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YKL-40: a Potential Biomarker and Therapeutic Target for Breast Cancer Diagnosis and Therapy

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Review Article

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ABSTRACT

Over the past two decades, emerging data have found that YKL-40, a secreted glycoprotein, is elevated in a broad spectrum of human diseases including cancers, liver injury, asthma, diabetes, inflammatory diseases, and cardiac disorders. In breast cancer, increased serum levels of YKL-40 are correlated with cancer metastasis and short survival, suggesting that serum levels of YKL-40 serve as a cancer biomarker. YKL-40 has the ability to stimulate vascular endothelial cell activation and suppress mammary epithelial cell differentiation, the pathophysiological events associated with tumor angiogenesis and poor differentiation. Neutralization of YKL-40 via an anti-YKL-40 monoclonal antibody in animal trials demonstrates the ability of YKL-40 blockade to impede tumor angiogenesis and tumor growth, thus holding therapeutic promise for cancer therapy. Apart from these findings, substantial efforts are urgently required to decipher the key molecular mechanisms that mediate cancer metastasis and malignancy, which is expected to significantly offer translational value for breast cancer diagnosis, prognosis and therapy. This review discusses the current status of research on YKL-40's expression, biophysiological and pathological activities and functional inhibition, which is instrumental for future clinical practice.

Keywords: YKL-40; cancer biomarker; therapeutic target; breast cancer.

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INTRODUCTION

YKL-40, also known as human cartilage glycoprotein-39 or chitinase-3-like-1, is a secreted glycoprotein originally identified from culture medium of a human osteosarcoma cell line MG-63 (Johansen et al., 1992). Structural analyses of YKL-40 have demonstrated that YKL-40 is highly conserved in mammals including: human (Hakala et al., 1993), porcine (Shackelton et al., 1995), cow (Rejman and Hurley, 1988), mouse (Lian et al., 2006), rabbit (De Ceuninck et al., 2001) and goat (Mohanty et al., 2003). Putative YKL-40-like proteins were also identified in *Drosophila* (Kawamura et al., 1999), bacteria (Kzhyshkowska et al., 2007) and oyster Crassostrea gigas (Badariotti et al., 2006). Human YKL-40 protein contains an open reading frame of 383 amino acids with a molecular mass of 40 kDa and it is a member of glycoside hydrolase family 18. This family contains chitinases, but YKL-40 does not have chitinase/hydrolase activity because of the substitution of an essential glutamic acid with leucine in the chitinase-3-like catalytic domain; it only binds to chitin-like oligosaccharides (Fusetti et al., 2003; Renkema et al., 1998). YKL-40 is normally expressed by a number of different cell types that include chondrocytes (Hu et al., 1996), synoviocytes (Nyirkos and Golds, 1990), vascular smooth muscle cells (Shackelton et al., 1995), macrophages (Rehli et al., 1997) and neutrophils (Kzhyshkowska et al., 2007). However, its biophysiological function in those cells is incompletely understood.

Mounting evidence has indicated that YKL-40 mediates pathogenesis of multiple inflammatory diseases, including bacterial infections (Kronborg et al., 2002), rheumatoid arthritis (Nielsen et al., 2011), osteoarthritis (Volck et al., 2001), hepatic fibrosis (Pizano-Martinez et al., 2011) and hepatitis (Fontana et al., 2010; Johansen et al., 2000), asthma and chronic obstructive pulmonary diseases (Park et al., 2010), neuroinflammation (Bonneh-Barkay et al., 2011) and bowel lesion (Vind et al., 2003). Though molecular mechanisms underlying these inflammatory disorders are largely elusive, it has been suggested that YKL-40 is associated with substantial remodeling of extracellular matrix and extensive infiltration and differentiation of macrophages, the primary leukocytes in response to inflammation. Studies with YKL-40 deficient mice offered strong evidence supporting this hypothesis, as these mice exhibited markedly diminished antigen-induced Th2 inflammation and impaired macrophage activation and differentiation (Lee et al., 2009). In addition, YKL-40 was found to regulate mitogenesis and survival of fibroblastic cells that participate in tissue injury and wound repairing (Recklies et al., 2002).

Over the past decade, multiple independent studies have demonstrated that high serum levels of YKL-40 are correlated with metastasis and poor survival in a variety of human carcinomas such as breast cancer (Jensen et al., 2003), colorectal cancer (Cintin et al., 1999), ovarian cancer (Hogdall et al., 2003), leukemia (Bergmann et al., 2005), lymphoma (Hottinger et al., 2011) and glioblastoma (Pelloski et al., 2005), suggesting that serum levels of YKL-40 serve as a diagnostic and prognostic cancer biomarker. A crucial regulatory mechanism was reported to be associated with an angiogenic signature of YKL-40 in the development of breast cancer and glioblastoma (Francescone et al., 2011; Shao et al., 2009). The primary focus of this article is to discuss pathophysiological properties of YKL-40 that were identified recently in breast cancer development, thus shedding light on translational significance in cancer diagnosis and unveiling a novel target potential for cancer therapy.

1. YKL-40 in Normal Mammary Gland Development

The adult mammary gland primarily consists of a lobuloalveolar structure with three distinct cell lineages: myoepithelial cells that form the basal layer of ducts and alveoli, ductal epithelial cells that line the lumen of ducts and alveolar epithelial cells that synthesize milk proteins (Russo et al., 1982). During puberty, these cells are able to proliferate and orchestrate epical-basal luminal buds also referred to as acini, a basic functional unit of the mammary gland (Hennighausen and Robinson, 2001). Varied levels of YKL-40 were found in ductal epithelial cells of non-pregnant human and mouse mammary tissue (Figure 1) (Scully et al., 2011; Shao et al. 2011). During pregnancy and lactation, the mammary glands undergo vigorous proliferation and differentiation into fully branched ductal network that develops a secreted duct system capable of producing and collecting milk protein. YKL-40 levels were noticeably evaluated in the ductal epithelial cells from weaning tissue in mice (Figure 1B). But this strong induction is transient; after involution, the remaining ducts markedly decreased expression of YKL-40 (Figure 1B), implicating that its function is associated with mammary gland remodeling and regression. Consistent with these findings, milk levels of YKL-40 in goat and bovine were increasingly detectable during weaning (Mohanty et al., 2003; Rejman and Hurley, 1988; Yamada et al., 2002). YKL-40 secretion was also found in human lactating mammary gland (Roslind et al., 2007a).

