Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance

Nuray Erin, Jelena Grahovac, Anamaria Brozovic, Thomas Efferth

PII: S1368-7646(20)30044-3

DOI: https://doi.org/10.1016/j.drup.2020.100715

Reference: YDRUP 100715

To appear in: *Drug Resistance Updates*

Received Date: 15 November 2019

Revised Date: 29 May 2020

Accepted Date: 7 June 2020

Please cite this article as: Erin N, Grahovac J, Brozovic A, Efferth T, Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance, *Drug Resistance Updates* (2020), doi: https://doi.org/10.1016/j.drup.2020.100715

Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance

Nuray Erin[1], Jelena Grahovac [2], Anamaria Brozovic [3], and Thomas Efferth[4]

[1] Department of Pharmacology, School of Medicine, Antalya, Turkey

[2] Laboratory for Experimental Pharmacology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

[3] Division of Molecular Biology, Ruđer Bošković Institute, Zagreb, Croatia.

[4] Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany

Corresponding author: Nuray Erin
Department of Medical Pharmacology,
School of Medicine, Akdeniz University
B-blok kat 1 Immunoloji
Antalya 07070, Turkey
Email: nerin@akdeniz.edu.tr
Phone 24222496159
ORCID : 0000-0002-6116-1970

Running title: Tumor microenvironment and overcoming chemoresistance

Abstract

It is well established that multifactorial drug resistance hinders successful cancer treatment. Tumor cell interactions with the tumor microenvironment (TME) is crucial in epithelial-mesenchymal transition (EMT) and multidrug resistance (MDR). TME-induced factors secreted by cancer cells and cancer-associated fibroblasts (CAFs) create an inflammatory microenvironment by recruiting immune cells. CD11b+/Gr-1+ myeloid-derived suppressor cells (MDSCs) and inflammatory tumor

associated macrophages (TAMs) are main immune cell types which further enhance chronic inflammation. Chronic inflammation nurture tumor-initiating/cancer stem-like cells (CSCs) induce both EMT and MDR leading to tumor relapses. Pro-thrombotic microenvironment created by inflammatory cytokines and chemokines from TAMs, MDSCs and CAFs is also involved in EMT and MDR. MDSCs are the most common mediators of immunosuppression and are also involved in resistance to targeted therapies, e.g. BRAF inhibitors and oncolytic viruses-based therapies. Expansion of both cancer and stroma cells causes hypoxia by hypoxia-inducible transcription factors (e.g. HIF-1α) resulting in drug resistance. TME factors induce the expression of transcriptional EMT factors, MDR and metabolic adaptation of cancer cells. Promoters of several ATP-binding cassette (ABC) transporter genes contain binding sites for canonical EMT transcription factors, e.g. ZEB, TWIST and SNAIL. Changes in glycolysis, oxidative phosphorylation and autophagy during EMT also promote MDR. Conclusively, EMT signaling simultaneously increases MDR.

Owing to the multifactorial nature of MDR, targeting one mechanism seems to be non-sufficient to overcome resistance. Targeting inflammatory processes by immune modulatory compounds such as mTOR inhibitors, demethylating agents, low-dosed histone deacetylase inhibitors may decrease MDR. Targeting EMT and metabolic adaptation by small molecular inhibitors might also reverse MDR. In this review, we summarize evidence for TME components as causative factors of EMT and anticancer drug resistance.

Abbreviations:5-FU, 5-fluorouracil; ABC, ATP-binding cassette; ABCA2/3, ABC transporter, subfamily A 2/3; ABCB1, ABC transporter, subfamily B 1 (MDR1, P-gp); ABCC1/4/5/10, ABC transporter, subfamily C 1/4/5/10; AKT, Akt serine/threonine kinase; AMPK, AMP-activated protein kinase; AXIN 2, axin 1-like (or axis inhibition protein 2); BCNU, bis-chlorethyl-nitroso-urea (carmustin); BCRP, breast cancer resistance protein; BMP2, bone morphogenetic protein 2; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BSO, buthionine sulfoximine; CAF, cancer-associated fibroblast; Cav-1/2, caveolin-1/2; CCL, chemokine (C-C motif) ligand; CCL1/2/5/11/15, C-C motif chemokine 1/2/511/15; CCR1, CC chemokine Receptor 1; CD8, cluster of differentiation 8; cDDP, cisplatin; CHK1, checkpoint kinase 1; CIC, cancer-initiating cell; CNT3, concentrative nucleoside transporter; COX2, cyclooxygenase 2; CRC, colorectal cancer; CSC, cancer stem-like cell; CSF-1R, colony stimulating factor 1 receptor, CXCL1,

chemokine (C-X-C motif) ligand 1; CXCR4/14, C-X-C chemokine receptor type 4/14; DM, double minute; EGF, epidermal growth factor; EGFL7, epidermal growth factor-like domain 7; EGFR, EGF receptor; EMT, epithelial-mesenchymal transition; EMT-TFs, EMT transcription factors; ENT1, equilibrative nucleoside transporter; ERK, extracellular regulated protein kinase; ETC1, MYB-like transcription factor; FGF, fibroblast growth factor; FOXC2/F2/M1, forkhead box transcription factors C2/F2/M1; G-CSF, granulocyte colony-stimulating factor; GLUT1; glucose transporter 1; GPER, G protein-coupled estrogen receptor; Hbx, hepatitis B virus X protein; HDM2/HDMX, aliases for MDM2, mouse double minute 2 homologue; HES1; hairy and enhancer of split 1; HGF, hepatocyte growth factor; HIF-1α, hypoxia-induced factor 1 alpha; HK2, hexokinase 2; HMBG1, extracellular high mobility group box 1; HNSCC, head and neck squamous cell carcinoma; HPOC, hybrid protein oxygen carrier; HSR, homogeneously stained region; IFN-β, interferon beta; IL-6/10/17A, interleukin 6/10/17A; IGF, insulin-like growth factor; JNK, c-jun N-terminal kinase; KLF5/8, Krüppel-like factor 5/8; KRAS, Kirsten Ras proto-oncogene; MAPK, mitogen-activated protein kinase; MCP1, monocyte chemotactic protein-1; M-CSF, macrophage colony stimulating factor; MDR, multidrug resistance; MDR1, multidrug resistance gene 1; MDSCs, myeloid-derived suppressor cells; MEK, mitogen-activated kinase kinase; MFG-E8, milk fat globule-epidermal growth factor 8 protein; miRNA/miR, microRNA; M-MDSC, monocytic MDSC; MRP1, multidrug resistance-related protein 1; mTOR, mammalian target of rapamycin; MYC; Myc proto-oncogene; basic helix-loop-helix transcription factor; NMSCs, human mesenchymal stem/stromal cells; NF-κB, nuclear factor kappa B cells; NOTCH, Notch homologue, translocation-associated (*Drosophila*); NOX1, NADPH oxidase 1; NSCLC, non-small cell lung cancer; oxidative phsphorylation (OXPHOS), oxidative phosphorylation protein; PAK1, p21 (RAC1) activated kinase 1; PDAC, pancreatic ductal adenocarcinoma; PDCD4, programmed cell death 4; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; P-gp, P-glycoprotein; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PMN-MDSC polymorphonuclear MDSC; pS6, phospho ribosomal protein S6; pSTAT3, phospho-signal transducer and activator of transcription 3; RNAi, RNA interference; RTK, receptor tyrosine kinase; SASP, senescence-associated secretory phenotype; SDF-1α, stromal cell-derived factor-1 alpha; shRNA, small hairpin RNA; siRNA, small interfering RNA; SIRT1, sirtuin 1; SLUG, Snail 2 zinc finger transcription factor; SMAD, human homology of Mad and Sma; SNAIL1, Snail 1 zinc finger transcription factor; SOX2, Sry-related high mobility group (HMG) box 2;

STAT1/3, signal transducer and activator of transcription 1/3; TAM, tumor-associated macrophages; TGF-β, tumor growth factor β; TIAM, T-lymphoma invasion and metastasis-inducing protein 1; TKI, tyrosine kinase inhibitor; TME, tumor microenviroment; TNBC, triple negative breast cancer; TNF-α, tumor necrosis factor α; TRAIL, tumour necrosis factor (TNF)-α-related apoptosis-inducing ligand; TWIST1, class A basic helix-loop-helix transcription factor 1; UCB, urothelial cancer of the bladder; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; WNT1, wingless Int-1 signal transducer; ZEB1, zinc finger E-box binding homeobox 1.

Key words: Chemotherapy; Hypoxia; Inflammation; Microenvironment, Multidrug resistance; Small molecules; Targeted therapy,

Table of contents:

1 Introduction
2 Tumor-associated macrophages
2.1 Function of tumor-associated macrophages
2.2 Mechanisms of TAM-related drug resistance
3 Myeloid-derived suppressor cells in the tumor microenvironment
3.1 Function of myeloid-derived suppressor cells
3.2 Mechanisms of MDSC-related drug resistance
3.3 MDSC-targeting therapeutic approaches
4 Cancer-associated fibroblasts
4.1 Function of cancer-associated fibroblasts
4.2 Correlation of cancer-associated fibroblasts with multidrug resistance and metastasis
5 Role of the EMT transcription factors and EMT-related metabolic adaptations in MDR
5.1. Micronenvironment signals involved in activation of EMT
5.2 Role of EMT transcription factors in MDR
5.3 Targeting of EM-TFs as a potential therapeutic approach
5.4 Effects of metabolic rewiring in EMT on MDR
5.5 Targeing of metabolic adaptations in EMT as a potential therapeutic approach
6 Role of hypoxia for metastasis and drug resistance

6.1. Hypoxia in tumor progression
6.2 Coexpression of HIF-1α and P-glycoprotein in clinical tumor biopsies
6.3 Molecular modes of action of hypoxia-induced MDR
6.4 Approaches to overcome hypoxia-induced MDR
7 Conclusion and perspectives
References

1 Introduction

Activation of the epithelial-mesenchymal transition (EMT) program in cancer cells results in increased invasive and metastatic properties as well as multidrug resistance (MDR). Factors provided by the tumor microenvironment (TME) play a major role in EMT, metastasis and MDR phenotype. MDR due to EMT and metastasis could be caused by (1) transmembrane pumps belonging to the ATP-binding cassette (ABC transporter) family (2) mechanisms independent of ABC transporters. Owing to the multifactorial nature of MDR, targeting one mechanism is not sufficient to overcome the resistance (Assaraf et al., 2019; Cui et al., 2018; Gacche and Assaraf, 2018; Gonen and Assaraf, 2012; Li et al., 2016b; Livney and Assaraf, 2013; Milman et al., 2019; Niewerth et al., 2015; Shapira et al., 2011; Vasconcelos et al., 2019; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016; Zhong and Virshup, 2020). Although ABC transporters have been extensively reported as a clinically relevant mechanism of MDR (Assaraf, 2006; Gottesman et al., 2002; Li et al., 2016b; Robey et al., 2007), the effectiveness of combination therapy with ABC transporter inhibitors in clinical trials were limited (Linn et al., 1995; Middleton et al., 2013; Weroha et al., 2011). Hence other drug-resistance mechanisms also have to be taken into account to overcome therapeutic failure in cancer patients. There is mounting evidence demonstrating a significant role of factors originating from tumor microenviroment (TME) for both responsiveness or resistance to various structurally and mechanistically unrelated anticancer drugs. The persistent production of inflammatory factors has been reported in TME-mediated EMT, metastasis and chemotherapy resistance (Acharyya et al., 2012; Bunt et al., 2006; Hartmann et al., 2005) (Gao et al., 2020; Krchniakova et al., 2020; Shaked, 2019). This may be due to inflammation-induced expansion and recruitment of macrophages and $CD11b^{+}/Gr\text{-}1^{+}$ myeloid-derived suppressor cells (MDSCs) (Szebeni et al., 2017; Xu et al., 2017) as well cancer-

associated fibroblasts (CAFs) (Bharti et al., 2016). Specifically, inflammatory cytokines such as tumor growth factor β (TGF-β) and interleukin 6 (IL-6) as well as chemokines that directly or indirectly induce EMT and metastasis are also involved in MDR (Bharti et al., 2016; Ghandadi and Sahebkar, 2016).

In the first part of the review, we therefore discuss the role of tumor-associated macrophages (TAMs), MDSCs and CAFs on MDR. In the second part of the review, we discuss the mechanisms of EMT-related drug resistance at the cellular and transcriptional level. We summarize the findings on the transcriptional factors and cell metabolism changes that are causative of EMT and which sustain the MDR phenotype in cancer cells. Finally, we focus on the indirect mechanisms of hypoxia-induced MDR and the relevance of ABC efflux transporters in this context.

2 Tumor-associated macrophages (Shapira et al., 2011)

2.1 Function of tumor-associated macophages

TAMs are derived from circulating monocytes recruited within the TME by chemokines such as (C–C motif) ligand-2 (CCL-2), CCL-3, CCL-4, CCL-5, CCL-7, CCL-8, CXCL-12 and cytokines, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), macrophage colony-stimulating factor (M-CSF), and interleukin (IL)-10 (Allavena et al., 2008; Cassetta et al., 2019; Chen et al., 2019; Condeelis and Pollard, 2006; Dudas et al., 2020; Li et al., 2020; Li et al., 2019; Lin et al., 2019; Mantovani et al., 2004; Murdoch et al., 2008; Sarode et al., 2020; Yamaguchi and Perkins, 2020; Zhang et al., 2020; Zins and Abraham, 2020). Macrophages are actively recruited to the TME from the bone marrow (Dalton et al., 2017). TAMs are abundant components of the TME and are highly plastic in nature. Macrophage phenotypes present in the TME represent a continuum and cannot be satisfactorily captured with the M1–M2 dichotomy, as previously reviewed in detail (Ginhoux et al., 2016; Hsieh and Wang, 2018). Similarly, the tumor-promoting role of TAMs has been extensively described (De Palma and Lewis, 2013; Li et al., 2020; Lin et al., 2019; Ruffell et al., 2012; Sarode et al., 2020; Zins and Abraham, 2020). Emerging evidence demonstrates that TAMs are also important components of microenvironment-related drug resistance.

Resistance to chemotherapy. Platinum-containing chemotherapy induced differentiation of monocytes into M2-like macrophages by enhancing the secretion of IL-6 and prostaglandin E2 (PGE2) from cervical and ovarian cancer cell lines, thus indirectly inducing chemoresistance

(Dijkgraaf et al., 2013). Accordingly, the prevention of TAM infiltration by an antibody against placental growth factor enhanced the efficacy of chemotherapy (Fischer et al., 2007).

Resistance to targeted therapies and immunotherapy. Receptor tyrosine kinase inhibitor (TKI) sorafenib induces recruitment of TAMs, which leads to drug resistance. Depletion of TAMs by zoledronic acid significantly enhanced the anti-tumor effect of sorafenib (Zhang et al., 2010). The macrophage levels within the tumor tissue increased with the emergence of resistance towards anti-VEGF therapy and depletion of macrophages restored sensitivity of tumors that were initially resistant to anti-VEGF therapy (Dalton et al., 2017). Similarly, TAM depletion restored T cell migration and infiltration into tumor islets. It also improved the efficacy of anti–PD-1 immunotherapy demonstrating that TAMs are responsible for intrinsic resistance to immunotherapy (Peranzoni et al., 2018).

2.2 Mechanisms of TAM-related drug resistance

Role of IL-6. Several cytokines, chemokines and growth factors secreted by TAMs are likely to mediate MDR. The pro-inflammatory cytokine IL-6 was secreted by TAMs (Xu et al., 2014) and induced signal transducer and activator of transcription 3 (STAT3) activation in cancer cells, leading to therapeutic resistance (Borsellino et al., 1995; Gritsko et al., 2006; Wu et al., 2013) (Diesendruck and Benhar, 2017; Kon and Benhar, 2019; Yin et al., 2019; Yin et al., 2017). IL-6 contributed markedly to poor therapeutic outcome, tumor relapse and aggressive tumor growth (Chang et al., 2013; Ghandadi and Sahebkar, 2016; Grivennikov and Karin, 2008; Kumari et al., 2016; Wu et al., 2013). Specifically, IL-6 induced immunosuppression in patients with advanced cancers (Bromberg and Wang, 2009; Grivennikov et al., 2010) and conferred therapeutic resistance in patients with prostate cancer (Culig and Puhr, 2012; Wu et al., 2013). IL-6-induced resistance was also due to increased cancer stem cell populations, which are mainly responsible for tumor refractoriness (Bharti et al., 2016). IL-6 was a potent inducer of resistance against TKIs directed against epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) (Yao et al., 2010) due to STAT3 activation (Yu et al., 2014; Zhong et al., 1994). Similarly, stromal cell-derived factor 1α (SDF-1α)-induced IL-6 upregulation mediated chemoresistance and apoptosis in multiple myeloma cells (Liu et al., 2019b). A neutralizing antibody for IL-6 increased the effectiveness of chemotherapy and gefitinib in various tumor models, including trastuzumab-resistant tumors (Zhong et al., 2016).

TAMs and cancer stem cells. Heterogeneous signals from the TME nurture tumor-initiating/cancer stem-like cells (CSCs), which are responsible for therapy resistance and tumor relapses (Chen et al., 2018; Colak and Medema, 2014; Paldino et al., 2014; Rycaj and Tang, 2014; Wang et al., 2014) (Assaraf et al., 2019; Leonetti et al., 2019b). TGF-β is one of the master players of stemness and is highly expressed in TAMs (Chen et al., 2018; Fan et al., 2014). It may also contribute to TAM-induced resistance towards anti-angiogenic treatments (Qin et al., 2015; Rolny et al., 2011). TAMs activated CSC properties in hepatocellular carcinoma by TGF-β1-induced EMT (Fan et al., 2014), which may led to resistance towards chemo- and targeted therapies (Dal Bo et al., 2020). For instance, TGF-β is primarily involved in erlotinib resistance, EMT and increased activation of the IL-6 axis in drug resistant bronchoalveolar metastatic carcinoma H1650 cells (Yao et al., 2010). Inhibition of the TGF-β activity using shRNA and TGF-β inhibitors increased the efficiency of sorafenib (Kang et al., 2017) in hepatocellular carcinoma. Silencing of TGF-β1 enhanced sensitivity of A549/DDP cells to cisplatin through the reversal of EMT (Wang et al., 2018).TAMs also provide survival signals to CSCs. Specifically, TAMs release milk fat globule-epidermal growth factor 8 protein (MFG-E8), which protected lung and colon CSCs from the cytotoxic effects of cisplatin. Similar to IL-6, MFG-E8 activated STAT3 in CSCs, enhancing their drug resistance (Jinushi et al., 2011). In accordance, TAM depletion also improved antitumor T cell responses and the efficacy of chemotherapy in a pancreatic cancer model (Mitchem et al., 2013).

Growth factors secreted by TAMs. Growth factors secreted by TAMs may also lead to MDR. Specifically, TAMs are a significant source of the epidermal growth factor (EGF) and insulin-like growth factor (IGF) in tumor tissues (Ireland et al., 2018; Vlaicu et al., 2013). EGF-triggered resistance to sunitinib, vandetanib, and sorafenib by transducing bypass survival signaling through ERK and AKT via activation EGFR in lung cancer cells (Chang et al., 2017) (Leonetti et al., 2019a; Leonetti et al., 2019b). In addition, blocking of IGF increased the efficacy of paclitaxel, a chemotherapeutic agent commonly used for the treatment of invasive breast cancer (Ireland et al., 2018). VEGF, a pro-angiogenic growth factor, is highly expressed in TAMs (Colegio et al., 2014; Qian and Pollard, 2010). Anti-VEGF therapy with bevacizumab (Cohen et al., 2009; Friedman et al., 2009; Lu-Emerson et al., 2015) or multiple RTK inhibitor sunitinib failed to improve survival

in patients with recurrent glioblastoma multiforme (Grisanti et al., 2019). This is likely due to M2-like macrophages, which promoted tumor angiogenesis and vascular abnormalization (Mazzieri et al., 2011; Qin et al., 2015; Rolny et al., 2011). TAMs, resistant to anti-VEGF therapy, showed increased secretion of alternative pro-angiogenic cytokines and chemokines, including platelet-derived growth factor (PDGF) and granulocyte-colony stimulating factor (G-CSF). The expression of VEGFR in macrophages was lower in patients who did not respond to anti-VEGF therapy compared to responders. Hence, VEGFR expression in macrophages may be a predictor of response to anti-angiogenic therapy (Dalton et al., 2017). Hence, increased expression of PDGF and G-CSF in macrophages is likely to be involved in drug resistance.

Other factors involved in drug resistance. TAMs induced gefitinib resistance in head and neck squamous carcinoma cells (HNSCC) by releasing chemokine (C-C motif) ligand 15 (CCL-15), a chemokine mainly expressed in the intestine and liver (Li et al., 2016d). Specifically, chemokine CCL-15 decreased the sensitivity to gefitinib through CC chemokine receptor 1 (CCR1) and NF-κB pathway signaling. Furthermore, serum CCL-15 levels in HNSCC patients were significantly correlated with patient prognosis (Yin et al., 2019).

TAMs mediated the suppression of T cells *in vitro* and *in vivo* in FVB PyMT mice (DeNardo et al., 2011). In addition, TAMs were responsible for the T cell-excluded tumor phenotype. Specifically, TAMs prevented migration and invasion of tumor nests containing $CD8^+$ T cells (Peranzoni et al., 2018), which are required for the efficiency of immunotherapy. Defective T cell migration into and within tumors was a determinant of resistance to cancer immunotherapy (Melero et al., 2014). Melanoma tumors of patients, who responded well to treatment with anti–PD-1 antibodies were characterized by the presence of $CD8^+$ T cells in the core of the tumor in contact with malignant cells (Herbst et al., 2014). Conversely, tumors of patients, who did not respond to anti–PD-1 antibodies either were devoid of T cells or contained T cells preferentially located around tumor cell regions (Herbst et al., 2014). Macrophage depletion by PLX3397 in tumor-bearing mice increased the infiltration of tumor nests with $CD8^+$ T enhancing anti-tumoral effects of anti–PD-1 treatment (Peranzoni et al., 2018).

In conclusion, TAMs represent an important component of TME-related drug resistance as illustrated in Figure 1. Therefore, strategies to deplete TAMs or block cancer-induced M2-like macrophage programming, bear the potential to increase treatment efficiency and to decrease

resistance to anti-cancer agents (Coussens et al., 2013; Hagemann et al., 2008; Jaiswal et al., 2010). Spesifically combination of TAM depletion with dendritic cell immunotherapy generated robust and durable antitumor immunity. Depletion of TAMs using colony stimulating factor 1 receptor (CSF-1R) kinase inhibitor PLX3397 (pexidartinib) alone, however, did not improve survival. These results demonstrated that decreasing local TAM-mediated immune suppression was only effective in the presence of immune activation (Dammeijer et al., 2017). Given the fact that the phenotype of TAMs varied and that under certain conditions TAMs cooperated with T cells to promote tumor regression (Saha et al., 2017; Thoreau et al., 2015), the complete depletion of macrophages may exert unwanted consequences. Several alternative approaches were under evaluation, *e.g.* reprogramming macrophages toward an antitumor phenotypic state (Schultze, 2016). Nevertheless, clinical studies are in progress in several solid tumor types, where macrophages are targeted by CSF-1R inhibitors (Cannarile et al., 2017). It can be expected that these clinical studies will yield better approaches targeting TAMs to reverse MDR and tumor progression.

3 Myeloid-derived suppressor cells in the tumor microenvironment

3.1 Function of myeloid-derived suppressor cells

Tumor-infiltrating myeloid-derived suppressor cells (MDSCs) are the most common mediators of immunosuppression in tumors. They orignate from immature myeloid cells that fail to differentiate into granulocytes, macrophages, or dendritic cells. MDSCs co-express Gr-1 and CD11b myeloid lineage differentiation markers in mouse as well as either or both of the common myeloid markers CD33 or CD11b in cancer patients (Gabrilovich et al., 2012; Talmadge and Gabrilovich, 2013) (Hsu et al., 2019; Zhang et al., 2018b). MDSCs consist of two large groups of cells: granulocytic or polymorphonuclear (PMN-MDSCs) and monocytic MDSCs (M-MDSCs). PMN-MDSCs are phenotypically and morphologically similar to neutrophils, whereas M-MDSCs are more similar to monocytes (Gabrilovich et al., 2007; Gabrilovich et al., 2012; Sasidharan Nair et al., 2020). Both the monocytic and the granulocytic subsets display immunosuppressive activity in tumors (Di Mitri et al., 2015). The existence of a third small population of MDSCs represented by cells with colony forming activity was demonstrated in human studies (Dumitru et al., 2012).

Inflammatory cytokines and chemokines mediate the recruitment and expansion of MDSCs. Specifically IL-6, CXCL1, CCL5, CCL2/monocyte chemotactic protein-1 and CXCL12 caused

accumulation and expansion of MDSCs (Acharyya et al., 2012; Blattner et al., 2018; Gabrilovich et al., 2012; Hartmann et al., 2005; Hawila et al., 2017; Hsu et al., 2015; Huang et al., 2007; Panka et al., 2013; Schlecker et al., 2012; Veglia et al., 2018; Xu et al., 2017; Zhang et al., 2013). Among the other chemokines/receptors, CXCR2 and CX3CR1 (the cognate receptor for CX3CL1) activation mediated granulocytic MDSC trafficking into tumors (Hart et al., 2014). Among the chemokine receptors, CCR5 expressed on MDSCs in melanoma patients played an important role for their recruitment to the TME by CCR5 ligands (CCL3, CCL4 and CCL5) ((Blattner et al., 2018; Hawila et al., 2017). $CCR5^+$ MDSCs displayed higher immunosuppressive potential than their $CCR5^-$ counterpart (Blattner et al., 2018), pointing to the heterogeneous nature of MDSCs. MDSCs suppressed both innate and adaptive immunity in various cancer types (Kumar et al., 2016; Ostrand-Rosenberg and Fenselau, 2018; Parker et al., 2015; Tcyganov et al., 2018; Umansky and Sevko, 2012). Hence, MDSCs hindered the anti-cancer activity of immunotherapies including immune checkpoint inhibitors (Weber et al., 2018). Growing evidence also demonstrated, however, that MDSCs were involved in resistance to therapeutic approaches other than immunotherapies as explained below. Factors involved in the expansion and recruitment of MDSCs as well as inflammatory factors secreted by MDSCs were likely to mediate chronic inflammation (Meyer et al., 2011) and consequently MDR.

Resistance to anti-angiogenic therapy. The frequent emergence of resistance to anti-angiogenic therapy is a major hindrance towards curative cancer therapy (El Alaoui-Lasmaili and Faivre, 2018; Gacche and Assaraf, 2018; Haibe et al., 2020)**.** Inherent anti-VEGF refractoriness was associated with infiltration of the tumor tissue by $CD11b^+Gr1^+$ myeloid cells. Specifically, combining anti-VEGF treatment with a monoclonal antibody that targets myeloid cells inhibited growth of refractory tumors more effectively than anti-VEGF therapy alone (Shojaei et al., 2007a). Similarly, increased MDSCs and related inflammatory chemokines within the TME enhanced angiogenesis and metastasis and were involved in resistance to small molecule inhibitors of VEGFR2 (Ebos et al., 2009; Shojaei et al., 2007b; Yang et al., 2004; Yang et al., 2008). Inhibition of SDF-1 production with the HDM2/HDMX antagonist MI-319 prevented the emergence of resistance to small molecular inhibitors of VEGFR2 in renal cell carcinoma xenograft tumors and inhibited the influx of MDSCs (Panka et al., 2013).

Resistance to targeted therapies. MDSCs also mediated resistance to targeted therapies such as BRAF inhibitors (vemurafenib and dabrafenib) in melanoma (Steinberg et al., 2017). Classically, reactivation of the MAPK pathway is involved in tumor resistance to BRAF inhibitors ((Johnson et al., 2015). However, acquired resistance to BRAF inhibitors still developed in the presence of MEK inhibitors (Long et al., 2014). Resistance to therapy was, in part, due to extrinsic factors present in the TME, including chemokines such as CCL2. This chemokine is also referred to as monocyte chemotactic protein-1 (MCP-1) ((Knight et al., 2013), which recruits MDSCs (Steinberg et al., 2017). CCL2 was also associated with anti-PD-1 resistance (Hugo et al., 2016; Peng et al., 2016) and was connected to increased tumorigenesis in different tumor types (Yao et al., 2012; Zollo et al., 2012).

