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Chapter 8

YKL-40: The Search for New Biomarkers in Rheumatoid Arthritis

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Abstract

There is a need for biomarkers to detect early joint inflammation and destruction of cartilage in different types of arthritis. YKL-40, a 39 kDa heparin- and chitin-binding secreted glycoprotein (also known as human cartilage gp39), has been recently discovered. Its exact biological function is still unclear. Specific receptors for YKL-40 have not been identified yet. The clinical significance of YKL-40 as a biomarker is discussed in different aspects. High level of YKL-40 is found in various human i`nflammatory and neoplastic diseases. We present a review highlighting the information available on YKL-40 and its significance in inflammatory joint diseases, like rheumatoid arthritis (RA). We also report original personal data on the topic concerning YKL-40 levels in serum and synovial fluid of patients with RA in comparison with ultrasonographic parameters and cytokine levels. The findings suggest that YKL-40 might be implicated in the pathogenesis of the disease and could indicate the level of joint inflammation.

Keywords: YKL-40, biomarkers, ultrasonography, cytokines, chitinases

1. Introduction

Identification of new biomarkers would be beneficial for improving biomedical research and drug development. Understanding the relationship between biological processes and clinical outcomes is significant for choosing optimal therapy [1].

A "biomarker" is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" [2]. The acceptance of novel biomarkers in clinical settings requires detailed validation process before they could be used in routine clinical practice.

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Utility of new biomarkers depends on several aspects: whether the method for detection of the biomarker is a specific, sensitive, fast, and affordable, if the level of the biomarker provides new information about the disease, if the concentration of the biomarker could help the patient's treatment [3].

The current review summarizes our investigations and presents evidences for the role of YKL-40 in the diagnosis and prognosis monitoring of rheumatoid arthritis (RA).

2. YKL-40: gene, protein, regulation, and proposed functions

2.1. YKL-40: protein and gene

YKL-40 is a glycoprotein that is encoded by the *CHI3L1* gene and belongs to the mammalian chitinase-like proteins [4].

Chitinases are enzymes that digest chitin, providing cellular and tissue remodeling during homeostasis in fungi, helminths, insects, and crustaceans [5]. Mammals express both enzymatically active chitinases and enzymatically inactive chitinase-like proteins. The exact biologic role of chitinase-like proteins, such as human YKL-40 protein, is still unclear.

YKL-40 was found out in 1989 as the most abundant protein secreted by MG63 human osteosarcoma cell line [6]. It is also known as human cartilage glycoprotein-39 [4], chitinase 3-like-1 protein [7], chondrex [8], and breast regression protein 39 kDa [9].

The human *YKL-40* gene is located on chromosome 1q32.1 and consists of 10 exons [7]. The promoter sequence contains binding sites for several known factors. The Sp1-family transcription factor had a dominant role in controlling YKL-40 promoter activity [10]. It contains a single polypeptide chain, comprising 383 amino acids, where the three N-terminal amino acids are Y (tyrosine), K (lysine), and L (leucine) and had a molecular mass of 40 kDa [4]. Two mutations of the catalytic glutamic and aspartic acids to leucine and to alanine, respectively, are responsible for the lack of hydrolase activity of YKL-40 [10]. The crystallographic structure of human YKL-40 exhibits two globular domains, forming a groove which corresponds to the active cite of the protein [10].

2.2. YKL-40 ligands

Recent studies suggested different ligands for YKL-40. It was determined that the glycoprotein could facilitate the cross-link between syndecan-1 and integrin [11]. Syndecan-1 is a heparan sulfate proteoglycan acting as a transmembrane receptor. Its coupling with other receptors such as integrins might induce cell adhesion and angiogenesis [12]. It was suggested that YKL-40 could activate key signaling cascades—PI3K/AKT and MAPK/ERK resulting in high rate of cell proliferation and tumor cell survival [13, 14].

These signaling pathways could promote proliferation of synoviocytes and altered innate immunity in inflammatory arthritis [15, 16]. Kjaergaard et al. [17] suggested that another heparan sulfate proteoglycan, perlecan, might be a possible ligand for YKL-40. It was revealed that perlecan comprised distinct effects on angiogenesis dependent on integrin coupling [17, 18].

It was shown that lectin-glycan associations determined the organization of plasma membrane and modulated interactions between surface glycoproteins and receptors [19]. Recently, He et al. [20] identified the interleukin-13 subunit α2 (IL-13Rα2) as a possible receptor for YKL-40. They found that the activation of YKL-40 was not dependent on interaction with IL-13Rα2, suggesting that a coreceptor should be considered. The authors supposed that IL-13, IL-13Rα2, and Chi3l1/YKL-40/formed a multimeric complex, but they did not provide details [20].