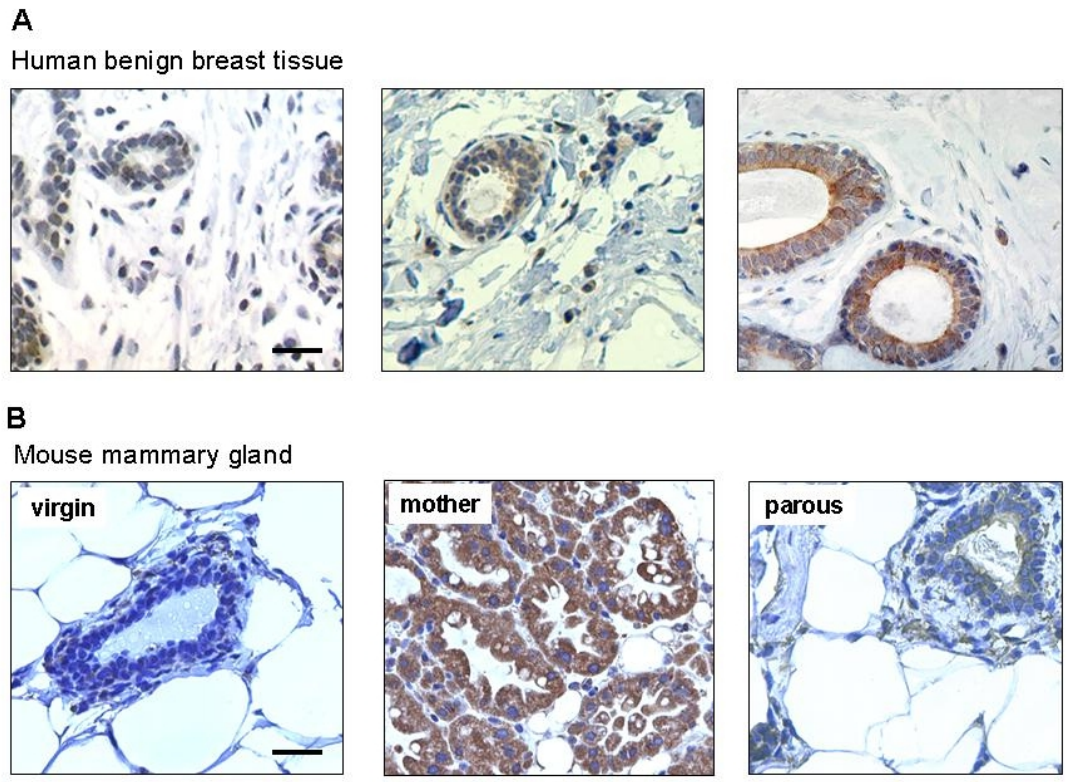

Fig. 1. Expression of YKL-40 in normal breast tissue from human and mice

A. *In humans at age between 30 and 40,* ***s****ome of benign breast tissue does not express levels of YKL-40 and some expresses YKL-40 by ductal epithelial cells.* ***B.*** *In mice, mammary tissue of virgin (12-week old) and parous (10-month old) animals expresses low levels of YKL-40, whereas the tissue at the initiation of involution (3-weeks after giving birth) demonstrates extensive accumulation of YKL-40 in secreted duct lumen. Bars: 100 «m.*

To simulate an *in vivo* environment for ductal morphogenesis, a 3-D Matrigel culture system was established as an *in vitro* model capable of recapitulating ductal epithelial properties including cell differentiation, secretion and polarization in the presence of lactogenic hormones (Debnath et al., 2003; Lee et al., 2007). YKL-40 exhibits the ability to inhibit ductal epithelial differentiation and polarization (Scully et al. 2011). This inhibitory property of YKL-40 was found to be at least partially associated with decreased expression of E-cadherin and increased expression of MMP-9. Reduced E-cadherin led to the loss of intercellular adhesion and impaired the integrity of apical-basal polarity, the process that occurs during mammary gland involution (Vallorosi et al., 2000). In addition, decreased E-cadherin in mouse mammary epithelial cells correlated with increased expression of MMPs, both of which synergistically disrupt cell polarity and contribute to increased cell motility (Xian et al., 2005). In animal models, xenotransplantation of pre-cleared mouse mammary fat-pad tissue with a normal mammary epithelial cell line 76N MEC ectopically expressing YKL-40 did not commit the mammary gland to undergo pathogenesis towards epithelial dysplasia, hyperplasia, or carcinogenesis, indicating that over-expressed YKL-40 alone is insufficient to develop mammary tumors (Scully et al., 2011). However, it remains to be determined whether YKL-40 in coordination with other oncogenic factors (*e.g.* Ras) is essential for the formation of breast cancer.

2. Serum Levels of YKL-40 in Cancer Patients—a Potential Diagnostic and Prognostic Marker

A multitude of clinical studies have revealed that serum levels of YKL-40 were elevated in patients with a series of carcinomas including breast (Jensen et al., 2003), colorectum (Cintin et al., 1999), ovary (Hogdall et al., 2003), prostate (Kucur et al., 2008), brain (Pelloski et al., 2005) and blood (Bergmann et al., 2005). These increased levels were correlated with poorer survival of cancer patients (Bergmann et al., 2005; Cintin et al., 1999, 2002; Hogdall et al., 2003; Jensen et al., 2003; Johansen et al., 2003; Pelloski et al., 2005), suggesting that serum levels of YKL-40 serve as a prognostic cancer biomarker (Johansen et al., 2009). In breast cancer, increased serum levels of YKL-40 were found in 19% of patients with primary cancer (Johansen et al., 2003) and 30% of patients with metastatic cancer (Jensen et al., 2003), supporting the notion that YKL-40 is associated with cancer aggressiveness (Cintin et al., 2002; Jensen et al., 2003; Johansen et al., 2004).

Jensen et al. surveyed 78 age-matched healthy females and 100 breast cancer patients with local regional metastasis and distant metastasis including bone, lung and liver tumor and found that serum levels of cancer patients were significantly higher than those observed in healthy subjects (an average of 137 ng/ml vs. 97 ng/ml, $p<0.0001$) (Jensen et al., 2003). In addition, an analysis of over 5-year survival showed that the median survival of patients with serum level of YKL-40 ≤168 ng/ml was 2.4-fold longer than patients with its levels >168 ng/ml (95% CI:1.8-4.3, $p=0.00003$). 93% (28 of 30) of the latter cancer populations developed distant metastasis in which patients with liver metastasis demonstrated the highest serum levels of YKL-40 (an average of 230 ng/ml, 96-832 ng/ml). They also reported that high serum levels of YKL-40 were a stronger predictor of survival *vs.* other breast cancer markers such as Her2/*neu* and estrogen receptor (ER), thus serving as an independent, sensitive biomarker. These findings were supported by a different study (Yamac et al., 2008), validating that the serum levels of YKL-40 are a prognostic marker of breast cancer.

