Chapter 8

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

Maria H. Kazakova and Victoria S. Sarafian

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66832

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.

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].

http://dx.doi.org/10.5772/66832

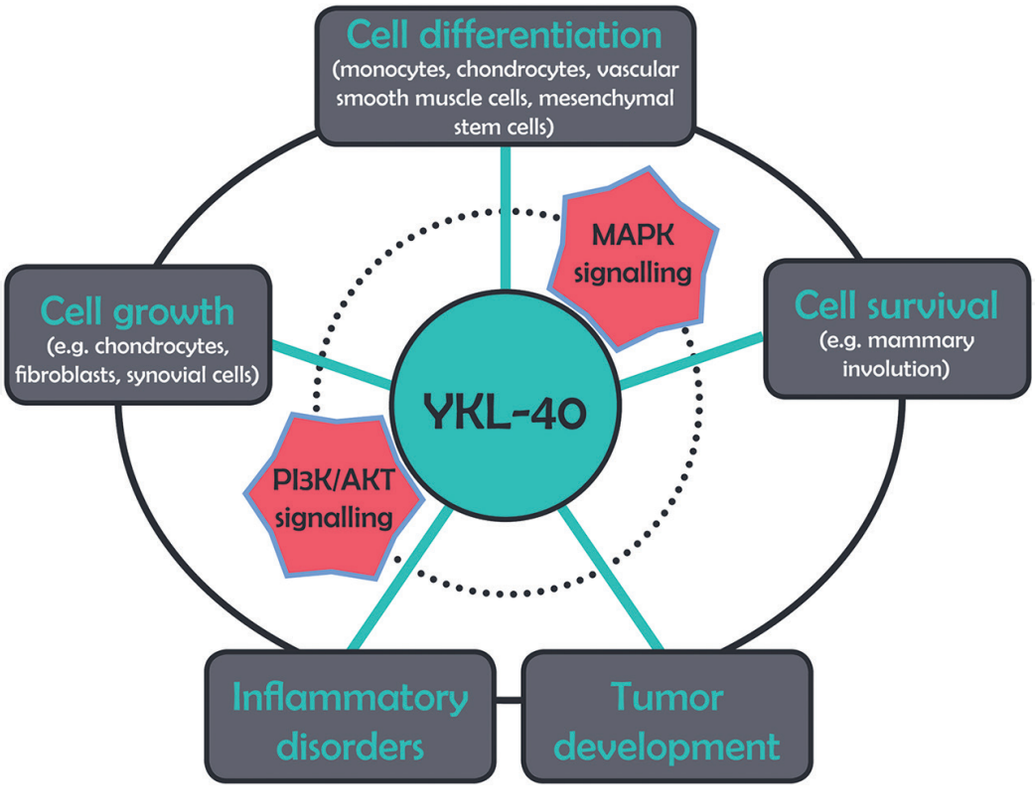

Figure 1. Biological functions of YKL-40. Involvement in cell growth and differentiation, cell survival, inflammatory disorders and tumor development; participation in two basic cell signaling cascades.

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.

Acknowledgements

The studies are supported by Medical University–Plovdiv—Grants No-01/2009, NO-01/2010, DP-08/2012 and partially by DUNK 01/2009 from the Ministry of Education and Science—Bulgaria.

The authors thank Yana Feodorova, PhD for the help in the design of the figure.

Author details

Maria H. Kazakova and Victoria S. Sarafian*

*Address all correspondence to: victoriasarafian@gmail.com

Department of Medical Biology, Faculty of Medicine, Medical University-Plovdiv, Bulgaria

References

[1] Strimbu K, Tavel J. What are biomarkers? Curr Opin HIV AIDS. 2010;6:463–466. doi:10.1097/COH.0b013e32833ed177

[2] Atkinson AJ. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.

[3] Morrow D, Cannon C, Jesse R, et al. Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation. 2007;13:356–375.