Still unanswered questions are as follows: how YKL-40 interacts with perlecan? how IL-13, YKL-40, and IL-13Rα2 cooperate? whether the glycoprotein binds to other receptors?

2.3. YKL-40 regulation

Studies focused on YKL-40 regulation revealed controversial data and diverse effects.

Insulin growth factor-I (IGF-I) and insulin growth factor-II (IGF-II) were shown to trigger YKL-40 secretion in guinea pig chondrocytes but not in human chondrocytes [21, 22]. The results might be due to differences in the investigated species.

Proinflammatory interleukins, such as IL-2, IL-6, IL-12, IL-13, IL-17, and IL-18, did not induce YKL-40 transcription in astrocytes [23], while IL-6 and IL-17 showed enhanced production in human primary chondrocyte culture [22, 24].

Different kinds of stressors (hypoxia, ionizating radiation, treatment with TNF-α, bFGF, p53 inhibition, serum depletion) were shown to influence YKL-40 induction on three human malignant glioma cell lines:U87, U118, and U373 [25]. It was found that corticosteroids inhibited YKL-40 protein and mRNA levels in subsets of macrophages (proinflammatory or classically activated macrophages) [26]. Zhang et al. determined that resveratrol inhibited YKL-40 expression by influencing its promoter activity and mRNA transcription levels in U87 cells in vitro [27].

Alterations in the extracellular microenvironment also alter YKL-40 synthesis. Microarray gene expression analysis showed that the gene was overexpressed in dedifferentiated human fetal chondrocytes in comparison with differentiated chondrocytes [28].

YKL-40 secretion is activated by cartilage resection or by replacement of chondrocytes from their native environment. The level of YKL-40 secreted by normal cartilage explants is low during the first day of culture and increases significantly after a few days [22].

A study on the expression of YKL-40 in normal mouse mammary gland development found that YKL-40 was upregulated in ductal epithelial cells. The glycoprotein had the ability to inhibit epithelial secretion and differentiation and to facilitate cell migration under hormone stimulation [29].

The available data regarding the regulation of YKL-40 are quite controversial. These results emphasize the differences in *in vitro* and *in vivo* effects of YKL-40 on cellular and systemic response. We could suggest that YKL-40 might play various roles depending on the cell type it is expressed by.

2.4. Proposed functions for YKL-40

Little is known about the functions of YKL-40 in normal conditions. The glycoprotein is detected during early human embryonic development which is related to rapid proliferation and morphogenetic changes [30].

There is no fixed reference value for YKL-40 in healthy people. It was determined that the level of the glycoprotein increased with age, and it was assumed to be used with an age-matched control group [31]. Johansen proposed serum YKL-40 concentration higher than 20% to be considered as elevated [32]. Published levels of YKL-40 in healthy individuals differ among populations [33–35] and are shown in **Table 1**. We could speculate that divergent YKL-40 levels could be explained with differences in sample collection and assays, genetic polymorphisms, or even epigenetics.

Researchers suggest that YKL-40 protects the extracellular matrix during tissue remodeling via suppression of different types of metalloproteinases [40]. Another study showed that the glycoprotein defined which cells to survive during mammary involution [41] and provided protection against apoptosis [42].

YKL-40 was supposed to induce signaling cascades in connective tissue and functioned as a growth factor for synovial cells and chondrocytes [32]. It was found that YKL-40 worked synergistically with insulin growth factor-1 (IGF-1) to induce fibroblasts growth [21]. YKL-40 was discussed as a differentiation marker for monocytes [7], mesenchymal stem cells [43], and chondrocytes [44].

YKL-40 functions as a migration and adhesion factor for vascular cells and helps the formation of branching tubules. Thus, the glycoprotein could play a role in angiogenesis [11].

A variety of independent investigations demonstrated that high levels of YKL-40 were related to metastasis and poor survival in different human carcinomas, such as breast cancer [11], colorectal cancer [45], ovarian cancer [46], high-grade glioma [47], and lymphoma [48], suggesting that YKL-40 might serve as a diagnostic, risk assessment, and prognostic biomarker. Other studies indicated that YKL-40 increased also in inflammatory disorders associated with tissue remodeling and destruction [24, 49].

	Population	Serum YKL-40 levels	References
1.	Danish	43	[33]
2.	French	59	[36]
3.	Chinese	61.1	[37]
4.	Bulgarian	84.19	[35]
5.	Japanese	101.7	[38]
6.	Turkish	114	[34]

Table 1. Mean serum YKL-40 levels (ng/ml) in healthy individuals from different populations [39].

