PHARMACIA

Pharmacia 70(2): 337–349
DOI 10.3897/pharmacia.70.e104097

Review Article

Pharmaco-epigenetics: Histone modification and personalized medicine

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Received 26 March 2023 ♦ **Accepted** 23 April 2023 ♦ **Published** 30 May 2023

Citation: Sabi SH, Qnais EYA, Al Tall YR, Almaaytah AM, Masaadeh MM (2023) Pharmaco-epigenetics: Histone modification and personalized medicine. Pharmacia 70(2): 337–349. https://doi.org/10.3897/pharmacia.70.e104097

Abstract

Epigenetic changes have a major effect in both normal and disease cases of organism. Multiple types of epigenetic changes as acetylation, methylation on either DNA or histone proteins, phosphorylation, or ubiquitination. Epigenetic changes are associated with multiple diseases; one of the major diseases that bind with epigenetic changes is cancer. However, DNA methylation is one of the most important epigenetic changes that leads to disease such as cancer. Moreover, patients respond differently to drugs due to different genetic makeup or what called molecular changes in their cells. Both genetic and epigenetic are important to determine the personalized medicine "precise medicine". This review will discuss the epigenetic changes in our body and how it's affected personalized medicine for each person.

Keywords

Histone modification, Precise medicine, Epigenetics, TPMT, Omics

Introduction

Epigenetic changes were defined as the changes at the protein level rather than in the DNA sequence. A British biologist Conrad Waddington in 1950s was the first time to discover the epigenetics. Conrad Waddington said that "some genetic alteration doesn't cause new phenotype". The differences between genetics and epigenetic is that the genetic processes are irreversible but the epigenetic is a reversible process (Kunysz et al. 2021). These changes lead to several diseases; including bone and skin with autoimmune diseases, neurodegenerative diseases as schizophrenia and cancer. It can be inherited from the daughter cells during the division (Esteller 2008; Josep and Maria 2022). The genome of an organism can be altered by many chemical compounds which can lead to gene expression alteration; These are called the "epigenome". One thing that can lead to epigenetic changes is internal or external stress such as the oxidative stress in the cells which affect the organism's genotype and phenotype (Allis and Jenuwein 2016; Rothstein et al. 2017).

Multiple forms of epigenetic changes like: DNA methylation, histone modifications, chromatin remodeling and microRNAs, that's have a regulation function (Mikkelsen et al. 2007; Diane et al. 2011). All these mechanisms play a role in the regulation of genes as well as multiple biological functions that's linked to several diseases (Skvortsova 2018).

Conventional therapies are ineffective for treatment the patients with epigenetic causes of disease. Because of that scientists can find personalized medicine or what is called "patient-specific medicine". Cancer develops through many genetic accumulation changes, as point mutations, gene amplifications and genes deletions which are responsible for stimulation of "oncogenes" and inhibition

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of "tumor suppressor genes" (Peramaiyan et al. 2022). But on the other side, some studies mention that the cancer cells are "addicts oncogenes maintenance of the malignant phenotype" (Weinstein and Joe 2008). Due to the increasing the studies that demonstrate the concept of "oncogene addiction" by showing the efficacy of the antibodies and drugs that target the human cancer like EGFR mutation indicates sensitivity gefitinib (Lujambio and Lowe 2012). Now, how is the response to chemotherapy predicted? The answer is by knowing specifically the data about the gene expression, and basically the cancer cell expression gives a relationship between the gene expression inside the cells and the cell response to chemotherapy (Paster et al. 2021).

Epigenetic changes in term of "DNA methylation" are one of the hallmarks of the cancers that are responsible for inhibition a gene expression by using enzyme called DNA methyltransferases (DNMTs) and the processes reversed by using demethylation enzyme. The sensitivity to chemotherapeutic drug can be predicted by know specifically what the genetic alteration in the cancer is. (Orlando et al. 2012).

Several drugs can be developed just by understanding the role of epigenetic changes in the cells. Two DNMT inhibitors 5-azacytidine and decitabine, by the US FDA approval for the treatment of myelodysplastic syndromes (MDS) and hematologic malignancies (Kumer et al. 2020). Drug responses affected by DNA methylation that coding enzymes drug metabolism (EMD), drug transporters and drug targets (Cossio et al. 2020).

Another thing that affects gene expression is single Nucleotide Polymorphisms (SNPs) which are located adjacent to DNA methylation sites (Shoemaker et al. 2010). Both these mechanisms can lead to inter-individual differences in drug response. Here are multiple genes involved in methylation processes; in DNA repair and maintenance of genome integrity (as, MGMT, hMLH1, WRN, and FANCF), and genes checkpoint of the cell cycle (as RFHC and 14-3-3 σ, CDK10, and p73), all of them affect the response to chemotherapeutic agents (Castilho et al. 2017).

In this review, we focus on the consequences of epigenetic changes in term of DNA methylation in measuring a therapeutic effectiveness of the chemotherapeutic drugs in cancer treatment by giving a thiopurine methyltransferase as a model system for epigenetic and DNA methylation.

The function of epigenetic in personalized medicine design

Epigenetic deregulation is a reason for cancer in humans

Concept of epigenetic

Multiple types of genetic abnormalities (mutations) can cause abnormal signaling pathways and sometimes propel diseases. This part gives us a solid foundation for the discovery of road-based drug, in which the targeted therapy against both mutant is oncoproteins built (KIT, BCR / ABL) and wild type effectors residing before or after the abnormal way (Zhang et al. 2018).