[4] Hakala B, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem. 1993;268:25803–25810.

[5] Chaplin D. Overview of the immune response. J Allergy Clin Immunol. 2010;125:S3–23. doi:10.1016/j.jaci.2009.12.9802012

[6] Johansen JS, Williamson MK, Rice JS, et al. Identification of proteins secreted by human osteoblastic cells in culture. J Bone Miner Res. 1992;7:501–512.

[7] Rehli M, Krause SW, Andreesen R. 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. 1997;43:221–225.

[8] Harvey S, Whaley J, Eberhardt K. The relationship between serum levels of YKL-40 and disease progression in patients with early rheumatoid arthritis. Scand J Rheumatol. 2000;29:391–393.

[9] Morrison BW, Leder P. neu and ras initiate murine mammary tumors that share genetic markers generally absent in c-myc and int-2-initiated tumors. Oncogene. 1994;9:3417–3426.

[10] Fusetti F, Pijning T, Kalk KH, Bos E, Dijkstra BW. Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. J Biol Chem. 2003;278:37753–37760.

[11] Shao R. YKL-40 acts as an angiogenic factor to promote tumor angiogenesis. Front Physiol. 2013;4:122.

[12] McQuade KJ, Beauvais DM, Burbach BJ, Rapraeger AC. Syndecan-1 regulates alphavbeta5 integrin activity in B82L fibroblasts. J Cell Sci. 2006;119:2445–2456.

[13] Faibish M, Francescone R, Bentley B, Yan W, Shao R. A YKL-40-neutralizing antibody blocks tumor angiogenesis and progression: a potential therapeutic agent in cancers. Mol Cancer Ther. 2011;10:742–751. doi:10.1158/1535-7163.MCT-10-0868

[14] Kim H, Lee B, Song Y, et al. Potential association between coronary artery disease and the inflammatory biomarker YKL-40 in asymptomatic patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2012;11:84. doi:10.1186/1475-2840-11-84

[15] Malemud Ch. Intracellular signaling pathways in rheumatoid arthritis. J Clin Cell Immunol. 2013. doi:10.4172/2155-9899.1000160

[16] Wisler BA, Dennis JE, Malemud CJ. New organ-specific pharmacological strategies interfering with signaling pathways in inflammatory disorders/autoimmune disorders. Curr Signal Transduct Ther. 2011;6:279–291.

[17] Kjaergaard A, Johansen J, Bojesen S, Nordestgaard B. Role of inflammatory marker YKL-40 in the diagnosis, prognosis and cause of cardiovascular and liver diseases. Crit Rev Clin Lab Sci. 2016. doi:10.1080/10408363.2016.1190683

[18] Clarke DN, Al Ahmad A, Lee B, et al. Perlecan domain V induces VEGf secretion in brain endothelial cells through integrin α5β1 and ERK-dependent signaling pathways. PLoS One. 2012;7:e45257.

[19] Rabinovich D, Croci G. Regulatory circuits mediated by lectin-glycan interactions in autoimmunity and cancer. Immunity. 2012;36:322–335.

[20] He C, Lee CG, Cruz C, Lee CM, Zhou Y,Ahangari F, et al. Chitinase 3-like 1 regulates cellular and tissue responses via IL-13 receptor α2. Cell Rep. 2013;4(4):830–841. doi:10.1016/j.celrep.2013.07.032

[21] De Ceuninck F, Gaufillier S, Bonnaud A, Sabatini M, Lesur C, Pastoureau P. YKL-40 (Cartilage gp-39) induces proliferative events in cultured chondrocytes and synoviocytes and increases glycosaminoglycan synthesis in chondrocytes. Biochem Biophys Res Commun. 2001;285:926–931.

[22] Johansen JS, Olee T, Price PA, Hashimoto S, Ochs RL, Lotz M. Regulation of YKL-40 production by human articular chondrocytes. Arthritis Rheum. 2001;44:826–837.

