DOI: 10.21294/1814-4861-2018-17-4-99-105
УДК: 616-006.04:577.112

Для цитирования: *Ларионова И.В., Севастьянова Т.Н., Ракина А.А., Чердынцева Н.В., Кжышковска Ю.Г.* Хитиназоподобные белки как перспективные маркеры при злокачественных новообразованиях. Сибирский онкологический журнал. 2018; 17 (4): 99–105. – doi: 10.21294/1814-4861-2018-17-4-99-105.
For citation: *Larionova I.V., Sevastyanova T.N., Rakina A.A., Cherdyntseva N.V., Kzhyshkowska Ju.G.* Chitinase-like proteins as promising markers in cancer patients. Siberian Journal of Oncology. 2018; 17 (4): 99–105. – doi: 10.21294/1814-4861-2018-17-4-99-105.

ХИТИНАЗОПОДОБНЫЕ БЕЛКИ КАК ПЕРСПЕКТИВНЫЕ МАРКЕРЫ ПРИ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЯХ

И.В. Ларионова[1,2], Т.Н. Севастьянова[1,3], А.А. Ракина[4], Н.В. Чердынцева[1,2], Ю.Г. Кжышковска[1,3,5]

Национальный исследовательский Томский государственный университет, г. Томск, Россия[1]
Россия, 634050, г. Томск, пр. Ленина, 36[1]
Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук, г. Томск, Россия[2]
Россия, 634009, г. Томск, пер. Кооперативный, 5[2]
Институт трансфузионной медицины и иммунологии, Медицинский факультет, Маннхайм, Университет Гейдельберга, Маннхайм, Германия[3]
Германия, 68167, Маннхайм, Theodor-Kutzer-Ufer, 1-3[3]
Национальный исследовательский Томский политехнический университет, г. Томск, Россия[4]
Россия, 634009, г. Томск, пр.Ленина, 32[4]
Служба крови Немецкого Красного Креста Баден-Вюртемберг-Гессен, Маннхайм, Германия[5]
Германия, 68167, Маннхайм, Friedrich-Ebert, 107[5]

Аннотация

В обзоре проанализированы данные о роли хитиназоподобных белков (CLP), принадлежащих к семейству белков, содержащих Glyco_18 домен и не обладающих ферментативной активностью, при различных злокачественных новообразованиях. У человека идентифицировано 3 таких белка: YKL-40 (CHI3L1), YKL-39 (CHI3L2) и стабилин-связывающий CLP (SI-CLP). Хитиназоподобные белки, продуцируемые различными типами клеток, в том числе опухолевыми, проявляют активность как цитокины и ростовые факторы, а также они вовлечены в процессы воспаления. Высокий уровень CLP определяется в циркулирующей крови при воспалительных заболеваниях и разных локализациях злокачественных опухолей. Освещены данные о ключевых функциях CLP в физиологических и патологических условиях. Проанализированы сведения о вовлечении CLP в процессы инвазии, метастазирования, ангиогенеза, их связи с опухолевой прогрессией. Представлены собственные результаты, подтверждающие перспективность разработки прогностических и предсказательных маркеров на основе CLP при злокачественных новообразованиях.

Ключевые слова: хитиназоподобные белки, CLP, YKL-30, YKL-40, SI-CLP, злокачественные новообразования, опухолевая прогрессия.

CHITINASE-LIKE PROTEINS AS PROMISING MARKERS IN CANCER PATIENTS

I.V. Larionova[1,2], T.N. Sevastyanova[1,3], A.A. Rakina[4], N.V. Cherdyntseva[1,2], Ju.G. Kzhyshkowska[1,3,5]

Nadezhda V. Cherdyntseva, nvch@tnimc.ru

Tomsk State University, Tomsk, Russia[1]
36, Lenina av., 634050-Tomsk, Russia. E-mail: mitrof_@mail.ru[1]
Cancer Research Institute, Tomsk National Research Medical Center,
Russian Academy of Sciences, Tomsk, Russia[2]
5, Kooperativny Street, Tomsk, Russia, 634050[2]
Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim,
University of Heidelberg, Mannheim, Germany[3]
1-3, Theodor-Kutzer-Ufer, 68167-Mannheim, Germany[3]
National Research Tomsk Polytechnic University, Tomsk, Russia[4]
30, Lenina av., Tomsk, Russia, 634050[4]
German Red Cross Blood Service Baden-Württemberg-Hessen, Mannheim, Germany[5]
107, Friedrich-Ebert Str., 68167-Mannheim, Germany[5]