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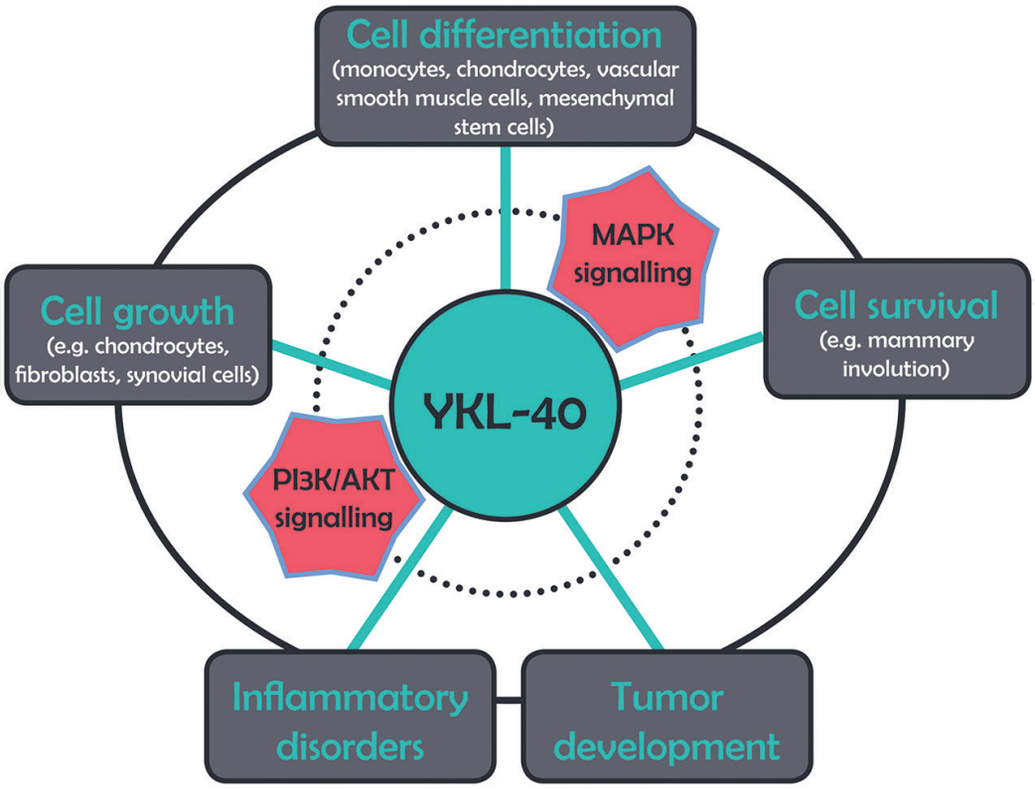


Figure 1. Biological functions of YKL-40. Involvement in cell growth and differentiation, cell survival, inflammatory disorders and tumor development; participation in two basic cell signaling cascades.

YKL-40 is a member of an evolutionary highly conserved protein family, described not only in humans [9, 30], proposing important biological role in normal and pathological conditions. The summarized functions of YKL-40 are presented in **Figure 1**.

3. YKL-40 and rheumatoid arthritis

It is believed that genetic and environmental factors are implicated in the etiology of RA. It is a chronic inflammatory disease which affects about 0.5–1% of the population. Patients suffer from chronic synovial inflammation, joint degradation, and functional disability [50]. Even though some clinical laboratory parameters are related to the risk of radiographic progression, they do not illustrate individual features in the pathogenesis of disease [51].

There is a lack of specific markers for early diagnosis, prognosis, and monitoring of effective treatment. Reliable biomarkers of joint inflammation and destruction in RA should be proteins produced by cells in the synovial fluid and leading to pathological alterations. YKL-40 is expressed and secreted by activated macrophages and neutrophils, fibroblast-like synovial cells, chondrocytes, and vascular smooth muscle cells [32]. Our immunocytochemical study also found that YKL-40 was present in polymorphonuclear cells in the synovial fluid of RA patients [52]. We suppose that it might reflect more precisely the local inflammatory process.

The investigations on the significance of serum YKL-40 as a novel inflammatory biomarker are polar. Some researchers show that it could be useful as an informative parameter in disease diagnosis and monitoring [53], and others state that it is merely a marker of joint inflammation [54].