[23] Bonneh-Barkay D, Bissel S, Kofler J, Starkey A, Guoji Wang G, Clayton A. Wiley Astrocyte and macrophage regulation of YKL-40 expression and cellular response in neuroinflammation. Brain Pathol. 2012;22:530–546. doi:10.1111/j.1750-3639.2011.00550.x

[24] Väänänen T, Koskinen A, Paukkeri E, et al. YKL-40 as a novel factor associated with inflammation and catabolic mechanisms in osteoarthritic joints. Mediat Inflamm. 2014. doi:10.1155/2014/215140

[25] Junker N, Johansen JS, Hansen LT, Lund EL, Kristjansen PEG. Regulation of YKL-40 expression during genotoxic or microenvironmental stress in human glioblastoma cells. Cancer Sci. 2005;96:183–190.

[26] Kunz L, Wout E, Schadewijk A, Postma D, Kerstjens, Sterk P, Hiemstra P. Regulation of YKL-40 expression by corticosteroids: effect on pro-inflammatory macrophages in vitro and its modulation in COPD in vivo. Respir. Res. 2015;16:154–164.

[27] Zhang W, Kawanishi M, Miyake K et al. Association between YKL-40 and adult primary astrocytoma. Cancer. 2010;116:2688–2697.

[28] Stokes DG, Liu G, Coimbra IB, Piera-Velazquez S, Crowl RM, Jimenez SA. Assessment of the gene expression profile of differentiated and dedifferentiated human fetal chondrocytes by microarray analysis. Arthritis Rheum. 2002;46:404–419.

[29] Scully S, Yan W, Bentley B, Cao Q, Shao R. Inhibitory activity of YKL-40 in mammary epithelial cell differentiation and polarization induced by lactogenic hormones: a role in mammary tissue involution. PLoS One. 2011;6:e25819. doi:10.1371/journal.pone.0025819

[30] Johansen JS, Høyer PE, Larsen LA, Price PA, Møllgård K. YKL-40 protein expression in the early developing human musculoskeletal system. J Histochem Cytochem. 2007;55:1213–1228.

[31] Bojesen SE, Johansen JS, Nostegaard BG. Plasma YKL-40 levels in healthy subjects from the general population. Clin Chim Acta. 2011. doi:10.1016/j.cca.2011.01.022

[32] Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. Dan Med Bull. 2006;53:172–209.

[33] Johansen JS, Lottenburger T, Nielsen HJ, Jensen JE, Svendsen MN, Kollerup G, Christensen IJ. Weekly, and long-time variation in serum concentrations of YKL-40 in healthy subjects. Cancer Epidemiol Biomarkers Prev. 2008:2603–2608.

[34] Gungen G, Ardic F, Findikoglu G, Rota S. The effect of mud pack therapy on serum YKL-40 and hsCRP levels in patients with knee osteoarthritis. Rheumatol Int. 2009. doi:10.1007/s00296-010-1727-4

[35] Kazakova M, Batalov A, Deneva T, Mateva N, Kolarov Z, Sarafian V. Relationship between sonographic parameters and YKL-40 levels in rheumatoid arthritis. Rheumatol Int. 2013;33:341–346.

[36] Conrozier Th, Carlier M-C, Mathieu P, Colson F, Debard AL, Richard S, et al. Serum levels of YKL-40 and C reactive protein in patients with hip osteoarthritis and healthy subjects: a cross sectional study. Ann Rheum Dis. 2000;59:828–831.

[37] Zou X, Zhang W. The efficacy of YKL-40 and CA125 as biomarkers for epithelial ovarian cancer. Braz J Med Biol Res. 2010;43:1232–1238.

[38] Yamamori H, Hashimoto R, Ohi K, Yasuda Y, Fukumoto M, Kasahara E, et al. A promoter variant in the chitinase 3-like 1 gene is associated with serum YKL-40 level and personality trait. Neurosci Lett. 2012;513:204–208.