Resistance to oncolytic viruses-based therapies. MDSCs are critical determinants of resistance to oncolytic viruses-related therapies (Hou et al., 2016). Oncolytic viruses are vectors designed to selectively replicate in, and destroy cancer cells. Various treatments based on oncolytic viruses are currently undergoing clinical testing (Andtbacka et al., 2016; Heo et al., 2013). TME was also involved in the anti-tumoral effects of oncolytic viruses, since oncolytic virus-mediated immunotherapeutic activity was more important than oncolytic virus-related cytotoxicity (Hou et al., 2016). COX2-mediated production of prostaglandin E2 (PGE2) is one of the key determinant of MDSC tumor infiltration (Fujita et al., 2011; Kalinski, 2012; Obermajer et al., 2011; Rodriguez et al., 2005). In accordance, inhibiting PGE2, the main product of cyclooxygenases in myeloid and stromal cells, reduced MDSC within TME and re-sensitized resistant tumors to therapy with oncolytic viruses (Hou et al., 2016).

Resistance to chemotherapy. Although many studies documented an indirect contribution of MDSCs to drug resistance (see below), a recent study demonstrated the direct contribution of MDSCs to chemoresistance. Spesifically, depletion of MDSC by administration of an anti-Gr-1 antibody sensitized 5-fluorouracil-resistant H22 hepatoma to chemotherapy in immunocompetent C57BL/6N mice(Xu et al., 2017) (Xu et al., 2017).

3.2 Mechanisms of MDSC-related drug resistance

Granulocyte colony-stimulating factor (G-CSF), a well-known hematopoietic cytokine regulating granulopoiesis, is required for progenitor cells to differentiate into granulocytic lineage, such as neutrophils, eosinophils and basophils (Natori et al., 2002). G-CSF and its receptor (G-CSFR) were aberrantly expressed in various human tumors including gastric and colon (Morris et al., 2014), bladder (Chakraborty and Guha, 2007), pancreatic (Liongue et al., 2009), ovarian and cervical cancers (Savarese et al., 2001). G-CSF production was associated with poor clinical outcome and MDR (Kawano et al., 2015; Kowanetz et al., 2010; Shojaei et al., 2009). As shown in tumor cell lines, *in vivo* models, and clinical samples of cervical carcinoma, G-CSF expression was significantly associated with increased number of MDSCs, decreased survival, and chemoresistance. The depletion of MDSC by splenectomy or the administration of anti-Gr-1 antibody, sensitized G-CSF-producing cervical cancer cells to cisplatin (Kawano et al., 2015). Similarly, in a colitis-associated cancer, G-CSF promoted MDSCs survival and activation through the STAT3 signaling pathway. Inhibition of G-CSF activity with monoclonal antibody treatment reduced MDSC accumulation and decreased size and number of the tumors (Li et al., 2016c).

Increased coagulation: A pro-thrombotic microenvironment revealed enhanced inflammatory responses (Levi et al., 2004; Vendramini-Costa and Carvalho, 2012) and induced chemoresistance (Nierodzik and Karpatkin, 2006), as observed following cytotoxic treatment by cisplatin and cyclophosphamide (Alexander et al., 2015; Alexander et al., 2016; Swystun et al., 2011). A cross-talk between coagulation system and an inflammatory microenvironment further heightened the inflammatory activity (Danckwardt et al., 2011; Levi et al., 2004). Thrombin increased TGF-β release and activation (Alexander et al., 2015) leading to chronic inflammation, accumulation and expansion of MDSCs (Bunt et al., 2006; Levi and van der Poll, 2010). Accordingly, dabigatran etexilate, a direct thrombin inhibitor and cisplatin co-treatment exhibited significantly greater anti-tumor efficacy than cisplatin alone. In a murine ovarian cancer model, co-treatment decreased MDSCs and pro-tumorigenic cytokines leading to a concomitant increase in $CD8^+$ effector T-cell activity (Levi and van der Poll, 2010). Similarly, in breast cancer, dabigatran etexilate and cyclophosphamide co-treatment reduced the accumulation of immunosuppressive MDSCs and TGF-β and induced markedly more potent anti-tumor and anti-metastatic effects (Alexander et al., 2016).

Transforming growth factor β1 (TGF-β1). MDSCs are an abundant source of TGF-β1 production within TME (Bierie and Moses, 2010). TGF-β1 secreted by MDSCs (Colak and Ten Dijke, 2017; Oshimori et al., 2015) may facilitate resistance to a wide range of anti-cancer agents. TGF-β1 inhibited antigen-specific CD8+ T-cell effector functions as demonstrated in melanoma (Ahmadzadeh and Rosenberg, 2005) and increased the number and immunosuppressive capacity of regulatory T cells (Hu et al., 2018; Huber et al., 2004; Marie et al., 2005; Polanczyk et al., 2019). TGF-β also abolished T cell activation by inhibiting the DC maturation processes (Weber et al., 2005), which thus impeded anti-tumor immune response. In addition, TGF-β-induced EMT and enrichment of CSCs as well as immune suppression were likely to be responsible for drug-resistance and metastasis ((Daroqui et al., 2012; Erin et al., 2018a; Kajiyama et al., 2007; Liu et al., 2017a; Mallini et al., 2014; Singh and Settleman, 2010; Wang et al., 2018). These effects of TGF-β1 play a significant role in resistance to targeted therapies such as TKI (Huang et al., 2012; Kang et al., 2017; Weber et al., 2018) and to cytotoxic agents (Kajiyama et al., 2007; Mallini et al., 2014; Singh and Settleman, 2010). Hence, MDSCs by secreting TGF-β were involved in MDR. Reciprocally, TGF-β may mediate MDSCs-induced resistance to immune-check point inhibitors (Weber et al., 2018).

Other factors: In a hepatocellular carcinoma model, cancer cell-derived IL-6 activated MDSCs-mediated chemoresistance, which was prevented by an IL-6-neutralizing antibody or by depleting MDSCs(Xu et al., 2017) (Xu et al., 2017). MDSC were also a source for the production of the EF-hand calcium-binding proteins S100A8 and S100A9 (Sade-Feldman et al., 2013; Turovskaya et al., 2008). S100A8 and S100A9 are pro-inflammatory factors, which were associated with chemoresistance (Wang et al., 2013; Yang et al., 2014). Besides certain chemotherapeutic and targeted therapies, commonly used adjuvants (*i.e.* corticosteroids) also induced MDSCs (Varga et al., 2008). These results explained the faster progression of tumors in patients treated with glucocorticoids for prolonged periods (Karagas et al., 2001).

3.3 Therapeutic approaches targeting MDSCs

Therapies targeting MDSCs, and inflammatory factors activating MDSCs or secreted from MDSCs (Weber et al., 2018) are warranted as adjunct therapy to directly treat malignant tumors. Certain cytotoxic agents such as paclitaxel (Sevko et al., 2013) or gemcitabine (Eriksson et al., 2016),

decreased MDSC frequency and increased therapeutic efficiency. Inhibiting STAT3, a main regulator of MDSC immunosuppressive activity (Condamine and Gabrilovich, 2011; Kumar et al., 2016; Vasquez-Dunddel et al., 2013), may also prevent or attenuate the development of drug resistance.

PGE2 is a main product of cyclooxygenases in myeloid and stromal cells and is one of the key mediators of immunopathology in cancer (Kalinski, 2012). PGE2 was shown to be necessary for the development of suppressive TAMs (Heusinkveld et al., 2011; Stolina et al., 2000)) and MDSC (Fujita et al., 2011; Obermajer et al., 2011; Sinha et al., 2007). In addition, MDSCs expressed high levels of COX2 and were a major source of PGE2 secretion in human cancer (Obermajer et al., 2011). Hence, inhibition of PGE2 production using non-selective or COX2-selective blockers as well as selective antagonists of PGE2 receptors (Ganesh et al., 2018; Markovic et al., 2017) is likely to prevent MDSC-related MDR.

Lenalidomide, an immune modulatory compound, was included in several current regimens to treat myeloma due to its beneficial efficacy and safety profile (Bartlett et al., 2004; Rollig et al., 2015). Lenalidomide alone decreased the number of systemic MDSCs and regulatory T cell in tumor-bearing but not in naive mice (Sakamaki et al., 2014). Lenalidomide also induced strong anti-inflammatory effects (Yamamoto et al., 2019), which may have been responsible for the suppression of MDSCs, since inhibition of inflammation using CD200 mimetics also decreased MDSCs (Erin et al., 2015; Erin et al., 2018b) and increased the therapeutic potential of doxorubicin (Erin et al., 2020).

Inhibition of mTOR activity with everolimus is a relatively new therapeutic approach for various carcinomas, including breast, prostate, neuroendocrine tumors and renal cell carcinoma (Deniz et al., 2019; George et al., 2019; Huijts et al., 2019; Larouche et al., 2019; Schmid et al., 2019; Wen et al., 2019). Everolimus in combination with metronomic cyclophosphamide led to a reduction in MDSCs and a sustained level of the $CD8^+$ T-cell population in patients with prostate cancer. This result further demonstrated that inhibition of MDSC activity also enhanced the efficacy of cytotoxic chemotherapy (Huijts et al., 2019).

Decitabine, a demethylating agent with immunoregulatory effects, depleted MDSCs *in vivo* by inducing apoptosis at relatively low doses (Zhou et al., 2017) and inhibited myeloma growth *in vivo* (Zhou et al., 2019). Histone deacetylase inhibitors are another class of drugs for various carcinomas, including hematological malignancies as well as common solid tumors (lung, breast

and prostate cancer) (Halsall and Turner, 2016). Histone deacetylase inhibitors decreased accumulation of MDSCs in the spleen, blood and tumor bed and increased the proportion of cytotoxic T cells in Balb-c mice with 4T1 mammary tumors (Wang et al., 2017a). This result demonstrated that these group of drugs may also enhance anti-tumor effects of chemotherapeutics in tumors abundantly infiltrated with MDSCs. The role of MDSCs in MDR is illustrated in Figure 2.

4 Cancer-associated fibroblasts

4.1. The functions of cancer-associated fibroblasts

Apart from the tumor itself, the TME is a heterogeneous population of different cells. The tumor recruits endogenous stromal cells in its neighbourhood (Bussard et al., 2016; Cammarota and Laukkanen, 2016). These cells promoted extracellular matrix remodelling, angiogenesis, cellular migration, invasion and drug resistance. Furthermore, these cells generated an environment, which was capable of evading the immunosurveillance through production and secretion of various chemokines, cytokines and growth factors (Liu et al., 2019b). Tumor-associated stromal cells arose from at least six distinct cellular origins: fibroblasts, pericytes, bone marrow-derived mesenchymal stem cells (MSCs), adipocytes, endothelial cells that underwent EMT, or tumor cells that underwent EMT. The transition of these cells occurs by soluble factors, microRNAs (miRNAs) or exosomes, and results in the formation of the different cell subtypes: CAFs, cancer-associated adipocytes, or cancer-associated endothelial cells.

4.2 Correlation of cancer-associated fibroblasts with multidrug resistance and metastasis

There is mounting evidence for the role of CAFs in tumor drug resistance and metastasis (Chen and Song, 2019; Fiori et al., 2019; Kadel et al., 2019; Liu et al., 2019b)The concept of EMT has gained tremendous attention in cancer research. Here, we are discussing the evidence showing the role of CAFs and related events, as well as possible key molecules, which are important for both, drug resistance and metastasis. These molecules are either produced by CAFs directly or secreted from tumor cells influencing further CAFs or other cells in the stroma, which reprogram them to become supporters of tumor growth and progeression (Kadel et al., 2019). For example, cell-free medium collected from CAF cultures induced EMT in human head and neck carcinoma cells enhancing their viability as well as decreasing their sensitivity to cisplatin treatment (Steinbichler

et al., 2016). Activated gastric CAFs correlated with poor prognosis of cancer patients and contributed to the malignant phenotype and the development of resistance to 5-fluorouracil by paracrine signalling in gastric cancer (Ma et al., 2018).

There are different types of molecules that are involved in chemoresistance and promotion of metastasis including chemokines, cytokines, membrane proteins, and chromatin proteins (Figure 3). Caveolin-1 (Cav-1) plays a role in tumorigenesis via its various functions in lipid transport, membrane trafficking, gene regulation, and signal transduction (Koleske et al., 1995) (Ketteler and Klein, 2018; Lamaze and Torrino, 2015). It is down-regulated in CAFs from human breast cancer compared to normal fibroblasts isolated from the same patient (Mercier et al., 2008). Breast cancer patients lacking stromal Cav-1 benefit from tamoxifen therapy, since Cav-1 acts as a tumor suppressor in the stromal environment. More specifically, loss of Cav-1 in CAFs predicted early tumor recurrence, lymph node metastasis, and tamoxifen-resistance (Witkiewicz et al., 2009). In addition, Cav-1-deficient stromal fibroblasts contribute to tumor growth and angiogenesis by providing energy-rich metabolites in a paracrine fashion. This phenomenon has been termed *reverse Warburg effect* (Pavlides et al., 2009) (Martinez-Outschoorn et al., 2014; Wilde et al., 2017). A two-component human tumor xenograft model system, was established in nude mice, in which the animals were co-injected with human MDA-MB-231 breast cancer cells and wild-type versus Cav-$1^{(-/-)}$ deficient stromal fibroblasts. These mice were treated with glycolysis inhibitors, which were functionally blocking the positive effects of Cav-1-deficient stromal fibroblasts on breast cancer growth. Thus, pharmacologically induced metabolic restriction (by treatment with glycolysis inhibitors) may be a promising new therapeutic strategy for breast cancers that lack stromal Cav-1 expression (Bonuccelli et al., 2010). Furthermore, CAFs of MCF-7 breast cancer lacking caveolin-2 (Cav-2) better induced EMT, indicating that CAFs contributed to a more malignant phenotype. Their role in therapy resistance should therefore be considered for breast cancer treatment (Soon et al., 2013). A possible role of another membrane located protein, β1-integrin, in anti-hormone therapy response in breast cancer patients was suggested too. G protein-coupled estrogen receptor (GPER) and epidermal growth factor receptor/extracellular regulated protein kinase (EGFR/ERK) signalling upregulated β1-integrin expression and activated downstream kinases, which contributed to CAF-induced cell migration and EMT in tamoxifen-resistant MCF-7R cells. GPER contributed to tamoxifen resistance by interaction with the TME in a β1-integrin-dependent pattern ((Yuan et al., 2015).

Conditioned media collected from CAFs isolated from human breast cancer tissues significantly induced migration of MDA-MB-231 breast cancer cells and protected them from doxorubicin-induced cell death probably by extracellular high mobility group box 1 (HMBG1) protein released from dying cancer cells (Amornsupak et al., 2014). Furthermore, lung fibroblasts reduced melanoma sensitivity to the BRAF inhibitor vemurafenib. In the presence of fibroblasts, the melanoma cells acquired a de-differentiated mesenchymal-like phenotype. Upon drug treatment, melanoma cells maintained high levels of phosphorylated ribosomal protein S6 (pS6), *i.e.* active mammalian target of rapamycin (mTOR) signalling, which was suppressed in vemurafenib-sensitive cells without stromal contacts (Seip et al., 2016).

Tumors recruited human MSCs and induced their conversion into CAFs (Jung et al., 2013; Mishra et al., 2008). The cross-talk between stromal cells and TRAIL-sensitive cancer cells reduced metastatic features of triple-negative MDA-MB-231 breast cancer cells (Yoon et al., 2016). T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1) mediated resistance to chemotherapeutic agents via enhancement of stemness. Clinical data supported the importance of TIAM1 in colorectal cancer drug resistance. Furthermore, CAFs induced TIAM1 overexpression in colorectal cancer cells and enhanced drug resistance (Izumi et al., 2019).

miRNAs are involved in the regulation of gene expression at the posttranscriptional level by degrading their target mRNAs and/or inhibiting their translation. They are important molecules affecting tumor drug resistance and metastasis (Brozovic, 2017; Si et al., 2019)(Leonetti et al., 2019a; Naser Al Deen et al., 2019). Oncogenic miR-21 was overexpressed in most solid tumors (Feng and Tsao, 2016). This miRNA protected colorectal cancer cells from oxaliplatin-induced cell death. Ectopic stromal miR-21 expression increased cell invasiveness (Bullock et al., 2013). Gemcitabine-resistant pancreatic ductal adenocarcinoma (PDAC) patients displayed higher miR-21 levels and more activated CAFs. CAFs with high miR-21 expression had elevated MMP-3, MMP-9, PDGF, and CCL7 expression and promoted the invasiveness of PDAC tumor cell lines. MiR-21 overexpression also contributed to the activation of CAFs by regulating the programmed cell death 4 (*PDCD4*) gene (Zhang et al., 2018a). By secreting stromal cell-derived factor-1/ chemokine (C-X-C motif) ligand 12 (SDF-1/CXCL12), which was regulated by miR-1, CAFs enhanced cell proliferation and cisplatin resistance in lung cancer A549 and 95D cells by the C-X-C chemokine receptor type 4 (CXCR4)-mediated signalling pathway (Li et al., 2016a). CXCL1 was expressed in human urothelial bladder cancer, especially in high-grade and late-stage tumors

and was secreted into the stromal area or bloodstream. The disruption of signalling of this chemokine may represent a promising therapeutic approach for bladder cancer (Miyake et al., 2016). Down-regulation of miR-29b in CAFs promoted cell growth and metastasis of SK-BR-3 and MCF-7 breast cancer cells by activating p38-STAT1 (signal transducer and activator of transcription 1), which regulated CXCL11 and CXCL14 (Liu et al., 2017b). The importance of chemokines was further confirmed by results showing that CAFs-derived CXCL12 activated CXCR4 in MDA-MB-231 cells and, thereby, significantly enhanced cell proliferation (Ham et al., 2018).

Interestingly, chemotherapy itself activated CAFs, which further promoted self-renewal of colorectal cancer-initiating cells (CIC; characterized by intrinsic drug resistance). Moreover, chemotherapy induced cancer growth *in vivo* associated with the secretion of different chemokines and cytokines such as interleukin-17A (IL-17A). As CICs contributed to tumor invasion and metastasis, the exogenous IL-17A nearly doubled the CIC migration rate (Lotti et al., 2013). IL-6 as an upstream regulator played an important role in increasing CXCR7 expression as a major inducer of tumor cell proliferation and drug resistance (Qiao et al., 2018). After docetaxel therapy, MDA-MB-231 cells co-cultured with primary CAFs displayed increased adhesive, invasive and proliferative properties as compared with MDA-MB-231 cells without CAFs co-culture. Additionally, 35 differentially expressed genes were identified among CAFs before and after chemotherapy (Rong et al., 2013). Gemcitabine-resistant CAFs expressed a pro-inflammatory senescence-associated secretory phenotype with enhanced migration capacity, viability and drug resistance of human MiaPaCa-2 and PANC-1 pancreatic ductal adenocarcinoma cells. Signalling pathways controlling senescence-associated secretory phenotype induction after chemotherapy, including stress-associated MAPK activation, represent potential therapeutic targets to enhance the efficacy of chemotherapeutic regimens (Toste et al., 2016). A recent review paper reported a detailed analysis about the interplay between tumor cells and CAFs (Fiori et al., 2019). In conclusion, CAFs and other TME factors represent important regulators of tumor behavior and additional *in vivo* studies should be performed to explore possibilities for therapeutic intervention that could be translated to clinical practice.

5 Role of the EMT transcription factors and EMT-related metabolic adaptations in MDR

5.1 Micronenvironmental signals involved in activation of EMT

EMT is the differentiation program necessary for tissue morphogenesis during embryonic development, in which cells lose some of their epithelial characteristics and acquire mesenchymal migratory properties. Activation of EMT in cancer cells results in increased invasive and metastatic potential as well as drug resistance. EMT is regulated by a limited number of transcription factors, mainly from the SNAIL, TWIST and ZEB family (De Craene and Berx, 2013; Dongre and Weinberg, 2019; Ribatti et al., 2020; Wilson et al., 2020; Yang and Weinberg, 2008). Various molecules in the extracellular microenvironment derived from CAFs, tumor-infiltrating immune cells and vessels – TGF-β, FGF, EGF, HGF, IGF-1 as well as members of the Hedgehog, Notch and Wnt signaling pathway – can induce EMT. Here, we briefly mention environmental signals directly inducing the expression of EMT transcription factors (EMT-TFs) that contribute to MDR to set the stage for reviewing the role of EMT-TFs in multidrug resistance.

Transforming growth factor β1 (TGF-β1).

Induction of EMT by TGF-β is regulated through SMAD-dependent and SMAD-independent transcriptional regulation of transcription factors of the SNAIL, TWIST and ZEB family as well as miRNAs (*e.g.* miR-34, miR200) (Moustakas and Heldin, 2012; Xu et al., 2009). TGF-β and FGF cooperated in the induction of SNAIL expression (Peinado et al., 2003), and TGF-β induced SNAIL in both cancer cells and CAFs, which led to EMT and fibroblast activation, respectively (Lambies et al., 2019). Adult fibroblasts did not express SNAIL, but SNAIL was found in fibroblasts of malignant tumors. In colorectal cancer, SNAIL overexpressing CAFs induced chemoresistance of colon cancer cells to 5-FU and paclitaxel *in vitro* and *in vivo.* This resistance was mediated by CAF-derived CCL1 and TGF-β (Li et al., 2018a). Perivascular TGF-β could also promote the survival of carcinoma progenitor cells, by reprogramming glutathione metabolism, thus increasing porgenitor cell drug resistance and cancer recurrence (Oshimori et al., 2015). In gastric cancer, the TGF-β/ZEB axis played a role in trastuzumab resistance (Zhou et al., 2018).

Additional factors.

Various receptor tyrosine kinases (RTKs) promoted EMT through ERK, JNK and MAPK signaling pathway induction of EMT transcription factors (Gonzalez and Medici, 2014). Hepatocyte growth factor (HGF) induced EMT by induction of SNAIL and SLUG (Grotegut et al., 2006; Savagner et

al., 1997), insulin-like growth factor 1 (IGF-1) by induction of SNAIL and ZEB1 (Graham et al., 2008; Kim et al., 2007) and epidermal growth factor (EGF) by induction of TWIST (Lo et al., 2007).

WNT ligands and WNT/β catenin signaling pathway promoted EMT on several levels (Gonzalez and Medici, 2014). In terms of induction of EMT transcription factors, the WNT/GSK-3β/AXIN 2 axis stabilized *SNAIL* (Yook et al., 2006; Zhou et al., 2004), and WNT1 upregulated TWIST expression (Howe et al., 2003). SLUG and SNAIL were also induced by NOTCH (Leong et al., 2007) and Hedgehog signaling (Li et al., 2005), respectively.

5.2 Role of EMT transcription factors in multidrug resistance

It has long been postulated that EMT-TFs contribute to phenotypic acquired resistance (Goossens et al., 2017). Most recently, it has been shown by single cell sequencing that a subpopulation with the upregulated EMT and stemness genes with a predisposition to drug resistance was also present in the parental drug-naive cancer cell population (Prieto-Vila et al., 2019). The promoters of many ABC transporter genes contain binding sites for EMT-TFs, hence, EMT program activation simultaneously increased drug resistance (Saxena et al., 2011; Xin et al., 2013). EMT-TFs also induced drug resistance independently of ABC transporters by increasing cellular resistance to drug-induced apoptosis (Li et al., 2018a; Tomono et al., 2017). It has even been suggested that the expression of EMT-TFs in tumor biopsies may serve as predictive marker for therapy-sensitive or -resistant subgroups (Goossens et al., 2017). Here, we focus on the major EMT-TFs implicated in the MDR phenotype.

SNAIL (SNAIL1) and SLUG (SNAIL2) are zinc-finger transcriptional repressors, which induce EMT by epithelial gene repression (i.e. repressing the E-cadherin, occludin, and claudin genes). SNAIL induced both expression of P-glycoprotein/MDR1 (Li et al., 2011) and BCRP (Chen et al., 2010) as well as P-glycoprotein (P-gp) drug efflux activity (Tomono et al., 2017). SNAIL and SLUG also induced chemoresistance independently of ABC transporters. SNAIL repressed cyclin D2 transcription, thus impairing cell cycle progression and conferring resistance to both intrinsic and extrinsic apoptotic pathways (Vega et al., 2004). In cancer, this contributed to drug resistance by repression of apoptosis mediated by the DNA-damage response pathway (Haslehurst et al., 2012; Kajita et al., 2004), antagonism of p53-induced apoptosis and promotion of the CSC

phenotype (Kurrey et al., 2009). Concomitantly with EMT, SNAIL overexpression also induced metabolic reprogramming in cancer cells, *i.e.* increased glucose uptake and lactate production as well as reduced mitochondrial respiration (Kim et al., 2017; Lee et al., 2012; Liu et al., 2019a; Thoreau et al., 2015), thus enhancing chemoresistance (see the section on the metabolic rewiring in EMT).

TWIST1 and TWIST2 are basic helix-loop-helix TFs that are major regulators of the mesenchymal phenotype during embryonic development. They are highly upregulated in multiple cancers and are associated with poor prognosis and invasive potential. TWIST1 conferred increased resistance to both P-gp and non-P-gp substrate drugs (Li et al., 2009). It regulated P-gp (MDR1/ABCB1) expression and drug efflux activity (Deng et al., 2016; Li et al., 2018a; Zhu et al., 2012), as well as expression of other ABC transporters: MRP1 (ABCC1) (Liu et al., 2017c), ABCA2, ABCA3, ABCC5 and ABCC10 (Saxena et al., 2011). TWIST and SNAIL both suppressed the expression of nucleoside transporters, thus inducing chemoresistance to nucleoside analogues (Zheng et al., 2015). In a PDAC mouse model with genetic deletion of TWIST1 or SNAIL1, equilibrative nucleoside transporter 1(ENT1) and concentrative nucleoside transporter 3 (CNT3) were significantly upregulated. This contributed to response to gemcitabine (Zheng et al., 2015). TWIST/*TWIST* and SNAIL/*SNAIL* were frequently co-expressed in human cancers. In breast cancer, SNAIL2 (SLUG) expression was directly dependent on TWIST1. TWIST1 also increased the expression of the proto-oncogene AKT serine/threonine kinase 2 (AKT2), and decreased chemosensitivity to paclitaxel by increased cell survival signaling (Cheng et al., 2007). Given the role of SLUG in conferring resistance to programmed cell death (Kajita et al., 2004), the TWIST/SLUG/SNAIL axis strongly contributes to MDR (Shen et al., 2017; Tomono et al., 2017).
ZEB1 is a zinc-finger E-box binding homeobox 1 transcription factor that induces EMT mostly by transcriptional upregulation. ZEB1 induced resistance to conventional chemotherapeutic drugs with divergent mechanisms of action (Arumugam et al., 2009; Lazarova and Bordonaro, 2017; Siebzehnrubl et al., 2013). ZEB1 increased the expression of multiple ABC transporters (MRP1, BCRP, ABCC4 and ABCC5) in several breast cancer cell lines *in vitro* (Saxena et al., 2011). ZEB1 also protected cells from genotoxic stress caused by chemotherapy by checkpoint kinase 1 (CHK1) and promotion of recombinant-dependent DNA repair (Zhang et al., 2014) in radioresistant human

breast cancer cells. In non-small lung cancer model, ZEB1 contributed to acquired resistance to EGFR inhibitors (*e.g.* erlotinib) as well (Yoshida et al., 2016).

Other TFs.

There is ample evidence that other EMT-related transcription factors also promote chemoresistance. Several members of the FOX transcription factor superfamily promoted drug resistance through induction of EMT: FOXC2 (Zhou et al., 2015), FOXM1 (Chiu et al., 2015; Hou et al., 2017) and FOXF2 (Cai et al., 2015). SOX2, a transcription factor important for the maintenance of embryonic stem cell characteristics and represents a cancer stem cell marker (Chen et al., 2012; Leis et al., 2012). It regulated the expression of BCRP and SNAIL, thus contributing to chemoresistance (Lee et al., 2014). Overexpression of hairy and enhancer of split 1 (HES1) , a transcription factor that triggers EMT (Wang et al., 2015), increased the expression of P-gp, MRP1 and BCRP (Sun et al., 2017). Colon cancer cells with HES1 overxpression were resistant to 5-FU. Whole-genome cDNA microarray analyses showed that pathways related to drug metabolism were up-regulated (including ABC transporters), whereas pathways associated with adherens junctions, focal adhesions and actin cytoskeleton, were down-regulated (Sun et al., 2017).