In an attempt to determine if testing serum levels of YKL-40 can be utilized to evaluate therapeutic efficacy, Coskun et al. measured serum levels of YKL-40, MMP-2 and MMP-9 in

27 patients with locally metastatic breast cancers after receiving neoadjuvant therapy (5-Fluorouracil, Doxorubicin and Cyclophosphamide) (Coskun et al., 2007). In a subset responsive to these therapies (n=21), the serum levels of YKL-40 were decreased by 26.7% (from an average of 146.4 to 107.3 ng/ml), whereas its serum levels from the non-responsive group (n=6) were unchanged. In contrast, neither MMP-2 nor MMP-9 was altered in these enrolled populations. These data suggest that testing serum levels of YKL-40 informs additional value for directing therapeutic strategies in breast cancer treatment.

Apart from above described potential applications of YKL-40, its serum levels were also implicated in early detection of some cancers including breast and ovarian cancer (Dupont et al., 2004; Qin et al., 2007). For example, Dupont et al. (2004), compared sensitivity of three ovarian cancer biomarkers YKL-40, CA125, CA15-3 in 30 ovarian cancer patients with stage I and II and found that preoperative serum levels of YKL-40, CA125 and CA15-3 were evaluated in 20(65%), 11(35%) and 4(13), respectively, suggesting that YKL-40 was more likely to detect early stages of the cancer than CA125 and CA15-3 ($p=0.039$). In breast cancer, a high incidence (95%) of the cancer was diagnosed in menopausal women at age over 40 when estrogen dramatically declines and the majority of these cancers (60-90%) are estrogen-dependent and responsive to ER-directed therapy, demonstrating a favorable prognosis. But, the population of estrogen-independent patients may be associated with increased levels of YKL-40, based on the findings that YKL-40 expression by cancers was negatively correlated with ER (see below) and serum levels of YKL-40 were more sensitive in prediction of patient survival than ER (Jensen et al., 2003). Therefore, testing serum levels of YKL-40 may hold promise for the early diagnosis of breast cancer, a population that probably predicts worse outcome.

3. Breast Cancer Expression of YKL-40

Analyses of differential gene expression profiling have showed significantly higher expression levels of YKL-40 in carcinoma tissues from breast, ovary and brain than those in adjacent normal tissues, including gene microarray and serial analysis of gene expression (SAGE) (Lal et al., 1999; Lau et al., 2006). Consistent with these data, several independent studies with large cancer cohorts from different laboratories including ours demonstrate that YKL-40 expressed by breast cancer is associated with clinical outcomes (Kim et al., 2007; Roslind et al., 2007b; Shao et al., 2011). Breast cancers at early stages such as ductal carcinoma *in situ* (DCIS) expressed low and medium levels of YKL-40 (Shao et al., 2011). In a survey of 203 cases of infiltrating ductal carcinomas (IDC), we found that 121 of 203 cases (59.6%) exhibited negative or low expression of YKL-40 and 82 patients (40.4%) were YKL-40-positive in which 43 patients (21.1%) displayed strong expression of YKL-40 and 39 patients (19.2%) expressed medium levels of YKL-40 (Shao et al., 2011). Elevated YKL-40 expression was strongly associated with high tumor grade ($p<0.0001$). This population (21.1%) of strong YKL-40-positive cancers was similar to patients containing elevated serum levels of YKL-40 reported previously (20-24% of patients) (Johansen et al., 2003; Johansen et al., 1995), implicating that serum levels of YKL-40 may reflect its strong tissue expression. However, in the study of relationship between tissue levels of YKL-40 and tumor malignancy, we found that cancer tissue expression, contrary to its levels in the blood, was not correlated with distant metastasis, overall survival or disease-free survival in 8-year follow-up studies (Shao et al., 2011). This finding was reinforced by the others surveying 630 breast cancer patients (Roslind et al., 2007b), indicating that testing tissue levels of YKL-40 alone is not sufficient to predict cancer prognosis. YKL-40 levels in cancer were associated with expression of Her2/*neu* ($p<0.01$), but were inversely correlated with ER, progesterone receptor (PR) ($p<0.0001$), GATA3 ($p=0.0137$) and E-cadherin ($p=0.0417$) (Kim et al., 2007;

Shao et al., 2011), suggestive of its association with cancer dedifferentiation. Interestingly, some of their divergent relationships were also reported. For instance, elevated expression of YKL-40 in breast cancer was found to correlate with both positive levels of ER and PR (Roslind et al., 2007b) and short disease-free survival (Kim et al., 2007). The reasons for these discrepancies are still unclear and may be attributed to the different quantification analyses and agents engaged for IHC analysis in cancers (Shao et al. 2011). Nevertheless, all the data demonstrate that expression levels of YKL-40 by cancer tissue are associated with cancer dedifferentiation and other breast cancer markers, which may enhance cancer diagnosis.

4. Pathological Function and Molecular Mechanisms of YKL-40 in Breast Cancer Development

Owing to lack of its chitinase activity, the pathological role of YKL-40 in cancer development is not fully understood. Recently, Chen et al. have reported that a chitin-binding motif located between 325 and 339 amino acid residues at the C terminus of YKL-40 is critical for YKL-40 activities in colonic epithelial cells (Chen et al., 2011a; Chen et al., 2011b). But it needs to be further identified if a single amino acid residue is the key element for YKL-40 function. In breast cancer, evidence from patient's specimens and xenografted animal models has provided new mechanistic insights into YKL-40-induced tumor development (Shao et al., 2009). Cancer tissue expression of YKL-40 from IDC patients was positively correlated with CD34 density, a vascular endothelial cell marker ($p=0.006$). In animal studies, a breast cancer line MDA-MB-231 and a colon cancer line HCT-116 engineered to express ectopic YKL-40 gave rise to four and eightfold larger tumors than ones formed from their corresponding control cells. Accordingly, the levels of blood vasculature formed in YKL-40-expressing HCT-116 and MDA-MB-231 tumors were 1.8 to 2.0-fold greater than those in control tumors, demonstrating that YKL-40 acts as an angiogenic factor to promote tumor development. Such angiogenic signature of YKL-40 was also validated in glioblastoma, the most lethal primary brain tumor characterized by strong vascularization (Francescone et al. 2011). Furthermore, YKL-40 is appreciated to regulate VEGF production in glioblastomas, thus synergistically enhancing tumor angiogenesis.