Abstract

In the present review we collected the main studies regarding the role of chitinase-like proteins (CLPs), belonging to the family of Glyco_18 domain-containing proteins, in different cancers. In humans, 3 chitinase-like proteins have been identified: YKL-40 (CHI3L1), YKL-39 (CHI3L2) and stabilin-1-interacting chitinase-like protein (SI-CLP). CLPs are produced by several types of cells and combine the properties of cytokines and growth factors. The high levels of CLPs were identified in the circulation of the patients with inflammatory diseases and various types of tumors. We highlighted the main known functions of CLPs in normal and pathological conditions, their contribution to metastasis development, angiogenesis, invasion and other processes in cancer, the correlation of the levels of CLPs with tumour progression. Our data also contribute to the understanding of question how CLP could be useful for cancer patient benefit.

Keywords: chitinase-like proteins, CLP, YKL-30, YKL-40, SI-CLP, cancer, tumor progression.

Common features of CLPs family

Chitinase-like proteins (CLPs) are structurally resemble chitinases that belong to a group of proteins, which are widely expressed in nature, and distributed in a wide range of organisms, including mammals, bacteria, plants, insects, viruses. Proteins with chitinase activity represent evolutionary ancient enzymes responsible for degradation of chitin, which is the second most abundant natural compound [1].

Mammalian chitinases and CLPs belong to glycosyl hydrolase family 18 (GH18) [2] due to presence of highly conserved Glyco_18 domain, responsible for sugar-binding, and catalytic site, which is essential for hydrolysis of chitin. The prehistoric purpose of GH18 existence is the degradation of complex sugar compounds, such as cellulose or chitin, via disruption of strong covalent or glycosylic bonds in polysaccharidic chains that compose polymer molecules. There are only two mammalian chitinases identified as functionally active enzymes, which are known as Acidic Mammalian Chitinase (AMCase) and Chitotriosidase (CHIT1) and they are both expressed in human [3, 4]. AMCase was firstly revealed in macrophages from patients with Gaucher disease [5]. The source of secreted chitotriosidase is abnormal lipid-laden macrophages that can be classified as a variation of alternatively activated macrophages, expressing CD68, CD14, HLA class II, CD163, CCL18 and IL-1-receptor antagonist, but not CD11b, CD40 and pro-inflammatory cytokines [6].

Chitinase-lake proteins predominantly contain Glyco-18 domain but not catalytic site (glycosyl hydrolase function). These proteins are also known as enzymatically inactive chi-lectins [2]. There are 4 known mammalian CLPs: YKL-40 (CHI3L1), YKL-39 (CHI3L2), stabilin-1-interacting chitinase-like protein (SI-CLP), and YM1/YM2 [7-10]. YM1/YM2 proteins are only found in rodents. YKL-39 is only present in humans and absent in rodents. All CLPs have specific characteristics in carbohydrate binding site. The binding region is located in (α/β)8 TIM-barrel domain, which allows CLPs to interact with chitin oligosaccharides with high affinity [10, 11]. It is crucial to be aware about the binding characteristics of CLP, because it allows prediction of the binding partners and, therefore, prediction of biological functions related to that binding.

YKL-39 is known to bind to chitooligosaccharides (GlcNac)5 and (GlcNac)6 [11, 12], that was demonstrated by glycan array screening, intrinsic tryptophan fluorescence and isothermal titration calorimetry (ITC). There are more binding targets known for YKL-40; it can bind to type I collagen that was revealed by affinity chromatography and surface plasmon resonance [13], to chitooligosaccharides, that shown in protein X-ray crystallography assay [14]; (GlcNac)5 and (GlcNac)4 that revealed by the Western blot [15] and heparin demonstrated by heparin affinity and HPLC chromatography [16]. ITC analysis showed that SI-CLP can bind to galactosamine, glucosamine, chitooligosacharide, (GlcNac)4, ribose and mannose [17]. It was demonstrated by surface plasmon resonance analysis that YM1 can bind to glucosamine, galactosamine and glucosamine polymers [18].