5.3 Targeting of EMT-TFs as a potential therapeutic approach

The correlation between EMT, CSCs, and drug resistance provides a rationale for therapeutic targeting of EMT in combination with chemotherapy in solid tumors. Targeting TFs themselves might be technically challenging, although a number of small molecule inhibitors of EMT have been proposed to target drug resistance: curcumin, mocetinostat, palbociclib, icaritin, zerumbone etc. (reviewed in (Du and Shim, 2016). Mocetinostat is an HDAC inhibitor that interferes with ZEB1 function and restores sensitivity to chemotherapy by epigenetic regulation; this has been shown for gemcitabine in highly resistant PANC1 cell line and freshly-established patient-derived PDAC cells, as well as for docetaxel in docetaxel-resistant DU145-DR prostate cancer cells (Meidhof et al., 2015). The anti-diabetic drug metformin also modulated EMT; it caused transcriptional reprogramming and decreased ZEB1, TWIST1 and SLUG, thus decreasing EMT, stemness and drug resistance in four genetically different breast cancer models (Hirsch et al., 2009; Vazquez-Martin et al., 2010). Metformin down-regulated the expression of P-gp and MRP1, as well as HIF1α through the AMPK/mTOR pathway and sensitized cells to 5-FU in 5-FU-resistant

hepatocellular carcinoma cells *in vitro* (Ling et al., 2014). Metformin reversed acquired resistance to 5-FU in 5-FU resistant MCF7-FU breast cancer cells (Qu et al., 2014), to doxorubicin in MCF7-ADR cells (Kim et al., 2011) and increased the sensitivity of radiation- and 5-FU-resistant rectal cancer cells via attenuation of anti-apoptotic gene expression and inhibition of EMT (Park et al., 2019). Small chemical inhibitors of SNAIL-p53 interaction (Lee et al., 2010) or of the zinc finger-binding domain have been similarly proposed as anti-EMT agents and chemosensitizers. For example, screening of a small molecule library of over 500 compounds yielded specific inhibitors of the SNAIL-p53 interaction, which activated p53 in a KRAS-dependent manner and induced apoptosis in both p53-wt and p53-mutated (one allele) pancreatic and breast cancer cell lines (Lee et al., 2010). This makes these inhibitors of potential interest for the overcoming of MDR. On the other hand, oligonucleotide-conjugated Co (III) complexes prevented SLUG and SNAIL from binding to their DNA targets (Harney et al., 2009). Thus, inactivation of their transcriptional activity may be used in combating MDR.

5.4 Effects of metabolic rewiring in EMT on MDR

Metabolic rewiring towards increased anaerobic glycolysis (Warburg effect) and mitochondrial dysfunction have a seminal role in tumor progression (Kang et al., 2019). During EMT, cancer cells acquire an enhanced glycolytic phenotype, maintained by increased glucose uptake and lactate secretion, which drive an undifferentiated cellular state (Li and Li, 2015; Liu et al., 2016). Increased extracellular lactate levels activated SNAIL and maintained the EMT phenotype (Li et al., 2018b). SNAIL caused a range of metabolic adaptations during EMT depending on the cellular context: mitochondrial repression (Lee et al., 2012; Liu et al., 2019a), concomitant elevation of intracellular ATP levels and oxygen consumption (Jiang et al., 2015) as well as a switch in glucose flux towards the pentose phosphate pathway (Kim and Lee, 2017). Nevertheless, all these adaptations that maintain EMT can at the same time sustain the MDR phenotype.

Increased intracellular ATP production represents an extraordinary determinant of chemoresistance (Zhou et al., 2012). In oxaliplatin-resistant colon cancer cells with increased glycolytic capacity and increased expression of glucose transporter (GLUT1) and hexokinase (HK2), depletion of intracellular ATP resulted in partial reversal of MDR and increased sensitivity to oxaliplatin and 5-FU (Zhou et al., 2012). In addition to increased production, cancer cells also took up ATP by macropinocytosis (Qian et al., 2014), which led to resistance to both standard chemotherapy and

targeted kinase inhibitors. Elevated extracellular ATP levels increased resistance to sunitinib, sorafenib, gefitinib, erlotinib, imatinib, paclitaxel, doxorubicin and cisplatin in lung, liver, breast, colon and pancreatic cancer cell lines (Wang et al., 2017b). In a model system with sunitinib (which binds to the ATP-binding site of receptor tyrosine kinases) in mice xenografted with A549 tumors, macropinocytosis of ATP enhanced resistance. The macropinocytosis inhibitor IPA3 and siRNA against serine/threonine-protein kinase PAK1, an enzyme involved in macropinocytosis, both mitigated this effect (Wang et al., 2017b). In another study, inhibition of macropinocytosis with EIPA (Author: Spell out EIPA) reduced intracellular ATP in A549 cells and reduced the efficacy of sunitinib and pazopanib (Qian et al., 2014). Extracellular ATP also increased ABC transporter drug efflux and increased the transcript levels of P-gp and MRP1 (Wang et al., 2017b). Taken together, increased ATP levels fuel ABC efflux transporters, increase their expression, compete with TKI inhibitors for binding sites and increase phosphorylation of growth factor receptors (Wang et al., 2017b), thus contributing to MDR towards both conventional and targeted therapeutics.

EMT, metabolic reprogramming, and MDR are molecularly intertwined and are summarized in Figure 4. Consequently, biochemical overexpression of ABC transporters in cancer cells influences cellular metabolism: MDR efflux transporters increased the glycolytic rate and glutathione consumtion and decreased the pentose phosphate pathway and the oxidative phosphorylation rate (Lopes-Rodrigues et al., 2017). One should keep in mind that the genetic landscape of the cancer cell and the TME (*e.g.* mutational status of proto-oncogenes such are KRAS, BRAF or p53, hypoxia, and stromal cells) strongly influence the outcome of metabolic alterations on the MDR phenotype. For example, increased OXPHOS in metastasis contributed to reduced expression of ABCB1, ABCC1, ABCC5 and ABCG2 in wild-type p53-expressing cells and to increased expression of the same transporters in mutated or null p53-expressing cells (Belkahla et al., 2017). The interplay between EMT, MDR and autophagy, another cellular process hijacked during the metabolic adaptation in cancer cells, is also two-sided. Autophagy protected cells from nutrient deprivation and recycled damaged cellular components. Early during tumor progression, autophagy restricted EMT by selective degradation of specific EMT proteins. However, during the metastatic dissemination, EMT induced autophagy to enable cell survival under conditions of low oxygen and nutrient deprivation (reviewed in (Gugnoni et al., 2016)). Autophagy acted in a pro-survival manner in the context of MDR (Ajabnoor et al., 2012; Bao et

al., 2015; Liang et al., 2016; Sui et al., 2013; Sun et al., 2011). By contrast, it also enhanced the anti-cancer efficacy of drugs by inducing autophagic cell death (Li et al., 2017; Sotelo et al., 2006; Sui et al., 2013) depending on the underlying cellular conditions. For example, in cisplatin- or vincristine-resistant ovarian cancer cells autophagy had cytoprotective role, and its inhibition by chloroquine or 3-methyladenine re-sensitized cells and potentiated apoptosis (Bao et al., 2015; Liang et al., 2016). Furthermore, autophagy was also cytoprotective and induced resistance to epirubicin and paclitaxel in MCF7 cells (Ajabnoor et al., 2012; Sun et al., 2011). Inhibition of autophagy in triple-negative breast cancer (TNBC) *in vitro* and *in vivo* significantly improved drug response of both anthracycline-sensitive and -resistant TNBC (Chittaranjan et al., 2014). Adding the autophagy inhibitor chloroquine to standard chemotherapy in glioblastoma multiforme patients increased mid-term survival (Sotelo et al., 2006). On the other hand, induction of autophagy led to autophagic cell death in cells with altered apoptotic pathways. For example, in cisplatin-resistant urothelial cancer cells the activation of autophagic flux with dual PI3K and mTOR inhibitor induced cytotoxicity (Li et al., 2013). Plant alkaloids that potentiated autophagy induced autophagic cell death in drug-resistant cells (Donadelli et al., 2011; Meschini et al., 2008).

Tumor cells have a deregulated oxidative mitochondrial machinery that supplies ATP (via OXPHOS), but still enables catabolism of glucose and glutamine (DeBerardinis and Chandel, 2016) for the supply of precursors for DNA, protein and lipid synthesis (Ahn and Metallo, 2015). Down-regulation of mitochondrial genes was strongly correlated with EMT across 20 different cancer types (Gaude and Frezza, 2016). The depletion of mitochondrial DNA provided survival advantages though AKT2 signaling and anoikis resistance (Moro et al., 2009), thus decreasing chemosensitivity. On the other hand, disseminating cancer cells displayed increased OXPHOS (LeBleu et al., 2014), and one of the emerging mechanisms of chemotherapy-induced drug resistance induced a switch from glycolysis to OXPHOS (Vellinga et al., 2015). For example, in samples from liver metastases of colon cancer patients that were exposed to chemotherapy before surgery, genes that are involved in oxidative phosphorylation were upregulated compared to the samples from untreated patients. 5-FU and oxaliplatin caused an upregulation of sirtuin-1 (SIRT1) (Vellinga et al., 2015). SIRT1 is a protein deacetylase, known to regulate multiple physiological functions by deacetylating different protein substrates. Cumulative studies revealed key roles of SIRT1 in different aspects of cancers including genomic instability, metabolism, cell proliferation, and drug resistance (Farcas et al., 2019). SIRT1 was activated in response to DNA damage and

initiated mitochondrial biogenesis (Knight and Milner, 2012). Therefore, mitochondria acted as a hub between metabolism and cell signaling, with temporally defined metabolic adaptations along EMT route, where increased mitochondrial metabolism promoted resistance to apoptosis, whereas mitochondrial dysfunction favored metastasis (reviewed in (Porporato et al., 2016).

EMT-related changes in protein glycosylation patterns also influenced the MDR phenotype. Incomplete glycosylation of ABC transporters prevented their proper membrane localization and, thus, decreased their efficacy as drug efflux pumps ((da Fonseca et al., 2016; Wojtowicz et al., 2015). EMT was also accompanied with a change in lipid metabolism providing alternative energy sources(Sanchez-Martinez et al., 2015) (Sánchez-Martínez et al., 2015) and reorganization of lipid rafts and increased migration ((Babina et al., 2014; Luo et al., 2017). Composition of the membrane lipids and membrane recycling contributed to resistance in MDR cells: altered lipid composition limited drug entry across the plasma membrane and altered kinetics of internalization preventing drug accumulation (Omran et al., 2017).

5.5 Targeting metabolic adaptations in EMT as a potential therapeutic approach

Control over the metabolic adaptation may be an effective modality to overcome drug resistance. It remains to be explored, whether targeting glycolysis, autophagy or OXPHOS may serve as promising therapeutic strategies against MDR tumors. For example, inhibition of glycolysis in MDR cells with activated AKT/mTOR/MYC pathway restored sensitivity to doxorubicin (Zhang et al., 2017). The glycolysis inhibitor, 3-bromopyruvate, sensitized MDR cells (Zhou et al., 2012). The specific lactate dehydrogenase-A inhibitor, oxamate, sensitized paclitaxel-resistant cells (Zhou et al., 2010). The antidiabetic drug metformin, a dual AMPK activator and mitochondrial electron transport chain complex I inhibitor (Wheaton et al., 2014), decreased glucose oxidation (Fendt et al., 2013), modulated autophagy (Kim and You, 2017) and eradicated CSCs when combined with chemotherapy (Hirsch et al., 2009).

6 Role of hypoxia in metastasis and drug resistance

6.1 Hypoxia in tumor progression

During tumor progression, the velocity of proliferation exceeds the tumor's capacity to supply enough oxygen and nutrients by passive diffusion from the sourrounding normal tissues. This situation results in hypoxia, a hallmark of most solid tumors. The role of the TME, which consists

not only of the tumor cells themselves, but also of immune cells, CAFs, endothelial cells, adipocites etc., cannot be underestimated for invasion, metastasis and development of drug resistance (Almeida et al., 2019). Tumors have the capacity to adapt to hypoxic stress by several mechanisms such as the induction of neoangiogenesis, the metabolic shift and apoptosis resistance (Kim and Lee, 2017). These mechanisms are orchestrated by hypoxia-inducible factors (HIF), which act as transcription factors for a plethora of genes involved in tumor progression and metastasis (Bhattarai et al., 2018; Tong et al., 2018). EMT also contributes to chemoresistance(Sui et al., 2014). Stem-like cancer cells are not only crucial for EMT, but are also drug- and radiation-resistant at the same time. Hypoxia can mediate resistance either directly or indirectly. Direct resistance due to hypoxia occurs to radiation and some anticancer drugs (Raz et al., 2014), which need oxygen for full activity, while indirect modes of hypoxia-mediated resistance represent alterations of cellular signaling or increased genetic instability (Teicher, 1994; Kim and Lee, 2017; Salem et al., 2018). Here, we focus on indirect mechanisms of hypoxia-induced MDR and the relevance of ABC transporters in this context.

6.2 Coexpression of HIF-1α and P-glycoprotein in clinical tumor biopsies

Hints that hypoxia may be relevant for the development of resistance to chemotherapy response emreged from investigations with clinical tumor biopsies. Interestingly, in diverse tumor types statistically significant correlations have been observed between the expression of HIF-1α and P-gp, including common epithelial tumors (carcinomas of the breast, lung, larynx or colon) and hematological malignancies (multiple myeloma) as well as rare tumors (such as chordoma) (**Table 1**). This was not only true for primary tumors but also for lymph node metastases (Badowska-Kozakiewicz et al., 2017; Lu et al., 2016). In chordoma, HIF-1α expression did, however, not correlate with MRP1 expression – a result that deserves verification in other tumor types. There is also a clue from advanced colon carcinoma that the simultaneous expression of HIF-1α and P-gp has clinical impact, since tumors with co-expression of these two proteins poorly responded to chemotherapy when compared to those devoid of co-expression (Chen et al., 2014).

Table 1: Expression of HIF-1α and P-glycoprotein in clinical tumor samples.

Tumor type	Biomarker expression	Reference

Breast cancer and lymph node metastases	Significant correlation between HIF-1α and P-gp expression	Badowska-Kozakiewicz et al., 2017
Multiple myeloma	Significant correlation between HIF-1α and P-gp expression	Muz et al., 2017
Lymph node metastaes of non-small cell lung cancer	Significant correlation between HIF-1α and P-gp expression	Lu et al., 2016
Advanced colon carcinoma patients	Patients with HIF-1α and P-gp co-expression were more resistant to chemotherapy than those lacking expression	Chen et al., 2014
Laryngeal squamous cell carcinoma	Significant correlation between HIF-1α and P-gp expression	Xie et al., 2013
Chordoma	Significant correlation between HIF-1α and P-gp expression, but not MRP1 expression	Ji et al., 2010
Colon carcinoma	Significant correlation between HIF-1α and P-gp expression	Ding et al., 2010

6.3 Molecular modes of action of hypoxia-induced MDR

The statistically significant co-expression of HIF-1α and P-gp supported the hypothesis that HIF-1α may regulate the expression of ABC transporter genes and thereby induce resistance to anticancer drugs. Numerous authors investigated this hypothesis, and it turned out that hypoxia seems to induce drug resistance by both ABC-transporter dependent and -independent mechanisms in cancer and also in normal tissues (**Table 2**).

A considerable portion of papers reported on the hypoxia-induced activation of HIF-1α leading to transcriptional activation of the *ABCB1* promoter and expression of *ABCB1* mRNA and P-gp, which in turn caused resistance to typical drug substrates of P-gp such as doxorubicin (**Table 2**). While the majority of papers focused on P-gp, a few authors also analyzed other ABC transporters such as MRP1, BCRP, and ABCB5. A similar trend as with P-gp was found, *i.e.* hypoxia caused overexpression of these drug efflux pumps. In addition to HIF-1α, the tightly related HIF-2α seems to play a role for these ABC transporters.

While the vast majority of authors found HIF-1α-mediated ABC transporter overexpression, some papers reported on P-gp overexpression as a consequence of amplification of the gene encoding for the murine, rodent and human P-gp (Assaraf and Borgnia, 1994; Assaraf et al., 1989; Genovese et al., 2017; Luk et al., 1990; Sharma et al., 1991). Hypoxia was shown to induce fragile sites in the genome, which favor genomic rearrangements. Breaks at these fragle sites initiate DNA amplifications and the generation of intrachromosomally localized gene amplifications

(cytogenetically visible as homogenously stained regions, HSR) or extrachromosomally organized elements (double minutes, DMs) (Coquelle et al., 1998).

In some cases, resistance to anticancer drugs which are known to be non-ABC transporter substrates was also observed, *e.g.* BCNU, ifosfamide and methotrexate (Takeshita et al., 1996; Harrison and Schwartz, 2017; Nikolova et al., 2017). This result is a clue that ABC transporters may be overexpressed under hypoxic conditions, but that resistance to these non-MDR drugs may occur via additional P-gp-independent mechanisms. Indeed, a number of investigations came to the conclusion that hypoxia-mediated drug resistance can occur in an ABC transporter-independent manner (**Table 2**). These authors searched for alternative mechanisms and suggested cell cycle related effects (up-regulation of cell cycle inhibitors and down-regulation of cyclins) or regulation of genes that affect drug response by their modes of actions (*e.g.* KLF8, KFL8, NOX1, EGFL7 etc.).

Hypoxia-mediated resistance is not restricted to cancer cells, but has also been observed in normal tissues and cells (**Table 2**). Here, hypoxia also induced HIF-1α activation followed by P-gp or BCRP overexpression or other mechanisms. This may have important implications for healthy organisms, which have to cope with a plethora of xenobiotic and partwise harmful compounds from the environment. Tissue hypoxia may support the detoxicifaction of xenobiotics taken up with food or breathing air. While hypoxia-induced resistance can cause chemotherapy failure with fatal outcome in cancer patients, it may contribute to salutogenesis in healthy subjects by keeping them off from the detrimental effects of harmful exogenous compounds.

Table 2: Role of hypoxia and hypoxia-inducible factors (HIF-1α, HIF-2α) for the expression of ABC transporters (P-gp, MRP1, BCRP, ABCB5) in tumor cells and normal cells and tissues.

Model	Mechanism	Reference
ABC-transporter-dependent drug resistance by hypoxia:		
OVCAR-3 S and CAOV-3 S ovarina cancer cells	Hypoxia induced HIF-1α, HIF-2α expression and doxorubicin resistance. HIF-1α knockdown sensitizied to and HIF-1α overexpression induced resistance to doxorubicin. HIF-2α directly promoted transcription/expression of BCRP	He et al., 2019
SKOV3 ovarian cancer cells	Hypoxia induced P-gp and MRP1 expression	Cai et al., 2018
	Hypoxia induced HIF-1α and P-gp expression and P-gp internalization, lysosomal doxorubicin accumulation, and doxorubicin resistance	Al-Akra et al., 2018
Multiple myeloma	Hypoxia induced P-gp expression and resistance to carfilzomib and bortezomib	Muz et al., 2017

HT-29 colon cancer cells	Hypoxia induced HIF-1α, P-gp and BCRP expression	Pinzón-Daza et al., 2017
A549/DDP non-small lung cancer cells	Hypoxia induced P-gp and EGFL7 expression and drug resistance	Shen et al., 2017
CH27, CH27/DOX, A549, H1299, H460 lung cancer cell lines	Hypoxia-induced inhibition of MRP1 and P-gp expression in a HIF-1α-dependent manner and DOX resistance	Chen et al., 2016
Laryngeal cancer cells	Hypoxia-induced P-gp expression was dowregulated by *ABCB1* RNAi leading to chemosensitization and increased drug accumulation	Li et al., 2016
LoVo colon cancer cells	Chemical hypoxia by cobalt chloride induced HIF-1α, P-gp and MRP1 expression and decreased intracellular doxorubicin retention	Yang et al., 2016
Colon cancer cells	Chemical hypoxia by cobalt chloride induced HIF-1α, P-gp and MRP1 expression. HIF-1α bound to *ABCC1* promoter	Lv et al., 2015
Melanoma cells	Hypoxia-mediated downregulation of miR-340-5p induced upregulation of ABCB5 regulation	Wozniak et al., 2015
Gastric cancer cells	Hypoxia-induced KLF8 and HIF-1α expression, KFL8-mediated *ABCB1* promoter activation and P-gp expression	Zhang et al., 2014
LoVo colon cancer cells	Hypoxia-induced HIF-1α and P-gp expression, HIF-1α silencing reduced P-gp expression and sensitized celld to four drugs, HIF-1α bound to the *ABCB1* promoter	Chen et al., 2014
Osteosarcoma cells	HIF-1α induced P-gp expression and doxorubicin efflux	Roncuzzi et al., 2014
Hep-2 lanyngeal squamous carcinoma cells	Hypoxia induced HIF-1α and P-gp expression, HIF-1α downregulation also inhibited P-gp expression in hypoxic cells	Xie et al., 2013
HT-29 colon cancer cells	Digoxin increased intracellular [Ca^{2+}] and activated calmodulin kinase II, which activated HIF-1α and P-gp expression	Riganti et al., 2009
SGC7901/VCR gastric cancer cells	Hypoxia induced doxorubicin efflux, *HIF1A* siRNA reversed this effect, HIF-1α overexpression induced P-gp and MRP1 expression	Liu et al., 2008
	Hepatitis-B-virus X protein (HBx) increased *ABCB1* activity through transcriptional activation by HIF-1α activation	Han et al., 2007
Colon cancer cells	Hypoxia alone had no effect, but together with acidosis the P-gp expression increased	Lotz et al., 2007
Oral squamous cell carcinoma cells	HIF-1α knockdown decreased P-gp expression and increased intracellular drug concentrations	Sasabe et al., 2007
A549 lung cancer cells	HIF-1α transfection increased P-gp expression and 5-fluorouracil expression	Zhang et al., 2006
A549 lung cancer cells	Hypoxia induced HIF-1α and P-gp expression and doxorubicin resistance	Xia et al., 2005
DU-145 prostate tumor spheroids	NOX-1-induced ROS generation reduced HIF-1α and P-gp expression and increased intracellular doxorubicin retention. Free radical scavengers (vitamin C and E) reversed this effect on the protein but not mRNA level	Wartenberg et al., 2005
	Hypoxia activated JNK activity and P-gp protein and *ABCB1* mRNA expression. JNK inhibition reversed this effect. Hypoxia-induced HIF-1α signaling depended on JNK activation	Comerford et al., 2004
DU-145 prostate cancer spheroids, Hepa1 hepatoma spheroids	Hypoxia and chemical hypoxia (by cobalt chloride or desferroxamine) induced HIF-1α and P-gp expression. Prooxidants	Wartenberg et al., 2003

	(H_2O_2, BSO) upregulated and antioxidants (N-acetylcysteine, vitamin E) upregulated HIF-1α and P-gp	
Murine KHT-LP1 cells	Hypoxia induced *mdr1a* gene amplification in the presence of doxorubicin	Luk et al., 1990
ABC-transporter-independent drug resistance by hypoxia:		
Non-small cell lung cancer cells	Hypoxia induced KLF5 expression. KLF5 knockdown suppressed hypoxia-induced cisplatin resistance and HIF-1α-dependent glycolysis	Gong et al., 2018
A549/DDP non-small lung cancer cells	Hypoxia induced P-gp and EGFL7 expression and drug resistance	Shen et al., 2017
Gallbladder cancer cells	NOX1-induced ROS generation and HIF-1α/P-gp pathway activation	Zhan et al., 2015
Oal suamous cell carcinoma cells	Hypoxia induced resistance to 5-fluorouracil by G1/S transition through upregulation of cell cycle inhibitors (p21, p27) and downregulation of cyclin D	Yoshiba et al., 2009
MIA PaCa-2, PANC-1, BxPC-3 pancreas cancer cells	Hypoxia did not induce ABCB1 expression	Lo et al., 2009
R3327-AT1 prostate cancer cells	Hypoxia mildly increased P-gp expression, but decreased MRP1 expression	Thews et al., 2008
MCF-7 and SW1573 breast cancer cells	Hypoxia induced resistance to mitoxantrone, but not doxorubicin. No changes in P-gp, MRP1 or BCRP expression under hypoxia	Greijer et al., 2005
Neuroblastoma cells	Hypoxia induced *ABCB1* downregulation	Jögi et al., 2004
Testicular germ cell tumors	Hypoxia induced resistance to cisplatin, etoposide, bleomycin, 4-OOH-ifosfamide, carboplatin, paclitaxel, gemcitabine, oxaliplatin, irinotecan, and mitomycin C	Koch et al., 2003
MCF-7 and MCF-7/VP breast cancer cells	Hypoxia reduced 99mTc-sestamibi and 99mTc-tetrofosmin radiotracer uptake independent of MRP1 function	Kinuya et al., 2003
U373 MG and PFAT-MT glioma cells	Hypoxia induced resistance to BCNU and cisplatin without change in drug resistance genes	Liang et al., 1996
MDA-468 and MCF-7/Adr	Hypoxia did not induce doxorubicin resistance and doxorubicin response was not increaed by the P-gp inhibior verapamil	Kalra et al., 1993
Murine EMT6/Ro cells	Hypoxia induced resistance to doxorubicin, 5-fluorouracil and actinomycin D, but not to colchicine, vincristine or cisplatin. Hypoxia did not induce *ABCB1* mRNA expression	Sakata et al., 1991
Hypoxia effects in normal tissues and cells:		
Human placenta	Hypoxia increased P-gp and *ABCB1* mRNA expression, but not BCRP expression	Javam et al., 2014
Rats	Hypoxia increased P-gp protein expression but not *ABCB1* mRNA expression	Fradette et al., 2007
Murine stem progenitor cells	Hypoxia induced HIF-1α-mediated BCRP expression	Krishnamurthy et al., 2004
Nontransformed, primary human microvascular endothelial cells	Hypoxia induced HIF-1α-mediated P-gp protein and *ABCB1* mRNA expression	Comerford et al., 2002
Chinese hamster lung fibroblasts	Hypoxia induced dodoxubicin resistance, which was not reversible with verapamil	Kalra et al., 1993

6.4 Approaches to overcome hypoxia-induced MDR

Given that many (though not all) forms of hypoxia-induced drug resistance are based on the HIF-1α mediated induction of P-gp overexpression, it is worthwhile to search for strategies to overcome resistance by targeting the HIF-1α/P-gp axis (**Table 3**). This has been attempted by the application of ribonucleotide drugs (siRNA, shRNA or RNAi against *HIF1A*) with or without encapsulation in nanoparticles. Remarkably, this approach led not only to down-regulation of HIF-1α, but also of P-gp, which can be taken as further evidence that P-gp overexpression is driven by HIF-1α under hypoxic conditions. Furthermore, nanoparticles have been used to encapsulate the anticancer drug doxorubicin with other drugs (*i.e.* metformin, chlorin E6) resulting in down-regulation of HIF-1α and P-gp as well as in increased doxorubicin concentrations in tumor cells. HIF-1α inhibitors (YC-1, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole) and other synthetic compounds (Buthionine sulfoximine and thiosemicarbazones) exhibited comparable effects in overcoming hypoxia-mediated drug resistance. Interestingly, hypoxia-induced and P-glycoprotein-mediated MDR has not only been reversed by synthetic compounds and nanoparticles, but also by natural products such as the dipeptide L-carnosin and phytochemicals. Epigallocatechin-3-gallate is a polyphenolic catechin and a major consistuent of green tea (*Camelia sinenis*), and hispulidin is a flavone found in plants of the genus *Artemisia* and *Salvia* and others.

Table 3: Strategies to overcome hypoxia-induced multidrug resistance by nanoparticles, synthetic compounds and phytochemicals.

Model	Compound	Mode of action	Reference
Ribonucleotide drugs with or without nanoparticle encaspulation:			
	HIF1A siRNA nanoparticle	Expression of HIF-1α and P-gp↓, drug efflux↓	Huang et al., 2019
PC3 prostate cancer cells	*HIF1A* siRNA nanoparticle	*ABCB1* expression↓, sensitization to doxorubicin	Liu et al., 2012
HT-29 colon cancer cells	*HIF1A* shRNA	Expression of HIF-1α and P-gp expression *in vitro* and *in vivo*↓	Zhang et al., 2017
MCF-7 breast cancer spheroids	*HIF1A* siRNA	P-gp expression↓, intracellular doxorubicin accumulation↑	Doublier et al., 2015
MCF-7 breast cancer cells	*HIF1A* siRNA		Li et al., 2006
SPCA1 and A549 non-small lung cancer cells	*HIF1A* RNAi	Expression of HIF-1α↓, doxorubicin and cisplatin resistance↓, but P-gp was not increased under hypoxia	Song et al., 2006
Chemical drug-containing nanoparticles:			

MCF-7/Adr breast cancer cells	Doxorubicin-metformin cationic liposomes	Hypoxic stress↓, expression of HIF-1α and P-gp↓	Li et al., 2019
	Encapsuled doxorubicin and chlorin e6 in tumor-targeted hybrid protein oxygen carriers	Expression of HIF-1α and P-gp↓, drug efflux↓	Luo et al., 2018
Synthetic compounds:			
Glioblastoma xenograft tumors	YC-1 (HIF-1α inhibitor)	*ABCB1* expression↓, survival rate to BCNU therapy↑	Chou et al., 2012
HepG2 liver cancer spheroids	YC-1 (HIF-1α inhibitor)	Doxorubicin accumulation↑	Liu et al., 2017
MCF-7 breast cancer spheroids	3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (HIF-1α inhibitor)	P-gp expression↓, intracellular doxorubicin accumulation↑	Doublier et al., 2015
	Lysosomal targeted thiosemicarbazones	Hypoxia-induced doxorubicin resistance↓	Al-Akra et al., 2018
HepG2 liver cancer cells	BSO	HIF-1α and P-gp expression↓	Jin et al., 2011
Natural products:			
HT-29 colon cancer cells	L-carnosine	Cell viability↓, HIF-1α and P-gp expression↓	Iovine et al., 2016
Gallbladder cancer cells	Hispidulin	HIF-1α protein expression, but not mRNA↓, AMPK signaling↑, HIF-1α/P-gp signaling↓, sensitization to gemcitabine and 5-fluorouracil	Gao et al., 2015
PANC-1 pancreas cancer cells	Epigallocatechin-3-gallate	HIF-1α expression↓, P-gp protein and *ABCB1* mRNA↓, cell proliferation↓	Zhu et al., 2012

7 Conclusions and perspectives

It is known that tumor drug resistance is frequently multifactorial(Kadioglu et al., 2016). However, nowadays it becomes evident that drug resistance is much more complex than initially thought some decades ago. A plethora of distinct yet intertwined mechanisms contribute to drug resistance. Many cancer patients succumb to the metastastatic disease that is typically non-responsive to therapeutic interventions. Hence, the metastatic process and the development of drugresistance are seemingly interconnected by common molecular modes of action.