In concert with these findings *in vivo*, YKL-40 is able to induce endothelial cell migration and tube formation *in vitro* (Malinda et al., 1999). The molecular mechanisms underlying YKL-40-induced angiogenesis involve the co-activation of membrane receptor syndecan-1 and integrin $\alpha_v\beta_3$ through binding to heparan sulfate that is present in syndecan-1 on the cell surface (Shao et al., 2009). YKL-40 activates intracellular signaling effectors focal adhesion kinase (FAK) and MAP Kinase that mediate endothelial cell adhesion and motility. Although membrane receptors specific for YKL-40 binding have not yet been identified, the heparin-binding affinity of YKL-40 appears to be essential for its activity, resembling the heparin-binding property of other proteins such as the extracellular matrix protein vitronectin and angiogenic factors bFGF and VEGF (Beauvais et al., 2004; Bernfield et al., 1999; Shao et al., 2009).

In addition to the ability of YKL-40 to drive tumor vessel formation, YKL-40 directly enhances tumor cell mobility and invasiveness. For instance, YKL-40, induced by transcription factors NFI-X3 and STAT3, promotes glioma cell migration and invasion (Singh et al., 2011). YKL-40 up-regulates other tumor-promoting factors (*e.g.* MMP-2) that participate in tumor metastasis (Ku et al., 2011). In addition, YKL-40 also demonstrates the capability of stimulating inflammatory mediators such as C-chemokine ligand 2(CCL2) and chemokine

CX motif ligand 2(CXCL2) from splenic macrophages; thereby, enhancing tumor metastasis in xenotransplanted animal models (Libreros et al., 2012).

5. YKL-40 Blockade Potential for Therapeutic Application

To date, little is known about specific inhibition of YKL-40's function. A key barrier of inhibitory approaches is insufficient knowledge about functional domain(s) of YKL-40. We recently developed a neutralizing anti-YKL-40 antibody (named mAY) from mice immunized against recombinant YKL-40 (Faibish et al., 2011). mAY markedly suppressed YKL-40-induced angiogenesis both in cultured cells and xenografted animal models. In addition, mAY abolished YKL-40-induced activation of membrane receptor VEGF receptor 2 (Flk-1/KDR) and intracellular signaling MAP kinase Erk 1 and Erk 2 in vascular endothelial cells. mAY was also found to facilitate death response of tumor cells U87 to γ-irradiation through decreased expression of pAKT and AKT. Such pre-clinical studies offered therapeutic promise for the possible development of a humanized anti-YKL-40 antibody in treatment of advanced breast cancers. YKL-40 gene knockdown is another YKL-40-directed approach to suppressing YKL-40 expression (Ku et al., 2011; Zhang et al., 2010). Tumor cells expressing YKL-40 siRNA abrogated tumor angiogenesis and tumor growth *in vivo* (Shao et al., 2009). In order to eliminate YKL-40 action, Iragavarapu-Charyulu's group utilized a YKL-40 ligand chitin to bind YKL-40 and found that treatment of mammary tumor-bearing mice with chitin suppressed lung metastasis (Libreros et al., 2012). Other alternative approaches that block YKL-40 signaling pathways may also suffice to prevent YKL-40 activity or be synergistic in conjunction therapies with YKL-40-directed inhibitors, which remains to be explored. A number of neutralizing antibodies or small molecules are available for possible blockade of signaling pathways employed by YKL-40 such as monoclonal anti-integrins $\alpha v\beta 3$ (LM609) or $\alpha v\beta 5$ (P1F6) antibodies, MAPK inhibitor SU1498, and/or AKT inhibitor GSK690693. Some of these inhibitors have demonstrated the ability to inhibit YKL-40-induced angiogenesis *in vitro* (Shao et al., 2009), but their therapeutic efficacies have not been yet validated in tumor models *in vivo*.

6. Future Challenges

Elevated serum levels of YKL-40 are not limited in cancers; instead, they are also involved in a vast array of other diseases including: chronic inflammation (Johansen, 2006), type 2 diabetes (Persson et al., 2011), obesity and insulin resistance in children (Kyrgios et al., 2011), Alzheimers' diseases (Perrin et al., 2011), heart failure (Harutyunyan et al., 2011) and other cardiovascular disorders (Kjaergaard et al., 2010), liver injury and hepatitis (Fontana et al., 2010) and lung cystic fibrosis (Lee et al., 2011). These findings suggest that YKL-40 may also serve as a diagnostic biomarker for these diseases as well. However, there are many unsolved questions remaining to be addressed, as YKL-40 may mediate pathogenesis of these diseases. First, it is unknown whether YKL-40 functions identically or distinctively in different diseases, as we currently don't understand mechanistically the common event of why YKL-40 is elevated in these individual diseases. Second, in breast cancer, little is known whether tissue expression of YKL-40 contributes to its serum levels, as its expression by breast cancer cells, in contrast to its serum levels, was not correlated with cancer metastasis and short survival. In cancer microenvironment, infiltrating leukocytes, in addition to cancer cells, may also contribute to its serum concentrations. It would be quite interesting to know whether there is an intimate association between tissue expression levels and serum concentrations of YKL-40 in the same cancer patients, and whether leukocytes are the primary determinator of serum levels of YKL-40. Genetic impacts in its tissue expression and

serum levels should be taken into account as well because several independent studies have unveiled their close relationship in different diseases. For instance, a promoter single nucleotide polymorphism (SNP) (-131→G) is positively correlated with serum levels of YKL-40 ($P=1.1x10^{-13}$), asthma (P=0.047) and bronchial hyperresponsiveness (P=0.002) in pulmonary diseases (Ober et al., 2008). Likewise, the SNP (-131→G) is also associated with the severity of hepatitis C virus-induced liver fibrosis (Berres et al., 2009). Agreed with these reports, varied levels of YKL-40 in individual benign breast tissue (Figure 1A) may also implicate the genetic influence in its distinct expression patterns. Interestingly, similar investigation of this SNP in glioblastomas demonstrated no significant correlation with patient survival (Boisselier et al., 2009). In addition to this relationship required to be established in breast cancer, it is urgent to add significant efforts to identify pathologic role(s) of YKL-40 in breast cancer metastasis and malignancy, based on our current knowledge of YKL-40 in endothelial cell angiogenesis. Third, regulation of YKL-40 gene expression in breast cancer development is largely undefined. Understanding its regulation at transcriptional and translational levels will give rise to therapeutic value in impeding its expression, thus reducing its activity. Fourth, it is still enigmatic if YKL-40 also stimulates angiogenesis in the development of normal mammary gland, as different levels of YKL-40 were observed in normal tissue. It remains to be explored if distinct microenvironment and/or cues present in normal *vs.* abnormal breast tissue contribute to its diverse functions. Such studies will enhance our understanding of different functional roles of YKL-40 in normal mammary tissue and carcinomas. Finally, one of the most challenging research approaches is to identify membrane receptor(s) specific for YKL-40 binding, which would not only provide new mechanistic insights into YKL-40's actions, but also establish proof-of-principle for offering a novel mechanistically-directed target for treatment of a number of cancers as well as other types of diseases.