The main sources and functions of CLPs

The secretion of chitinase-like proteins was found in macrophages, neutrophils, epithelial

cells, chondrocytes and synovial cells, vascular smooth muscle cells as well as tumor cells (including breast, colon, kidney, lung, ovarian, prostate, uterine, osteosarcoma, glioblastoma) and their expression was regulated by various cytokines and hormones [1, 12].

YKL-39 is predominantly secreted by chondrocytes and synoviocytes and is recognized as a biochemical marker for the activation of chondrocytes and progression of osteoarthritis in humans [19].

YKL-40 is secreted by chondrocytes, synoviocytes, differentiated vascular smooth muscle cells, fibroblast-like synovial cells, by macrophages in the atherosclerotic plaque, tumor cells in many cancers [1, 20, 21]. In vivo, YKL-40 expression was found in places with intensive tissue remodeling [1]. YKL-40 regulates cell proliferation, migration, adhesion, macrophage differentiation, as well as extracellular matrix assembly and correlates with an elevated level of YKL-40 in chronic inflammation and connective tissue turnover [1, 22]. YKL-40 promotes the proliferation of chondrocytes and fibroblasts, migration and reorganization of vascular endothelial cells as well as inflammation and remodeling of extracellular matrix [1, 16]. It induces the migration of vascular smooth muscle cells (VSMC) [16] and promotes the growth of human synovial cells, skin and fibroblasts. High YKL-40 level was detected in serum of patients with rheumatoid arthritis (RA) and in patients with type 2 diabetes [1].

SI-CLP expression was found in various tumor cell lines, Raji cells, Jurkat cells, as well as in CD3+ T-cells, in the synovial fluid of patients with osteoarthritis or rheumatoid arthritis [17].

Expression of YKL-40 mRNA in human monocyte was strongly upregulated by IFN-gamma, and inhibited by IL-4 and dexamethasone [9]. There are also evidences that YKL-40 is secreted by macrophages during the late stages of differentiation. YKL-40 gene expression was up-regulated in monocytes stimulated with granulocyte-macrophage colony-stimulating factor, in colony-stimulating factor stimulated monocytes and in lipopolysaccharide stimulated monocytes [23, 24].

For YKL-39, no specific effects of IFN-gamma, IL-4 or dexamethasone were detected, but YKL-39 was upregulated in macrophages differentiated in the presence of IL-4+TGF-beta, but not IL-4 alone [25].

Human macrophages produce also SI-CLP and its expression is induced by Th2 cytokine IL-4 and glucocorticoid dexamethasone [9]. In vivo, high amounts of SI-CLP were detected in macrophages from bronchoalveolar lavage of patients with chronic airway inflammation [17].

In macrophages, SI-CLP is primarily localized in the secretory lysosomes. Kzhyshkowska et al. demonstrated that the intracellular sorting of SI-CLP in alternatively activated macrophages was mediated by the scavenger receptor stabilin-1, which was specifically expressed on subpopulations of tissue macrophages and sinusoidal endothelial cells in liver, spleen, lymph node and bone marrow. Stabilin-1 recognized SI-CLP in trans-Golgi network and delivered it to the late endosomes and consequently into Lamp1-positive and CD63-positive lysosomes [9]. The pattern of intracellular YKL-39 distribution was similar to the pattern demonstrated for SI-CLP suggesting that YKL-39 can be secreted by the lysosomal secretory pathway. Endogenous YKL-39 was found in the trans-Golgi network, where it was partially co-localized with stabilin-1. Using GST pull-down assay we showed that stabilin-1 can act as an intracellular sorting receptor for YKL-39 [25].

The role of CLPs in angiogenesis and chemotaxis

Among all chitinases and chitinase-like proteins, the pro-angiogenic activity and function of YKL-40 in various types of cancer progression were well studied. Angiogenic properties of YKL-40 in cancer development were demonstrated in breast and brain cancers where the expression level of YKL-40 was associated with tumor vascular formation [26, 27]. Immunohistochemical analysis of human breast cancer demonstrated a correlation between blood vessel density and YKL-40 protein expression [26]. In mouse model of breast cancer, YKL-40 was demonstrated to promote tumor growth by supporting angiogenesis. In mouse model of melanoma and glioblastoma, the inhibiting effect of anti-YKL-40 monoclonal antibody on tumor growth was shown [28, 29]. It was revealed that YKL-40 can facilitate tumor angiogenesis by interacting with syndecan-1 on endothelial cells and metastasis by stimulating production of MMP-9, CCL2 and CXCL2 [30].