This situation may explain, at least in part, why drug resistance phenomena dogged oncology during the past 7 decades. This situation underscores, how complex drug resistance really is in the clinical context. The more we understand the individual factors contributing to the entire phenomenon of therapy failure, the more we have tools to develop sophisticated individualized

strategies to surmount drug resistance, which ultimately would improve the survival rates of cancer patients.

The emerging questions that arise are: how should we cope with the complexity of drug resistance and would it be ever possible to develop efficient strategies to overcome and reverse chemoresistance? With the expansion of the integrative research fields of genomics, transcriptomics, proteomics, interactomics, and metabolomics of tumors in the past decade, a large amount of information was generated. We are yet to grasp and consolidate the impact of these new findings in the context of MDR. The future of cancer therapy will be revolutionized by cutting-edge technologies to handle big data such as artificial intelligence. The future of drug resistance research lies in the bioinformatic handling of big data from experimental and clinical settings, in order to develop personalized, patient-tailored protocols that will hopefully overcome drug resistance in each individual tumor (Efferth et al., 2017; Efferth and Volm, 2005; Volm and Efferth, 2015).

To come closer to this final goal, a first step is to develop a hierarchy of mechanisms of drug resistance. This is still non-sufficiently understood, i.e. which mechanisms contribute more to drug resistance than others in well defined tumors. Based on experimental results *in vitro* and *in vivo*, the clinial relevance of the prioritized mechanisms should be verified in translational settings. While the entire field of drug resistance becomes increasingly complex, the chances and opportunities to fight tumor refractoriness also increase, which presents a hope for novel treatment strategies for cancer patients worldwide.

Acknowledgements: This article is based upon work from COST Action 17104 STRATAGEM, supported by COST (European Cooperation in Science and Technology).

Funding: NE is supported by grant no:118S378 from TUBITAK (The Scientific and Technological Research Council of Turkey); JG is supported by the grant III41026 from the Serbian Ministry of Education, Science and Technological Development. AB is supported by the Croatian Science Foundation (CSF, Project No. IP-2016-06-1036). TE is grateful for funding by the Germany Science Foundation (DFG), the German Cancer Aid, the Chinese Scholarship Council (CSC), and the German Academic Exchange Service (DAAD).

Conflicts of interest

NE, JG, AB and TE have no conflict of interest to disclosure.

Reference List

Acharyya, S., Oskarsson, T., Vanharanta, S., Malladi, S., Kim, J., Morris, P.G., Manova-Todorova, K., Leversha, M., Hogg, N., Seshan, V.E., Norton, L., Brogi, E., Massague, J., 2012. A CXCL1 paracrine network links cancer chemoresistance and metastasis. Cell 150, 165-178.

Ahmadzadeh, M., Rosenberg, S.A., 2005. TGF-beta 1 attenuates the acquisition and expression of effector function by tumor antigen-specific human memory CD8 T cells. J Immunol 174, 5215-5223.

Ahn, C.S., Metallo, C.M., 2015. Mitochondria as biosynthetic factories for cancer proliferation. Cancer Metab 3, 1.

Ajabnoor, G.M.A., Crook, T., Coley, H.M., 2012. Paclitaxel resistance is associated with switch from apoptotic to autophagic cell death in MCF-7 breast cancer cells. Cell Death Dis 3, e260-e260.

Al-Akra, L., Bae, D.H., Sahni, S., Huang, M.L.H., Park, K.C., Lane, D.J.R., Jansson, P.J., 2018. Richardson, D.R. Tumor stressors induce two mechanisms of intracellular P-glycoprotein-mediated resistance that are overcome by lysosomal-targeted thiosemicarbazones. J Biol Chem 293, 3562-3587.

Alexander, E.T., Minton, A.R., Hayes, C.S., Goss, A., Van Ryn, J., Gilmour, S.K., 2015. Thrombin inhibition and cyclophosphamide synergistically block tumor progression and metastasis. Cancer Biol Ther 16, 1802-1811.

Alexander, E.T., Minton, A.R., Peters, M.C., van Ryn, J., Gilmour, S.K., 2016. Thrombin inhibition and cisplatin block tumor progression in ovarian cancer by alleviating the immunosuppressive microenvironment. Oncotarget 7, 85291-85305.

Allavena, P., Sica, A., Solinas, G., Porta, C., Mantovani, A., 2008. The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. Crit Rev Oncol Hematol 66, 1-9.

Almeida, F.V., Douglass, S.M., Fane, M.E., Weeraratna, A.T., 2019. Bad company: Microenvironmentally mediated resistance to targeted therapy in melanoma. Pigment Cell Melanoma Res 32, 237-247.

Amornsupak, K., Insawang, T., Thuwajit, P., O-Charoenrat, P., Eccles, S.A., Thuwajit, C., 2014. Cancer-associated fibroblasts induce high mobility group box 1 and contribute to resistance to doxorubicin in breast cancer cells. BMC Cancer 14, 955.

Andtbacka, R.H., Ross, M., Puzanov, I., Milhem, M., Collichio, F., Delman, K.A., Amatruda, T., Zager, J.S., Cranmer, L., Hsueh, E., Chen, L., Shilkrut, M., Kaufman, H.L., 2016. Patterns of clinical response with Talimogene Laherparepvec (T-VEC) in patients with melanoma treated in the OPTiM Phase III clinical trial. Ann Surg Oncol 23, 4169-4177.

Arumugam, T., Ramachandran, V., Fournier, K.F., Wang, H., Marquis, L., Abbruzzese, J.L., Gallick, G.E., Logsdon, C.D., McConkey, D.J., Choi, W., 2009. Epithelial to mesenchymal transition contributes to drug resistance in pancreatic cancer. Cancer Res 69, 5820-5828.

Assaraf, Y.G., 2006. The role of multidrug resistance efflux transporters in antifolate resistance and folate homeostasis. Drug Resist Updat 9, 227-246.

Assaraf, Y.G., Borgnia, M.J., 1994. Probing the interaction of the multidrug-resistance phenotype with the polypeptide ionophore gramicidin D via functional channel formation. Eur J Biochem 222, 813-824.

Assaraf, Y.G., Brozovic, A., Goncalves, A.C., Jurkovicova, D., Line, A., Machuqueiro, M., Saponara, S., Sarmento-Ribeiro, A.B., Xavier, C.P.R., Vasconcelos, M.H., 2019. The multi-factorial nature of clinical multidrug resistance in cancer. Drug Resist Updat 46, 100645.

Assaraf, Y.G., Molina, A., Schimke, R.T., 1989. Sequential amplification of dihydrofolate reductase and multidrug resistance genes in Chinese hamster ovary cells selected for stepwise resistance to the lipid-soluble antifolate trimetrexate. J Biol Chem 264, 18326-18334.

Babina, I.S., McSherry, E.A., Donatello, S., Hill, A.D., Hopkins, A.M., 2014. A novel mechanism of regulating breast cancer cell migration via palmitoylation-dependent alterations in the lipid raft affiliation of CD44. Breast Cancer Res 16, R19.

Badowska-Kozakiewicz, A.M., Sobol, M., Patera, J., 2017. Expression of multidrug resistance protein P-glycoprotein in correlation with markers of hypoxia (HIF-1alpha, EPO, EPO-R) in invasive breast cancer with metastasis to lymph nodes. Arch Med Sci 13, 1303-1314.

Bao, L., Jaramillo, M.C., Zhang, Z., Zheng, Y., Yao, M., Zhang, D.D., Yi, X., 2015. Induction of autophagy contributes to cisplatin resistance in human ovarian cancer cells. Mol Med Rep 11, 91-98.

Bartlett, J.B., Dredge, K., Dalgleish, A.G., 2004. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer 4, 314-322.

Belkahla, S., Khan, A.U.H., Gitenay, D., Alexia, C., Gondeau, C., Vo, D.-N., Orecchioni, S., Talarico, G., Bertolini, F., Cartron, G., Hernandez, J., Daujat-Chavanieu, M., Allende-Vega, N., Gonzalez, M.V., 2017. Changes in metabolism affect expression of ABC transporters through ERK5 and depending on p53 status. Oncotarget 9, 1114-1129

Bharti, R., Dey, G., Mandal, M., 2016. Cancer development, chemoresistance, epithelial to mesenchymal transition and stem cells: A snapshot of IL-6 mediated involvement. Cancer Lett 375, 51-61.

Bhattarai, D., Xu, X., Lee, K., 2018. Hypoxia-inducible factor-1 (HIF-1) inhibitors from the last decade (2007 to 2016): A "structure-activity relationship" perspective. Medicinal research reviews 38, 1404-1442.

Bierie, B., Moses, H.L., 2010. Transforming growth factor beta (TGF-beta) and inflammation in cancer. Cytokine Growth Factor Rev 21, 49-59.

Blattner, C., Fleming, V., Weber, R., Himmelhan, B., Altevogt, P., Gebhardt, C., Schulze, T.J., Razon, H., Hawila, E., Wildbaum, G., Utikal, J., Karin, N., Umansky, V., 2018. CCR5(+) myeloid-derived suppressor cells are enriched and activated in melanoma lesions. Cancer Res 78, 157-167.

Bonuccelli, G., Whitaker-Menezes, D., Castello-Cros, R., Pavlides, S., Pestell, R.G., Fatatis, A., Witkiewicz, A.K., Vander Heiden, M.G., Migneco, G., Chiavarina, B., Frank, P.G., Capozza, F., Flomenberg, N., Martinez-Outschoorn, U.E., Sotgia, F., Lisanti, M.P., 2010. The reverse Warburg effect: glycolysis inhibitors prevent the tumor promoting effects of caveolin-1 deficient cancer associated fibroblasts. Cell Cycle 9, 1960-1971.

Borsellino, N., Belldegrun, A., Bonavida, B., 1995. Endogenous interleukin 6 is a resistance factor for cis-diamminedichloroplatinum and etoposide-mediated cytotoxicity of human prostate carcinoma cell lines. Cancer Res 55, 4633-4639.

Bromberg, J., Wang, T.C., 2009. Inflammation and cancer: IL-6 and STAT3 complete the link. Cancer Cell 15, 79-80.

Brozovic, A., 2017. The relationship between platinum drug resistance and epithelial-mesenchymal transition. Arch Toxicol 91, 605-619.

Bullock, M.D., Pickard, K.M., Nielsen, B.S., Sayan, A.E., Jenei, V., Mellone, M., Mitter, R., Primrose, J.N., Thomas, G.J., Packham, G.K., Mirenzami, A.H., Mirnezami, A.H., 2013. Pleiotropic actions of miR-21 highlight the critical role of deregulated stromal microRNAs during colorectal cancer progression. Cell Death Dis 4, e684.

Bunt, S.K., Sinha, P., Clements, V.K., Leips, J., Ostrand-Rosenberg, S., 2006. Inflammation induces myeloid-derived suppressor cells that facilitate tumor progression. J Immunol 176, 284-290.

Bussard, K.M., Mutkus, L., Stumpf, K., Gomez-Manzano, C., Marini, F.C., 2016. Tumor-associated stromal cells as key contributors to the tumor microenvironment. Breast Cancer Res 18, 84.

Cai, J., Tian, A.X., Wang, Q.S., Kong, P.Z., Du, X., Li, X.Q., Feng, Y.M., 2015. FOXF2 suppresses the FOXC2-mediated epithelial-mesenchymal transition and multidrug resistance of basal-like breast cancer. Cancer Lett 367, 129-137.

Cai, Y., Huang, J., Xing, H., Li, B., Li, L., Wang, X., Peng, D., Chen, J., 2018. Contribution of FPR and TLR9 to hypoxia-induced chemoresistance of ovarian cancer cells. Onco Targets Ther. 12, 291-301.

Cammarota, F., Laukkanen, M.O., 2016. Mesenchymal stem/stromal cells in stromal evolution and cancer progression. Stem Cells Int 2016, 4824573.

Cannarile, M.A., Weisser, M., Jacob, W., Jegg, A.M., Ries, C.H., Ruttinger, D., 2017. Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. J Immunother Cancer 5, 53.

Cassetta, L., Fragkogianni, S., Sims, A.H., Swierczak, A., Forrester, L.M., Zhang, H., Soong, D.Y.H., Cotechini, T., Anur, P., Lin, E.Y., Fidanza, A., Lopez-Yrigoyen, M., Millar, M.R., Urman, A., Ai, Z., Spellman, P.T., Hwang, E.S., Dixon, J.M., Wiechmann, L., Coussens, L.M., Smith, H.O., Pollard, J.W., 2019. Human tumor-associated macrophage and monocyte transcriptional landscapes reveal cancer-specific reprogramming, biomarkers, and therapeutic targets. Cancer Cell 35, 588-602 e510.

Chakraborty, A., Guha, S., 2007. Granulocyte colony-stimulating factor/granulocyte colony-stimulating factor receptor biological axis promotes survival and growth of bladder cancer cells. Urology 69, 1210-1215.

Chang, C.H., Hsiao, C.F., Yeh, Y.M., Chang, G.C., Tsai, Y.H., Chen, Y.M., Huang, M.S., Chen, H.L., Li, Y.J., Yang, P.C., Chen, C.J., Hsiung, C.A., Su, W.C., 2013. Circulating interleukin-6 level is a prognostic marker for survival in advanced nonsmall cell lung cancer patients treated with chemotherapy. Int J Cancer 132, 1977-1985.

Chang, H., Sung, J.H., Moon, S.U., Kim, H.S., Kim, J.W., Lee, J.S., 2017. EGF induced RET inhibitor eesistance in CCDC6-RET lung cancer cells. Yonsei Med J 58, 9-18.

Chen, J., Ding, Z., Peng, Y., Pan, F., Li, J., Zou, L., Zhang, Y., Liang, H., 2014. HIF-1alpha inhibition reverses multidrug resistance in colon cancer cells via downregulation of MDR1/P-glycoprotein. PloS One 9, e98882.

Chen, S., Xu, Y., Chen, Y., Li, X., Mou, W., Wang, L., Liu, Y., Reisfeld, R.A., Xiang, R., Lv, D., Li, N., 2012. SOX2 gene regulates the transcriptional network of oncogenes and affects tumorigenesis of human lung cancer cells. PLoS One 7, e36326.

Chen, W.J., Wang, H., Tang, Y., Liu, C.L., Li, H.L., Li, W.T., 2010. Multidrug resistance in breast cancer cells during epithelial-mesenchymal transition is modulated by breast cancer resistant protein. Chin J Cancer 29, 151-157.

Chen, X., Song, E., 2019. Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discov 18, 99-115.

Chen, X.J., Deng, Y.R., Wang, Z.C., Wei, W.F., Zhou, C.F., Zhang, Y.M., Yan, R.M., Liang, L.J., Zhong, M., Liang, L., Wu, S., Wang, W., 2019. Hypoxia-induced ZEB1 promotes cervical cancer progression via CCL8-dependent tumour-associated macrophage recruitment. Cell Death Dis 10, 508.

Chen, Y., Tan, W., Wang, C., 2018. Tumor-associated macrophage-derived cytokines enhance cancer stem-like characteristics through epithelial-mesenchymal transition. Onco Targets Ther 11, 3817-3826.

Chen, Y.L., Yang, T.Y., Chen, K.C., Wu, C.L., Hsu, S.L., Hsueh, C.M., 2016. Hypoxia can impair doxorubicin resistance of non-small cell lung cancer cells by inhibiting MRP1 and P-gp expression and boosting the chemosensitizing effects of MRP1 and P-gp blockers. Cell Oncol 39, 411-433.

Cheng, G.Z., Chan, J., Wang, Q., Zhang, W., Sun, C.D., Wang, L.H., 2007. Twist transcriptionally up-regulates AKT2 in breast cancer cells leading to increased migration, invasion, and resistance to paclitaxel. Cancer Res 67, 1979-1987.

Chittaranjan, S., Bortnik, S., Dragowska, W.H., Xu, J., Abeysundara, N., Leung, A., Go, N.E., DeVorkin, L., Weppler, S.A., Gelmon, K., Yapp, D.T., Bally, M.B., Gorski, S.M., 2014. Autophagy inhibition augments the anticancer effects of epirubicin treatment in anthracycline-sensitive and -resistant triple-negative breast cancer. Clin Cancer Res 20, 3159-3173.

Chiu, W.T., Huang, Y.F., Tsai, H.Y., Chen, C.C., Chang, C.H., Huang, S.C., Hsu, K.F., Chou, C.Y., 2015. FOXM1 confers to epithelial-mesenchymal transition, stemness and chemoresistance in epithelial ovarian carcinoma cells. Oncotarget 6, 2349-2365.

Chou, C.W., Wang, C.C., Wu, C.P., Lin, Y.J., Lee, Y.C., Cheng, Y.W., Hsieh, C.H., 2012. Tumor cycling hypoxia induces chemoresistance in glioblastoma multiforme by upregulating the expression and function of ABCB1. Neuro Oncol 14, 1227-1238.

Cohen, M.H., Shen, Y.L., Keegan, P., Pazdur, R., 2009. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist 14, 1131-1138.

Colak, S., Medema, J.P., 2014. Cancer stem cells--important players in tumor therapy resistance. FEBS J 281, 4779-4791.

Colak, S., Ten Dijke, P., 2017. Targeting TGF-beta Signaling in Cancer. Trends Cancer 3, 56-71.

Colegio, O.R., Chu, N.Q., Szabo, A.L., Chu, T., Rhebergen, A.M., Jairam, V., Cyrus, N., Brokowski, C.E., Eisenbarth, S.C., Phillips, G.M., Cline, G.W., Phillips, A.J., Medzhitov, R., 2014. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 513, 559-563.

Comerford, K.M., Cummins, E.P., Taylor, C.T., 2004. c-Jun NH2-terminal kinase activation contributes to hypoxia-inducible factor 1alpha-dependent P-glycoprotein expression in hypoxia. Cancer Res 64, 9057-9061.

Comerford, K.M., Wallace, T.J., Karhausen, J., Louis, N.A., Montalto, M.C., Colgan, S.P. Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. Cancer Res. 62, 3387-3394 (2002)Condamine, T., Gabrilovich, D.I., 2011. Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function. Trends Immunol 32, 19-25.

Condeelis, J., Pollard, J.W., 2006. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 124, 263-266.

Coquelle, A., Toledo, F., Stern, S., Bieth, A., Debatisse, M., 1998. A new role for hypoxia in tumor progression: induction of fragile site triggering genomic rearrangements and formation of complex DMs and HSRs. Mol Cell 2, 259-265.

Coussens, L.M., Zitvogel, L., Palucka, A.K., 2013. Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science 339, 286-291.

Cui, Q., Wang, J.Q., Assaraf, Y.G., Ren, L., Gupta, P., Wei, L., Ashby, C.R., Jr., Yang, D.H., Chen, Z.S., 2018. Modulating ROS to overcome multidrug resistance in cancer. Drug Resist Updat 41, 1-25.

Culig, Z., Puhr, M., 2012. Interleukin-6: a multifunctional targetable cytokine in human prostate cancer. Mol Cell Endocrinol 360, 52-58.

da Fonseca, L.M., da Silva, V.A., Freire-de-Lima, L., Previato, J.O., Mendonca-Previato, L., Capella, M.A., 2016. Glycosylation in Cancer: Interplay between Multidrug Resistance and Epithelial-to-Mesenchymal Transition? Front Oncol 6, 158.

Dal Bo, M., De Mattia, E., Baboci, L., Mezzalira, S., Cecchin, E., Assaraf, Y.G., Toffoli, G., 2020. New insights into the pharmacological, immunological, and CAR-T-cell approaches in the treatment of hepatocellular carcinoma. Drug Resist Updat 51, 100702.

Dalton, H.J., Pradeep, S., McGuire, M., Hailemichael, Y., Ma, S., Lyons, Y., Armaiz-Pena, G.N., Previs, R.A., Hansen, J.M., Rupaimoole, R., Gonzalez-Villasana, V., Cho, M.S., Wu, S.Y., Mangala, L.S., Jennings, N.B., Hu, W., Langley, R., Mu, H., Andreeff, M., Bar-Eli, M., Overwijk, W., Ram, P., Lopez-Berestein, G., Coleman, R.L., Sood, A.K., 2017. Macrophages Facilitate Resistance to Anti-VEGF Therapy by Altered VEGFR Expression. Clin Cancer Res 23, 7034-7046.

Dammeijer, F., Lievense, L.A., Kaijen-Lambers, M.E., van Nimwegen, M., Bezemer, K., Hegmans, J.P., van Hall, T., Hendriks, R.W., Aerts, J.G., 2017. Depletion of Tumor-Associated Macrophages with a CSF-1R Kinase Inhibitor Enhances Antitumor Immunity and Survival Induced by DC Immunotherapy. Cancer Immunol Res 5, 535-546.

Danckwardt, S., Gantzert, A.S., Macher-Goeppinger, S., Probst, H.C., Gentzel, M., Wilm, M., Grone, H.J., Schirmacher, P., Hentze, M.W., Kulozik, A.E., 2011. p38 MAPK controls prothrombin expression by regulated RNA 3' end processing. Mol Cell 41, 298-310.

Daroqui, M.C., Vazquez, P., Bal de Kier Joffe, E., Bakin, A.V., Puricelli, L.I., 2012. TGF-beta autocrine pathway and MAPK signaling promote cell invasiveness and in vivo mammary adenocarcinoma tumor progression. Oncol Rep 28, 567-575.

De Craene, B., Berx, G., 2013. Regulatory networks defining EMT during cancer initiation and progression. Nat Rev Cancer 13, 97-110.

De Palma, M., Lewis, C.E., 2013. Macrophage regulation of tumor responses to anticancer therapies. Cancer Cell 23, 277-286.

DeBerardinis, R.J., Chandel, N.S., 2016. Fundamentals of cancer metabolism. Sci Adv 2, e1600200.

DeNardo, D.G., Brennan, D.J., Rexhepaj, E., Ruffell, B., Shiao, S.L., Madden, S.F., Gallagher, W.M., Wadhwani, N., Keil, S.D., Junaid, S.A., Rugo, H.S., Hwang, E.S., Jirstrom, K., West, B.L., Coussens, L.M., 2011. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. Cancer Discov 1, 54-67.

Deng, J.J., Zhang, W., Xu, X.M., Zhang, F., Tao, W.P., Ye, J.J., Ge, W., 2016. Twist mediates an aggressive phenotype in human colorectal cancer cells. Int J Oncol 48, 1117-1124.

Deniz, B., Ambavane, A., Yang, S., Altincatal, A., Doan, J., Rao, S., Michaelson, M.D., 2019. Treatment sequences for advanced renal cell carcinoma: A health economic assessment. PLoS One 14, e0215761.

Di Mitri, D., Toso, A., Alimonti, A., 2015. Molecular Pathways: Targeting Tumor-Infiltrating Myeloid-Derived Suppressor Cells for Cancer Therapy. Clin Cancer Res 21, 3108-3112.

Diesendruck, Y., Benhar, I., 2017. Novel immune check point inhibiting antibodies in cancer therapy-Opportunities and challenges. Drug Resist Updat 30, 39-47.

Dijkgraaf, E.M., Heusinkveld, M., Tummers, B., Vogelpoel, L.T., Goedemans, R., Jha, V., Nortier, J.W., Welters, M.J., Kroep, J.R., van der Burg, S.H., 2013. Chemotherapy alters monocyte differentiation to favor generation of cancer-supporting M2 macrophages in the tumor microenvironment. Cancer Res 73, 2480-2492.

Ding, Z., Yang, L., Xie, X., Xie, F., Pan, F., Li, J., He, J., Liang, H., 2010. Expression and significance of hypoxia-inducible factor-1 alpha and MDR1/P-glycoprotein in human colon carcinoma tissue and cells. J Cancer Res Clin Oncol 136, 1697-1707 (2010)

Donadelli, M., Dando, I., Zaniboni, T., Costanzo, C., Dalla Pozza, E., Scupoli, M.T., Scarpa, A., Zappavigna, S., Marra, M., Abbruzzese, A., Bifulco, M., Caraglia, M., Palmieri, M., 2011. Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism. Cell Death Dis 2, e152-e152.

Dongre, A., Weinberg, R.A., 2019. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nature Rev Mol Cell Biol 20, 69-84.

Du, B., Shim, J.S., 2016. Targeting epithelial-mesenchymal transition (EMT) to overcome drug resistance in cancer. Molecules 21.

Doublier, S., Belisario, D.C., Polimeni, M., Annaratone, L., Riganti, C., Allia, E., Ghigo, D., Bosia, A., Sapino, A., 2012. HIF-1 activation induces doxorubicin resistance in MCF7 3-D spheroids via P-glycoprotein expression: a potential model of the chemo-resistance of invasive micropapillary carcinoma of the breast. BMC Cancer 12, 4.

Doublier, S., Belisario, D.C., Polimeni, M., Annaratone, L., Riganti, C., Allia, E., Ghigo, D., Bosia, A., Sapino, A., 2012. HIF-1 activation induces doxorubicin resistance in MCF7 3-D spheroids via P-glycoprotein expression: a potential model of the chemo-resistance of invasive micropapillary carcinoma of the breast. BMC Cancer 12, 4.

Dudas, J., Ladanyi, A., Ingruber, J., Steinbichler, T.B., Riechelmann, H., 2020. Epithelial to mesenchymal transition: A mechanism that fuels cancer radio/chemoresistance. Cells 9, 428.

Dumitru, C.A., Moses, K., Trellakis, S., Lang, S., Brandau, S., 2012. Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. Cancer Immunol Immunother 61, 1155-1167.

Ebos, J.M., Lee, C.R., Kerbel, R.S., 2009. Tumor and host-mediated pathways of resistance and disease progression in response to antiangiogenic therapy. Clin Cancer Res 15, 5020-5025.

Efferth, T., Saeed, M.E.M., Mirghani, E., Alim, A., Yassin, Z., Saeed, E., Khalid, H.E., Daak, S., 2017. Integration of phytochemicals and phytotherapy into cancer precision medicine. Oncotarget 8, 50284-50304.

Efferth, T., Volm, M., 2005. Pharmacogenetics for individualized cancer chemotherapy. Pharmacol Ther 107, 155-176.

El Alaoui-Lasmaili, K., Faivre, B., 2018. Antiangiogenic therapy: Markers of response, "normalization" and resistance. Critical Rev Oncolog Hematol 128, 118-129.

Eriksson, E., Wenthe, J., Irenaeus, S., Loskog, A., Ullenhag, G., 2016. Gemcitabine reduces MDSCs, tregs and TGFbeta-1 while restoring the teff/treg ratio in patients with pancreatic cancer. J Transl Med 14, 282.

Erin, N., Dilmac, S., Curry, A., Duymus, O., Tanriover, G., Prodeus, A., Gariepy, J., Gorczynski, R.M., 2020. CD200 mimetic aptamer PEG-M49 markedly increases the therapeutic effects of pegylated liposomal doxorubicin in a mouse model of metastatic breast carcinoma: an effect independent of CD200 receptor 1. Cancer Immunol Immunother CII 69, 103-114.

Erin, N., Ogan, N., Yerlikaya, A., 2018a. Secretomes reveal several novel proteins as well as TGF-beta1 as the top upstream regulator of metastatic process in breast cancer. Breast Cancer Res Treat 170, 235-250.

Erin, N., Podnos, A., Tanriover, G., Duymus, O., Cote, E., Khatri, I., Gorczynski, R.M., 2015. Bidirectional effect of CD200 on breast cancer development and metastasis, with ultimate outcome determined by tumor aggressiveness and a cancer-induced inflammatory response. Oncogene 34, 3860-3870.