The neutralizing anti-YKL-40 antibody mAY may hold therapeutic promise; thus, it can be anticipated that development of a humanized anti-YKL-40 antibody will pave a novel therapeutic avenue for anti-angiogenic therapy in cancer patients. In particular, blockade of YKL-40-induced tumor angiogenesis may benefit patients that are resistant to other anti-angiogenic drugs or develop angiogenic rebound following anti-angiogenic therapies. There is growing evidence showing that the benefits of anti-angiogenic agents (*e.g.* sunitinib, an anti-VEGF receptor kinase inhibitor and bevacizumab, an anti-VEGF antibody) appear to be transitory in the treatment of several types of advanced cancers, as drug resistance, tumor regrowth and extensive vascular recovery rapidly develop once the therapy is terminated (Bergers and Hanahan, 2008; Burstein et al., 2008; Verhoeff et al., 2009; Wick et al., 2010). In line with these clinical trials, treatment of xenografted models with an anti-VEGF receptor 2 antibody unexpectedly resulted in extensive tumor revascularization, increased invasiveness and rapidly ectopic dissemination (Casanovas et al., 2005; Paez-Ribes et al., 2009). In addition, a short-term therapy with sunitnib, AG-013736 or AG-028262 (VEGF receptor inhibitors) and SU11248 (VEGF and platelet-derived growth factor receptor kinase inhibitor) accelerated local tumor invasion and multiple distant metastases after intravenous injection of tumor cells or removal of primary tumors (Ebos et al., 2009; Mancuso et al., 2006). This immediately acquired adaption to the anti-angiogenic therapies is realized to be associated with a distinct angiogenic switch by which tumors undergo robust revascularization and malignant transformation. It is also noteworthy that bevacizumab has recently been removed by the Food and Drug Administration from monotreatment of metastatic breast cancers. Therefore, it should be taken into account for alternative anti-angiogenic therapy in breast cancer in the future such as an anti-YKL-40 antibody.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

Badariotti, F., Kypriotou, M., Lelong, C., Dubos, M.P., Renard, E., Galera, P., Favrel, P. (2006). The phylogenetically conserved molluscan chitinase-like protein 1 (Cg-Clp1), homologue of human HC-gp39, stimulates proliferation and regulates synthesis of extracellular matrix components of mammalian chondrocytes. Journal of Biological Chemistry, 281, 29583-29596.

Beauvais, D.M., Burbach, B.J., Rapraeger, A.C. (2004). The syndecan-1 ectodomain regulates alphavbeta3 integrin activity in human mammary carcinoma cells. Journal of Cell Biology, 167, 171-181.

Bergers, G., Hanahan, D. (2008). Modes of resistance to anti-angiogenic therapy. Nature Reviews Cancer, 8, 592-603.

Bergmann, O.J., Johansen, J.S., Klausen, T.W., Mylin, A.K., Kristensen, J.S., Kjeldsen, E., Johnsen, H.E. (2005). High serum concentration of YKL-40 is associated with short survival in patients with acute myeloid leukemia. Clinical Cancer Research, 11, 8644-8652.

Bernfield, M., Gotte, M., Park, P.W., Reizes, O., Fitzgerald, M.L., Lincecum, J., Zako, M. (1999). Functions of cell surface heparan sulfate proteoglycans. Annual Review of Biochemistry, 68, 729-777.

Berres, M.L., Papen, S., Pauels, K., Schmitz, P., Zaldivar, M.M., Hellerbrand, C., Mueller, T., Berg, T., Weiskirchen, R., Trautwein, C. et al. (2009). A functional variation in CHI3L1 is associated with severity of liver fibrosis and YKL-40 serum levels in chronic hepatitis C infection. Journal of Hepatology, 50, 370-376.

Boisselier, B., Marie, Y., El Hallani, S., Kaloshi, G., Iershov, A., Kavsan, V., Psimaras, D., Thillet, J., Hoang-Xuan, K., Delattre, J.Y. et al. (2009). No association of (-131C-->G) variant of CHI3L1 gene with risk of glioblastoma and prognosis. Journal of Neuro-Oncology, 94, 169-172.

Bonneh-Barkay, D., Wang, G., Starkey, A., Hamilton, R.L., Wiley, C.A. (2011). In vivo CHI3L1 (YKL-40) expression in astrocytes in acute and chronic neurological diseases. Journal of neuroinflammation, 7, 34.

Burstein, H.J., Elias, A.D., Rugo, H.S., Cobleigh, M.A., Wolff, A.C., Eisenberg, P.D., Lehman, M., Adams, B.J., Bello, C.L., DePrimo, S.E. et al. (2008). Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of Clinical Oncology, 26, 1810-1816.

Casanovas, O., Hicklin, D.J., Bergers, G., Hanahan, D. (2005). Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. In Cancer Cell, 299-309.

Chen, C.C., Llado, V., Eurich, K., Tran, H.T., Mizoguchi, E. (2011a). Carbohydrate-binding motif in chitinase 3-like 1 (CHI3L1/YKL-40) specifically activates Akt signaling pathway in colonic epithelial cells. Clinical Immunology (Orlando, Fla), 140, 268-275.

Chen, C.C., Pekow, J., Llado, V., Kanneganti, M., Lau, C.W., Mizoguchi, A., Mino-Kenudson, M., Bissonnette, M., Mizoguchi, E. (2011b). Chitinase 3-like-1 expression in colonic epithelial cells as a potentially novel marker for colitis-associated neoplasia. The American Journal of Pathology, 179, 1494-1503.

Cintin, C., Johansen, J.S., Christensen, I.J., Price, P.A., Sorensen, S., Nielsen, H.J. (1999). Serum YKL-40 and colorectal cancer. British Journal of Cancer, 79, 1494-1499.

Cintin, C., Johansen, J.S., Christensen, I.J., Price, P.A., Sorensen, S., Nielsen, H.J. (2002). High serum YKL-40 level after surgery for colorectal carcinoma is related to short survival. Cancer, 95, 267-274.