Several studies on in vitro tube formation and endothelial cell migration have demonstrated that YKL-40 has stimulating effect on the endothelial cells that is similar to the effect of endothelial growth factor (VEGF) [27]. YKL-40-heparin interaction promotes the interaction with syndecan-1 and αvβ3 integrin, leading to activation of the ERK1/2 pathway and stimulation of VEGF [26, 27]. In glioblastoma, transient suppression of VEGF substantially increased YKL-40 expression and promoted tumor angiogenesis [31]. Anti-VEGF neutralizing antibody did not improve HMVECs tube formation and migration induced by YKL-40, thus confirming that pro-angiogenic effects of YKL-40 on HMVECs were not affected by VEGF [26].

Chitinase-like proteins can influence chemotactic activity of various cells directly or indirectly. Using an in vitro microchemotaxis transwell system model, Nio et al. demonstrated that YM1 acted as a chemotactic factor for eosinophils, T-lymphocytes and bone marrow cells [32]. YKL-40 was shown to affect chemotaxis of VSMC [16], THP-1 cells [33] and bronchial smooth muscle cells [34]. For THP-1 and VSMC cells, purified YKL-40 induced chemotaxis directly. In contrary, for

bronchial smooth muscle cells and SW480, YKL-40 enhanced secreted levels of IL-8, thus providing a chemotactic effect.

YKL-40 significantly increased the migration and invasion ability of CL1-1 NSCLC (non-small cell lung cancer) cell lines by regulating EMT (Epithelial Mesenchimal Transition) genes. In YKL-40 overexpressed cell line, the expression of E-cadherin, a marker of epithelial cells, was significantly lower; and the expression of markers of mesenchymal cells (N-cadherin, Vimentin) was significantly higher as well as other EMT regulators (Snail, Slug, and Twist) [35]. Moreover, inhibition of YKL-40 reduced the tube formation in vitro and suppressed tumor growth, angiogenesis, and progression of brain tumors [28].

Analysis of biological functions of YKL-39 demonstrated that it is unique that CLP combines monocyte attracting and pro-angiogenic activities, which essential for tumor progression [25]. The angiogenesis assay showed that recombinant YKL-39 induced tube formation of HUVEC cells 6 times higher than that observed in the negative control group, and this induction was more than 60% of positive control. The chemotactic effect of YKL-39 on primary monocytes was approximately 2 times higher after 1 h and more than 5 times higher after 3 h compared to control, and this effect was comparable with the effect of MCP-1/CCL2 chemokines [25].

CLPs in cancer

YKL-40 is expressed by several types of solid tumors including breast, colon, lung, kidney, head and neck, liver, bladder, prostate, stomach, ovary, pancreas, osteosarcoma, thyroid, glioblastoma and endometrial cancers. Microarray analysis identified YKL-40 gene as one of the most overexpressed genes in glioblastoma, papillary thyroid carcinoma, and chondrosarcoma [36]. YKL-40 protein expression was found in biopsies of glioblastomas, breast cancer and colon cancer. In vitro YKL-40 was secreted by the following human cancer cell lines: osteosarcoma, glioblastoma, colon cancer, ovarian cancer, prostate cancer and malignant melanoma [37]. YKL-40 protein expression was found in tumor associated macrophages (TAM) in patients with melanoma [37]. YKL-40 protein was not expressed in small cell lung cancer cells, but YKL-40 mRNA expression was elevated in TAM [36].

In tumors, YKL-40 may contribute to the proliferation and differentiation of malignant cells, protect the cancer cells from apoptosis, stimulate angiogenesis, and regulate extracellular tissue remodeling [23]. In non-small cell lung cancer, YKL-40 may also regulate (PI3K)/AKT/mTOR pathway, which is related with cell transformation, tumor survival, invasion and metastasis, and is a central feature of EMT [23]. In breast cancer, YKL-40 levels were inversely correlated with expression of GATA3 and E-cadherin, which regulate cell-cell contacts and act as tumor inhibitors [37]. The high risk of tumor progression may be explained either by the fact that cancer cells and TAM produce YKL-40, or that chronic inflammation causes both elevated plasma YKL-40 and cancer.