Erin, N., Tanriover, G., Curry, A., Akman, M., Duymus, O., Gorczynski, R., 2018b. CD200fc enhances anti-tumoral immune response and inhibits visceral metastasis of breast carcinoma. Oncotarget 9, 19147-19158.

Fan, Q.M., Jing, Y.Y., Yu, G.F., Kou, X.R., Ye, F., Gao, L., Li, R., Zhao, Q.D., Yang, Y., Lu, Z.H., Wei, L.X., 2014. Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352, 160-168.

Farcas, M., Gavrea, A.A., Gulei, D., Ionescu, C., Irimie, A., Catana, C.S., Berindan-Neagoe, I., 2019. SIRT1 in the development and treatment of hepatocellular carcinoma. Front Nutr 6, 148.

Fendt, S.M., Bell, E.L., Keibler, M.A., Davidson, S.M., Wirth, G.J., Fiske, B., Mayers, J.R., Schwab, M., Bellinger, G., Csibi, A., Patnaik, A., Blouin, M.J., Cantley, L.C., Guarente, L., Blenis, J., Pollak, M.N., Olumi, A.F., Vander Heiden, M.G., Stephanopoulos, G., 2013. Metformin decreases glucose oxidation and increases the dependency of prostate cancer cells on reductive glutamine metabolism. Cancer Res 73, 4429-4438.

Feng, Y.H., Tsao, C.J., 2016. Emerging role of microRNA-21 in cancer. Biomed Rep 5, 395-402.
Fiori, M.E., Di Franco, S., Villanova, L., Bianca, P., Stassi, G., De Maria, R., 2019. Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance. Mol Cancer 18, 70.

Fischer, C., Jonckx, B., Mazzone, M., Zacchigna, S., Loges, S., Pattarini, L., Chorianopoulos, E., Liesenborghs, L., Koch, M., De Mol, M., Autiero, M., Wyns, S., Plaisance, S., Moons, L., van Rooijen, N., Giacca, M., Stassen, J.M., Dewerchin, M., Collen, D., Carmeliet, P., 2007. Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. Cell 131, 463-475.

Fradette, C., Batonga, J., Teng, S., Piquette-Miller, M., du Souich, P., 2007. Animal models of acute moderate hypoxia are associated with a down-regulation of CYP1A1, 1A2, 2B4, 2C5, and 2C16 and up-regulation of CYP3A6 and P-glycoprotein in liver. Drug Metab Dispos 35, 765-771.

Friedman, H.S., Prados, M.D., Wen, P.Y., Mikkelsen, T., Schiff, D., Abrey, L.E., Yung, W.K., Paleologos, N., Nicholas, M.K., Jensen, R., Vredenburgh, J., Huang, J., Zheng, M., Cloughesy, T., 2009. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27, 4733-4740.

Fujita, M., Kohanbash, G., Fellows-Mayle, W., Hamilton, R.L., Komohara, Y., Decker, S.A., Ohlfest, J.R., Okada, H., 2011. COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. Cancer Res 71, 2664-2674.

Gabrilovich, D.I., Bronte, V., Chen, S.H., Colombo, M.P., Ochoa, A., Ostrand-Rosenberg, S., Schreiber, H., 2007. The terminology issue for myeloid-derived suppressor cells. Cancer Res 67, 425; author reply 426.

Gabrilovich, D.I., Ostrand-Rosenberg, S., Bronte, V., 2012. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 12, 253-268.

Gacche, R.N., Assaraf, Y.G., 2018. Redundant angiogenic signaling and tumor drug resistance. Drug Resist Updat 36, 47-76.

Ganesh, T., Banik, A., Dingledine, R., Wang, W., Amaradhi, R., 2018. Peripherally restricted, highly Potent, Selective, Aqueous-Soluble EP2 Antagonist with Anti-Inflammatory Properties. Mol Pharm 15, 5809-5817.

Gao, Y., Fan, X., Li, N., Du, C., Yang, B., Qin, W., Fu, J., Markowitz, G.J., Wang, H., Ma, J., Cheng, S., Yang, P., 2020. CCL22 signaling contributes to sorafenib resistance in hepatitis B virus-associated hepatocellular carcinoma. Pharmacol Res 157, 104800.

Gao, H., Xie, J., Peng, J., Han, Y., Jiang, Q., Han, M., Wang, C., 2015. Hispidulin inhibits proliferation and enhances chemosensitivity of gallbladder cancer cells by targeting HIF-1α. Exp. Cell Res 332, 236-246.

Gaude, E., Frezza, C., 2016. Tissue-specific and convergent metabolic transformation of cancer correlates with metastatic potential and patient survival. Nat Commun 7, 13041.

Genovese, I., Ilari, A., Assaraf, Y.G., Fazi, F., Colotti, G., 2017. Not only P-glycoprotein: Amplification of the ABCB1-containing chromosome region 7q21 confers multidrug resistance upon cancer cells by coordinated overexpression of an assortment of resistance-related proteins. Drug Resist Updat 32, 23-46.

George, D.J., Halabi, S., Healy, P., Jonasch, D., Anand, M., Rasmussen, J., Wood, S.Y., Spritzer, C., Madden, J.F., Armstrong, A.J., 2019. Phase 2 clinical trial of TORC1 inhibition with everolimus in men with metastatic castration-resistant prostate cancer. Urol Oncol 79, 1752-1761.

Ghandadi, M., Sahebkar, A., 2016. Interleukin-6: A Critical Cytokine in Cancer Multidrug Resistance. Curr Pharm Des 22, 518-526.

Ginhoux, F., Schultze, J.L., Murray, P.J., Ochando, J., Biswas, S.K., 2016. New insights into the multidimensional concept of macrophage ontogeny, activation and function. Nat Immunol 17, 34-40.

Gonen, N., Assaraf, Y.G., 2012. Antifolates in cancer therapy: structure, activity and mechanisms of drug resistance. Drug Resist Updat 15, 183-210.

Gong, T., Cui, L., Wang, H., Wang, H., Han, N., 2018. Knockdown of KLF5 suppresses hypoxia-induced resistance to cisplatin in NSCLC cells by regulating HIF-1α-dependent glycolysis through inactivation of the PI3K/Akt/mTOR pathway. J Transl Med 16, 164.

Goossens, S., Vandamme, N., Van Vlierberghe, P., Berx, G., 2017. EMT transcription factors in cancer development re-evaluated: Beyond EMT and MET. Biochim Biophys Acta Rev Cancer 1868, 584-591.

Gottesman, M.M., Fojo, T., Bates, S.E., 2002. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2, 48-58.

Graham, T.R., Zhau, H.E., Odero-Marah, V.A., Osunkoya, A.O., Kimbro, K.S., Tighiouart, M., Liu, T., Simons, J.W., O'Regan, R.M., 2008. Insulin-like growth factor-I-dependent up-regulation of ZEB1 drives epithelial-to-mesenchymal transition in human prostate cancer cells. Cancer Res 68, 2479-2488.

Greijer, A.E., de Jong, M.C., Scheffer, G.L., Shvarts, A., van Diest, P.J., van der Wall, E., 2005. Hypoxia-induced acidification causes mitoxantrone resistance not mediated by drug transporters in human breast cancer cells. Cell Oncol 27, 43-49.

Grisanti, S., Ferrari, V.D., Buglione, M., Agazzi, G.M., Liserre, R., Poliani, L., Buttolo, L., Gipponi, S., Pedersini, R., Consoli, F., Panciani, P., Roca, E., Spena, G., Triggiani, L., Berruti, A., Gruppo Neuro-Oncologico, B., 2019. Second line treatment of recurrent glioblastoma with sunitinib: results of a phase II study and systematic review of literature. J Neurosurg Sci 63, 458-467.

Gritsko, T., Williams, A., Turkson, J., Kaneko, S., Bowman, T., Huang, M., Nam, S., Eweis, I., Diaz, N., Sullivan, D., Yoder, S., Enkemann, S., Eschrich, S., Lee, J.H., Beam, C.A., Cheng, J., Minton, S., Muro-Cacho, C.A., Jove, R., 2006. Persistent activation of stat3 signaling induces survivin gene expression and confers resistance to apoptosis in human breast cancer cells. Clin Cancer Res 12, 11-19.

Grivennikov, S., Karin, M., 2008. Autocrine IL-6 signaling: a key event in tumorigenesis? Cancer Cell 13, 7-9.

Grivennikov, S.I., Greten, F.R., Karin, M., 2010. Immunity, inflammation, and cancer. Cell 140, 883-899.

Grotegut, S., von Schweinitz, D., Christofori, G., Lehembre, F., 2006. Hepatocyte growth factor induces cell scattering through MAPK/Egr-1-mediated upregulation of Snail. EMBO J 25, 3534-3545.

Gonzalez, D.M., Medici, D., 2014. Signaling mechanisms of the epithelial-mesenchymal transition. Sci Signal 7, re8-re8.

Gugnoni, M., Sancisi, V., Manzotti, G., Gandolfi, G., Ciarrocchi, A., 2016. Autophagy and epithelial-mesenchymal transition: an intricate interplay in cancer. Cell Death Dis 7, e2520.

Hagemann, T., Lawrence, T., McNeish, I., Charles, K.A., Kulbe, H., Thompson, R.G., Robinson, S.C., Balkwill, F.R., 2008. "Re-educating" tumor-associated macrophages by targeting NF-kappaB. J Exp Med 205, 1261-1268.

Haibe, Y., Kreidieh, M., El Hajj, H., Khalifeh, I., Mukherji, D., Temraz, S., Shamseddine, A., 2020. Resistance mechanisms to anti-angiogenic therapies in cancer. Front Oncol 10, 221.

Halsall, J.A., Turner, B.M., 2016. Histone deacetylase inhibitors for cancer therapy: An evolutionarily ancient resistance response may explain their limited success. Bioessays 38, 1102-1110.

Ham, S.L., Thakuri, P.S., Plaster, M., Li, J., Luker, K.E., Luker, G.D., Tavana, H., 2018. Three-dimensional tumor model mimics stromal - breast cancer cells signaling. Oncotarget 9, 249-267.

Han, H.K., Han, C.Y., Cheon, E.P., Lee, J., Kang, K.W., 2007. Role of hypoxia-inducible factor-alpha in hepatitis-B-virus X protein-mediated MDR1 activation. Biochem Biophys Res Commun 357, 567-573.

Harrison, D.J., Schwartz, C.L., 2017. Osteogenic sarcoma: Systemic chemotherapy options for localized disease. Curr Treatm Options Oncol 18, 24.

Hart, K.M., Usherwood, E.J., Berwin, B.L., 2014. CX3CR1 delineates temporally and functionally distinct subsets of myeloid-derived suppressor cells in a mouse model of ovarian cancer. Immunol Cell Biol 92, 499-508.

Hartmann, T.N., Burger, J.A., Glodek, A., Fujii, N., Burger, M., 2005. CXCR4 chemokine receptor and integrin signaling co-operate in mediating adhesion and chemoresistance in small cell lung cancer (SCLC) cells. Oncogene 24, 4462-4471.

Haslehurst, A.M., Koti, M., Dharsee, M., Nuin, P., Evans, K., Geraci, J., Childs, T., Chen, J., Li, J., Weberpals, J., Davey, S., Squire, J., Park, P.C., Feilotter, H., 2012. EMT transcription factors snail and slug directly contribute to cisplatin resistance in ovarian cancer. BMC Cancer 12, 91.

Hawila, E., Razon, H., Wildbaum, G., Blattner, C., Sapir, Y., Shaked, Y., Umansky, V., Karin, N., 2017. CCR5 directs the mobilization of CD11b+Gr1+Ly6C(low) polymorphonuclear myeloid cells from the bone marrow to the blood to support tumor development. Cell Rep 21, 2212-2222.

He, M., Wu, H., Jiang, Q., Liu, Y., Han, L., Yan, Y., Wei, B., Liu, F., Deng, X., Chen, H., Zhao, L., Wang, M., Wu, X., Yao, W., Zhao, H., Chen, J., Wie, M., 2019. Hypoxia-inducible factor-2α directly promotes BCRP expression and mediates the resistance of ovarian cancer stem cells to adriamycin. Mol Oncol 13, 403-421.

Heo, J., Reid, T., Ruo, L., Breitbach, C.J., Rose, S., Bloomston, M., Cho, M., Lim, H.Y., Chung, H.C., Kim, C.W., Burke, J., Lencioni, R., Hickman, T., Moon, A., Lee, Y.S., Kim, M.K., Daneshmand, M., Dubois, K., Longpre, L., Ngo, M., Rooney, C., Bell, J.C., Rhee, B.G., Patt, R., Hwang, T.H., Kirn, D.H., 2013. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. Nat Med 19, 329-336.

Herbst, R.S., Soria, J.C., Kowanetz, M., Fine, G.D., Hamid, O., Gordon, M.S., Sosman, J.A., McDermott, D.F., Powderly, J.D., Gettinger, S.N., Kohrt, H.E., Horn, L., Lawrence, D.P., Rost, S., Leabman, M., Xiao, Y., Mokatrin, A., Koeppen, H., Hegde, P.S., Mellman, I., Chen, D.S., Hodi, F.S., 2014. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515, 563-567.

Heusinkveld, M., de Vos van Steenwijk, P.J., Goedemans, R., Ramwadhdoebe, T.H., Gorter, A., Welters, M.J., van Hall, T., van der Burg, S.H., 2011. M2 macrophages induced by prostaglandin E2 and IL-6 from cervical carcinoma are switched to activated M1 macrophages by CD4+ Th1 cells. J Immunol 187, 1157-1165.

Hirsch, H.A., Iliopoulos, D., Tsichlis, P.N., Struhl, K., 2009. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res 69, 7507-7511.

Hou, W., Sampath, P., Rojas, J.J., Thorne, S.H., 2016. Oncolytic virus-mediated targeting of PGE2 in the tumor alters the immune status and sensitizes established and resistant tumors to immunotherapy. Cancer Cell 30, 108-119.

Hou, Y., Zhu, Q., Li, Z., Peng, Y., Yu, X., Yuan, B., Liu, Y., Liu, Y., Yin, L., Peng, Y., Jiang, Z., Li, J., Xie, B., Duan, Y., Tan, G., Gulina, K., Gong, Z., Sun, L., Fan, X., Li, X., 2017. The FOXM1–ABCC5 axis contributes to paclitaxel resistance in nasopharyngeal carcinoma cells. Cell Death Dis 8, e2659-e2659.

Howe, L.R., Watanabe, O., Leonard, J., Brown, A.M., 2003. Twist is up-regulated in response to Wnt1 and inhibits mouse mammary cell differentiation. Cancer Res 63, 1906-1913.

Hsieh, C.C., Wang, C.H., 2018. Aspirin disrupts the crosstalk of angiogenic and inflammatory cytokines between 4T1 breast cancer cells and macrophages. Mediators Inflamm 2018, 6380643.

Hsu, Y.L., Hung, J.Y., Tsai, E.M., Wu, C.Y., Ho, Y.W., Jian, S.F., Yen, M.C., Chang, W.A., Hou, M.F., Kuo, P.L., 2015. Benzyl butyl phthalate increases the chemoresistance to doxorubicin/cyclophosphamide by increasing breast cancer-associated dendritic cell-derived CXCL1/GROalpha and S100A8/A9. Oncol Rep 34, 2889-2900.

Hsu, Y.L., Yen, M.C., Chang, W.A., Tsai, P.H., Pan, Y.C., Liao, S.H., Kuo, P.L., 2019. CXCL17-derived CD11b(+)Gr-1(+) myeloid-derived suppressor cells contribute to lung metastasis of breast cancer through platelet-derived growth factor-BB. Breast Cancer Res 21, 23.

Hu, Y., Qi, W., Sun, L., Zhou, H., Zhou, B., Yang, Z., 2018. Effect of TGF-beta1 on blood CD4+CD25(high) regulatory T cell proliferation and Foxp3 expression during non-small cell lung cancer blood metastasis. Exp Ther Med 16, 1403-1410.

Huang, C., Tan, W., Zheng, J., Zhu, C., Huo, J., Yang, R., 2019. Azoreductase-responsive metal-organic framework-based nanodrug for enhanced cancer therapy via breaking hypoxia-induced chemoresistance. ACS Appl. Mater. Interfaces 11, 25740-25749. Harney, A.S., Lee, J., Manus, L.M., Wang, P., Ballweg, D.M., LaBonne, C., Meade, T.J., 2009. Targeted inhibition of Snail family zinc finger transcription factors by oligonucleotide-Co(III) Schiff base conjugate. Proc Natl Acad Sci U S A 106, 13667-13672.

Huang, B., Lei, Z., Zhao, J., Gong, W., Liu, J., Chen, Z., Liu, Y., Li, D., Yuan, Y., Zhang, G.M., Feng, Z.H., 2007. CCL2/CCR2 pathway mediates recruitment of myeloid suppressor cells to cancers. Cancer Lett 252, 86-92.

Huang, S., Holzel, M., Knijnenburg, T., Schlicker, A., Roepman, P., McDermott, U., Garnett, M., Grernrum, W., Sun, C., Prahallad, A., Groenendijk, F.H., Mittempergher, L., Nijkamp, W., Neefjes, J., Salazar, R., Ten Dijke, P., Uramoto, H., Tanaka, F., Beijersbergen, R.L., Wessels, L.F., Bernards, R., 2012. MED12 controls the response to multiple cancer drugs through regulation of TGF-beta receptor signaling. Cell 151, 937-950.

Huber, S., Schramm, C., Lehr, H.A., Mann, A., Schmitt, S., Becker, C., Protschka, M., Galle, P.R., Neurath, M.F., Blessing, M., 2004. Cutting edge: TGF-beta signaling is required for the in vivo expansion and immunosuppressive capacity of regulatory CD4+CD25+ T cells. J Immunol 173, 6526-6531.

Hugo, W., Zaretsky, J.M., Sun, L., Song, C., Moreno, B.H., Hu-Lieskovan, S., Berent-Maoz, B., Pang, J., Chmielowski, B., Cherry, G., Seja, E., Lomeli, S., Kong, X., Kelley, M.C., Sosman, J.A., Johnson, D.B., Ribas, A., Lo, R.S., 2016. Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. Cell 165, 35-44.

Huijts, C.M., Lougheed, S.M., Bodalal, Z., van Herpen, C.M., Hamberg, P., Tascilar, M., Haanen, J.B., Verheul, H.M., de Gruijl, T.D., van der Vliet, H.J., Dutch, W.I.N.O.C., 2019. The effect of everolimus and low-dose cyclophosphamide on immune cell subsets in patients with metastatic

renal cell carcinoma: results from a phase I clinical trial. Cancer Immunol Immunother 68, 503-515.

Ireland, L., Santos, A., Campbell, F., Figueiredo, C., Hammond, D., Ellies, L.G., Weyer-Czernilofsky, U., Bogenrieder, T., Schmid, M., Mielgo, A., 2018. Blockade of insulin-like growth factors increases efficacy of paclitaxel in metastatic breast cancer. Oncogene 37, 2022-2036.

Izumi, D., Toden, S., Ureta, E., Ishimoto, T., Baba, H., Goel, A., 2019. TIAM1 promotes chemoresistance and tumor invasiveness in colorectal cancer. Cell Death Disease 10, 267.

Jaiswal, S., Chao, M.P., Majeti, R., Weissman, I.L., 2010. Macrophages as mediators of tumor immunosurveillance. Trends Immunol 31, 212-219.

Javam, M., Audette, M.C., Iqbal, M., Bloise, E., Gibb, W., Matthews, S.G., 2014. Effect of oxygen on multidrug resistance in term human placenta. Placenta 35, 324-330.

Ji, Z., Long, H., Hu, Y., Qiu, X., Chen, X., Li, Z., Fan, D., Ma, B., Fan, Q., 2010. Expression of MDR1, HIF-1α and MRP1 in sacral chordoma and chordoma cell line CM-319. J Exp Clin Cancer Res 29, 158.

Jiang, L., Xiao, L., Sugiura, H., Huang, X., Ali, A., Kuro-o, M., Deberardinis, R.J., Boothman, D.A., 2015. Metabolic reprogramming during TGFbeta1-induced epithelial-to-mesenchymal transition. Oncogene 34, 3908-3916.

Jin, W.S., Kong, Z.L., Shen, Z.F., Jin, Y.Z., Zhang, W.K., Chen, G.F. Regulation of hypoxia inducible factor-1α expression by the alteration of redox status in HepG2 cells. J Exp Clin Cancer Res. 30, 61.

Jinushi, M., Chiba, S., Yoshiyama, H., Masutomi, K., Kinoshita, I., Dosaka-Akita, H., Yagita, H., Takaoka, A., Tahara, H., 2011. Tumor-associated macrophages regulate tumorigenicity and anticancer drug responses of cancer stem/initiating cells. Proc Natl Acad Sci U S A 108, 12425-12430.

Johnson, D.B., Menzies, A.M., Zimmer, L., Eroglu, Z., Ye, F., Zhao, S., Rizos, H., Sucker, A., Scolyer, R.A., Gutzmer, R., Gogas, H., Kefford, R.F., Thompson, J.F., Becker, J.C., Berking, C., Egberts, F., Loquai, C., Goldinger, S.M., Pupo, G.M., Hugo, W., Kong, X., Garraway, L.A., Sosman, J.A., Ribas, A., Lo, R.S., Long, G.V., Schadendorf, D., 2015. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur J Cancer 51, 2792-2799.

Jögi, A., Vallon-Christersson, J., Holmquist, L., Axelson, H., Borg, A., Påhlman, S., 2014. Human neuroblastoma cells exposed to hypoxia: induction of genes associated with growth, survival, and aggressive behavior. Exp Cell Res 295, 469-487.

Jung, Y., Kim, J.K., Shiozawa, Y., Wang, J., Mishra, A., Joseph, J., Berry, J.E., McGee, S., Lee, E., Sun, H., Wang, J., Jin, T., Zhang, H., Dai, J., Krebsbach, P.H., Keller, E.T., Pienta, K.J., Taichman, R.S., 2013. Recruitment of mesenchymal stem cells into prostate tumours promotes metastasis. Nat Commun 4, 1795.

Kadel, D., Zhang, Y., Sun, H.R., Zhao, Y., Dong, Q.Z., Qin, L.X., 2019. Current perspectives of cancer-associated fibroblast in therapeutic resistance: potential mechanism and future strategy. Cell Biol Toxicol 35, 407-421..

Kadioglu, O., Cao, J., Kosyakova, N., Mrasek, K., Liehr, T., Efferth, T., 2016. Genomic and transcriptomic profiling of resistant CEM/ADR-5000 and sensitive CCRF-CEM leukaemia cells for unravelling the full complexity of multi-factorial multidrug resistance. Sci Rep 6, 36754.

Kajita, M., McClinic, K.N., Wade, P.A., 2004. Aberrant expression of the transcription factors snail and slug alters the response to genotoxic stress. Mol Cell Biol 24, 7559-7566.

Kajiyama, H., Shibata, K., Terauchi, M., Yamashita, M., Ino, K., Nawa, A., Kikkawa, F., 2007. Chemoresistance to paclitaxel induces epithelial-mesenchymal transition and enhances metastatic potential for epithelial ovarian carcinoma cells. Int J Oncol 31, 277-283.

Kalinski, P., 2012. Regulation of immune responses by prostaglandin E2. J Immunol 188, 21-28.
Kang, D., Han, Z., Oh, G.H., Joo, Y., Choi, H.J., Song, J.J., 2017. Down-regulation of TGF-beta expression sensitizes the resistance of hepatocellular carcinoma cells to sorafenib. Yonsei Med J 58, 899-909.

Kalra, R., Jones, A.M., Kirk, J., Adams, G.E., Stratford, I.J., 1993. The effect of hypoxia on acquired drug resistance and response to epidermal growth factor in Chinese hamster lung fibroblasts and human breast-cancer cells in vitro. Int J Cancer 54, 650-655.

Kang, H., Kim, H., Lee, S., Youn, H., Youn, B., 2019. Role of metabolic reprogramming in epithelial(-)mesenchymal transition (EMT). Int J Mol Sci 20.

Karagas, M.R., Cushing, G.L., Jr., Greenberg, E.R., Mott, L.A., Spencer, S.K., Nierenberg, D.W., 2001. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer 85, 683-686.

Kawano, M., Mabuchi, S., Matsumoto, Y., Sasano, T., Takahashi, R., Kuroda, H., Kozasa, K., Hashimoto, K., Isobe, A., Sawada, K., Hamasaki, T., Morii, E., Kimura, T., 2015. The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer. Sci Rep 5, 18217.

Ketteler, J., Klein, D., 2018. Caveolin-1, cancer and therapy resistance. Int J Cancer 143, 2092-2104.

Kim, H.G., Hien, T.T., Han, E.H., Hwang, Y.P., Choi, J.H., Kang, K.W., Kwon, K.-i., Kim, B.-H., Kim, S.K., Song, G.Y., Jeong, T.C., Jeong, H.G., 2011. Metformin inhibits P-glycoprotein

expression via the NF-κB pathway and CRE transcriptional activity through AMPK activation. Br J Pharmacol 162, 1096-1108.

Kim, H.J., Litzenburger, B.C., Cui, X., Delgado, D.A., Grabiner, B.C., Lin, X., Lewis, M.T., Gottardis, M.M., Wong, T.W., Attar, R.M., Carboni, J.M., Lee, A.V., 2007. Constitutively active type I insulin-like growth factor receptor causes transformation and xenograft growth of immortalized mammary epithelial cells and is accompanied by an epithelial-to-mesenchymal transition mediated by NF-kappaB and Snail. Mol Cell Biol 27, 3165-3175.

Kim, J., You, Y.J., 2017. Regulation of organelle function by metformin. IUBMB Life 69, 459-469.

Kim, J.Y., Lee, J.Y., 2017. Targeting tumor adaption to chronic hypoxia: Implications for drug resistance, and how it can be overcome. Int J Mol Sci 18, 1854.

Kim, N.H., Cha, Y.H., Lee, J., Lee, S.H., Yang, J.H., Yun, J.S., Cho, E.S., Zhang, X., Nam, M., Kim, N., Yuk, Y.S., Cha, S.Y., Lee, Y., Ryu, J.K., Park, S., Cheong, J.H., Kang, S.W., Kim, S.Y., Hwang, G.S., Yook, J.I., Kim, H.S., 2017. Snail reprograms glucose metabolism by repressing phosphofructokinase PFKP allowing cancer cell survival under metabolic stress. Nat Commun 8, 14374.

Kinuya, S., Li, X.F., Yokoyama, K., Mori, H., Shiba, K., Watanabe, N., Shuke, N., Bunko, H., Michigishi, T., Tonami, N., 2003. Reduction of 99mTc-sestamibi and 99mTc-tetrofosmin uptake in MRP-expressing breast cancer cells under hypoxic conditions is independent of MRP function. Eur J Nucl Med Mol Imaging 30, 1529-1531.

Knight, D.A., Ngiow, S.F., Li, M., Parmenter, T., Mok, S., Cass, A., Haynes, N.M., Kinross, K., Yagita, H., Koya, R.C., Graeber, T.G., Ribas, A., McArthur, G.A., Smyth, M.J., 2013. Host immunity contributes to the anti-melanoma activity of BRAF inhibitors. J Clin Invest 123, 1371-1381.

Knight, J.R., Milner, J., 2012. SIRT1, metabolism and cancer. Curr Opin Oncol 24, 68-75.

Koch, S., Mayer, F., Honecker, F., Schittenhelm, M., Bokemeyer, C., 2003. Efficacy of cytotoxic agents used in the treatment of testicular germ cell tumours under normoxic and hypoxic conditions in vitro. Br J Cancer 89, 2133-2139.

Koleske, A.J., Baltimore, D., Lisanti, M.P., 1995. Reduction of caveolin and caveolae in oncogenically transformed cells. Proc Natl Acad Sci U S A 92, 1381-1385.

Kon, E., Benhar, I., 2019. Immune checkpoint inhibitor combinations: Current efforts and important aspects for success. Drug Resist Updat 45, 13-29.

Krishnamurthy, P., Ross, D.D., Nakanishi, T., Bailey-Dell, K., Zhou, S., Mercer, K.E., Sarkadi, B., Sorrentino, B.P., Schuetz, J.D., 2004. The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. J Biol Chem 279, 24218-24225.

Kowanetz, M., Wu, X., Lee, J., Tan, M., Hagenbeek, T., Qu, X., Yu, L., Ross, J., Korsisaari, N., Cao, T., Bou-Reslan, H., Kallop, D., Weimer, R., Ludlam, M.J., Kaminker, J.S., Modrusan, Z., van Bruggen, N., Peale, F.V., Carano, R., Meng, Y.G., Ferrara, N., 2010. Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G+Ly6C+ granulocytes. Proc Natl Acad Sci U S A 107, 21248-21255.