Critical signals can affect epigenetics

Different factors and points affect epigenetics. Environmental factors play a major role in epigenetic changes which induce "epigenome" as a biochemical record of relevant life events (Bock 2009). In case of environmental and life-style factors, pregnant woman, and it's behavioral also affect epigenetic alteration (Horsthemke 2018). And the example of that, age-related epigenetic changes in identical twins; due to DNA methylation these twins can be different in older than younger (Boks et al. 2009). These differences are due to alteration in lifestyle, even though they live in the same environment, and in more specifically, the activity of the enzyme that regulate the histone modification process are controlled by critical signals, which responsible for altering the chromatin structure and histone modifications (Schreiber and Bernstein 2002; Jorge et al. 2011; Alblas et al. 2019).

Changing in environmental and internal factors is different for each person and it's a dynamic process. 11-years before researcher found that epigenetic changes occur at specific regions which is the CpG region near the promoter (Johenson et al. 2020). From here on these dynamic processes affect epigenetic modification, all the factors including environmental factors are important to determine the specific dose for each state "personalized medicine" (Rauschert et al. 2020).

Epigenetic codes

The DNA is wrapped around the histone octamer (two H2A, H2B, H3 and H4) to form chromatin and the functional unit of chromatin called nucleosome. Around 147 base pairs of the DNA responsible for determining the basic structural units of chromatin, it's carried what called "epigenetically inherited codes" plays a role in the regulation pathway such as: DNA repair and chromosome remodeling. These epigenetic codes contain basically histone modification in case of histone level alteration or DNA methylation in case of DNA level. Recent studies show that multiple regulator factors either upstream or downstream regulate this pathway, also the microRNA and other non-coding RNA regulate these processes (Andersen et al. 2018). Histone modifications occur on the N-terminal ends, including (acetylation, methylation, phosphorylation, and ubiquitination). These processes contained different enzymes such as: HATs, HDACs, HMTs, HDMTs, kinase, phosphatase, ubiquitin ligases, deubiquitinate SUMO ligase, protease and so on. As mentioned above, methylation occurs at specific regions, so in case of S-adenosyl-methionine (SAM); a methyl donor, the 5-C methylated, and it becomes 5-methylcytosine. Methylation affects X-chromosome inactivation, genomic imprinting, transposon silencing, and gene transcription regulation (Mohn and Schubeler 2009).

HDAC alteration in driving cancer

Most of the studies focus on two processes of histone modification which are acetylation and deacetylation (histone methylation) that are regulated by two different enzymes HAT and HDAC. The histone acetylation correlates with gene activation and histone deacetylation correlates with gene silencing leads to chromatin condensation. In general, histone deacetylation term describes histone methylation. Researchers studied how these two terms affect driving force during cancer development by inactivation or mutation in HDAC that leads to silence its activity and converted into abnormal cells (Biswas and Rao 2017).

Based on the similarity in the sequence and the domain organization of HDACs, it's divided into four classes, Class I (HDAC1, 2, 3 and 8), class II (HDAC4, 5, 6, 7, 9, 10), HDAC III (sirtuins in mammals, sirts) and HDAC IV (HDAC 11) (Kinnaird et al. 2016). The first two classes with class four are considered as "classical" HDACs; represent as anticancer drug targets during therapy. Recent studies either in vitro or in vivo found multiple HDAC inhibitors (like, SAHA, valproic acid, TSA). This inhibitor blocks the activity of HDAC and switches the chromatin structure and the tumor suppressor gene (TSG) expression, which lead to a variety of anti-cancer activities. But one point must be mentioned that the HDAC inhibitor drugs efficient in patient and toxic in another patient. This is due to different epigenetic alteration (DNA methylation) and different histone tail modification. However, when the HDAC inhibitor alters that's lead also to DNMT alteration, both enzymes involved in acetylation and methylation process. From this point personalized medicine arises that can lead to better or bad response to drug based on different HDAC inhibitors isoform, so each person gets its specific dose (Shankar et al. 2016).

Abnormal DNA methylation in cancer therapy

As mentioned above, epigenetics occurs at protein level or at a DNA level. In the case of DNA methylation which involved DNA alteration, specifically it contains different enzymes that are responsible for methylation process to done such as DNMT1, DNMT1b, DNMT2 and DNMT3a and DNMT3b (Levine and Melnick 2010).

As such, ten to eleven translocation states of MLL genes were found in AML leukemia, and that's play a role in DNA methylation and determining its status (Ito et al. 2011; Williams et al. 2011). This gene family consists of three members: TET1, TET2 and TET3 that are responsible for 5-hydroxymethylcytosine (5hmC) production from methyl-cytosine (5mC) by deamination (Aimei et al. 2022). Recent studies found small RNA which regulate the gene expression as siRNA and miRNA, from that the scientist saw the effect of siRNA on the TET1 and 5hmC reduction level in the cells. (Tahiliani et al. 2009; Montano et al. 2020).

What specifically happened in cancer is that about 50% of genes become methylated that' means it gets silenced. Hypermethylation of CpG islands in promoter region leads to inactivation of tumor suppressor gene, cell cycle-related genes, DNA mismatch repair genes, hormone receptors and tissue or cell adhesion molecules (TSGs as FHIT, WWOX and RASSF1A in lung cancer, p15 and estrogen receptor in leukemia) (Majidinia et al. 2019; Renosi et al. 2021).