Coskun, U., Yamac, D., Gulbahar, O., Sancak, B., Karaman, N., Ozkan, S. (2007). Locally advanced breast carcinoma treated with neoadjuvant chemotherapy: are the changes in serum levels of YKL-40, MMP-2 and MMP-9 correlated with tumor response? Neoplasma, 54, 348-352.

De Ceuninck, F., Gaufillier, S., Bonnaud, A., Sabatini, M., Lesur, C., Pastoureau, P. (2001). YKL-40 (cartilage gp-39) induces proliferative events in cultured chondrocytes and synoviocytes and increases glycosaminoglycan synthesis in chondrocytes. Biochemical & Biophysical Research Communications, 285, 926-931.

Debnath, J., Muthuswamy, S.K., Brugge, J.S. (2003). Morphogenesis and oncogenesis of MCF-10A mammary epithelial acini grown in three-dimensional basement membrane cultures. Methods (Duluth), 30, 256-268.

Dupont, J., Tanwar, M.K., Thaler, H.T., Fleisher, M., Kauff, N., Hensley, M.L., Sabbatini, P., Anderson, S., Aghajanian, C., Holland, E.C. et al. (2004). Early detection and prognosis of ovarian cancer using serum YKL-40. Journal of Clinical Oncology, 22, 3330-3339.

Ebos, J.M., Lee, C.R., Cruz-Munoz, W., Bjarnason, G.A., Christensen, J.G., Kerbel, R.S. (2009). Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. [see comment]. Cancer Cell, 15, 232-239.

Faibish, M., Francescone, R., Bentley, B., Yan, W., Shao, R. (2011). A YKL-40-neutralizing antibody blocks tumor angiogenesis and progression: a potential therapeutic agent in cancers. Molecular Cancer Therapeutics, 10, 742-751.

Fontana, R.J., Dienstag, J.L., Bonkovsky, H.L., Sterling, R.K., Naishadham, D., Goodman, Z.D., Lok, A.S., Wright, E.C., Su, G.L. (2010). Serum fibrosis markers are associated with liver disease progression in non-responder patients with chronic hepatitis C. Gut, 59, 1401-1409.

Fontana, R.J., Litman, H.J., Dienstag, J.L., Bonkovsky, H.L., Su, G., Sterling, R.K., Lok, A.S. (2011). YKL-40 genetic polymorphisms and the risk of liver disease progression in patients with advanced fibrosis due to chronic hepatitis C. Liver Int., 32, 665-674.

Francescone, R.A., Scully, S., Faibish, M., Taylor, S.L., Oh, D., Moral, L., Yan, W., Bentley, B., Shao, R. (2011). Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. The Journal of Biological Chemistry, 286, 15332-15343.

Fusetti, F., Pijning, T., Kalk, K.H., Bos, E., Dijkstra, B.W. (2003). Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. Journal of Biological Chemistry, 278, 37753-37760.

Hakala, B.E., White, C., Recklies, A.D. (1993). Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. Journal of Biological Chemistry, 268, 25803-25810.

Harutyunyan, M., Christiansen, M., Johansen, J.S., Kober, L., Torp-Petersen, C., Kastrup, J. (2011). The inflammatory biomarker YKL-40 as a new prognostic marker for all-cause mortality in patients with heart failure. Immunobiology, in press.

Hennighausen, L., Robinson, G.W. (2001). Signaling pathways in mammary gland development. Developmental Cell, 1, 467-475.

Hogdall, E.V., Johansen, J.S., Kjaer, S.K., Price, P.A., Christensen, L., Blaakaer, J., Bock, J.E., Glud, E., Hogdall, C.K. (2003). High plasma YKL-40 level in patients with ovarian cancer stage III is related to shorter survival. Oncology Reports, 10, 1535-1538.

Hottinger, A.F., Iwamoto, F.M., Karimi, S., Riedel, E., Dantis, J., Park, J., Panageas, K.S., Lassman, A.B., Abrey, L.E., Fleisher, M. et al. (2011). YKL-40 and MMP-9 as serum markers for patients with primary central nervous system lymphoma. Annals of Neurology, 70, 163-169.

Hu, B., Trinh, K., Figueira, W.F., Price, P.A. (1996). Isolation and sequence of a novel human chondrocyte protein related to mammalian members of the chitinase protein family. Journal of Biological Chemistry, 271, 19415-19420.

Jensen, B.V., Johansen, J.S., Price, P.A. (2003). High levels of serum HER-2/neu and YKL-40 independently reflect aggressiveness of metastatic breast cancer. Clinical Cancer Research, 9, 4423-4434.

Johansen, J.S. (2006). Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodeling, fibroses and cancer. Danish Medical Bulletin, 53, 172-209.

Johansen, J.S., Christensen, I.J., Riisbro, R., Greenall, M., Han, C., Price, P.A., Smith, K., Brunner, N., Harris, A.L. (2003). High serum YKL-40 levels in patients with primary breast cancer is related to short recurrence free survival. Breast Cancer Research & Treatment, 80, 15-21.

Johansen, J.S., Christoffersen, P., Moller, S., Price, P.A., Henriksen, J.H., Garbarsch, C., Bendtsen, F. (2000). Serum YKL-40 is increased in patients with hepatic fibrosis. Journal of Hepatology, 32, 911-920.

Johansen, J.S., Cintin, C., Jorgensen, M., Kamby, C., Price, P.A. (1995). Serum YKL-40: a new potential marker of prognosis and location of metastases of patients with recurrent breast cancer. European Journal of Cancer, 31A, 1437-1442.

Johansen, J.S., Drivsholm, L., Price, P.A., Christensen, I.J. (2004). High serum YKL-40 level in patients with small cell lung cancer is related to early death. Lung Cancer, 46, 333-340.

Johansen, J.S., Schultz, N.A., Jensen, B.V. (2009). Plasma YKL-40: a potential new cancer biomarker? Future Oncology, 5, 1065-1082.

Johansen, J.S., Williamson, M.K., Rice, J.S., Price, P.A. (1992). Identification of proteins secreted by human osteoblastic cells in culture. Journal of Bone & Mineral Research, 7, 501-512.

Kawamura, K., Shibata, T., Saget, O., Peel, D., Bryant, P.J. (1999). A new family of growth factors produced by the fat body and active on Drosophila imaginal disc cells. Development, 126, 211-219.

Kim, S.H., Das, K., Noreen, S., Coffman, F., Hameed, M. (2007). Prognostic implications of immunohistochemically detected YKL-40 expression in breast cancer. World Journal of Surgical Oncology, 5, 17.