Krchniakova, M., Skoda, J., Neradil, J., Chlapek, P., Veselska, R., 2020. Repurposing tyrosine kinase inhibitors to overcome multidrug resistance in cancer: A focus on transporters and lysosomal sequestration. Int J Mol Sci 21, E3 157.

Kumar, V., Patel, S., Tcyganov, E., Gabrilovich, D.I., 2016. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 37, 208-220.

Kumari, N., Dwarakanath, B.S., Das, A., Bhatt, A.N., 2016. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol 37, 11553-11572.

Kurrey, N.K., Jalgaonkar, S.P., Joglekar, A.V., Ghanate, A.D., Chaskar, P.D., Doiphode, R.Y., Bapat, S.A., 2009. Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. Stem Cells 27, 2059-2068.

Lamaze, C., Torrino, S., 2015. Caveolae and cancer: A new mechanical perspective. Biomed J 38, 367-379.

Lambies, G., Miceli, M., Martinez-Guillamon, C., Olivera-Salguero, R., Pena, R., Frias, C.P., Calderon, I., Atanassov, B.S., Dent, S.Y.R., Arribas, J., Garcia de Herreros, A., Diaz, V.M., 2019. TGFbeta-activated USP27X deubiquitinase regulates cell migration and chemoresistance via stabilization of Snail1. Cancer Res 79, 33-46.

Larouche, V., Akirov, A., Alshehri, S., Ezzat, S., 2019. Management of small bowel neuroendocrine tumors. Cancers 11, 828.

Lazarova, D., Bordonaro, M., 2017. ZEB1 mediates drug resistance and EMT in p300-deficient CRC. J Cancer 8, 1453-1459.

LeBleu, V.S., O'Connell, J.T., Gonzalez Herrera, K.N., Wikman, H., Pantel, K., Haigis, M.C., de Carvalho, F.M., Damascena, A., Domingos Chinen, L.T., Rocha, R.M., Asara, J.M., Kalluri, R., 2014. PGC-1alpha mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. Nat Cell Biol 16, 992-1003.

Lee, S.H., Oh, S.Y., Do, S.I., Lee, H.J., Kang, H.J., Rho, Y.S., Bae, W.J., Lim, Y.C., 2014. SOX2 regulates self-renewal and tumorigenicity of stem-like cells of head and neck squamous cell carcinoma. Br J Cancer 111, 2122-2130.

Lee, S.H., Shen, G.N., Jung, Y.S., Lee, S.J., Chung, J.Y., Kim, H.S., Xu, Y., Choi, Y., Lee, J.W., Ha, N.C., Song, G.Y., Park, B.J., 2010. Antitumor effect of novel small chemical inhibitors of Snail-p53 binding in K-Ras-mutated cancer cells. Oncogene 29, 4576-4587.

Lee, S.Y., Jeon, H.M., Ju, M.K., Kim, C.H., Yoon, G., Han, S.I., Park, H.G., Kang, H.S., 2012. Wnt/Snail signaling regulates cytochrome C oxidase and glucose metabolism. Cancer Res 72, 3607-3617.

Leis, O., Eguiara, A., Lopez-Arribillaga, E., Alberdi, M.J., Hernandez-Garcia, S., Elorriaga, K., Pandiella, A., Rezola, R., Martin, A.G., 2012. Sox2 expression in breast tumours and activation in breast cancer stem cells. Oncogene 31, 1354-1365.

Leonetti, A., Assaraf, Y.G., Veltsista, P.D., El Hassouni, B., Tiseo, M., Giovannetti, E., 2019a. MicroRNAs as a drug resistance mechanism to targeted therapies in EGFR-mutated NSCLC: Current implications and future directions. Drug Resist Updat 42, 1-11.

Leonetti, A., Wever, B., Mazzaschi, G., Assaraf, Y.G., Rolfo, C., Quaini, F., Tiseo, M., Giovannetti, E., 2019b. Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer. Drug Resist Updat 46, 100644.

Leong, K.G., Niessen, K., Kulic, I., Raouf, A., Eaves, C., Pollet, I., Karsan, A., 2007. Jagged1-mediated Notch activation induces epithelial-to-mesenchymal transition through Slug-induced repression of E-cadherin. J Exp Med 204, 2935-2948.

Levi, M., van der Poll, T., 2010. Inflammation and coagulation. Crit Care Med 38, S26-34.

Levi, M., van der Poll, T., Buller, H.R., 2004. Bidirectional relation between inflammation and coagulation. Circulation 109, 2698-2704.

Li, D., Ji, H., Niu, X., Yin, L., Wang, Y., Gu, Y., Wang, J., Zhou, X., Zhang, H., Zhang, Q., 2020. Tumor-associated macrophages secrete CC-chemokine ligand 2 and induce tamoxifen resistance by activating PI3K/Akt/mTOR in breast cancer. Cancer science 111, 47-58.

Li, F., Kitajima, S., Kohno, S., Yoshida, A., Tange, S., Sasaki, S., Okada, N., Nishimoto, Y., Muranaka, H., Nagatani, N., Suzuki, M., Masuda, S., Thai, T.C., Nishiuchi, T., Tanaka, T., Barbie, D.A., Mukaida, N., Takahashi, C., 2019. Retinoblastoma inactivation induces a protumoral microenvironment via enhanced CCL2 secretion. Cancer Res 79, 3903-3915.

Li, J., Guan, J., Long, X., Wang, Y., Xiang, X., 2016a. mir-1-mediated paracrine effect of cancer-associated fibroblasts on lung cancer cell proliferation and chemoresistance. Oncol Rep 35, 3523-3531.

Li, J., Shi, M., Cao, Y., Yuan, W., Pang, T., Li, B., Sun, Z., Chen, L., Zhao, R.C., 2006. Knockdown of hypoxia-inducible factor-1alpha in breast carcinoma MCF-7 cells results in reduced tumor growth and increased sensitivity to methotrexate. Biochem Biophys Res Commun 342, 1341-1351.

Li, J.-r., Cheng, C.-L., Yang, C.-R., Ou, Y.-C., Wu, M.-J., Ko, J.-L., 2013. Dual inhibitor of phosphoinositide 3-kinase/mammalian target of rapamycin NVP-BEZ235 effectively inhibits cisplatin-resistant urothelial cancer cell growth through autophagic flux. Toxicol Lett 220, 267-276.

Li, L., Li, W., 2015. Epithelial-mesenchymal transition in human cancer: comprehensive reprogramming of metabolism, epigenetics, and differentiation. Pharmacol Ther 150, 33-46.

Li, Q.Q., Xu, J.D., Wang, W.J., Cao, X.X., Chen, Q., Tang, F., Chen, Z.Q., Liu, X.P., Xu, Z.D., 2009. Twist1-mediated adriamycin-induced epithelial-mesenchymal transition relates to multidrug resistance and invasive potential in breast cancer cells. Clin Cancer Res 15, 2657-2665.

Li, R., Wu, C., Liang, H., Zhao, Y., Lin, C., Zhang, X., Ye, C., 2018a. Knockdown of TWIST enhances the cytotoxicity of chemotherapeutic drugs in doxorubicin-resistant HepG2 cells by suppressing MDR1 and EMT. Int J Oncol 53, 1763-1773.

Li, W., Liu, C., Tang, Y., Li, H., Zhou, F., Lv, S., 2011. Overexpression of Snail accelerates adriamycin induction of multidrug resistance in breast cancer cells. Asian Pac J Cancer Prev 12, 2575-2580.

Li, W., Zhang, H., Assaraf, Y.G., Zhao, K., Xu, X., Xie, J., Yang, D.H., Chen, Z.S., 2016b. Overcoming ABC transporter-mediated multidrug resistance: Molecular mechanisms and novel therapeutic drug strategies. Drug Resist Upd 27, 14-29.

Li, W., Zhang, X., Chen, Y., Xie, Y., Liu, J., Feng, Q., Wang, Y., Yuan, W., Ma, J., 2016c. G-CSF is a key modulator of MDSC and could be a potential therapeutic target in colitis-associated colorectal cancers. Protein Cell 7, 130-140.

Li, X., Deng, W., Nail, C.D., Bailey, S.K., Kraus, M.H., Ruppert, J.M., Lobo-Ruppert, S.M., 2005. Snail induction is an early response to Gli1 that determines the efficiency of epithelial transformation. Oncogene 25, 609-621.

Li, Y., Luo, J., Lin, M.T., Zhi, P., Guo, W.W., Han, M., You, J., Gao, J.Q., 2019. Co-delivery of metformin enhances the antimultidrug resistant tumor effect of doxorubicin by improving hypoxic tumor microenvironment. Mol Pharm 16, 2966-2979.

Li, Y., Yu, H.P., Zhang, P., 2016d. CCL15 overexpression predicts poor prognosis for hepatocellular carcinoma. Hepatol Int 10, 488-492.

Li, Y.J., Lei, Y.H., Yao, N., Wang, C.R., Hu, N., Ye, W.C., Zhang, D.M., Chen, Z.S., 2017. Autophagy and multidrug resistance in cancer. Chin J Cancer 36, 52.

Li, Z., Chan, K., Qi, Y., Lu, L., Ning, F., Wu, M., Wang, H., Wang, Y., Cai, S., Du, J., 2018b. Participation of CCL1 in Snail-positive fibroblasts in colorectal cancer contribute to 5-fluorouracil/paclitaxel chemoresistance. Cancer Res Treat 50, 894-907.

Liang, B., Liu, X., Liu, Y., Kong, D., Liu, X., Zhong, R., Ma, S., 2016. Inhibition of autophagy sensitizes MDR-phenotype ovarian cancer SKVCR cells to chemotherapy. Biomed Pharmacother 82, 98-105.

Liang, B.C., 1996. Effects of hypoxia on drug resistance phenotype and genotype in human glioma cell lines. J Neurooncol 29, 149-155.

Lin, Y., Xu, J., Lan, H., 2019. Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. J Hematol Oncol 12, 76.

Ling, S., Tian, Y.U., Zhang, H., Jia, K., Feng, T., Sun, D., Gao, Z., Xu, F.E.I., Hou, Z., Li, Y.A.N., Wang, L., 2014. Metformin reverses multidrug resistance in human hepatocellular carcinoma Bel-7402/5-fluorouracil cells. Mol Med Rep 10, 2891-2897.

Linn, S.C., Giaccone, G., van Diest, P.J., Blokhuis, W.M., van der Valk, P., van Kalken, C.K., Kuiper, C.M., Pinedo, H.M., Baak, J.P., 1995. Prognostic relevance of P-glycoprotein expression in breast cancer. Ann Oncol 6, 679-685.

Liongue, C., Wright, C., Russell, A.P., Ward, A.C., 2009. Granulocyte colony-stimulating factor receptor: stimulating granulopoiesis and much more. Int J Biochem Cell Biol 41, 2372-2375.

Liu, J., Yan, F., Chen, H., Wang, W., Liu, W., Hao, K., Wang, G., Zhou, F., Zhang, J., 2017. A novel individual-cell-based mathematical model based on multicellular tumour spheroids for evaluating doxorubicin-related delivery in avascular regions. Br J Pharmacol 174, 2862-2879.

Liu, L., Ning, X., Sun, L., Zhang, H., Shi, Y., Guo, C., Han, S., Liu, J., Sun, S., Han, Z., Wu, K., Fan, D., 2008. Hypoxia-inducible factor-1 alpha contributes to hypoxia-induced chemoresistance in gastric cancer. Cancer Sci 99, 121-128.

Liu, M., Hancock, S.E., Sultani, G., Wilkins, B.P., Ding, E., Osborne, B., Quek, L.E., Turner, N., 2019a. Snail-overexpression induces epithelial-mesenchymal transition and metabolic reprogramming in human pancreatic ductal adenocarcinoma and non-tumorigenic ductal cells. J Clin Med 8, 822.

Liu, M., Quek, L.-E., Sultani, G., Turner, N., 2016. Epithelial-mesenchymal transition induction is associated with augmented glucose uptake and lactate production in pancreatic ductal adenocarcinoma. Cancer Metabol 4, 19.

Liu, Q., Tong, D., Liu, G., Xu, J., Do, K., Geary, K., Zhang, D., Zhang, J., Zhang, Y., Li, Y., Bi, G., Lan, W., Jiang, J., 2017a. Metformin reverses prostate cancer resistance to enzalutamide by targeting TGF-beta1/STAT3 axis-regulated EMT. Cell Death Dis 8, e3007.

Liu, T., Han, C., Wang, S., Fang, P., Ma, Z., Xu, L., Yin, R., 2019b. Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. J Hematol Oncol 12, 86.

Liu, X.Q., Xiong, M.H., Shu, X.T., Tang, R.Z., Wang, J., 2012. Therapeutic delivery of siRNA silencing HIF-1 alpha with micellar nanoparticles inhibits hypoxic tumor growth. Mol Pharm 9, 2863-2874.

Liu, Y., Zhang, J., Sun, X., Su, Q., You, C., 2017b. Down-regulation of miR-29b in carcinoma associated fibroblasts promotes cell growth and metastasis of breast cancer. Oncotarget 8, 39559-39570.

Liu, Y.R., Liang, L., Zhao, J.M., Zhang, Y., Zhang, M., Zhong, W.L., Zhang, Q., Wei, J.J., Li, M., Yuan, J., Chen, S., Zong, S.M., Liu, H.J., Meng, J., Qin, Y., Sun, B., Yang, L., Zhou, H.G., Sun, T., Yang, C., 2017c. Twist1 confers multidrug resistance in colon cancer through upregulation of ATP-binding cassette transporters. Oncotarget 8, 52901-52912.

Livney, Y.D., Assaraf, Y.G., 2013. Rationally designed nanovehicles to overcome cancer chemoresistance. Adv Drug Deliv Rev 65, 1716-1730.

Lo, H.-W., Hsu, S.-C., Xia, W., Cao, X., Shih, J.-Y., Wei, Y., Abbruzzese, J.L., Hortobagyi, G.N., Hung, M.-C., 2007. Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression. Cancer Res 67, 9066-9076.

Lo, M., Tsao, M.S., Hedley, D., Ling, V., 2009. Gene expression profiling of adenosine triphosphate-binding cassette transporters in response to K-ras activation and hypoxia in human pancreatic cancer cell cultures. Pancreas 38, 85-93.

Long, G.V., Stroyakovskiy, D., Gogas, H., Levchenko, E., de Braud, F., Larkin, J., Garbe, C., Jouary, T., Hauschild, A., Grob, J.J., Chiarion Sileni, V., Lebbe, C., Mandala, M., Millward, M., Arance, A., Bondarenko, I., Haanen, J.B., Hansson, J., Utikal, J., Ferraresi, V., Kovalenko, N., Mohr, P., Probachai, V., Schadendorf, D., Nathan, P., Robert, C., Ribas, A., DeMarini, D.J., Irani, J.G., Casey, M., Ouellet, D., Martin, A.M., Le, N., Patel, K., Flaherty, K., 2014. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 371, 1877-1888.

Lopes-Rodrigues, V., Di Luca, A., Mleczko, J., Meleady, P., Henry, M., Pesic, M., Cabrera, D., van Liempd, S., Lima, R.T., O'Connor, R., Falcon-Perez, J.M., Vasconcelos, M.H., 2017. Identification of the metabolic alterations associated with the multidrug resistant phenotype in cancer and their intercellular transfer mediated by extracellular vesicles. Sci Rep 7, 44541.

Lotti, F., Jarrar, A.M., Pai, R.K., Hitomi, M., Lathia, J., Mace, A., Gantt, G.A., Jr., Sukhdeo, K., DeVecchio, J., Vasanji, A., Leahy, P., Hjelmeland, A.B., Kalady, M.F., Rich, J.N., 2013. Chemotherapy activates cancer-associated fibroblasts to maintain colorectal cancer-initiating cells by IL-17A. J Exp Med 210, 2851-2872.

Lotz, C., Kelleher, D.K., Gassner, B., Gekle, M., Vaupel, P., Thews, O., 2007. Role of the tumor microenvironment in the activity and expression of the p-glycoprotein in human colon carcinoma cells. Oncol Rep 17, 239-244.

Lu, Y., Yu, L.Q., Zhu, L., Zhao, N., Zhou, X.J., Lu, X., 2016. Expression of HIF-1alpha and P-gp in non-small cell lung cancer and the relationship with HPV infection. Oncol Lett 12, 1455-1459.

Lu-Emerson, C., Duda, D.G., Emblem, K.E., Taylor, J.W., Gerstner, E.R., Loeffler, J.S., Batchelor, T.T., Jain, R.K., 2015. Lessons from anti-vascular endothelial growth factor and anti-vascular endothelial growth factor receptor trials in patients with glioblastoma. J Clin Oncol 33, 1197-1213.

Luk, C.K., Veinot-Drebot, L., Tjan, E., Tannock, I.F., 1990. Effect of transient hypoxia on sensitivity to doxorubicin in human and murine cell lines. J Natl Cancer Inst 82, 684-692.

Luo, X., Cheng, C., Tan, Z., Li, N., Tang, M., Yang, L., Cao, Y., 2017. Emerging roles of lipid metabolism in cancer metastasis. Mol Cancer 16, 76.

Luo, Z., Tian, H., Liu, L., Chen, Z., Liang, R., Chen, Z., Wu, Z., Ma, A., Zheng, M., Cai, L., 2018. Tumor-targeted hybrid protein oxygen carrier to simultaneously enhance hypoxia-dampened chemotherapy and photodynamic therapy at a single dose. Theranostics 8, 3584-3596.

Lv, Y., Zhao, S., Han, J., Zheng, L., Yang, Z., Zhao, L., 2015. Hypoxia-inducible factor-1α induces multidrug resistance protein in colon cancer. Onco Targets Ther. 8, 1941-1948.

Ma, Y., Zhu, J., Chen, S., Li, T., Ma, J., Guo, S., Hu, J., Yue, T., Zhang, J., Wang, P., Wang, X., Chen, G., Liu, Y., 2018. Activated gastric cancer-associated fibroblasts contribute to the malignant phenotype and 5-FU resistance via paracrine action in gastric cancer. Cancer Cell Int 18, 104.

Mallini, P., Lennard, T., Kirby, J., Meeson, A., 2014. Epithelial-to-mesenchymal transition: what is the impact on breast cancer stem cells and drug resistance. Cancer Treat Rev 40, 341-348.

Mantovani, A., Sica, A., Sozzani, S., Allavena, P., Vecchi, A., Locati, M., 2004. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25, 677-686.

Marie, J.C., Letterio, J.J., Gavin, M., Rudensky, A.Y., 2005. TGF-beta1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. J Exp Med 201, 1061-1067.

Markovic, T., Jakopin, Z., Dolenc, M.S., Mlinaric-Rascan, I., 2017. Structural features of subtype-selective EP receptor modulators. Drug Discov Today 22, 57-71.

Martinez-Outschoorn, U.E., Lisanti, M.P., Sotgia, F., 2014. Catabolic cancer-associated fibroblasts transfer energy and biomass to anabolic cancer cells, fueling tumor growth. Sem Cancer Biol 25, 47-60.

Mazzieri, R., Pucci, F., Moi, D., Zonari, E., Ranghetti, A., Berti, A., Politi, L.S., Gentner, B., Brown, J.L., Naldini, L., De Palma, M., 2011. Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myeloid cells. Cancer Cell 19, 512-526.

Meidhof, S., Brabletz, S., Lehmann, W., Preca, B.T., Mock, K., Ruh, M., Schuler, J., Berthold, M., Weber, A., Burk, U., Lubbert, M., Puhr, M., Culig, Z., Wellner, U., Keck, T., Bronsert, P., Kusters, S., Hopt, U.T., Stemmler, M.P., Brabletz, T., 2015. ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. EMBO Mol Med 7, 831-847.

Melero, I., Rouzaut, A., Motz, G.T., Coukos, G., 2014. T-cell and NK-cell infiltration into solid tumors: a key limiting factor for efficacious cancer immunotherapy. Cancer Discov 4, 522-526
.
Mercier, I., Casimiro, M.C., Wang, C., Rosenberg, A.L., Quong, J., Minkeu, A., Allen, K.G., Danilo, C., Sotgia, F., Bonuccelli, G., Jasmin, J.-F., Xu, H., Bosco, E., Aronow, B., Witkiewicz, A., Pestell, R.G., Knudsen, E.S., Lisanti, M.P., 2008. Human breast cancer-associated fibroblasts (CAFs) show caveolin-1 downregulation and RB tumor suppressor functional inactivation: Implications for the response to hormonal therapy. Cancer Biol Ther 7, 1212-1225.

Meschini, S., Condello, M., Calcabrini, A., Marra, M., Formisano, G., Lista, P., De Milito, A., Federici, E., Arancia, G., 2008. The plant alkaloid voacamine induces apoptosis-independent autophagic cell death on both sensitive and multidrug resistant human osteosarcoma cells. Autophagy 4, 1020-1033.

Meyer, C., Sevko, A., Ramacher, M., Bazhin, A.V., Falk, C.S., Osen, W., Borrello, I., Kato, M., Schadendorf, D., Baniyash, M., Umansky, V., 2011. Chronic inflammation promotes myeloid-derived suppressor cell activation blocking antitumor immunity in transgenic mouse melanoma model. Proc Natl Acad Sci U S A 108, 17111-17116.

Middleton, G., Brown, S., Lowe, C., Maughan, T., Gwyther, S., Oliver, A., Richman, S., Blake, D., Napp, V., Marshall, H., Wadsley, J., Maisey, N., Chau, I., Hill, M., Gollins, S., Myint, S., Slater, S., Wagstaff, J., Bridgewater, J., Seymour, M., 2013. A randomised phase III trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: results of the Panitumumab, Irinotecan & Ciclosporin in COLOrectal cancer therapy trial (PICCOLO). Eur J Cancer 49, 3507-3516.

Milman, N., Ginini, L., Gil, Z., 2019. Exosomes and their role in tumorigenesis and anticancer drug resistance. Drug Resist Updat 45, 1-12.

Mishra, P.J., Humeniuk, R., Medina, D.J., Alexe, G., Mesirov, J.P., Ganesan, S., Glod, J.W., Banerjee, D., 2008. Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res 68, 4331-4339.

Mitchem, J.B., Brennan, D.J., Knolhoff, B.L., Belt, B.A., Zhu, Y., Sanford, D.E., Belaygorod, L., Carpenter, D., Collins, L., Piwnica-Worms, D., Hewitt, S., Udupi, G.M., Gallagher, W.M., Wegner, C., West, B.L., Wang-Gillam, A., Goedegebuure, P., Linehan, D.C., DeNardo, D.G., 2013. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res 73, 1128-1141.

Miyake, M., Hori, S., Morizawa, Y., Tatsumi, Y., Nakai, Y., Anai, S., Torimoto, K., Aoki, K., Tanaka, N., Shimada, K., Konishi, N., Toritsuka, M., Kishimoto, T., Rosser, C.J., Fujimoto, K.,

2016. CXCL1-mediated interaction of cancer cells with tumor-associated macrophages and cancer-associated fibroblasts promotes tumor progression in human bladder cancer. Neoplasia 18, 636-646.

Moro, L., Arbini, A.A., Yao, J.L., di Sant'Agnese, P.A., Marra, E., Greco, M., 2009. Mitochondrial DNA depletion in prostate epithelial cells promotes anoikis resistance and invasion through activation of PI3K/Akt2. Cell Death Differ 16, 571-583.

Morris, K.T., Khan, H., Ahmad, A., Weston, L.L., Nofchissey, R.A., Pinchuk, I.V., Beswick, E.J., 2014. G-CSF and G-CSFR are highly expressed in human gastric and colon cancers and promote carcinoma cell proliferation and migration. Br J Cancer 110, 1211-1220.

Moustakas, A., Heldin, C.H., 2012. Induction of epithelial-mesenchymal transition by transforming growth factor beta. Semin Cancer Biol 22, 446-454.

Murdoch, C., Muthana, M., Coffelt, S.B., Lewis, C.E., 2008. The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer 8, 618-631.

Muz, B., Kusdono, H.D., Azab, F., de la Puente, P., Federico, C., Fiala, M., Vij, R., Salama, N.N., Azab, A.K., 2017. Tariquidar sensitizes multiple myeloma cells to proteasome inhibitors via reduction of hypoxia-induced P-gp-mediated drug resistance. Leuk Lymphoma 58, 2916-2925.

Naser Al Deen, N., Nassar, F., Nasr, R., Talhouk, R., 2019. Cross-roads to drug resistance and metastasis in breast cancer: miRNAs regulatory function and biomarker capability. Adv Exp Biol 1152, 335-364.

Natori, T., Sata, M., Washida, M., Hirata, Y., Nagai, R., Makuuchi, M., 2002. G-CSF stimulates angiogenesis and promotes tumor growth: Potential contribution of bone marrow-derived endothelial progenitor cells. Biochem Biophys Res Commun 297, 1058-1061.

Nierodzik, M.L., Karpatkin, S., 2006. Thrombin induces tumor growth, metastasis, and angiogenesis: Evidence for a thrombin-regulated dormant tumor phenotype. Cancer Cell 10, 355-362.

Niewerth, D., Jansen, G., Assaraf, Y.G., Zweegman, S., Kaspers, G.J., Cloos, J., 2015. Molecular basis of resistance to proteasome inhibitors in hematological malignancies. Drug Resist Updat 18, 18-35.

Nikolova, T., Roos, W.P., Kramer, O.H., Strik, H.M., Kaina, B., 2017. Chloroethylating nitrosoureas in cancer therapy: DNA damage, repair and cell death signaling. Biochim Biophys Acta. Rev Cancer 1868, 29-39.

Obermajer, N., Muthuswamy, R., Lesnock, J., Edwards, R.P., Kalinski, P., 2011. Positive feedback between PGE2 and COX2 redirects the differentiation of human dendritic cells toward stable myeloid-derived suppressor cells. Blood 118, 5498-5505.

Omran, Z., Scaife, P., Stewart, S., Rauch, C., 2017. Physical and biological characteristics of multi drug resistance (MDR): An integral approach considering pH and drug resistance in cancer. Semin Cancer Biol 43, 42-48.

Oshimori, N., Oristian, D., Fuchs, E., 2015. TGF-beta promotes heterogeneity and drug resistance in squamous cell carcinoma. Cell 160, 963-976.

Ostrand-Rosenberg, S., Fenselau, C., 2018. Myeloid-derived suppressor cells: Immune-suppressive cells that impair antitumor immunity and are sculpted by their environment. J Immunol 200, 422-431.

Paldino, E., Tesori, V., Casalbore, P., Gasbarrini, A., Puglisi, M.A., 2014. Tumor initiating cells and chemoresistance: which is the best strategy to target colon cancer stem cells? Biomed Res Int 2014, 859871.

Panka, D.J., Liu, Q., Geissler, A.K., Mier, J.W., 2013. Effects of HDM2 antagonism on sunitinib resistance, p53 activation, SDF-1 induction, and tumor infiltration by CD11b+/Gr-1+ myeloid derived suppressor cells. Mol Cancer 12, 17.

Park, J.H., Kim, Y.H., Park, E.H., Lee, S.J., Kim, H., Kim, A., Lee, S.B., Shim, S., Jang, H., Myung, J.K., Park, S., Lee, S.J., Kim, M.J., 2019. Effects of metformin and phenformin on apoptosis and epithelial-mesenchymal transition in chemoresistant rectal cancer. Cancer Sci 110, 2834-2845.

Parker, K.H., Beury, D.W., Ostrand-Rosenberg, S., 2015. Myeloid-derived suppressor cells: Critical cells driving immune suppression in the tumor microenvironment. Adv Cancer Res 128, 95-139.

Pavlides, S., Whitaker-Menezes, D., Castello-Cros, R., Flomenberg, N., Witkiewicz, A.K., Frank, P.G., Casimiro, M.C., Wang, C., Fortina, P., Addya, S., Pestell, R.G., Martinez-Outschoorn, U.E., Sotgia, F., Lisanti, M.P., 2009. The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. Cell Cycle 8, 3984-4001.

Peinado, H., Quintanilla, M., Cano, A., 2003. Transforming growth factor beta-1 induces snail transcription factor in epithelial cell lines: mechanisms for epithelial mesenchymal transitions. J Biol Chem 278, 21113-21123.

Peng, W., Chen, J.Q., Liu, C., Malu, S., Creasy, C., Tetzlaff, M.T., Xu, C., McKenzie, J.A., Zhang, C., Liang, X., Williams, L.J., Deng, W., Chen, G., Mbofung, R., Lazar, A.J., Torres-Cabala, C.A., Cooper, Z.A., Chen, P.L., Tieu, T.N., Spranger, S., Yu, X., Bernatchez, C., Forget, M.A., Haymaker, C., Amaria, R., McQuade, J.L., Glitza, I.C., Cascone, T., Li, H.S., Kwong, L.N., Heffernan, T.P., Hu, J., Bassett, R.L., Jr., Bosenberg, M.W., Woodman, S.E., Overwijk, W.W., Lizee, G., Roszik, J., Gajewski, T.F., Wargo, J.A., Gershenwald, J.E., Radvanyi, L., Davies, M.A., Hwu, P., 2016. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov 6, 202-216.