In our study we showed that the elevated levels of YKL-39 expression in tumors after neoadjuvant chemotherapy (NAC) were associated with increased risk of distant metastasis and poor response to NAC in patients with nonspecific invasive breast carcinoma [25]. Moreover, in the study of gene expression of M2 macrophage markers (YKL-39 and CCL18) we found that in breast cancer patients, who received anthracycline-containing NAC, the absence of clinical response was associated with the presence of M2+ macrophage phenotype (YKL-39-CCL18+or YKL-39+CCL18-) [38]. Kavsan et al. reported the increased expression of CHI3L2 gene in glioblastoma [39]. However, there is still insufficient data on the association of both YKL-39 gene and protein level with tumor progression, and no data on SI-CLP in tumor progression are available.

YKL-40 is a marker of late stages of cancer

Elevated plasma YKL-40 was found in patients with metastatic pancreatic and ovarian adenocarcinoma [36]. In patients with gastric cancer, serum levels of YKL-40 were significantly higher compared to those observed in healthy population, and the increased YKL-40 level indicated more aggressive phenotype of tumor [40]. Plasma YKL-40 level was elevated in approximately 80% of patients with metastatic renal cell carcinoma [37]. Dupont et al. showed that serum YKL-40 was upregulated in 65% of patients with stage I and II ovarian cancer in contrast to 74-91% of patients with stage III and IV cancer [41]. In patients with small cell lung cancer, the highest percentage of the patients who had elevated serum YKL-40 level was associated with advanced disease compared to local one. More than 80% of patients with metastatic renal cell cancer and more that 40% of patients with metastatic malignant melanoma and metastatic prostate cancer had also elevated serum YKL-40. In patients with glioblastoma, the serum YKL-40 level was higher in patients with glioblastoma multiforme compared to patients with lower grade gliomas [23]. In breast cancer, increased serum levels of YKL-40 were found more frequently in patients with metastatic cancer compared to patients with early cancer [23]. YKL-40 is associated with cancer aggressiveness. It was reported that not serum but urine YKL-40 level can be helpful in the diagnosis of bladder cancer in the assistance to BTA protein. Urine YKL-40 level was significantly higher in all invasive subgroups (T1, T2–T4, and T1–T4) compared to low stage (Ta) and can help determine treatment regimen in early invasive stages [42].

YKL-40 as an independent marker of tumor progression

Serum YKL-40 as a prognostic marker was independent of serum carcinoembryonic antigen in patients with colorectal cancer, of serum CA-125 and CA15-3 in patients with ovarian cancer, of estrogen receptor status, KRAS mutation status, of serum HER2 in patients with metastatic breast cancer, of serum prostate-specific antigen in patients with metastatic prostate cancer, and of serum lactate dehydrogenase in patients with small cell lung cancer or metastatic malignant melanoma and of clinical parameters (*i.e.*, age, performance status, tumor stage, histology), indicating that serum YKL-40 reflects other pathogenic aspects of tumor progression than these tumor markers [23]. Plasma YKL-40 in pre-treatment patients was shown to be an independent prognostic biomarker of short overall survival both at time of first cancer diagnosis and at time of relapse in patients with different types of adenocarcinoma (breast, colorectal, endometrial, non-small cell lung, ovary, cervix and prostate), in patients with head and neck and cervix squamous cell carcinoma [36].

In gastric cancer, high YKL-40 protein level was an independent biomarker of short survival and was associated with tumor invasion, lymph node metastasis [43]. In patients with localized or advanced small cell lung carcinoma, high plasma YKL-40 levels before chemotherapy independently predicted short survival [44]. Pre-treatment plasma and serum level of YKL-40 was an independent prognostic biomarker in patients with metastatic prostate cancer [36]. Serum level of YKL-40 is also an independent marker for the aggressiveness of metastatic breast cancer [1]. High plasma YKL-40 in patients with metastatic colorectal cancer before treatment was associated with short progression free survival and short overall survival, independently of KRAS status [45]. However, serum concentrations of YKL-40 do not show high sensitivity for early diagnostics of cancer and YKL-40 cannot be used as a single screening marker for diagnosis of cancer [1, 23].