[39] Kazakova M, Sarafian V. YKL-40 in health and disease: a challenge for joint inflammation. Biomed Rev. 2013;24:49–56.

[40] Ling H, Recklies AD. The chitinase 3-like protein human cartilage glycoproein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumor necrosis factor-alpha. Biochem J. 2004;380:651–659.

[41] Malinda KM, Ponce L, Kleinman HK, et al. Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Exp Cell Res 1999;250:168–173.

[42] Lee CG, Hartl D, Lee GR, Koller B, Matsuura H, Da Silva CA, Sohn MH, Cohn L, Homer RJ, Kozhich AA, et al. Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. J Exp Med. 2009;206:1149–1166.

[43] Hoover D, Zhu V, Chen R, Briley, Rameshwar P, et al. Expression of the chitinase family glycoprotein YKL-40 in undifferentiated, differentiated and trans-differentiated mesenchymal stem cells. PLoS One. 2013;8. doi:info:doi/10.1371/journal.pone.0096230

[44] Imabayashi H, Mori T, Gojo S, Kioyono T, Sugiyama T, Irie R, Isoga T, Hata J, Toyama Y, Umezawa A. Redifferentiation of dedifferentiated chondrocytes and chondrogenesis of human bone marrow stromal cells via chondrosphere formation with expression profiling by large-scale cDNA analysis. Exp Cell Res 2003;288:35–50.

[45] Johansen JS, Christensen IJ, Jørgensen L, Olsen J, Rahr H, Nielsen K, Laurberg S, Brünner N, Nielsen H. Serum YKL-40 in risk assessment for colorectal cancer: a prospective study of 4,496 subjects at risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2015;3:621–626. doi:10.1158/1055-9965.EPI-13-1281

[46] Chiang YC, Lin HW, Chang CF, Chang MC, Fu CF, Chen TC, et al. Overexpression of CHI3L1 is associated with chemoresistance and poor outcome of epithelial ovarian carcinoma. Oncotarget. 2015;6:39740–39755.

[47] Steponaitis G, Skiriute D, Kazlauskas A, Golubickaite I, Stakaitis R, Tamašauskas A, Vaitkiene P. High CHI3L1 expression is associated with glioma patient survival. Diagn Pathol. 2016;11:42. doi:10.1186/s13000-016-0492-4

[48] Hottinger A, Iwamoto F, Karimi S, Riedel E, Dantis J, Park J, et al. YKL-40 and MMP-9 as serum markers for patients with primary central nervous system lymphoma. Ann Neurol. 2011;70:163–169. doi:10.1002/ana.22360

[49] Létuvé S, Kozhich A, Arouche N, Grandsaigne M, Reed J, Dombret MC, et al. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. J Immunol. 2008;181:5167–5173.

[50] Mclnnes I, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205-2219.

[51] Liao KP, Weinblatt ME, Cui J, et al. Clinical predictors of erosion-free status in rheumatoid arthritis: a prospective cohort study. Rheumatology (Oxford). 2011;50:1473–1479.

[52] Kazakova M, Batalov A, Kolarov Z, Sarafian V. Serum and synovial YKL-40 levels in psoriatic arthritis. Sci Technnol. 2012;2:60–63.

[53] Kassem I, Mahmoud L, Salah W. Study of resistin and YKL-40 in rheumatoid arthritis. J Am Sci. 2010;6:1004–1012.

