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Expression of YKL-40, an Inflammatory Glycoprotein and its Prognostic Implications in Cancer

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Abstract

A cancer prognosticator refers to a substance or process that is a sign of the existence of cancer in the body and foretelling the course of cancer. It might be either a molecule oozed by a tumor or it can be a specific response of the body to the occurrence of cancer. YKL-40 is an inflammatory glycoprotein and a member of mammalian chitanase-like proteins (CHI3L1), is expressed and secreted by several types of solid tumor cells, inflammatory cells and stem cells. The precise physiological role of YKL-40 in cancer is not still clear and suggested that it has a role in cancer cell proliferation, differentiation, metastatic potential, cell attachment and migration, reorganization and tissue remodeling. Several clinical studies of patients with diverse types of cancer indicated that elevated serum level of YKL-40 may be a prognostic marker of cancer. The higher level of YKL-40 in serum also seems to correlate with short survival and poorer prognosis of several cancers including breast, ovary, colorectal, and glioblastoma melanoma. Serum YKL-40 level is often elevated compared to healthy subjects, in patients with disease characterized by inflammation, and increased extracellular remodeling or ongoing fibrosis such as infections. This review depict the present facts regarding YKL-40 and talk about its relation in cancer prediction.

Keywords: YKL-40; Cancer; Prognostic implication; Prognosticator; Inflammatory; Glycoprotein

Introduction

As said by the US national cancer institute "cancer" is the term mainly applied for diseases where in uncharacteristic cells split without control and are able to attack on other tissues, Cancer cells can mushroom to other parts of the body via blood and lymph tissues. Using statistics from the World Health Organization (WHO), it summarized that cancer has a bigger fiscal crash from premature death and disability than all reasons of death worldwide; it has the largest disturbing economic impact of any reason of death. The World Health Organization has long envisaged that cancer would surpass heart disease this year as the maximum death causing disorder. Around 7.6 million people departed their life from the cancer in 2008, and approximately 12.4 million most recent cases are solved per annum. Now cancer has come out as a major health crisis of the people in developing countries and it is estimated that there will be 16 million new cases every year by 2020 [1].

The major challenges in current cancer research are the discovery and justification of biomarkers that could be used to detect the initial stages of cancer whilst its development, to go after the succession or failure of cancer [2]. The cancer prognosticator or prognostic marker is the substance or process foretelling the course of cancer or might be either a molecule released by a tumor or it can be a specific comeback of the body to the occurrence of cancer [3].

YKL-40 or CH3L1 is a 40 kD glycosylated chitinase like glycoprotein secreted by some specific *in vivo* cancers cells, several *ex vivo* cancer cell lines, few non-cancer cells contiguous to some cancers, propagated chondrocytes, 'mature' macrophages and neutrophils, initially reported in whey proteins of non-lactating cows. The name YKL-40 is based on its three N-terminal amino acids Tyrosine (Y), Lysine (K) and Leucine (L) and 40 kDa of its molecular mass [4]. Human YKL-40 contain only one polypeptide chain of 383 amino acids and the molecular mass of about 40,476 Da [5]. The isoelectric point of YKL-40 is 7.6 [6] and sequence analysis of the amino acids of YKL-40 describes about chitinase (glycosyl hydrolase) protein family 18 [7] but does not has chitinase like glycosyl hydrolase activity. The protein has so many names such as: "YKL-40" [7], "Human Cartilage glycoprotein-39 (HC gp39)" [4], "Breast regressing protein 39 kDa (brp 39)", "38 kDa heparin-binding glycoprotein (gp38k)" [8], "Chitinase-3-like-1 (CHI3L1)", "Chondrex", and "40 kDa mammary gland protein (MGP-40)".

Role of YKL-40

YKL-40 is an inflammatory marker and it is suggested that YKL-40 is a secreted protein and the sites of actions are most likely to be extracellular [9-11]. Till today no specific cell-surface or soluble receptors for YKL-40 have been identified. The role of YKL-40 in cancer cells is still unclear [3], but several promising functions have been proposed.