Epigenetic treatment

Hypermethylation at CpG islands in the promoter is one feature of the cancer either histone modification or DNA methylation "Epigenetic alteration" that can be detected by a specific technique which is bisulfate conversion and PCR-based quantification or HPLC (Bailey et al. 2009; Li and Chen 2009). Nowadays, chemotherapy is the most potent therapy for all cancerous individuals, but don't forget that these therapies lead to epigenetic alteration, sister chromatid exchange and deletion on the chromosome level. For that, "pharmaco-epigenomics" arise to create patient-specific-dose not only for cancer, but also for (type 2 diabetes mellitus, psychosis). And from its name, it manipulates individual genome to develop specific therapy, specific profile for each state (Feinberg et al. 2016; Locke et al. 2019).

CpG islands vary between individuals but mostly it contains 50% of genes, one of these genes becomes methylated. Everyone has a CpG-specific type; CpG-specific methylation, and the reason of course is due to histone modification and epigenetic alteration between patients. The main idea is to activate TAG and suppress oncogene, by deactivation of DNMT enzyme and activating the acetylation enzymes to get better response for drugs (Kelly et al. 2010). Many drugs were developed as DNMT inhibitor such as Azacytidine (Vidaza) and decitabine (Dacogen), which tested in myelodysplastic syndromes (MDS) in AML (Issa et al. 2005). It gets FDA approval for DNMT and HDAC inhibitors drugs such as vorinostat (Zolinza) and romidepsin (Istodax). These are not the only drugs were used in treatment but to date no significant statistical for other drugs in increased the therapeutic index (Zou et al. 2018; Ankita et al. 2021).

Epigenetic has some barriers in treatment involved; inappropriate in the delivery of drugs, loss epigenetic biomarkers, lack some information about the exact mechanism for tumor resistance to drugs and other things (Marks 2011).

In some cases, cancer cells are converted from benign to metastatic cells due to ineffective drug therapy. One reason for that is due to heterogeneity of cancer; it's a complex pathway involved environmental and genetic alteration (Bilokapic et al. 2018). However, the most available chemotherapy is decitabine, it has different side effect such as inefficient in drug delivery, decreased the potency of DNA incorporation, loss some DNMT inhibitors like 3A, 3B, and the last one is due to different resistant profile for drugs (Hao et al. 2017). From all these reasons, the most

one that must be studied is the "drug delivery" if specific profile was determined this lead to increase effective cancer therapy (Villanueva et al. 2015) (Ramazi et al. 2020).

Pharmacogenomics and personalized medicine

Pharmacogenomics is defined as the studying of the drug response in whole genome (RNA, DNA). It contributes with multiple factors correlated with drug metabolism, drug transporter, receptors and drug metabolizing enzymes with a deviation affect a responsiveness of drugs in different disease and this is called polymorphisms; All these things regulated by epigenetic mechanism (Pirmohamed 2011).

One of the applications of Pharmacogenomics is to determine a particular patient in the exact concentration and at the right time and this is called "precision medicine". In the beginning, "one drug for all" arises but after studying the epigenetic and understanding what this term exactly means the second idea arises which is "patient specific dose". Different factors contribute to epigenetic alteration like, diet, age, body weight, sex, genetic behavior, infections, co-medications, and organ function, all these important in drug therapy and disease treatment. However, new techniques used to determine that as medical computer science which focus on identifying disease targeted therapy.

Two terms used to determine drug response and drug variability, pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetics basically determines the dose and pharmacodynamics study effectiveness and toxicity (Rajasri 2017).

The major enzyme responsible for the metabolizing of drug is cytochrome CYP450, variation in this enzyme lead to different drug response either by increase efficient state or toxicity state. CYP450 has multiple polymorphisms, it's about 38 families and different coding form (Shimizu and Kawano 2022). By using sensitive techniques like microarray, types of CYP450 genes can be determined whether CYP450 genes, CYP2D6, CYP2C19 etc. These genes affect the metabolism of 25% of all drugs (Megaraj et al. 2014).

Furthermore, multiple polymorphisms were detected within drug transporter and drug receptor. Mutations in transporters or receptors lead to different metabolism profiles, like the mutation within tyrosine kinases receptor encoded different cancers and neurodegenerative aberration. Another example of that is increasing the expression of ErbB2 (v-erb-b2 viral oncogene homolog 2 avian erythroblast leukemia) in breast cancer with trastuzumab treatment, the BCR / ABL fusion protein is very sensitive to imatinib in leukemia treatment and reactivating the mutations of the epidermal growth factor receptor (EGFR) shown to be correlated with gefitinib with different response (Corces et al. 2018).

Genotyping and phenotyping application are important to determine a disease-mutations "polymorphisms" and disease state. mRNA is a transcription product, genetic variation affects this product, also it's affected splicing machinery, some mutation located in exon region and other located in intronic region or splicing site. Alternative splicing contributes about 40–60% of mammalian genome. Scientists studied gene expression at mRNA level, and a result of that was catechol-O-methyltransferase gene (COMT) which is a gene that higher found in schizophrenia patients, because this gene related into the autopsy brain tissue of patient (Gao et al. 2020).