Kjaergaard, A.D., Bojesen, S.E., Johansen, J.S., Nordestgaard, B.G. (2010). Elevated plasma YKL-40 levels and ischemic stroke in the general population. Annals of Neurology, 68, 672-680.

Kronborg, G., Ostergaard, C., Weis, N., Nielsen, H., Obel, N., Pedersen, S.S., Price, P.A., Johansen, J.S. (2002). Serum level of YKL-40 is elevated in patients with Streptococcus pneumoniae bacteremia and is associated with the outcome of the disease. Scandinavian Journal of Infectious Diseases, 34, 323-326.

Ku, B.M., Lee, Y.K., Ryu, J., Jeong, J.Y., Choi, J., Eun, K.M., Shin, H.Y., Kim, D.G., Hwang, E.M., Yoo, J.C. et al. (2011). CHI3L1 (YKL-40) is expressed in human gliomas and regulates the invasion, growth and survival of glioma cells. Int J Cancer, 128, 1316-1326.

Kucur, M., Isman, F.K., Balci, C., Onal, B., Hacibekiroglu, M., Ozkan, F., Ozkan, A. (2008). Serum YKL-40 levels and chitotriosidase activity as potential biomarkers in primary prostate cancer and benign prostatic hyperplasia. Urologic Oncology, 26, 47-52.

Kyrgios, I., Galli-Tsinopoulou, A., Stylianou, C., Papakonstantinou, E., Arvanitidou, M., Haidich, A.B. (2011). Elevated circulating levels of the serum acute-phase protein YKL-40 (chitinase 3-like protein 1) are a marker of obesity and insulin resistance in prepubertal children. Metabolism: Clinical and Experimental, in press.

Kzhyshkowska, J., Gratchev, A., Goerdt, S. (2007). Human chitinases and chitinase-like proteins as indicators for inflammation and cancer. Biomarker Insights, 2, 128-146.

Lal, A., Lash, A.E., Altschul, S.F., Velculescu, V., Zhang, L., McLendon, R.E., Marra, M.A., Prange, C., Morin, P.J., Polyak, K. et al. (1999). A public database for gene expression in human cancers. Cancer Res, 59, 5403-5407.

Lau, S.H., Sham, J.S., Xie, D., Tzang, C.H., Tang, D., Ma, N., Hu, L., Wang, Y., Wen, J.M., Xiao, G. et al. (2006). Clusterin plays an important role in hepatocellular carcinoma metastasis. Oncogene, 25, 1242-1250.

Lee, C.G., Da Silva, C.A., Dela Cruz, C.S., Ahangari, F., Ma, B., Kang, M.J., He, C.H., Takyar, S., Elias, J.A. (2011). Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling and injury. Annual Review of Physiology, 73, 479-501.

Lee, C.G., Hartl, D., Lee, G.R., Koller, B., Matsuura, H., Da Silva, C.A., Sohn, M.H., Cohn, L., Homer, R.J., Kozhich, A.A. et al. (2009). Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. The Journal of Experimental Medicine, 206, 1149-1166.

Lee, G.Y., Kenny, P.A., Lee, E.H., Bissell, M.J. (2007). Three-dimensional culture models of normal and malignant breast epithelial cells. Nature Methods, 4, 359-365.

Lian, Z., De Luca, P., Di Cristofano, A. (2006). Gene expression analysis reveals a signature of estrogen receptor activation upon loss of Pten in a mouse model of endometrial cancer. Journal of Cellular Physiology, 208, 255-266.

Libreros, S., Garcia-Areas, R., Shibata, Y., Carrio, R., Torroella-Kouri, M., Iragavarapu-Charyulu, V. (2012). Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: Decreased tumor metastasis in a breast cancer model. Int J Cancer, in press.

Malinda, K.M., Ponce, L., Kleinman, H.K., Shackelton, L.M., Millis, A.J. (1999). Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Experimental Cell Research, 250, 168-173.

Mancuso, M.R., Davis, R., Norberg, S.M., O'Brien, S., Sennino, B., Nakahara, T., Yao, V.J., Inai, T., Brooks, P., Freimark, B. et al. (2006). Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Journal of Clinical Investigation, 116, 2610-2621.

Mohanty, A.K., Singh, G., Paramasivam, M., Saravanan, K., Jabeen, T., Sharma, S., Yadav, S., Kaur, P., Kumar, P., Srinivasan, A. et al. (2003). Crystal structure of a novel regulatory 40-kDa mammary gland protein (MGP-40) secreted during involution. Journal of Biological Chemistry, 278, 14451-14460.

Nielsen, K.R., Steffensen, R., Boegsted, M., Baech, J., Lundbye-Christensen, S., Hetland, M.L., Krintel, S.B., Johnsen, H.E., Nyegaard, M., Johansen, J.S. (2011). Promoter polymorphisms in the chitinase 3-like 1 gene influence the serum concentration of YKL-40 in Danish patients with rheumatoid arthritis and in healthy subjects. Arthritis Research & Therapy, 13, R109.

Nyirkos, P., Golds, E.E. (1990). Human synovial cells secrete a 39 kDa protein similar to a bovine mammary protein expressed during the non-lactating period. Biochemical Journal, 269, 265-268.

Ober, C., Tan, Z., Sun, Y., Possick, J.D., Pan, L., Nicolae, R., Radford, S., Parry, R.R., Heinzmann, A., Deichmann, K.A. et al. (2008). Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. New England Journal of Medicine, 358, 1682-1691.

Paez-Ribes, M., Allen, E., Hudock, J., Takeda, T., Okuyama, H., Vinals, F., Inoue, M., Bergers, G., Hanahan, D., Casanovas, O. (2009). Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. [see comment]. Cancer Cell, 15, 220-231.

Park, J.A., Drazen, J.M., Tschumperlin, D.J. (2010). The chitinase-like protein YKL-40 is secreted by airway epithelial cells at base line and in response to compressive mechanical stress. The Journal of Biological Chemistry, 285, 29817-29825.

Pelloski, C.E., Mahajan, A., Maor, M., Chang, E.L., Woo, S., Gilbert, M., Colman, H., Yang, H., Ledoux, A., Blair, H. et al. (2005). YKL-40 expression is associated with poorer response to radiation and shorter overall survival in glioblastoma. Clinical Cancer Research, 11, 3326-3334.