Peranzoni, E., Lemoine, J., Vimeux, L., Feuillet, V., Barrin, S., Kantari-Mimoun, C., Bercovici, N., Guerin, M., Biton, J., Ouakrim, H., Regnier, F., Lupo, A., Alifano, M., Damotte, D., Donnadieu, E., 2018. Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment. Proc Natl Acad Sci U S A 115, E4041-E4050.

Pinzón-Daza, M.L., Cuellar-Saenz, Y., Nualart, F., Ondo-Mendez, A., Del Riesgo, L., Castillo-Rivera, F., Garzón, R., 2017. Oxidative stress promotes doxorubicin-induced Pgp and BCRP expression in colon cancer cells under hypoxic conditions. J Cell Biochem 118, 1868-1878.

Polanczyk, M.J., Walker, E., Haley, D., Guerrouahen, B.S., Akporiaye, E.T., 2019. Blockade of TGF-beta signaling to enhance the antitumor response is accompanied by dysregulation of the functional activity of CD4(+)CD25(+)Foxp3(+) and CD4(+)CD25(-)Foxp3(+) T cells. J Transl Med 17, 219.

Porporato, P.E., Payen, V.L., Baselet, B., Sonveaux, P., 2016. Metabolic changes associated with tumor metastasis, part 2: Mitochondria, lipid and amino acid metabolism. Cell Mol Life Sci 73, 1349-1363.

Prieto-Vila, M., Usuba, W., Takahashi, R.U., Shimomura, I., Sasaki, H., Ochiya, T., Yamamoto, Y., 2019. Single-cell analysis reveals a preexisting drug-resistant subpopulation in the luminal breast cancer subtype. Cancer Res 79, 4412-4425.

Riganti, C., Campia, I., Polimeni, M., Pescarmona, G., Ghigo, D., Bosia, A., 2009. Digoxin and ouabain induce P-glycoprotein by activating calmodulin kinase II and hypoxia-inducible factor-1alpha in human colon cancer cells. Toxicol Appl Pharmacol 240, 385-392.

Roncuzzi, L., Pancotti, F., Baldini, N., 2014. Involvement of HIF-1α activation in the doxorubicin resistance of human osteosarcoma cells. Oncol Rep 32, 389-394.

Qian, B.Z., Pollard, J.W., 2010. Macrophage diversity enhances tumor progression and metastasis. Cell 141, 39-51.

Qian, Y., Wang, X., Liu, Y., Li, Y., Colvin, R.A., Tong, L., Wu, S., Chen, X., 2014. Extracellular ATP is internalized by macropinocytosis and induces intracellular ATP increase and drug resistance in cancer cells. Cancer Lett 351, 242-251.

Qiao, Y., Zhang, C., Li, A., Wang, D., Luo, Z., Ping, Y., Zhou, B., Liu, S., Li, H., Yue, D., Zhang, Z., Chen, X., Shen, Z., Lian, J., Li, Y., Wang, S., Li, F., Huang, L., Wang, L., Zhang, B., Yu, J., Qin, Z., Zhang, Y., 2018. IL6 derived from cancer-associated fibroblasts promotes chemoresistance via CXCR7 in esophageal squamous cell carcinoma. Oncogene 37, 873-883.

Qin, T., Wang, C., Chen, X., Duan, C., Zhang, X., Zhang, J., Chai, H., Tang, T., Chen, H., Yue, J., Li, Y., Yang, J., 2015. Dopamine induces growth inhibition and vascular normalization through reprogramming M2-polarized macrophages in rat C6 glioma. Toxicol Appl Pharmacol 286, 112-123.

Qu, C., Zhang, W., Zheng, G., Zhang, Z., Yin, J., He, Z., 2014. Metformin reverses multidrug resistance and epithelial-mesenchymal transition (EMT) via activating AMP-activated protein kinase (AMPK) in human breast cancer cells. Mol Cell Biochem 386, 63-71.

Raz, S., Sheban, D., Gonen, N., Stark, M., Berman, B., Assaraf, Y.G., 2014. Severe hypoxia induces complete antifolate resistance in carcinoma cells due to cell cycle arrest. Cell Death Dis 5, e1067

.

Ribatti, D., Tamma, R., Annese, T., 2020. Epithelial-mesenchymal transition in cancer: A historical overview. Transl Oncol 13, 100773.

Robey, R.W., Polgar, O., Deeken, J., To, K.W., Bates, S.E., 2007. ABCG2: determining its relevance in clinical drug resistance. Cancer Metastasis Rev 26, 39-57.

Rodriguez, P.C., Hernandez, C.P., Quiceno, D., Dubinett, S.M., Zabaleta, J., Ochoa, J.B., Gilbert, J., Ochoa, A.C., 2005. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. J Exp Med 202, 931-939.

Rollig, C., Knop, S., Bornhauser, M., 2015. Multiple myeloma. Lancet 385, 2197-2208.

Rolny, C., Mazzone, M., Tugues, S., Laoui, D., Johansson, I., Coulon, C., Squadrito, M.L., Segura, I., Li, X., Knevels, E., Costa, S., Vinckier, S., Dresselaer, T., Akerud, P., De Mol, M., Salomaki, H., Phillipson, M., Wyns, S., Larsson, E., Buysschaert, I., Botling, J., Himmelreich, U., Van Ginderachter, J.A., De Palma, M., Dewerchin, M., Claesson-Welsh, L., Carmeliet, P., 2011. HRG inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through downregulation of PlGF. Cancer Cell 19, 31-44.

Rong, G., Kang, H., Wang, Y., Hai, T., Sun, H., 2013. Candidate markers that associate with chemotherapy resistance in breast cancer through the study on Taxotere-induced damage to tumor microenvironment and gene expression profiling of carcinoma-associated fibroblasts (CAFs). PloS One 8, e70960.

Ruffell, B., Affara, N.I., Coussens, L.M., 2012. Differential macrophage programming in the tumor microenvironment. Trends Immunol 33, 119-126.

Rycaj, K., Tang, D.G., 2014. Cancer stem cells and radioresistance. Int J Radiat Biol 90, 615-621.

Sade-Feldman, M., Kanterman, J., Ish-Shalom, E., Elnekave, M., Horwitz, E., Baniyash, M., 2013. Tumor necrosis factor-alpha blocks differentiation and enhances suppressive activity of immature myeloid cells during chronic inflammation. Immunity 38, 541-554.

Saha, D., Martuza, R.L., Rabkin, S.D., 2017. Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade. Cancer Cell 32, 253-267 e255.

Sakamaki, I., Kwak, L.W., Cha, S.C., Yi, Q., Lerman, B., Chen, J., Surapaneni, S., Bateman, S., Qin, H., 2014. Lenalidomide enhances the protective effect of a therapeutic vaccine and reverses immune suppression in mice bearing established lymphomas. Leukemia 28, 329-337.

Sakata, K., Kwok, T.T., Murphy, B.J., Laderoute, K.R., Gordon, G.R., Sutherland, R.M., 1991. Hypoxia-induced drug resistance: comparison to P-glycoprotein-associated drug resistance. Br. J. Cancer 64, 809-814.

Salem, A., Asselin, M.C., Reymen, B., Jackson, A., Lambin, P., West, C.M.L., O'Connor, J.P.B., Faivre-Finn, C., 2018. Targeting hypoxia to improve non-small cell lung cancer outcome. J Natl Cancer Inst 110, doi: 10.1093/jnci/djx160.

Sanchez-Martinez, R., Cruz-Gil, S., Gomez de Cedron, M., Alvarez-Fernandez, M., Vargas, T., Molina, S., Garcia, B., Herranz, J., Moreno-Rubio, J., Reglero, G., Perez-Moreno, M., Feliu, J., Malumbres, M., Ramirez de Molina, A., 2015. A link between lipid metabolism and epithelial-mesenchymal transition provides a target for colon cancer therapy. Oncotarget 6, 38719-38736.
Sarode, P., Schaefer, M.B., Grimminger, F., Seeger, W., Savai, R., 2020. Macrophage and tumor cell cross-talk is fundamental for lung tumor progression: We need to talk. Front Oncol 10, 324.

Sasabe, E., Zhou, X., Li, D., Oku, N., Yamamoto, T., Osaki, T., 2007. The involvement of hypoxia-inducible factor-1alpha in the susceptibility to gamma-rays and chemotherapeutic drugs of oral squamous cell carcinoma cells. Int J Cancer 120, 268-277.

Sasidharan Nair, V., Saleh, R., Toor, S.M., Taha, R.Z., Ahmed, A.A., Kurer, M.A., Murshed, K., Alajez, N.M., Abu Nada, M., Elkord, E., 2020. Transcriptomic profiling disclosed the role of DNA methylation and histone modifications in tumor-infiltrating myeloid-derived suppressor cell subsets in colorectal cancer. Clin Epigenet 12, 13.

Savagner, P., Yamada, K.M., Thiery, J.P., 1997. The zinc-finger protein slug causes desmosome dissociation, an initial and necessary step for growth factor-induced epithelial-mesenchymal transition. J Cell Biol 137, 1403-1419.

Savarese, T.M., Mitchell, K., McQuain, C., Campbell, C.L., Guardiani, R., Wuu, J., Ollari, C., Reale, F., Nelson, B.E., Chen, A., Quesenberry, P.J., 2001. Coexpression of granulocyte colony stimulating factor and its receptor in primary ovarian carcinomas. Cancer Lett 162, 105-115.

Saxena, M., Stephens, M.A., Pathak, H., Rangarajan, A., 2011. Transcription factors that mediate epithelial-mesenchymal transition lead to multidrug resistance by upregulating ABC transporters. Cell Death Dis 2, e179.

Schlecker, E., Stojanovic, A., Eisen, C., Quack, C., Falk, C.S., Umansky, V., Cerwenka, A., 2012. Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J Immunol 189, 5602-5611.

Schmid, P., Zaiss, M., Harper-Wynne, C., Ferreira, M., Dubey, S., Chan, S., Makris, A., Nemsadze, G., Brunt, A.M., Kuemmel, S., Ruiz, I., Perello, A., Kendall, A., Brown, J., Kristeleit, H., Conibear,

J., Saura, C., Grenier, J., Mahr, K., Schenker, M., Sohn, J., Lee, K.S., Shepherd, C.J., Oelmann, E., Sarker, S.J., Prendergast, A., Marosics, P., Moosa, A., Lawrence, C., Coetzee, C., Mousa, K., Cortes, J., 2019. Fulvestrant plus vistusertib vs fulvestrant plus everolimus vs fulvestrant alone for women with hormone receptor-positive metastatic breast cancer: The MANTA Phase 2 randomized clinical trial. JAMA Oncol, 29, 1556-1563.

Schultze, J.L., 2016. Reprogramming of macrophages--new opportunities for therapeutic targeting. Curr Opin Pharmacol 26, 10-15.

Seip, K., Fleten, K.G., Barkovskaya, A., Nygaard, V., Haugen, M.H., Engesaeter, B.O., Maelandsmo, G.M., Prasmickaite, L., 2016. Fibroblast-induced switching to the mesenchymal-like phenotype and PI3K/mTOR signaling protects melanoma cells from BRAF inhibitors. Oncotarget 7, 19997-20015.

Sevko, A., Michels, T., Vrohlings, M., Umansky, L., Beckhove, P., Kato, M., Shurin, G.V., Shurin, M.R., Umansky, V., 2013. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. J Immunol 190, 2464-2471.

Shaked, Y., 2019. The pro-tumorigenic host response to cancer therapies. Nat Rev Cancer 19, 667-685.

Shapira, A., Livney, Y.D., Broxterman, H.J., Assaraf, Y.G., 2011. Nanomedicine for targeted cancer therapy: towards the overcoming of drug resistance. Drug Resist U 14, 150-163.

Sharma, R.C., Assaraf, Y.G., Schimke, R.T., 1991. A phenotype conferring selective resistance to lipophilic antifolates in Chinese hamster ovary cells. Cancer Res 51, 2949-2959.

Shen, C.J., Kuo, Y.L., Chen, C.C., Chen, M.J., Cheng, Y.M., 2017. MMP1 expression is activated by Slug and enhances multi-drug resistance (MDR) in breast cancer. PloS One 12, e0174487.

Shen, X., Zhi, Q., Wang, Y., Li, Z., Zhou, J., Huang, J., 2017. Hypoxia induces multidrug resistance via enhancement of epidermal growth factor-like domain 7 expression in non-small lung cancer cells. Chemotherapy 62, 172-180.

Shojaei, F., Wu, X., Malik, A.K., Zhong, C., Baldwin, M.E., Schanz, S., Fuh, G., Gerber, H.P., Ferrara, N., 2007a. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+Gr1+ myeloid cells. Nat Biotechnol 25, 911-920.

Shojaei, F., Wu, X., Qu, X., Kowanetz, M., Yu, L., Tan, M., Meng, Y.G., Ferrara, N., 2009. G-CSF-initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. Proc Natl Acad Sci U S A 106, 6742-6747.

Shojaei, F., Wu, X., Zhong, C., Yu, L., Liang, X.H., Yao, J., Blanchard, D., Bais, C., Peale, F.V., van Bruggen, N., Ho, C., Ross, J., Tan, M., Carano, R.A., Meng, Y.G., Ferrara, N., 2007b. Bv8 regulates myeloid-cell-dependent tumour angiogenesis. Nature 450, 825-831.

Si, W., Shen, J., Zheng, H., Fan, W., 2019. The role and mechanisms of action of microRNAs in cancer drug resistance. Clin Epigenet 11, 25.

Siebzehnrubl, F.A., Silver, D.J., Tugertimur, B., Deleyrolle, L.P., Siebzehnrubl, D., Sarkisian, M.R., Devers, K.G., Yachnis, A.T., Kupper, M.D., Neal, D., Nabilsi, N.H., Kladde, M.P., Suslov, O., Brabletz, S., Brabletz, T., Reynolds, B.A., Steindler, D.A., 2013. The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance. EMBO Mol Med 5, 1196-1212.

Singh, A., Settleman, J., 2010. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene 29, 4741-4751.

Sinha, P., Clements, V.K., Fulton, A.M., Ostrand-Rosenberg, S., 2007. Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. Cancer Res 67, 4507-4513.

Song, X., Liu, X., Chi, W., Liu, Y., Wei, L., Wang, X., Yu, J., 2006. Hypoxia-induced resistance to cisplatin and doxorubicin in non-small cell lung cancer is inhibited by silencing of HIF-1alpha gene. Cancer Chemother Pharmacol 58, 776-784.

Soon, P.S., Kim, E., Pon, C.K., Gill, A.J., Moore, K., Spillane, A.J., Benn, D.E., Baxter, R.C., 2013. Breast cancer-associated fibroblasts induce epithelial-to-mesenchymal transition in breast cancer cells. Endocr Relat Cancer 20, 1-12.

Sotelo, J., Briceno, E., Lopez-Gonzalez, M.A., 2006. Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 144, 337-343.

Steinberg, S.M., Shabaneh, T.B., Zhang, P., Martyanov, V., Li, Z., Malik, B.T., Wood, T.A., Boni, A., Molodtsov, A., Angeles, C.V., Curiel, T.J., Whitfield, M.L., Turk, M.J., 2017. Myeloid Cells That Impair Immunotherapy Are Restored in Melanomas with Acquired Resistance to BRAF Inhibitors. Cancer Res 77, 1599-1610.

Steinbichler, T.B., Metzler, V., Pritz, C., Riechelmann, H., Dudas, J., 2016. Tumor-associated fibroblast-conditioned medium induces CDDP resistance in HNSCC cells. Oncotarget 7, 2508-2518.

Stolina, M., Sharma, S., Lin, Y., Dohadwala, M., Gardner, B., Luo, J., Zhu, L., Kronenberg, M., Miller, P.W., Portanova, J., Lee, J.C., Dubinett, S.M., 2000. Specific inhibition of cyclooxygenase 2 restores antitumor reactivity by altering the balance of IL-10 and IL-12 synthesis. J Immunol 164, 361-370.

Sui, H., Zhu, L., Deng, W., Li, Q., 2014. Epithelial-mesenchymal transition and drug resistance: role, molecular mechanisms, and therapeutic strategies. Oncol Res Treatm 37, 584-589.

Sui, X., Chen, R., Wang, Z., Huang, Z., Kong, N., Zhang, M., Han, W., Lou, F., Yang, J., Zhang, Q., Wang, X., He, C., Pan, H., 2013. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. Cell Death Dis 4, e838.

Sun, L., Ke, J., He, Z., Chen, Z., Huang, Q., Ai, W., Wang, G., Wei, Y., Zou, X., Zhang, S., Lan, P., Hong, C., 2017. HES1 promotes colorectal cancer cell resistance to 5-FU by inducing of EMT and ABC transporter proteins. J Cancer 8, 2802-2808.

Sun, W.L., Chen, J., Wang, Y.P., Zheng, H., 2011. Autophagy protects breast cancer cells from epirubicin-induced apoptosis and facilitates epirubicin-resistance development. Autophagy 7, 1035-1044.

Swystun, L.L., Mukherjee, S., Levine, M., Liaw, P.C., 2011. The chemotherapy metabolite acrolein upregulates thrombin generation and impairs the protein C anticoagulant pathway in animal-based and cell-based models. J Thromb Haemost 9, 767-775.

Szebeni, G.J., Vizler, C., Kitajka, K., Puskas, L.G., 2017. Inflammation and cancer: Extra- and intracellular determinants of tumor-associated macrophages as tumor promoters. Mediators Inflamm 2017, 9294018.

Takeshita, H. Gebhardt, M.C., Springfield, D.S., Kusuzaki, K., Mankin, H.J., 1996. Experimental models for the study of drug resistance in osteosarcoma: P-glycoprotein-positive, murine osteosarcoma cell lines. J Bone Joint Surg Am 78,:366- 375.

Talmadge, J.E., Gabrilovich, D.I., 2013. History of myeloid-derived suppressor cells. Nat Rev Cancer 13, 739-752.

Tcyganov, E., Mastio, J., Chen, E., Gabrilovich, D.I., 2018. Plasticity of myeloid-derived suppressor cells in cancer. Curr Opin Immunol 51, 76-82.

Teicher, B.A., 1994. Hypoxia and drug resistance. Cancer Metast Rev 13, 139-168.

Thews, O., Gassner, B., Kelleher, D.K., Gekle, M., 2008. Activity of drug efflux transporters in tumor cells under hypoxic conditions. Adv Exp Med Biol 614, 157-164.

Thoreau, M., Penny, H.L., Tan, K., Regnier, F., Weiss, J.M., Lee, B., Johannes, L., Dransart, E., Le Bon, A., Abastado, J.P., Tartour, E., Trautmann, A., Bercovici, N., 2015. Vaccine-induced tumor regression requires a dynamic cooperation between T cells and myeloid cells at the tumor site. Oncotarget 6, 27832-27846.

Tomono, T., Yano, K., Ogihara, T., 2017. Snail-induced epithelial-to-mesenchymal transition enhances P-gp-mediated multidrug resistance in HCC827 Cells. J Pharmaceut Sci 106, 2642-2649.

Tong, W.W., Tong, G.H., Liu, Y., 2018. Cancer stem cells and hypoxia-inducible factors (Review). Int J Oncol 53, 469-476.

Toste, P.A., Nguyen, A.H., Kadera, B.E., Duong, M., Wu, N., Gawlas, I., Tran, L.M., Bikhchandani, M., Li, L., Patel, S.G., Dawson, D.W., Donahue, T.R., 2016. Chemotherapy-induced inflammatory gene signature and protumorigenic phenotype in pancreatic CAFs via stress-associated MAPK. Mol Cancer Res 14, 437-447.

Turovskaya, O., Foell, D., Sinha, P., Vogl, T., Newlin, R., Nayak, J., Nguyen, M., Olsson, A., Nawroth, P.P., Bierhaus, A., Varki, N., Kronenberg, M., Freeze, H.H., Srikrishna, G., 2008. RAGE, carboxylated glycans and S100A8/A9 play essential roles in colitis-associated carcinogenesis. Carcinogenesis 29, 2035-2043.

Umansky, V., Sevko, A., 2012. Melanoma-induced immunosuppression and its neutralization. Semin Cancer Biol 22, 319-326.

Varga, G., Ehrchen, J., Tsianakas, A., Tenbrock, K., Rattenholl, A., Seeliger, S., Mack, M., Roth, J., Sunderkoetter, C., 2008. Glucocorticoids induce an activated, anti-inflammatory monocyte subset in mice that resembles myeloid-derived suppressor cells. J Leukoc Biol 84, 644-650.

Vasconcelos, M.H., Caires, H.R., Abols, A., Xavier, C.P.R., Line, A., 2019. Extracellular vesicles as a novel source of biomarkers in liquid biopsies for monitoring cancer progression and drug resistance. Drug Resist Updat 47, 100647.

Vasquez-Dunddel, D., Pan, F., Zeng, Q., Gorbounov, M., Albesiano, E., Fu, J., Blosser, R.L., Tam, A.J., Bruno, T., Zhang, H., Pardoll, D., Kim, Y., 2013. STAT3 regulates arginase-I in myeloid-derived suppressor cells from cancer patients. J Clin Invest 123, 1580-1589.

Vazquez-Martin, A., Oliveras-Ferraros, C., Cufi, S., Del Barco, S., Martin-Castillo, B., Menendez, J.A., 2010. Metformin regulates breast cancer stem cell ontogeny by transcriptional regulation of the epithelial-mesenchymal transition (EMT) status. Cell Cycle 9, 3807-3814.

Vega, S., Morales, A.V., Ocana, O.H., Valdes, F., Fabregat, I., Nieto, M.A., 2004. Snail blocks the cell cycle and confers resistance to cell death. Genes Dev 18, 1131-1143.

Veglia, F., Perego, M., Gabrilovich, D., 2018. Myeloid-derived suppressor cells coming of age. Nat Immunol 19, 108-119.

Vellinga, T.T., Borovski, T., de Boer, V.C., Fatrai, S., van Schelven, S., Trumpi, K., Verheem, A., Snoeren, N., Emmink, B.L., Koster, J., Rinkes, I.H., Kranenburg, O., 2015. SIRT1/PGC1alpha-dependent increase in oxidative phosphorylation supports chemotherapy resistance of colon cancer. Clin Cancer Res 21, 2870-2879.

Vendramini-Costa, D.B., Carvalho, J.E., 2012. Molecular link mechanisms between inflammation and cancer. Curr Pharm Des 18, 3831-3852.

Vlaicu, P., Mertins, P., Mayr, T., Widschwendter, P., Ataseven, B., Hogel, B., Eiermann, W., Knyazev, P., Ullrich, A., 2013. Monocytes/macrophages support mammary tumor invasivity by co-secreting lineage-specific EGFR ligands and a STAT3 activator. BMC Cancer 13, 197.

Volm, M., Efferth, T., 2015. Prediction of cancer drug resistance and implications for personalized medicine. Front Oncol 5, 282.

Wang, H.F., Ning, F., Liu, Z.C., Wu, L., Li, Z.Q., Qi, Y.F., Zhang, G., Wang, H.S., Cai, S.H., Du, J., 2017a. Histone deacetylase inhibitors deplete myeloid-derived suppressor cells induced by 4T1 mammary tumors in vivo and in vitro. Cancer Immunol Immunother 66, 355-366.

Wang, J., Chen, Y., Xiang, F., Li, M., Li, H., Chi, J., Ren, K., 2018. Suppression of TGF-beta1 enhances chemosensitivity of cisplatin-resistant lung cancer cells through the inhibition of drug-resistant proteins. Artif Cells Nanomed Biotechnol 46, 1505-1512.

Wang, J., Li, Z.H., White, J., Zhang, L.B., 2014. Lung cancer stem cells and implications for future therapeutics. Cell Biochem Biophys 69, 389-398.

Wang, L., Chang, E.W., Wong, S.C., Ong, S.M., Chong, D.Q., Ling, K.L., 2013. Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage and plasma S100A8/A9 proinflammatory proteins. J Immunol 190, 794-804.

Wang, S.-C., Lin, X.-L., Wang, H.-Y., Qin, Y.-J., Chen, L., Li, J., Jia, J.-S., Shen, H.-F., Yang, S., Xie, R.-Y., Wei, F., Gao, F., Rong, X.-X., Yang, J., Zhao, W.-T., Zhang, T.-T., Shi, J.-W., Yao, K.-T., Luo, W.-R., Sun, Y., Xiao, D., 2015. Hes1 triggers epithelial-mesenchymal transition (EMT)-like cellular marker alterations and promotes invasion and metastasis of nasopharyngeal carcinoma by activating the PTEN/AKT pathway. Oncotarget 6, 36713-36730.

Wang, X., Li, Y., Qian, Y., Cao, Y., Shriwas, P., Zhang, H., Chen, X., 2017b. Extracellular ATP, as an energy and phosphorylating molecule, induces different types of drug resistances in cancer cells through ATP internalization and intracellular ATP level increase. Oncotarget 8, 87860-878677.

Wartenberg, M., Hoffmann, E., Schwindt, H., Grünheck, F., Petros, J., Arnold, J.R., Hescheler, J., Sauer, H., 2005. Reactive oxygen species-linked regulation of the multidrug resistance transporter P-glycoprotein in Nox-1 overexpressing prostate tumor spheroids. FEBS Lett. 579, 4541-4549.

Wartenberg, M., Ling, F.C., Müschen, M., Klein, F., Acker, H., Gassmann, M., Petrat, K., Pütz, V., Hescheler, J., Sauer, H., 2003. Regulation of the multidrug resistance transporter P-glycoprotein in multicellular tumor spheroids by hypoxia-inducible factor (HIF-1) and reactive oxygen species. FASEB J 17, 503-505.

Weber, F., Byrne, S.N., Le, S., Brown, D.A., Breit, S.N., Scolyer, R.A., Halliday, G.M., 2005. Transforming growth factor-beta1 immobilises dendritic cells within skin tumours and facilitates tumour escape from the immune system. Cancer Immunol Immunother 54, 898-906.

Weber, R., Fleming, V., Hu, X., Nagibin, V., Groth, C., Altevogt, P., Utikal, J., Umansky, V., 2018. Myeloid-Derived Suppressor Cells Hinder the Anti-Cancer Activity of Immune Checkpoint Inhibitors. Front Immunol 9, 1310.

Wen, W., Marcinkowski, E., Luyimbazi, D., Luu, T., Xing, Q., Yan, J., Wang, Y., Wu, J., Guo, Y., Tully, D., Han, E.S., Yost, S.E., Yuan, Y., Yim, J.H., 2019. Eribulin synergistically increases anti-tumor activity of an mTOR inhibitor by inhibiting pAKT/pS6K/pS6 in triple negative breast cancer. Cells 8, 1010.

Weroha, S.J., Oberg, A.L., Ziegler, K.L., Dakhilm, S.R., Rowland, K.M., Hartmann, L.C., Moore, D.F., Jr., Keeney, G.L., Peethambaram, P.P., Haluska, P., 2011. Phase II trial of lapatinib and topotecan (LapTop) in patients with platinum-refractory/resistant ovarian and primary peritoneal carcinoma. Gynecol Oncol 122, 116-120.

Wheaton, W.W., Weinberg, S.E., Hamanaka, R.B., Soberanes, S., Sullivan, L.B., Anso, E., Glasauer, A., Dufour, E., Mutlu, G.M., Budigner, G.S., Chandel, N.S., 2014. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. Elife 3, e02242.

Wijdeven, R.H., Pang, B., Assaraf, Y.G., Neefjes, J., 2016. Old drugs, novel ways out: Drug resistance toward cytotoxic chemotherapeutics. Drug Resist Updat 28, 65-81.

Wilde, L., Roche, M., Domingo-Vidal, M., Tanson, K., Philp, N., Curry, J., Martinez-Outschoorn, U., 2017. Metabolic coupling and the Reverse Warburg Effect in cancer: Implications for novel biomarker and anticancer agent development. Sem Oncol 44, 198-203.

Wilson, M.M., Weinberg, R.A., Lees, J.A., Guen, V.J., 2020. Emerging mechanisms by which EMT programs control stemness. Trends Cancer S2405-8033, 30120-30125.

Witkiewicz, A.K., Dasgupta, A., Sotgia, F., Mercier, I., Pestell, R.G., Sabel, M., Kleer, C.G., Brody, J.R., Lisanti, M.P., 2009. An absence of stromal caveolin-1 expression predicts early tumor recurrence and poor clinical outcome in human breast cancers. Am J Pathol 174, 2023-2034.