Specific epigenetic biomarkers are used to classify cancer in histological parts of the hospital by using either tissue or cells. Also, by using microarray multiple cancer types can be detected whether breast, colon or any other type and their stages also can be detected. In microarray, cDNA, fluorescent labeling was used to determine specific stages for each type of cancer. The principle of microarray was based on analyzing mRNA expression (Lo et al. 2010). The most sample type used in cancer diagnosis is serum. For example, one of the epigenetic biomarkers in prostate cancer is hypermethylation of glutathione S-transferase gene (GSTP1) which is used to determine the cells if its benign or metastasis so, this is a clue for DNA methylation (Rodriguez and Esteller 2011). If GSTP1 higher in serum or urine that's mean this biomarker become methylated and the cell get metastasis and vice a versa if GSTP1 level decreased in serum or urine that's mean low level of methylation and the cells get benign, by controlling this pathway; by personalized medicine; benign cells get smaller (Richiardi et al. 2009; Xu et al. 2017).

New horizons about using monoclonal antibodies specific for each type of cancer and using specific inhibitors to inhibit some point in the cancer pathway; this can lead to improved cancer treatment. Different molecular targets and pathways like Aurora kinases, the FOXO FOXM1 axis and PI3K / mTOR signaling were contributed to human cancers. For example, the small molecule VX-680 shows an inhibitory effect and cause cell death in leukemic cells with a specific aurora expression profile by the Bax / Bcl-2 ratio to increase, what with a high aurora-A expression apoptosis acute in the myeloid leukemia induced (Yan and Liu 2013). In the same way, fork-head transcription factors (FOXO and FOXM1) a crucial play a major role in cell division, differentiation, angiogenesis, apoptosis, DNA repair and tissue homeostasis. As such, the FOXO FOXM1have a major role in drug resistance regulation and tumor- genesis (Gomes et al. 2013).

Epigenetic alteration of drug-response-related genes and relation to clinical pharmacology

Inter-individual variation in drug-response-genes is very important to study drug response (toxicity or effectiveness). These differences are shown in ADME expression, drug carriers, drug targets and downstream signaling molecules. (Table 1).

Table 1. DNA methylation gene is related to drug response.

	DNA methylated region	Affected drugs
CYP450 family members	CYP1A1 promoter	Polycyclic aromatic hydrocarbon
	CYP1A2	Drug metabolism and synthesis of cholesterol and other lipids
	Promoter/	Oestrogen and 4-hydroxy esradiol
	enhancer	Vitamin D (Belinsky et al. 2006).
	CYP1B1	
	CYP24A1 promoter	
Phase II DME	GSTP1 promoter	Oxaliplatin
	NAT1	Tamoxifen (Ronneberg et al. 2008).
Drug transporter	MDR1/ABCC1 promoter	5-azacitidine and irinotecan
	SLC5A8	
	SLC22A1/OCT1	Dichloroacetate (DAC)
		Cisplatin (David et al. 2004).
Drug target and signal pathway genes	TFAP2E	Fluorouracil
	DEX1	Camptothecin (CPT)
	MGMT promoter	Temozolomide (Harst and de Boer. 2010).

Cytochrome P450 super-family play a role in phase I metabolism of approximately 75% drugs approved by FDA. Different studies have shown the robust role of epigenetic (DNA methylation) in the regulation of CYP1, CYP2 and CYP3 gene expression. CYP1A2; one enzyme belongs to CYP450 superfamilies. It's contributed to metabolism of drugs, steroid, hormones, and other lipid synthesis. Another member of the CYP450 family is CYP1A2, which is involved in drug metabolism and cholesterol, steroids, and other lipids synthesis (Bjornsson et al. 2004).

Study done by Miyajima et al, showed that a strong relationship between methylation and CYP1A2 expression in liver. When methylation increases, mRNA expression of this enzyme decreased in liver and vises a versa in case DNA methylation level increases (Miyajima et al. 2009).

Another enzyme from CYP450 families is CYP1B1 called "estrogen metabolite". It's more potent to study its effect in female because this enzyme plays a role in breast cancer. It regulates 4-hydroxy estradiol formation. Recent studies done by De Montellano, whose said that the methylation pattern within CYP1B1 promoter affect binding of transcription factor (AhR / ARNT and SP-1). Another type of cancer related to this enzyme is prostate cancer. When methylation status increases for this enzyme, level of expression becomes lower or decreased and cancer will develop (De Montellano 2013).

In general, all CYP450 families are regulated by epigenetic alteration (DNA methylation) such as CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP2R1, CYP2S1 and CYP2W1. Remember that acetylation processes or demethylation mechanisms are responsible for increased expression of these genes. One of the largest CYP450 families is CYP3A that's making about 70% of drug metabolizing in liver. Methylation is inhibited by small molecules of DNMT inhibitor, it's a sensitive mechanism affected by CYP3 expression whether CYP3A4, CYP3A5 or CYP3A7 in HepG2 cells. In vivo studies showed that the CpG hot spot regions are highly different within individual and within fatal, adult tissue. Methylation status is different in adults than fatal; high methylation status in fatal liver indicates low CYP3A4 expression. Drug response regulated by the methylation status of CYP3A, low level of DNA methylation required to get higher response. For this idea to complete, small DNMT inhibitors can be used in disease treatment and increase drug effectiveness.

As mentioned before, epigenetic affected by external factors like nutrition intake and diet like ingestion of vitamin D. One of the CYP450 enzymes that are responsible for vitamin D metabolism is CYP24A1. This enzyme is considered as "tissue specific". According to Novakovic et al studies that provided a clue for methylation relationship to CYP24A1 expression in human placenta samples that's related to gestation abnormalities. As such, one marker to determine inter-individual differences for calcitriol "active form of vitamin D3" is CYP24A1 that expressed on the endothelial cells. By using this enzyme, normal and tumor endothelial cells can be detected (Johnson et al. 2010).