3.1. YKL-40 in serum and synovial fluid

Johansen detected a 10-fold increase in the concentration of YKL-40 in synovial fluid compared to serum levels in RA patients and proposed that the level of YKL-40 might reflect cartilage degradation and synovial inflammation in RA [32]. These findings are in agreement with other studies, suggesting that YKL-40 is associated with the development of osteoarthritis and should be considered as a potential target for treatment [55].

Our observations focused on YKL-40 in RA patients also found significantly higher glycoprotein concentrations in the synovial fluid in comparison with serum levels [35]. However, we determined the same pattern of expression in other inflammatory joint diseases such as osteoarthritis, gout, and psoriatic arthritis [56].

Huber et al. established synovial antigen microarray technology to analyze antibody profile in RA patients. The synovial glycoprotein YKL-40 was one of the 225 peptides and proteins studied, and it was proved to generate autoantibody production [57]. YKl-40 was also detected as a target of T cells and as a specific and independent histologic marker in arthritic synovitis [58, 59].

There are a number of studies in which a multi-biomarker disease activity (MBDA) score is used to evaluate disease activity, prediction of radiographic progression, and prognosis in RA patients. MBDA score is estimated by measuring the concentrations of 12 serum biomarkers. YKL-40 is a part of the established panel of parameters [60, 61]. This fact confirms the potential significance of YKL-40 in the pathogenic route of RA.

The role of YKL-40 in inflammation still remains to be resolved. The question is whether YKL-40 is an active participant in the process of inflammation or is a result of the body response to it.

3.2. YKL-40 and conventional laboratory parameters

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the best known and frequently used conventional parameters at the time of diagnosis of RA, but they are not considered as predictors of poor prognosis. Radiological progression of joint destruction could often appear despite normal values. This is a common event in early RA stages [62].

Several studies investigated the significance of YKL-40 in relation to CRP and ESR [53]. We also determined a strong association between YKL-40 levels in serum and synovial fluid and CRP and ESR [35]. Thus, YKL-40 could be regarded as an informative proinflammatory biomarker.

3.3. YKL-40 and ultrasonography

Angiogenesis is a major result of synovial inflammation and maintenance of the pannus in RA [63]. Conventional radiology and tomography could not provide direct visualization of

the joint cartilage. The decreased in joint space is only an indirect evidence for joint destruction. Some authors use ultrasonograhy to measure and register early arthritic changes in joint thickness and to figure joint surfaces before they could be detected by routine radiologic methods [64]. We also applied ultrasonography as a sensitive technique for detecting synovial alteration. A relationship between ultrasonographic findings and YKL-40 was detected. Analysis of the data confirmed that the sonographic inflammation correlated with angiogenesis of the synovial membrane [35].

3.4. YKL-40 and angiogenesis

Vascular epidermal growth factor (VEGF) is a key factor in the pathogenesis of RA, serving both as a cell mitogen for endothelial cells and as a factor defining vascular permeability [65]. Several research groups revealed that secreted and expressed VEGF was related to the inflammatory response, to changes in the synovium, and to other conventional markers [65, 66].

YKL-40 also promotes attachment and migration of vascular endothelial cells, which indicates that the protein participates in angiogenesis [11]. Francescone et al. showed that YKL-40 induced VEGF expression in the U87 glioblastoma cell line and supposed that both molecules synergistically promoted endothelial cell angiogenesis [67].

VEGF was influenced by hypoxia, which contributed to RA development and altered response in arthritic synovium [64]. Similarly, YKL-40 was also upregulated by hypoxia in tumor cells [25]. It is assumed that the pathogenic features of arthritic synovium share the same characteristics with tumor cells.

3.5. YKL-40 and cytokines

Recent studies defined proinflammatory cytokines as major participants in RA pathogenesis resulting in identification of new molecular targets. It was shown that the production of tumor necrosis factor-alpha (TNF-α) is involved in the pathogenesis of RA [68], and biological inhibitors of this cytokine were approved for clinical use [69]. It was proved that levels of proinflammatory cytokines such as IL-1α, TNF-α, IL-6, and IFN-γ in the serum and synovial fluid of RA patients correlated with disease activity and progression [70]. Our investigations determined a strong link between serum and synovial levels of YKL-40 and serum TNF-α and IL-1β in patients with RA [71]. The cellular sources of TNF-α and IL-1β are circulating monocytes and macrophages [72]. It was shown that YKL-40 originated from the same cell types [32].

4. Conclusion

Investigations published so far determine YKL-40 as an important molecule in RA pathogenesis. It is assumed that circulating YKL-40 might reflect precisely the activity of local and systemic inflammation. The clinical utility of YKL-40 as diagnostic or prognostic marker in RA remains to be further clarified, but still it gives rise to serious expectations in the search of new promising biomarkers.

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