Wojtowicz, K., Januchowski, R., Nowicki, M., Zabel, M., 2015. Inhibition of protein glycosylation reverses the MDR phenotype of cancer cell lines. Biomed Pharmacother 74, 49-56.

Wozniak, M., Sztiller-Sikorska, M., Czyz, M., 2015. Diminution of miR-340-5p levels is responsible for increased expression of ABCB5 in melanoma cells under oxygen-deprived conditions. Exp Mol Pathol 99, 707-716.

Wu, C.T., Chen, M.F., Chen, W.C., Hsieh, C.C., 2013. The role of IL-6 in the radiation response of prostate cancer. Radiat Oncol 8, 159.

Xia, S., Yu, S., Yuan, X., 2005. Effects of hypoxia on expression of P-gp and multidrug resistance protein in human lung adenocarcinoma A549 cell line. J Huazhong Univ Sci Technol Med Sci 25, 279-281.

Xie, J., Li, D.W., Chen, X.W., Wang, F., Dong, P., 2013. Expression and significance of hypoxia-inducible factor-1α and MDR1/P-glycoprotein in laryngeal carcinoma tissue and hypoxic Hep-2 cells. Oncol Lett 6, 232-238.

Xin, H., Kong, Y., Jiang, X., Wang, K., Qin, X., Miao, Z.H., Zhu, Y., Tan, W., 2013. Multi-drug-resistant cells enriched from chronic myeloid leukemia cells by Doxorubicin possess tumor-initiating-cell properties. J Pharmacol Sci 122, 299-304.

Xu, H., Lai, W., Zhang, Y., Liu, L., Luo, X., Zeng, Y., Wu, H., Lan, Q., Chu, Z., 2014. Tumor-associated macrophage-derived IL-6 and IL-8 enhance invasive activity of LoVo cells induced by PRL-3 in a KCNN4 channel-dependent manner. BMC Cancer 14, 330.

Xu, J., Lamouille, S., Derynck, R., 2009. TGF-beta-induced epithelial to mesenchymal transition. Cell Res 19, 156-172.

Xu, M., Zhao, Z., Song, J., Lan, X., Lu, S., Chen, M., Wang, Z., Chen, W., Fan, X., Wu, F., Chen, L., Tu, J., Ji, J., 2017. Interactions between interleukin-6 and myeloid-derived suppressor cells drive the chemoresistant phenotype of hepatocellular cancer. Exp Cell Res 351, 142-149.

Yamaguchi, R., Perkins, G., 2020. An emerging model for cancer development from a tumor microenvironment perspective in mice and humans. Adv Exp Med Biol 1225, 19-29.

Yamamoto, K., Kitawaki, T., Sugimoto, N., Fujita, H., Kawase, Y., Takaori-Kondo, A., Kadowaki, N., 2019. Anti-inflammatory modulation of human myeloid-derived dendritic cell subsets by lenalidomide. Immunol Lett 211, 41-48.

Yang, G., Xu, S., Peng, L., Li, H., Zhao, Y., Hu, Y., 2016. The hypoxia-mimetic agent $CoCl_2$ induces chemotherapy resistance in LOVO colorectal cancer cells. Mol Med Rep 13, 2583-2589.

Yang, J., Weinberg, R.A., 2008. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. Dev Cell 14, 818-829.

Yang, L., DeBusk, L.M., Fukuda, K., Fingleton, B., Green-Jarvis, B., Shyr, Y., Matrisian, L.M., Carbone, D.P., Lin, P.C., 2004. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 6, 409-421.

Yang, L., Huang, J., Ren, X., Gorska, A.E., Chytil, A., Aakre, M., Carbone, D.P., Matrisian, L.M., Richmond, A., Lin, P.C., Moses, H.L., 2008. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. Cancer Cell 13, 23-35.

Yang, M., Zeng, P., Kang, R., Yu, Y., Yang, L., Tang, D., Cao, L., 2014. S100A8 contributes to drug resistance by promoting autophagy in leukemia cells. PLoS One 9, e97242.

Yao, H.L., Gao, F.H., Li, Z.Z., Wu, H.X., Xu, M.D., Zhang, Z., Dai, Q.Y., 2012. Monocyte chemoattractant protein-1 mediates angiotensin II-induced vascular smooth muscle cell proliferation via SAPK/JNK and ERK1/2. Mol Cell Biochem 366, 355-362.

Yao, Z., Fenoglio, S., Gao, D.C., Camiolo, M., Stiles, B., Lindsted, T., Schlederer, M., Johns, C., Altorki, N., Mittal, V., Kenner, L., Sordella, R., 2010. TGF-beta IL-6 axis mediates selective and adaptive mechanisms of resistance to molecular targeted therapy in lung cancer. Proc Natl Acad Sci U S A 107, 15535-15540.

Yin, X., Han, S., Song, C., Zou, H., Wei, Z., Xu, W., Ran, J., Tang, C., Wang, Y., Cai, Y., Hu, Q., Han, W., 2019. Metformin enhances gefitinib efficacy by interfering with interactions between tumor-associated macrophages and head and neck squamous cell carcinoma cells. Cell Oncol 42, 459-475.

Yin, Y., Yao, S., Hu, Y., Feng, Y., Li, M., Bian, Z., Zhang, J., Qin, Y., Qi, X., Zhou, L., Fei, B., Zou, J., Hua, D., Huang, Z., 2017. The immune-microenvironment confers chemoresistance of colorectal cancer through macrophage-derived IL6. Clin Cancer Res 23, 7375-7387.

Yook, J.I., Li, X.-Y., Ota, I., Hu, C., Kim, H.S., Kim, N.H., Cha, S.Y., Ryu, J.K., Choi, Y.J., Kim, J., Fearon, E.R., Weiss, S.J., 2006. A Wnt–Axin2–GSK3β cascade regulates Snail1 activity in breast cancer cells. Nat Cell Biol 8, 1398-1406.

Yoon, N., Park, M.S., Shigemoto, T., Peltier, G., Lee, R.H., 2016. Activated human mesenchymal stem/stromal cells suppress metastatic features of MDA-MB-231 cells by secreting IFN-beta. Cell Death Dis 7, e2191.

Yoshiba, S., Ito, D., Nagumo, T., Shirota, T., Hatori, M., Shintani, S., 2009. Hypoxia induces resistance to 5-fluorouracil in oral cancer cells via G(1) phase cell cycle arrest. Oral Oncol 45, 109-115

Yoshida, T., Song, L., Bai, Y., Kinose, F., Li, J., Ohaegbulam, K.C., Munoz-Antonia, T., Qu, X., Eschrich, S., Uramoto, H., Tanaka, F., Nasarre, P., Gemmill, R.M., Roche, J., Drabkin, H.A., Haura, E.B., 2016. ZEB1 Mediates acquired resistance to the epidermal growth factor receptor-tyrosine kinase inhibitors in non-small cell lung cancer. PLoS One 11, e0147344.

Yu, H., Lee, H., Herrmann, A., Buettner, R., Jove, R., 2014. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer 14, 736-746.

Yuan, J., Liu, M., Yang, L., Tu, G., Zhu, Q., Chen, M., Cheng, H., Luo, H., Fu, W., Li, Z., Yang, G., 2015. Acquisition of epithelial-mesenchymal transition phenotype in the tamoxifen-resistant breast cancer cell: a new role for G protein-coupled estrogen receptor in mediating tamoxifen resistance through cancer-associated fibroblast-derived fibronectin and beta1-integrin signaling pathway in tumor cells. Breast Cancer Res 17, 69.

Zhan, M., Wang, H., Chen, T., Chen, W., Yang, L., He, M., Xu, S., Wang, J., 2015. NOX1 mediates chemoresistance via HIF1α/MDR1 pathway in gallbladder cancer. Biochem Biophys Res Commun 468, 79-85.

Zhang, H., Sun, L., Xiao, X., Xie, R., Liu, C., Wang, Y., Wie, Y., Zhang, H., Liu, L., 2014. Krüppel-like factor 8 contributes to hypoxia-induced MDR in gastric cancer cells. Cancer Sci 105, 1109-1115.

Zhang, L., Yao, J., Li, W., Zhang, C., 2018a. Micro-RNA-21 regulates cancer-associated fibroblast-mediated drug resistance in pancreatic cancer. Oncol Res 26, 827-835.

Zhang, M., Chen, C., Su, F., Huang, Z., Li, X., Li, X., 2017. Knockdown of hypoxia-inducible factor 1α improved the efficacy of low-dose metronomic chemotherapy of paclitaxel in human colon cancer xenografts. Technol Cancer Res Treat 16, 609-619.

Zhang, P., Wei, Y., Wang, L., Debeb, B.G., Yuan, Y., Zhang, J., Yuan, J., Wang, M., Chen, D., Sun, Y., Woodward, W.A., Liu, Y., Dean, D.C., Liang, H., Hu, Y., Ang, K.K., Hung, M.C., Chen, J., Ma, L., 2014. ATM-mediated stabilization of ZEB1 promotes DNA damage response and radioresistance through CHK1. Nat Cell Biol 16, 864-875.

Zhang, W., Jiang, M., Chen, J., Zhang, R., Ye, Y., Liu, P., Yu, W., Yu, J., 2018b. SOCS3 Suppression Promoted the Recruitment of CD11b(+)Gr-1(-)F4/80(-)MHCII(-) Early-stage myeloid-derived suppressor cells and accelerated interleukin-6-related tumor invasion via affecting myeloid differentiation in breast cancer. Front Immunol 9, 1699.

Zhang, W., Zhang, H., 2006. Hypoxia-inducible factor-1alpha suppressing apoptosis and increasing tolerance of lung cancer cells to chemotherapy. J Huazhong Univ Sci Technol Med Sci 26, 520-523.

Zhang, W., Zhu, X.D., Sun, H.C., Xiong, Y.Q., Zhuang, P.Y., Xu, H.X., Kong, L.Q., Wang, L., Wu, W.Z., Tang, Z.Y., 2010. Depletion of tumor-associated macrophages enhances the effect of sorafenib in metastatic liver cancer models by antimetastatic and antiangiogenic effects. Clin Cancer Res 16, 3420-3430.

Zhang, X., Ai, Z., Chen, J., Yi, J., Liu, Z., Zhao, H., Wei, H., 2017. Glycometabolic adaptation mediates the insensitivity of drug-resistant K562/ADM leukaemia cells to adriamycin via the AKT-mTOR/c-Myc signalling pathway. Mol Med Rep 15, 1869-1876.

Zhang, X., Chen, L., Dang, W.Q., Cao, M.F., Xiao, J.F., Lv, S.Q., Jiang, W.J., Yao, X.H., Lu, H.M., Miao, J.Y., Wang, Y., Yu, S.C., Ping, Y.F., Liu, X.D., Cui, Y.H., Zhang, X., Bian, X.W., 2020. CCL8 secreted by tumor-associated macrophages promotes invasion and stemness of glioblastoma cells via ERK1/2 signaling. Lab Invest 100, 619-629.

Zhang, Y., Lv, D., Kim, H.J., Kurt, R.A., Bu, W., Li, Y., Ma, X., 2013. A novel role of hematopoietic CCL5 in promoting triple-negative mammary tumor progression by regulating generation of myeloid-derived suppressor cells. Cell Res 23, 394-408.

Zheng, X., Carstens, J.L., Kim, J., Scheible, M., Kaye, J., Sugimoto, H., Wu, C.C., LeBleu, V.S., Kalluri, R., 2015. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature 527, 525-530.

Zhitomirsky, B., Assaraf, Y.G., 2016. Lysosomes as mediators of drug resistance in cancer. Drug Resist Updat 24, 23-33.

Zhong, H., Davis, A., Ouzounova, M., Carrasco, R.A., Chen, C., Breen, S., Chang, Y.S., Huang, J., Liu, Z., Yao, Y., Hurt, E., Moisan, J., Fung, M., Tice, D.A., Clouthier, S.G., Xiao, Z., Wicha, M.S., Korkaya, H., Hollingsworth, R.E., 2016. A novel IL6 antibody sensitizes multiple tumor types to chemotherapy including trastuzumab-resistant tumors. Cancer Res 76, 480-490.

Zhong, Z., Virshup, D.M., 2020. Wnt signaling and drug resistance in cancer. Mol Pharmacol 97, 72-89.

Zhong, Z., Wen, Z., Darnell, J.E., Jr., 1994. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. Science 264, 95-98.

Zhou, B.P., Deng, J., Xia, W., Xu, J., Li, Y.M., Gunduz, M., Hung, M.-C., 2004. Dual regulation of Snail by GSK-3β-mediated phosphorylation in control of epithelial–mesenchymal transition. Nat Cell Biol 6, 931-940.

Zhou, J., Shen, Q., Lin, H., Hu, L., Li, G., Zhang, X., 2019. Decitabine shows potent anti-myeloma activity by depleting monocytic myeloid-derived suppressor cells in the myeloma microenvironment. J Cancer Res Clin Oncol 145, 329-336.

Zhou, J., Yao, Y., Shen, Q., Li, G., Hu, L., Zhang, X., 2017. Demethylating agent decitabine disrupts tumor-induced immune tolerance by depleting myeloid-derived suppressor cells. J Cancer Res Clin Oncol 143, 1371-1380.

Zhou, M., Zhao, Y., Ding, Y., Liu, H., Liu, Z., Fodstad, O., Riker, A.I., Kamarajugadda, S., Lu, J., Owen, L.B., Ledoux, S.P., Tan, M., 2010. Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol. Mol Cancer 9, 33.

Zhou, X., Men, X., Zhao, R., Han, J., Fan, Z., Wang, Y., Lv, Y., Zuo, J., Zhao, L., Sang, M., Liu, X.D., Shan, B., 2018. miR-200c inhibits TGF-beta-induced-EMT to restore trastuzumab sensitivity by targeting ZEB1 and ZEB2 in gastric cancer. Cancer Gene Ther 25, 68-76.

Zhou, Y., Tozzi, F., Chen, J., Fan, F., Xia, L., Wang, J., Gao, G., Zhang, A., Xia, X., Brasher, H., Widger, W., Ellis, L.M., Weihua, Z., 2012. Intracellular ATP levels are a pivotal determinant of chemoresistance in colon cancer cells. Cancer Res 72, 304-314.

Zhou, Z., Zhang, L., Xie, B., Wang, X., Yang, X., Ding, N., Zhang, J., Liu, Q., Tan, G., Feng, D., Sun, L.Q., 2015. FOXC2 promotes chemoresistance in nasopharyngeal carcinomas via induction of epithelial mesenchymal transition. Cancer Lett 363, 137-145.

Zhu, K., Chen, L., Han, X., Wang, J., Wang, J., 2012. Short hairpin RNA targeting Twist1 suppresses cell proliferation and improves chemosensitivity to cisplatin in HeLa human cervical cancer cells. Oncol Rep 27, 1027-1034.

Zins, K., Abraham, D., 2020. Cancer immunotherapy: Targeting tumor-associated macrophages by gene silencing. Methods Mol Biol 2115, 289-325.

Zollo, M., Di Dato, V., Spano, D., De Martino, D., Liguori, L., Marino, N., Vastolo, V., Navas, L., Garrone, B., Mangano, G., Biondi, G., Guglielmotti, A., 2012. Targeting monocyte chemotactic protein-1 synthesis with bindarit induces tumor regression in prostate and breast cancer animal models. Clin Exp Metast 29, 585-601.

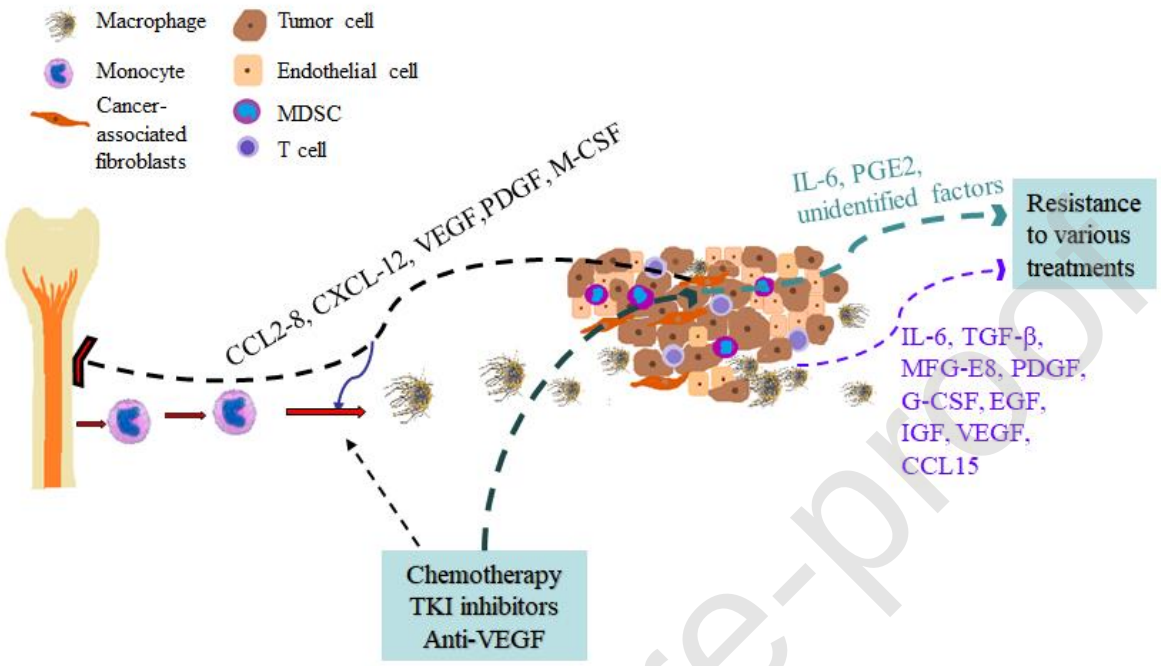

Figure 1. Factors involved in MDR due to TAMs. Factors originating from cancer cell and TME such as CCL-2 to 8, CXCL-12, VEGF, PDGF and M-CSF induce the formation of macrophages from monocytes. Factors secreted from TAMs (IL-6, TGF-β, MFG-E8, PDGF, G-CSF, EGF, IGF, VEGF, and CCL15) or from cancer cells (*e.g.* IL-6 and PGE2) that were exposed to chemotherapy are involved in MDR as described in detail in the text.

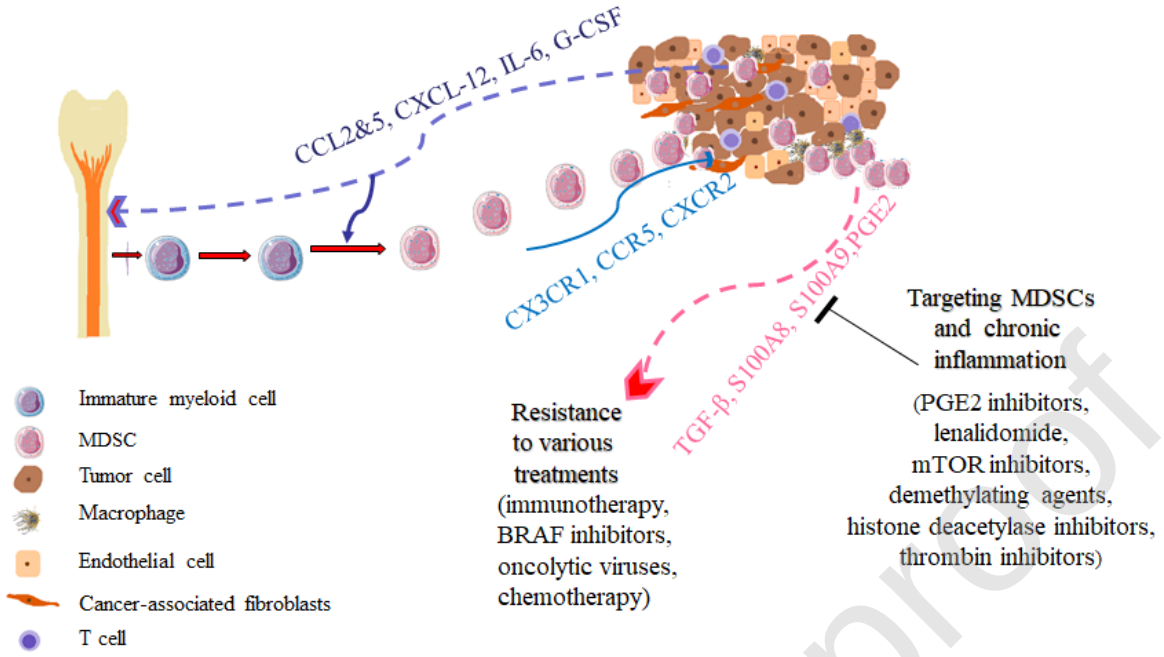

Figure 2. Factors involved in MDR due to MDSCs. Factors originating from cancer cell and TME such as CCL-2 and 5, CXCL-12, IL-6 and G-CSF induce the formation of MDSCs from immature myeloid cells. MDSCs expressing certain chemokine receptors (CX3CR1, CCR5 and CXCR2) are effectively recruited to TME and involved in MDR partly by secreting TGF-β, S100A8, S100A9 and PGE2. Targeting MDSCs and chronic inflammation with various therapeutic approaches may overcome MDR, as described in detail in the text.

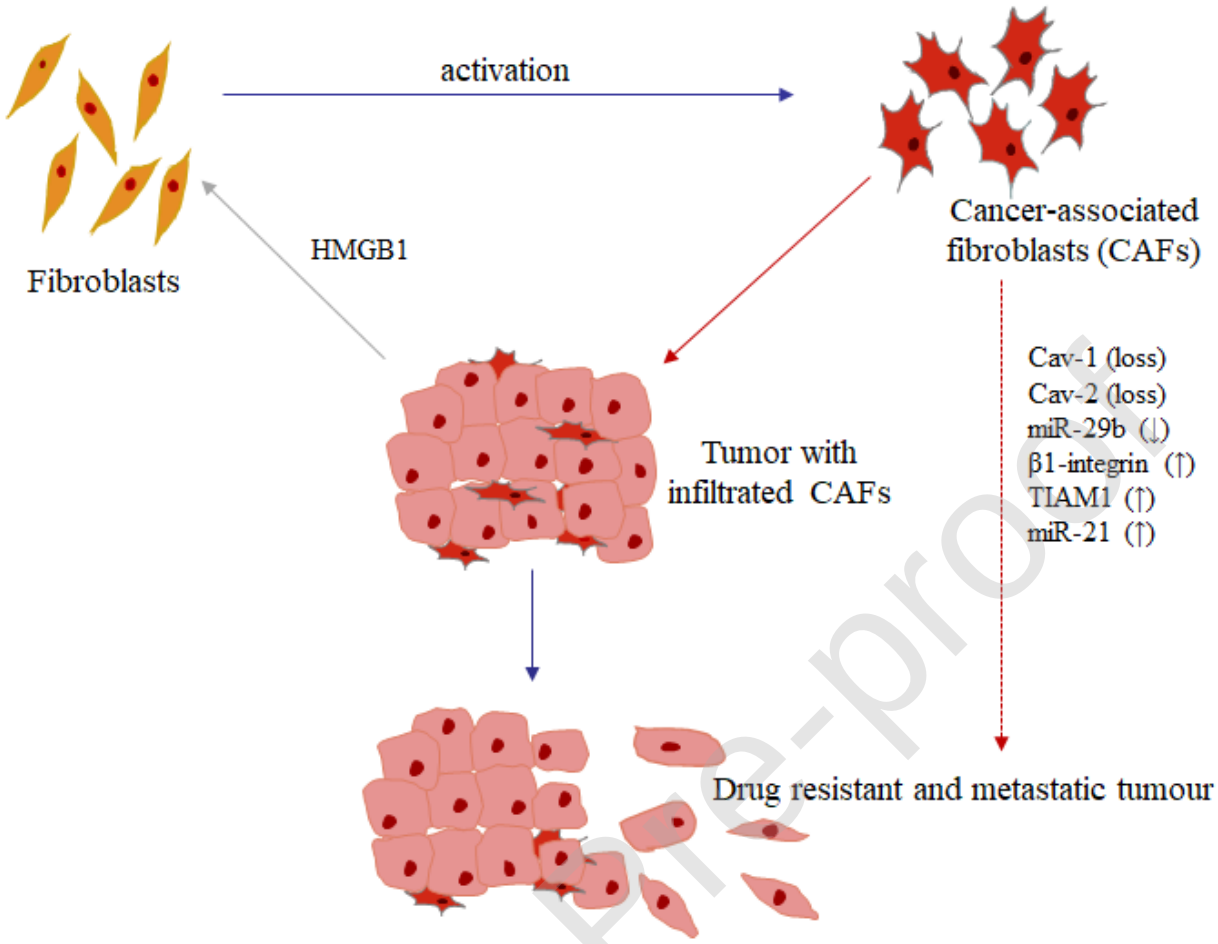

Figure 3. A mutual play between fibroblasts, CAFs and tumor cells resulting in metastatic drug-resistant tumors. Loss of Cav-1 or Cav-2, downregulation of miR-29b, upregulation of β1-integrin, TIAM1 or miR-21 in CAFs are involved in the formation of metastatic drug-resistant tumors. Dying tumor cells release HMGB1, which activates stromal fibroblasts and further development of metastatic drug-resistant tumors.

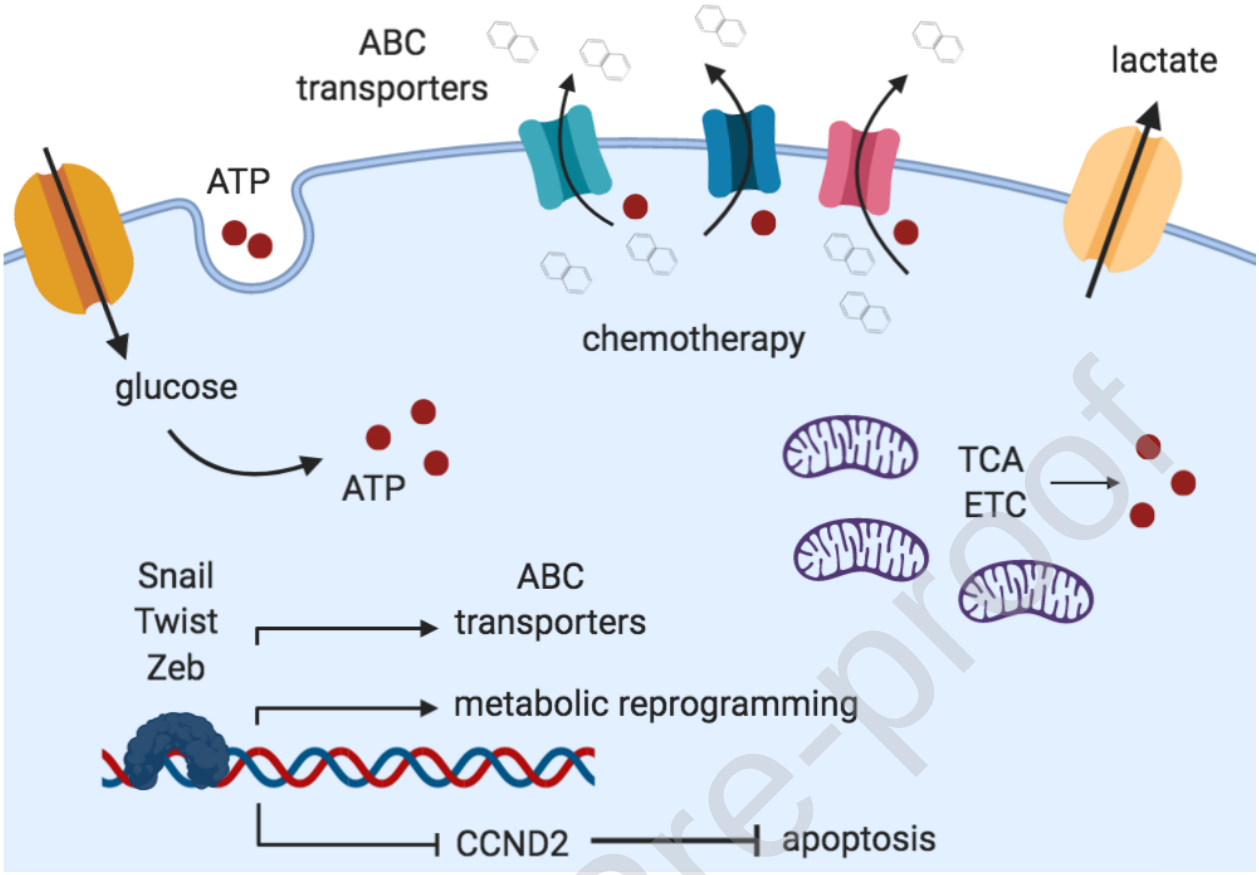

Figure 4. EMT transcription factors contribute to the MDR phenotype through ABC transporter-dependent and -independent mechanisms; among the latter is the metabolic rewiring in cancer cells.