DNA methylation with CYP1A1

One cause of DNA methylation is smoking. Smoking or occupational exposure are recognized as a major source of lung cancer. One of the compounds that are found within cigarette smoking is Polycyclic Aromatic Hydrocarbons (PAHs), which is an organic matter. This matter was considered as carcinogenic compound and it was used for inter-individual differences. Polymorphisms within the enzyme that metabolize PAHs are very important in studying drug response and effectiveness.

CYP1A1 (Cytochrome P4501A1) is a reactive HAP metabolite, that can play a role in starting of carcinogenesis by the formation of PAH-DNA bulky in adducts. From PAHs, CYP1A1 was formed, when PAHs level increased that's indicate lung cancer and vice versa if PAHs level low in human lung. CYP1A1 contain multiple polymorphisms and according to these polymorphisms drugs was adjusted. Everyone has specific polymorphism, which means specific dose (Mittal et al. 2015). Here, one of the biological markers that can be used to determine toxic dose threshold in the tissue is PAH-DNA adducts. One type of tumor suppressor gene is TP5, mutation in this gene plus K- Ras oncogene was shown about 50% in non-small cell lung cancerous (NSCLC). Higher expression of PAH-DNA adducts in TP53, and K-Ras mutations were considered as a molecular marker for lung cancer.

As such, CYP1A1 is an enzyme which is regulated by specific enhancer and may alter gene expression. Enhancer of this enzyme contains specific region called xenobiotic response elements (XREs), located upstream of start site of transcription, this region considered as transcriptional control region. XREs binds with AHR complex (aryl hydrocarbon classical motifs receptor) which is a grouped of enhancer domain. Gene expression can be altered based on this thing, silencing states occur when enhancer is absent and in other hand, when AHR binds to enhancer CYP1A1 activated and the transcription will

begin (Tekpli et al. 2012). In addition, DNA methylation here plays a role in regulating gene expression, the methylation of CpG islands leads to down regulate CYP1A1. Acetylation is a mechanism that enables AHR to XRE binding which is responsible for CYP1A1 activation and expression (Gomez and Ingelman-Sundberg 2009).

The conclusion from that; smoking alters methylation states and modifies the histone protein that surrounded the DNA, methylation alteration affects AHR binding to CYP1A1 enhancer that's lead to higher expression shown in lung cancerous tissue (Androutsopoulos et al. 2009).

DNA methylation with the regulation of drug transporter

The transporter responsible either for efflux or influx of drugs across the cell. To show how DNA methylation affects drug metabolizing enzymes, epigenetic mechanisms must be investigated. All the individuals worldwide have a difference in drug response due to variability in either genes or enzyme. Different drug responses are due to different genes which are called pharmacogenetics that involved pharmacokinetics which plays a role in absorption, distribution, metabolism, and excretion (ADME) of the drugs. So, more than one factor affects the changes in drug and drug metabolizing. (Zhang et al. 2008).

Juliana et al., showed that 2 genes (CYP1B1, CYP3A4) have a direct relationship between methylation and the transcription process. For example, up regulation in CYP1B1 was explained by hypermethylation in the 5'-promoter end of this gene (1B1) and Pregnane X Receptor (PXR) genes. To date scientists have discovered more than 50 ADME-related genes that target epigenetic regulation. Also, these ADME genes were controlled by epigenetic mechanisms in both tumor and normal cells. This is developed by several research about tumor suppressor genes field. One example of anticancer drug cation transporter is SLC22A1 in hepatocellular carcinoma. Hepatocellular carcinoma is one type of cancer that occurs by genetic and epigenetic alteration that collected in regulatory genes leading to inhibit tumor suppressor genes and activate oncogenes. And because the environmental factor in addition to genome alteration can affect the epigenetic mechanism, deregulation of epigenome by environmental stresses such as: (hepatitis B and C virus, chronic alcohol intake, and aflatoxins) could disrupt the cellular processes and increase the rash of hepatocellular carcinoma. Juliana et al showed how the gene expression of solute carrier families (SLC) regulated by DNA methylation. SLC is called organic cation transporter genes SLC22A1, SLC22A2, SLC22A3 encoding OCT1, OCT2, OCT3 respectively. In the case of normal hepatocytes this SLC solute carrier family 22, member 1, that encodes for organic cation transport 1 (OCT1), it's highly expressed due to nutrients, metabolite uptake. Also, this transporter could uptake drugs and some antineoplastic agents like imatinib, cisplatin, irinotecan and oxaliplatin. OCT1 transports these drugs and increase cancerous cells risk for these antineoplastic drugs. Methylation of OCT1 in hepatocellular carcinoma leads to inhibit its function of uptake some anticancer drugs. Because the potent role of OCT1 in increase efficiency of many anticancer drugs, SLC22A1 methylation may be used as epigenetic biomarker in disease diagnosis and drug response (Srijib et al. 2014; Falero-Perez et al. 2018).

Schaeffler et al., that exhibit the individuals with higher SLC22A1 methylation phenotype showed transport inhibition and chemoresistance, and vice versa in case of individuals with low methylation phenotype and respond to chemotherapy due to transporter activation. He suggests the DNA methylation of MIR193A promoter might be used as a molecular marker to detect how hepatocellular carcinoma response to 5-flourouracil (5-Fu). MIR193A promoter hypomethylation induced microRNA 193a-3p transcription that targets both serine/arginine rich splicing factor (SRSF2). This factor sensitizes hepatocellular carcinoma to 5-Fu chemotherapeutic drugs (Srijib et al. 2014).