Perrin, R.J., Craig-Schapiro, R., Malone, J.P., Shah, A.R., Gilmore, P., Davis, A.E., Roe, C.M., Peskind, E.R., Li, G., Galasko, D.R. et al. (2011). Identification and validation of novel cerebrospinal fluid biomarkers for staging early Alzheimer's disease. PloS One, 6, e16032.

Persson, F., Rathcke, C.N., Gall, M.A., Parving, H.H., Vestergaard, H., Rossing, P. (2011). High YKL-40 levels predict mortality in patients with type 2 diabetes. Diabetes Research and Clinical Practice, in press.

Pizano-Martinez, O., Yanez-Sanchez, I., Alatorre-Carranza, P., Miranda-Diaz, A., Ortiz-Lazareno, P.C., Garcia-Iglesias, T., Daneri-Navarro, A., Vazquez-Del Mercado, M., Fafutis-Morris, M., Delgado-Rizo, V. (2011). YKL-40 expression in CD14 liver cells in acute and chronic injury. World J Gastroenterol, 17, 3830-3835.

Qin, W., Zhu, W., Schlatter, L., Miick, R., Loy, T.S., Atasoy, U., Hewett, J.E., Sauter, E.R. (2007). Increased expression of the inflammatory protein YKL-40 in precancers of the breast. Int J Cancer, 121, 1536-1542.

Recklies, A.D., White, C., Ling, H. (2002). The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. Biochemical Journal, 365, 119-126.

Rehli, M., Krause, S.W., Andreesen, R. (1997). Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation. Genomics, 43, 221-225.

Rejman, J.J., Hurley, W.L. (1988). Isolation and characterization of a novel 39 kilodalton whey protein from bovine mammary secretions collected during the nonlactating period. Biochemical & Biophysical Research Communications, 150, 329-334.

Renkema, G.H., Boot, R.G., Au, F.L., Donker-Koopman, W.E., Strijland, A., Muijsers, A.O., Hrebicek, M., Aerts, J.M. (1998). Chitotriosidase, a chitinase, and the 39-kDa human cartilage glycoprotein, a chitin-binding lectin, are homologues of family 18 glycosyl hydrolases secreted by human macrophages. European Journal of Biochemistry, 251, 504-509.

Roslind, A., Johansen, J.S., Junker, N., Nielsen, D.L., Dzaferi, H., Price, P.A., Balslev, E. (2007a). YKL-40 expression in benign and malignant lesions of the breast: a methodologic study. Applied Immunohistochemistry & Molecular Morphology, 15, 371-381.

Roslind, A., Knoop, A.S., Jensen, M.B., Johansen, J.S., Nielsen, D.L., Price, P.A., Balslev, E. (2007b). YKL-40 protein expression is not a prognostic marker in patients with primary breast cancer. Breast Cancer Research and Treatment, 112, 275-85.

Russo, J., Tay, L.K., Russo, I.H. (1982). Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Research & Treatment, 2, 5-73.

Scully, S., Yan, W., Bentley, B., Cao, Q.J., Shao, R. (2011). Inhibitory Activity of YKL-40 in Mammary Epithelial Cell Differentiation and Polarization Induced by Lactogenic Hormones: A Role in Mammary Tissue Involution. PloS One, 6, e25819.

Shackelton, L.M., Mann, D.M., Millis, A.J. (1995). Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. Journal of Biological Chemistry, 270, 13076-13083.

Shao, R., Cao, Q.J., Arenas, R.B., Bigelow, C., Bentley, B., Yan, W. (2011). Breast cancer expression of YKL-40 correlates with tumour grade, poor differentiation, and other cancer markers. Br J Cancer, 105, 1203-1209.

Shao, R., Hamel, K., Petersen, L., Cao, Q.J., Arenas, R.B., Bigelow, C., Bentley, B., Yan, W. (2009). YKL-40, a secreted glycoprotein, promotes tumor angiogenesis. Oncogene, 28, 4456-4468.

Singh, S.K., Bhardwaj, R., Wilczynska, K.M., Dumur, C.I., Kordula, T. (2011). A complex of nuclear factor I-X3 and STAT3 regulates astrocyte and glioma migration through the secreted glycoprotein YKL-40. The Journal of Biological Chemistry, 286, 39893-39903.

Vallorosi, C.J., Day, K.C., Zhao, X., Rashid, M.G., Rubin, M.A., Johnson, K.R., Wheelock, M.J., Day, M.L. (2000). Truncation of the beta-catenin binding domain of E-cadherin precedes epithelial apoptosis during prostate and mammary involution. Journal of Biological Chemistry, 275, 3328-3334.

Verhoeff, J.J., van Tellingen, O., Claes, A., Stalpers, L.J., van Linde, M.E., Richel, D.J., Leenders, W.P., van Furth, W.R. (2009). Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme. BMC Cancer, 9, 444.

Vind, I., Johansen, J.S., Price, P.A., Munkholm, P. (2003). Serum YKL-40, a potential new marker of disease activity in patients with inflammatory bowel disease. Scandinavian Journal of Gastroenterology, 38, 599-605.

Volck, B., Johansen, J.S., Stoltenberg, M., Garbarsch, C., Price, P.A., Ostergaard, M., Ostergaard, K., Lovgreen-Nielsen, P., Sonne-Holm, S., Lorenzen, I. (2001). Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. Osteoarthritis & Cartilage, 9, 203-214.

Wick, W., Weller, M., van den Bent, M., Stupp, R. (2010). Bevacizumab and recurrent malignant gliomas: a European perspective. Journal of Clinical Oncology, 28, e188-189; Author Reply, e190-182.

Xian, W., Schwertfeger, K.L., Vargo-Gogola, T., Rosen, J.M. (2005). Pleiotropic effects of FGFR1 on cell proliferation, survival and migration in a 3D mammary epithelial cell model. Journal of Cell Biology, 171, 663-673.

Yamac, D., Ozturk, B., Coskun, U., Tekin, E., Sancak, B., Yildiz, R., Atalay, C. (2008). Serum YKL-40 levels as a prognostic factor in patients with locally advanced breast cancer. Advances in Therapy, 25, 801-809.

Yamada, M., Murakami, K., Wallingford, J.C., Yuki, Y. (2002). Identification of low-abundance proteins of bovine colostral and mature milk using two-dimensional electrophoresis followed by microsequencing and mass spectrometry. Electrophoresis, 23, 1153-1160.

Zhang, W., Murao, K., Zhang, X., Matsumoto, K., Diah, S., Okada, M., Miyake, K., Kawai, N., Fei, Z., Tamiya, T. (2010). Resveratrol represses YKL-40 expression in human glioma U87 cells. BMC Cancer, 10, 593.