Activation of Ras/Raf Signaling Pathways

The study by a group of researchers suggested, YKL-40 may play a role in the regulation of Ras/Map kinase pathway or Ras/Raf/MEK/ERK cascade (Figure 1), one of the best-studied signal transduction pathways connected with the control of mitogenesis [12,13]. It is most importantly concerned in the conduction of anti-apoptotic and mitogenic signals as it communicates information initiating from membrane receptors to transcription factors, having over gene expression power. Ras is all over expressed and often mutated in human cancer and it is a first oncogene acknowledged as a prospective chemotherapeutic target by pharmaceutical companies [14,15]. It is a small monomeric GTP-binding protein which linked with its

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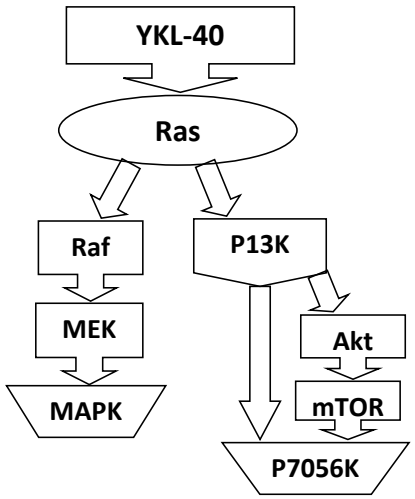

Figure1: Activation of Ras signaling pathways.

downstream intermediate in their GTP-bound form, in some cases known as Raf.

Antiapoptotic Protein

Through the phosphorylation of both the extracellular signal-regulated kinase-1/2 mitogen-activated protein kinase and protein kinase B (AKT)-mediated signaling cascades, YKL-40 begins mitogen-activated protein (MAP) kinase and phosphoinositide-3-kinase signaling cascades in fibroblasts [12,13,15]. These are linked with the control of mitogenesis and point out towards the role of YKL-40 as an antiapoptotic protein. The roll of YKL-40 in cell survival is strongly related with the PI-3K pathway, and in particular the phosphorylation of AKT [12].

Growth Properties

The accurate physiological role of YKL-40 is undisclosed, but a short time ago it has been reported that YKL-40 work as a growth factor which encourage the growth of fibroblasts cell lines obtained from human osteoarthritic synovium fetal lung and adult skin, chondrocytes and synovial cells [16]. YKL-40 may also play a physiological role in the embryonic development and in developing mouse heart expression, and agreed with alteration in morphology concerning cell relocation, altered cell adhesion and remodeling signifying a responsibility for YKL-40 in cardiac morphogenesis consistent with its established activities *in vitro* of sustaining cell migration and adhesion [17].

Heparin and Chitin Binding Affinity

On the cell surfaces or in extra cellular matrix YKL-40 may interact with heparin-like molecules. YKL-40 binds heparin with an affinity greater than fibronectin and have a distinct putative heparin-binding site at location 144-147 [8]. Researchers publicized by means of crystallization methods that heparan sulfate is a more plausible physiological ligand of YKL-40 compared to heparin [18]. YKL-40 also has powerful binding affinity for chitin [5,6] and have amino acid sequence which shows high homology to bacterial chitinases [5,19] but YKL-40 is deficient in chitinase activity [5,6,16]. Chito-oligosaccharides bind to YKL-40 with high affinity and could be a physiological ligand for YKL-40, while binding of additional carbohydrate polymers cannot be expelled.

Regulation of YKL-40 Expression

In vivo Expression of YKL-40 has been reported in the subpopulation of macrophages taking part in inflammatory and extracellular matrix (ECM) remodeling processes in different tissues [9,16,20,21]. In human YKL-40 there are two mutations become visible to eliminate the hydrolase activity, both mutation of the catalytic aspartic acid to alanine (A, residue 138) and glutamic acid to leucine (L, residue 140). Human YKL-40 binds chitin of distinctive lengths and in a related fashion as noticed in Family 18 chitinases, although it is not a chitinase [18]. It was found that the Sp1-family transcription factors looks like to control a prevailing role of YKL-40 promoter activity. In macrophages YKL-40 expression is maturity dependent, probably higher while inflammation and infections. Experiments confirmed M1 cytokines/factors amplified YKL-40 expression even as the M2 cytokines/factors did not; attracting results in view of YKL-40 knockout mice were reported defective in Th2 responses [22].

Prognostic Implication and YKL-40 Expression in Various Type of Cancer

YKL-40 or Chitinase 3-like-1 (CHI3L1), belongs to the mammalian chitinase family, and inflammation is a major factor responsible for their induction in some disorders like inflammatory bowel disease, asthma and hepatitis. Furthermore, in some solid tumors including glioblastoma, colon cancer, breast cancer and malignant melanoma, YKL-40 is also expressed and secreted by malignant cells [23,24].

Researchers found that significant higher levels of YKL-40 were observed in patients with gastric cancer compared to healthy individuals ($P<0.0001$). Besides, they showed the major differences in serum YKL-40 levels of male and female patients having gastric cancer ($P<0.01$) [24]. Higher serum level of YKL-40 is a prognosticator of poorer survival of patients with primary and metastatic solid tumors for instance glioblastoma, breast, colorectal, ovary, lung, prostate, squamous cell carcinoma, head and neck cancer and renal cancer [3,9,11,15,25,26].