DNA methylation of phase II drug metabolizing enzymes (DMEs)

Glutathione S-transferase P1 (GSTP1) is one of the most potent DME phase II that regulate drug metabolism of Oxaliplatin and Adriamycin. Mostly, GSTP1 promoter is highly regulated, because if this enzyme downregulated or hypermethylated this indicates prostate cancer. 5-azacytidine and decitabine GSTM1 and GSTP1are DNMT inhibitors that lead to reactivation of the GSTP1 promoter and its expression. Generally, GSTP1 can be used as epigenetic biomarkers to study the response of tissue for 5-azacytidine (Goering et al. 2012).

N-acetyltransferase 1 (NAT1) is a DME phase II which is more potent in the metabolism of drugs and other xenobiotics. NAT1 was observed, inside the tissue of breast cancer, to be methylated in 62.2% tamoxifen-resistant tumors, significantly greater than 33.8% shown in normal tissues proportion. In addition, in the case of tamoxifen therapy, NAT1 is seen to get a lower expression in comparison to normal cells. These studies showed that the NAT1 methylation can be subscribed to tamoxifen resistance, after addition studies will do (Levesque et al. 2019).

DNA methylation of drug targets and signal pathway genes

DNA methylation can alter drug sensitivity and it can change the drug target expression, also the downstream signaling molecules. Hypermethylation of some transcription factors can affect cancer development and metastasis. One example of that is Transcription factor AP-2 epsilon (*TFAP2E*) which belongs to AP-2 transcription factor family. DNA methylation of the *TFAP2E* causes low

level of *TFAP2E* expression in benign cancer which leads to metastatic cancer. Dickkopf homolog 4 protein (DKK4) is one of the target proteins for *TFAP2E*, over expression of the gene coding DKK4 can be developed for fluorouracil resistance. Nowadays, several studies have seen that the *TFAP2E* methylation causes fluorouracil resistance due to DKK4 higher expression. Additionally, patients whose suffer from colorectal cancer showed *TFAP2E* hypermethylation (Ebert et al. 2012).

The best example of colorectal cancer causing is a hypermethylation of tumor suppressor genes (TSG) and transcription silencing. Hypermethylation and inhibition of TSG can be affected the responsiveness for drugs. Several studies in colorectal-cancer field show that patient whose have a hypermethylated epidermal growth factor receptor (*EGFR*) promoter, treated with both irinotecan and cetuximab exhibit a higher resistance, increase disease metastasis and shorter median overall survival (OS) (Scartozzi et al. 2011).

Furthermore, Camptothecin (CPT) is involved Glucocorticoid-induced protein-coding gene (*DEXI*) showed a resistance by apoptosis inhibition. So, inhibition of *DEXI gene* using small interference RNA (siRNA), a type of non-coding RNA which plays a role in gene regulation, decreased CPT-induced apoptosis. In comparison, reactivation of *DEXI* expression via 5-aza-2'-deoxycytidine increases CPT sensitivity. *DEXI* is hypermethylated in both colorectal and gastric cancer (49%, 31% patients respectively). Patients with colorectal cancer have a not good response and get worse after 5-Fluorouracil +CPT- 11 treatments. From that, *DEXI* was used as a molecular marker in disease prognosis after CPT-11-based chemotherapy (Miyaki et al. 2012).

One of the best examples of tumor suppressor genes is the breast cancer genes *BRCA1* and *BRCA2* which encoding for proteins responsible for DNA repair. A hypermethylation in *BRCA1* promoter leads to loss BRCA1 expression, while a silencing mutation in these two genes leads to increased sensitivity to Poly-ADP ribose polymerase-inhibitors (Ibragimova and Cairns 2011).

One of the genes that control the cell division processes is mitotic checkpoint with fork head-associated and ring finger (CHFR) gene. Again, *CHFR* gene can be used as biomarker for gastric cancer and endometrial cancer prognosis by studying the methylation pattern (Hiraki et al. 2010).

Nowadays, evaluated hypermethylation within CpG hot spot region correlated to 35 mammalian cell lines from the National Cancer Institute (NCI) Drug Screening Panel (NCI-60 panel). Hypermethylation profile of some tumor suppressor genes (TIMP3, APC, and IGSF4) in the NCI panel-60 has been found to show a strong relationship with sensitivity for antimetabolites like fluorouracil (5-FU) (Duan and Maki 2016).

Abaan and his colleagues (Aban et al. 2013) determine a strong pattern between hypermethylation profile of P15, CDH (E-cadherin) and HIC (hypermethylated in cancer 1) gene in the outcome of traditional chemotherapy in myelodysplastic syndromes high risk (MDS) and acute myelogenous leukemia (Abaan et al. 2013).

Methylation pharmacogenetics

Thiopurine methyltransferase as a model system

Thiopurine methyltransferase system is a potent system in drug transformation process. This enzyme (TPMT) involved different forms of "polymorphism" responsible for different mechanisms of metabolism either ultra, poor, or moderate metabolized. From that, studying the polymorphisms within this enzyme is very important is very important to determine dose-specific patient "personalized medicine".

TPMT enzyme is affected by internal factors and environmental factors. Because of that, epigenetics here must be taken into consideration. Specific epigenetic biomarkers can be used to determine methyl status as well as dose of drug and drug response. TPMT activate a methylation pathway for different thiopurine drugs like; 6-mercaptopurine. It is regulated by SNPs presence within it; some SNPs are responsible for toxicity; others are responsible for increase effectiveness especially when drug-drug interaction can be used which lead to stimulate signaling pathway.