[54] Syversen SW, Goll GL, Heijde D, Landeve R, Lie BA, Odegard S, et al. Prediction of radiographic progression in rheumatoid arthritis and the role of antibodies against mutated citrullinated vimentin: results from a 10-year prospective study. Ann Rheum Dis. 2009;69:345–351. doi:10.1136/ard.2009.113092

[55] Szychlinska M, Trovato F, Di Rosa M, Malaguarnera L, Puzzo L, Leonardi R, Castrogiovanni P, Musumeci G. Co-expression and co-localization of cartilage glycoproteins CHI3L1 and lubricin in osteoarthritic cartilage: morphological, immunohistochemical and gene expression profiles. Int J Mol Sci. 2016:17:359. doi:10.3390/ijms17030359

[56] Kazakova M, Batalov A, Mateva N, Kolarov Z, Sarafian V. Comparative significance of YKL-40 in different types of arthritis. In: Front. Immunol. Conference 15th International Congress of Immunology (ICI); 22-28 August 2013; Milan. Italy: doi:10.3389/conf.fiL

[57] Hueber W, Kidd B, Tomooka B, Lee B, Bruce B, Fries J, et al. Antigen microarray profiling of autoantibodies in rheumatoid arthritis. Arthritis Rheum. 2005;52:2645–2655. doi::10.1002/art.21269

[58] Cope A, Sonderstrup G. Evaluating candidate autoantigens in rheumatoid arthritis. Springer Semin Immunopathol. 1998;20:23–39.

[59] Baeten D, Steenbakkers PG, Rijnders AM, Boots AM, Veys EM, de Keyser F. Detection of major histocompatibility complex/human cartilage gp-39 complexes in rheumatoid arthritis synovitis as a specific and independent histologic marker. Arthritis Rheum. 2004;50:444–451.

[60] Bakker M, Cavet G, WG Jacobs J, Bijlsma J, Haneym D, Shen Y, Hesterberg L, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis. 2012;71:1692–1697.

[61] Hambardzumyan K, Bolce R, Saevarsdottir S, Cruickshank S, Sasso E, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis. 2015;74:1102–1109.

[62] Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis. 1995;54:944–947.

[63] Paleolog E. The vasculature in rheumatoid arthritis: cause or consequence? Int J Exp Pathol. 2009;90:249–261.

[64] Batalov A, Kuzmanova S, Penev D. Ultrasonographic evaluation of knee joint cartilage in rheumatoid arthritis patients. Folia Med. 2000;4:23–26.

[65] Lee S, Joo Y, Kim W, et al. Vascular endothelial growth factor levels in the serum and synovial fluid of patients with rheumatoid arthritis. Clin Exp Rheumatol. 2001;19:321–324.

[66] Sone H, Sakauchi M, Takahashi A, et al. Elevated levels of vascular endothelial growth factor in the sera of patients with rheumatoid arthritis correlation with disease activity. Life Sci. 2001;69:1861–1869.

[67] Francescone RA, Scully S, Faibish M, et al. Role of YKL-40 in the angiogenesis, radioresistance, and progression og glioblastoma. J Biol Chem. 2011. doi:10.1074/jbc.M110.212514

[68] Feldmann M, Maini R. Discovery of TNF-alpha as a therapeutic target in rheumatoid arthritis: preclinical and clinical studies. Joint Bone Spine. 2002;69:12–18.

[69] Maini R, Taylor P. Anti-cytokine therapy for rheumatoid arthritis. Annu Rev Med. 2000;51:207–229.

[70] Kolarov Z, Altunkova I, Baleva M, Martinova F, Monov S, Shumnalieva R. Relation between serum and synovial fluei levels of IL-1-alpha, TNF-alpha, IL-6, IFN-gamma and sIL-6r and clinical, immunological and genetic factors in rheumatoid arthritis patients. In: Ann. Rheum. Dis Annual European Congress of Rheumatol. EULAR 2015; 10-13 June 2015; Italy: p. 914.

[71] Kazakova-Velinova M. Immunobiological studies on YKL-40 in inflammatory joint and tumor processes [PhD thesis]. Medical University, Plovdiv; 2013.

[72] Arleevskaya M, Gabdoulkhakova A, Filina J, et al. Mononuclear phagocytes in rheumatoid arthritis patients and their relatives-family similarity. Open Rheumatol J. 2011;5:36–44.

IntechOpen