Clinical correlation in a study showed, the detection of YKL-40 antigen was related with larger tumor size, poorer differentiation of tumor, and a more chances of estrogen and progesterone receptor negativity. Further-more, it was showed that the YKL-40 immuno reactivity related with less disease-free survival in both uni-variate and multivariate analysis [27].

In vitro glioblastoma cell lines studies showed that the expression of YKL-40 mRNA and protein related with the distinct types of stress, and suggesting that YKL-40 play a role as a cellular survival factor [20] (Table 1). YKL-40 may also play a role in proliferation and differentiation of the cancer cells, and may protect the cells undergoing apoptosis, stimulate angiogenesis and remodeling.

Findings recommended that YKL-40 is an upbeat supervisory body in the proliferation and invasiveness of glioma cells. It is also determined that the invasion ability of U87 cells is sharply weakened after the silencing of YKL-40 gene [28].

YKL-40 has been implicated as an intermediary of collagen synthesis and extracellular matrix remodeling as well as mitogenesis. Eminent serum levels of YKL-40 have been related with worse survival in an array of malignancies in addition to breast cancer [15,28]. Raised levels of serum YKL-40 and interleukin 6 (IL-6) are preoccupied markers of inflammation and both were established to be significantly amplified in pretreatment samples from Hodgkin lymphoma cases,

Serum Levels of YKL-40 in Patients with Cancer						
S. No.	**Diagnosis**	**Number of Patients**	**Serum YKL-40 (µg/l)**	**Detection Limit (µg/l)**	**High YKL-40 %**	**References**
1	Gastric Cancer	100	132	20	-	Itik et al., 26
2	Metastatic prostate cancer	153	112	20	43	-
3	Primary Breast Cancer	271	57	22	19	Johansan et al., 15
4	Metastatic breast cancer	54	80	20	41	-
5	Colorectal cancer	324	160	56	62	Cintinn et al., 9
6	Ovarian cancer	473	125	20	67	Hogdall et al., 20
7	Small cell lung cancer	131	82	23	32	Johansan et al., 11
8	Metastatic malignant melanoma	110	95	20	45	Schmidt *et al.,* 29
9	Metastatic renal cell cancer	58	235	45	83	-
10	Squamous Cell carcinoma of Head and neck	144	121	20	53	Roslind et al., 18

Table 1: Serum levels of YKL-40 in patients with cancer.

being 4-fold and 8-fold higher than in healthy age- and sex-matched controls, in that order [29].

YKL-40 is more profuse in GBMs than AOs, is directly secreted by neoplastic cells, and accounts for the preeminent part in high-grade gliomas. An inverse relationship exists between EGFR and YKL-40 in GBMs, even as a straight correlation exists with 10q23 LOH and YKL-40 in AOs. This molecule become visible to be an essential cause in loads of glooms and, as the mechanisms of YKL-40 action and regulation turn into more correctly defined, the significance of this molecule in appreciative of gloom biology will be better understood [30]. With regard to the role of YKL-40 in patients with hepatobiliary malignancies, earlier studies have verified that clusterin, a molecule greatly associated with YKL-40, plays an essential role in the metastasis of HCC. Whether serum YKL-40 has any diagnostic and/or prognostic role in patients with HCC and other hepatobiliary malignancies have not been studied [31].

Conclusion and Future Detection

YKL-40 is an inflammatory glycoprotein belongs to the chitanase family but excludes chitin hydrolase activity because of the mutation in the catalytic glutamic acid to leucine (L, residue 140) and mutation of the aspartic acid to alanine (A, residue 138). Human YKL-40 binds chitin of different lengths and in a similar fashion as seen in family 18 chitinases [18].

The exact physiological role of YKL-40 in cancer is not however clear [3] and recommended that it has a role in cancer cell proliferation, differentiation, metastatic potential, cell attachment and migration, reorganization and tissue remodeling. The clarification of the physiological role of YKL-40 is an important goal of future studies. It has been suggested that YKL-40 play a role in the regulation of Ras/MAP kinase signaling pathway which are connected with the control of mitogenesis [12,13]. This specifies the role of YKL-40 as an anti apoptotic protein.

It is concluded that raised levels of serumYKL-40 are preoccupied markers and prognosticator of poorer survival of patients with solid tumors and other types of cancer disorders, such as glioblastoma, breast, colorectal, ovary, lung, prostate, and renal cancer [3,9,10,11,15,25]. YKL-40 immunoreactivity was also related with larger tumor size, poorer differentiation of tumor, and a more chances of estrogen and progesterone receptor negativity and less disease-free survival [27].

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