Different experiments show that patients with low level of TPMT suffer from myelosuppression, but in case of increased level of TPMT in RBCs, those patients continued the treatment. Studies done in mice used as animal model to study pharmacogenetics and adverse drug reaction for these drugs. A deeper comprehension of methylation with pharmacogenetics is important to study individual differences, therapeutic index for methyl conjugation of some compounds.

Thiopurine S-methyltransferase (TPMT) genes affect inter-individual dosing of thiopurine drugs, multiple SNPs located in this enzyme, and it can play a role in optimizing the dose for patients with high efficacy and low toxicity and without adverse drug reaction. This enzyme converts 6-mercaptopurine (6-MP) into 6-MeMP and the 6-MP can be converted by hypoxanthine-guanine phosphoribosyl transferase (HPRT) into 6-thioguanine nucleotide (6-TGN) that's incorporated to DNA and RNA molecules and express the cytotoxic effect. This mechanism can be used for cancer treatment because one of the hallmarks of cancer is nucleotide synthesis and once the nucleotide inhibited cancerous cells goes to apoptosis. The most identified TPMT alleles are TPMT*2, *3A, *3C. Predictive genotyping is most important to optimize the drug with specific dose.

TPMT plays an important role in the response to thiopurine drugs, so that decreases the activity of TPMT. It gets together with TGN elevated in the tissue (thioguanine nucleotides) which leads to toxicity in our body. Studies show that Caucasian populations have a TPMT variation;

it's divided into three groups' normal, intermediate, low metabolized with about (89%, 11%, 0.3% respectively). As shown in Table 2 that represents different TPMT polymorphisms with different activities. The most TPMT polymorphisms are TPMT2, 3A and *3C. Making phenotype and genotype assay is very important to determine dose-specific for each patient, and this is approved by FDA in 2004.

Table 2. Summary of the currently known SNPs in the TPMT gene.

TPMT variant allele	Genetic variant	Molecular alteration	Position in the TPMT gene
TPMT*1	Wt		
TPMT*1A	-178C>T		Exon1 (Spire-Vayron de la Moureyre et al. 1998)
TPMT*5	c.146T>C	p. Leu49Ser	Exon4 (Raju et al. 2010)
TPMT*8	c.644G>A	p. Arg215His	Exon10 (Raju et al. 2010)
TPMT*3B	c.460G>A	p. Ala154Thr	Exon7 (Somrudee et al. 2004)
TPMT*3C	c.719A>G	p. Tyr240Cys	Exon10 (Somrudee et al. 2004)
TPMT*2	c.238G>C	p. Ala80Pro	Exon5 (Somrudee et al. 2004)
TPMT*10	c.430G>C	p. Gly144Arg	Exon7 (Liewei et al. 2010)
TPMT*13	c.83A>T	p. Glu28Val	Exon3 (Liewei et al. 2010)

Patients that inherited a defect copy of TPMT respond from 6-MP treatment higher than the wild type patients because of TGN elevated in cancerous cell, but still, they have a higher risk of haematotoxicity and secondary tumors in normal cells. In the other side in case of ultra-rapid metabolized patients which result in increased 6-MPlevel that leads to hepatotoxicity (Jardin et al. 2011). Homozygous patients that have both defect copies of TPMT have dose-reduction by about 90%, and patients who's inherited just one copy defect have about 30–70% reduction to first dose. All this genotype polymorphism must be detected, by either polymerase chain reaction (PCR) or Pyrosequencing or any type of genotype detection, prior give a drug to patients to avoid toxicity or discontinuation of therapy (Savard 2013).

DNA methylation-related SNPs in pharmacogenomics

Single nucleotide polymorphism (SNPs) is the most polymorphism affect the human genome. It's a type of variation and has a frequency of more than 1%. It's also played a role in the modification of multigame diseases and in inter-individual differences to the response of drugs. DNA methylation-related SNPs lead to gene expression alteration, disease developed due to change TPMT activity. SNPs within *CYP2A6-CYP2A7* gene families are considered to affect the level of nicotine in blood. Studies have shown the SNPs within *CYP2C* locus can be caused by "allele-specific DNA methylation" for these gene families. A non-synonymous SNP rs3815710 (Arg128Leu) in *CYP2A7* was shown something called "allele-specific mRNA expression". This polymorphism (*CYP2A7*) can be altered smoking status by hypermethylation alteration and mRNA expression. Another polymorphism in *MGMT* promoter (rs16906252 C/T) was shown, and it was shown that altering *MGMT* methylation can affect drug response. Recent studies reported 95 malignant pleural mesothelioma patients with a heterozygous genotype (rs16906252 C/T), have T allele (rs16906252) in colorectal cancer patients which correlated to *MGMT* promoter methylation. A mechanism is still not clear while the SNPs can be altered the binding of some transcription factor that affect DNMT binding and methylation mechanism (Kristensen et al. 2011).

Dynorphin is an endogenous ligand of κ opioid receptor, it's also considered as strong analgesic. Studies showed that the associations between 3'-UTR SNPs (rs910080, rs910079 and rs2235749) in prodynorphin gene (*PDYN*) in cocaine dependence. These SNPs (rs910080C-rs910079C-rs2235749T) haplotype was correlated with cocaine dependence. With rs910079 C allele, *PDYN* expression was very low as well as in the patients with (rs910080C-rs910079C-rs2235749T) haplotype. These three SNPs that are associated with alcoholism showed that there are methylated in brain according to post-mortem specimens' analysis from dorsolateral prefrontal cortex (dl-PFC) in alcoholics. With this SNP (rs2235749 C) exhibits an increase in *PDYN* methylation, which binds positively with the levels of dynorphin. It was shown that the (rs2235749) A/T polymorphism can affect *PDYN* methylation; this is approved by studying the DNA-binding factor that revealed a variation in methylated T allele or unmethylated C allele binding affinity (Yuferov et al. 2009).

There are two factors that play a major role in the growth of fetal and post-natal growth which are insulin-like growth factor 1 (IGF-I) and insulin-like growth factor-binding protein 3 (IGFBP3). In shorter children of gestational age (SGA), the IGFBP3 level in plasma was decreased. Patients specifically SGA adults which took growth factor therapy, *IGFBP3* mRNA expression elevated. *IGFBP3* promoters have a variation of SNPs such as -202 A/C, -185 C/T which regulate IGFBP3 mRNA level. Also, hypermethylation may affect IGFBP3 level via transcription factor binding alteration. SGA children whose have -202 AA genotype have elevated IGFBP-3 levels from the -202 C allele patients. Children with -202C/-185C haplotype showed a significant lowering in IGFBP-3 levels compared with children whose carrying the202A/-185C haplotype. The methylation of CpGs islands affecting the transcription factor binding which was elevated within short young SGA adult in comparing with the controls. Studies showed that -202A/C and -185C/T polymorphisms may regulate a response of growth hormone by DNA methylation changes within *IGBP3* promoter region. And of evidence of what happened for the child with the -202A/-185C haplotype and with growth hormone treatment which have elevated within IGFBP3 level in comparison with child haplotype (Van der et al. 2009).

MDR1 exon 26 has a unique polymorphism (C3435T) which regulates the *MDR1mRNA* expression. This SNP may affect the absorption and distribution of some drugs like, digoxin, phenytoin, tacrolimus, carbamazepine, doxorubicin, and vincristine. Ulcerative colitis subjects with polymorphism (3435C allele) were higher suscepti-

ble for *MDR1* methylation in comparison of 3435TT carrier's patients by six times. For example, on patient that taking tacrolimus drug, studies involved 1327 renal transplant patients was carried C3435T allele can be affected the pharmacokinetics of tacrolimus drug. Although, CC Patients genotyped have a lower dose of tacrolimus in comparison with T allele carrier. Three main things that affected by *MDR1* C3435T polymorphism: I) The concentration of drug in the plasma. II) Distribution of that drug in the tissue distribution. III) Drug reactivity of chemotherapy drugs (Li et al. 2012).

What is new and conclusion?

To date, pharmacogenomics has two main approaches: candidate gene approach and whole genome approach. Both resolve the genetic alteration like SNPs to determine the response for drugs. Besides variations within DNA sequences, heritable epigenetic is a non-genetic system even though they include have been involved in gene regulation which can be affected the drug response.

In the beginning, all research concentrates on DNA sequence studying rather than DNA methylation on the drug response. Nowadays, several studies arise to focus on epigenetic alteration. Epigenetic or methylation mechanism is a reversible process unlike genetic variants; it's correlated with drug response alteration. In addition, genetic alteration like polymorphism changes the cancerous cell response for chemotherapy which can be predicted by different methods like microarrays and next generation sequencing. From that, analyzing promoter methylation status was very important thing before using any type of chemotherapy or drug treatment.

This article focuses on precision "personalized" medicine related to epigenetic or methylation status in the case of cancer treatment. Nowadays, there is no treatment without epigenetic analysis because epigenetics is considered as a basal level in the clinical trials of cancer treatment. Not all the patients have the same response to drug treatment; discontinuation or toxicity that developed is due to one-dose giving for all patients. By analyzing epigenetic factors, dose-specific patients can be determined, increase efficiency, and reduce adverse drug reactions and toxicity.

Although still some patients have a failure in drug therapy because until now low of information about epigenetic and genetic variants may developed. The term pharmacogenetics developed to include pharmacogenomics because "omics" is a term used generally to predict all the things in the genome whether DNA or RNA. By using this term, drug response detection becomes easier. As such, molecular biomarkers make this process easier. Proteomics must obtain an enormous potential to answer directly about the pharmacological issues such as transcription profiling. While inconsistency for the modification of proteins makes the application of proteomic markers for personalized medicine limited.

"Omics" term includes lipidomic, transcriptomics, and "Epigenomics" which play an important role in the development of personalized medicine, which covered both internal and external like food, environment conditions, etc.…, that produce SNPs affected gene regulation. However, pharmacogenetics and epigenetics until now has been the most studied in cancer treatment. Because there is a relationship or some information between chemotherapy and epigenetic or DNA methylation by selecting specific epigenetic markers to get a better therapy. Chemotherapy if it's given to all patients may produce efficient in person and toxicity in another. But epigenetic biomarkers that determine the specific dose for each person will reduce the toxicity. So, represent epigenetic alteration completely personalized features and demonstrate specifically the reason for the collaboration of epigenetic personalized area improves medicine.

Overall, the final thing for pharmaco-epigenomics with personalized medicine is to be contemplated the cancer treatment. A dynamic movement between cancerous cells, normal cells, and immune system. One of the barriers in this article is using epigenetic and personalized medicine to treat not just cancer but also for heart failure and osteoarthritis disease. In general, information patient-proteome, epigenetic and drug metabolism can be integrated to adapt individual health care.

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