Elevated YKL-40 level may serve as a useful potential prognostic biomarker for cancer patients

Serum levels of YKL-40 are indicative for the poor prognosis of metastatic process. Increased plasma concentration of YKL-40 is related to poor prognosis and shorter survival in patients with breast cancer, gastric cancer, ovarian cancer, colorectal carcinoma, metastatic prostate carcinoma, melanoma and many other cancers. High plasma YKL-40 levels predicted an absolute 10-year risk of gastrointestinal cancer in patients who were >70 years and smokers [46].

For advanced pancreatic cancer it was shown that the combination of plasma YKL-40, CA-19-9 and osteopontin was more sensitive compared to CA-19-9 alone [47]. High plasma YKL-40 was a predictor of chemoresistance in patients with ovarian cancer and breast cancer during treatment [36]. In recurrent breast cancer, high serum YKL-40 was associated with metastasis and high tumor grade and was elevated mostly in case of visceral and bone metastasis and less in case of lymph nodes metastasis. Moreover, the highest serum YKL-40 levels were found in patients with more than two different metastatic sites [23].

It was found that colorectal cancer patients with elevated serum YKL-40 after surgery had significantly shorter recurrence-free period and overall survival than patients with normal serum YKL-40, indicating that YKL-40 may be useful for the monitoring of cancer patients [23].

Conclusion remarks

In the present review we shortly highlighted the main features of CLPs, their key function and their ability to contribute to tumor progression. Nowadays we have clear evidences about the correlation with survival, invasion, metastasis etc. only for YKL-40 protein. There are a lot of studies related to the YKL-40 serum levels with cancer aggressiveness and disease progression. However, many fundamental aspects regarding the function, mechanisms of action and regulation of YKL-40 as well as YKL-39 and SI-CLP in cancer remain unclear. Problems regarding the direct or indirect contribution of YKL-39 and SI-CLP to tumor progression remain to be solved.

Future translational researches combining basic and clinical basis are needed and should give the answers on the main questions: “Are CLPs useful clinical biomarker for patients with cancer?” and “Can CLPs potentially become new targets for cancer therapy?”.

ЛИТЕРАТУРА/REFERENCES

1. *Kzhyshkowska J., Gratchev, A., Goerdt, S.* Human chitinases and chitinase-like proteins as indicators for inflammation and cancer. Biomark Insights. 2007 May 3; 2: 128–46.

2. *Shuhui L., Mok Y.K., Wong W.S.* Role of mammalian chitinases in asthma. Int Arch Allergy Immunol. 2009; 149(4): 369–77. doi: 10.1159/000205583.

3. *Donnelly L.E., Barnes, P.J.* Acidic mammalian chitinase–a potential target for asthma therapy. Trends Pharmacol Sci. 2004 Oct; 25(10): 509–11. doi: 10.1016/j.tips.2004.08.002.

4. *Zhu Z., Zheng T., Homer R.J., Kim Y.-K., Chen N.Y., Cohn L., Hamid Q., Elias J.A.* Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science. 2004 Jun 11; 304(5677): 1678–82. doi: 10.1126/science.1095336.

5. *Boot R.G., Renkema G.H., Strijland A., van Zonneveld A.J., Aerts J.M.* Cloning of a cDNA encoding chitotriosidase, a human chitinase produced by macrophages. J Biol Chem. 1995 Nov 3; 270(44): 26252–6.

6. *Boven L.A., van Meurs M., Boot R.G., Mehta A., Boon L., Aerts J.M., Laman J.D.* Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. Am J Clin Pathol. 2004 Sep; 122(3): 359–69. doi: 10.1309/BG5V-A8JR-DQH1-M7HN.

7. *Hu B., Trinh K., Figueira W.F., Price P.A.* Isolation and sequence of a novel human chondrocyte protein related to mammalian members of the chitinase protein family. J Biol Chem. 1996 Aug 9; 271(32): 19415–20.

8. *Jin H.M., Copeland N.G., Gilbert D.J., Jenkins N.A., Kirkpatrick R.B., Rosenberg M.* Genetic characterization of the murine Ym1 gene and identification of a cluster of highly homologous genes. Genomics. 1998 Dec 1; 54(2): 316–22. doi: 10.1006/geno.1998.5593.

9. *Kzhyshkowska J., Mamidi S., Gratchev A., Kremmer E., Schmuttermaier C., Krusell L., Haus G., Utikal J., Schledzewski K., Scholtze J., Goerdt S.* Novel stabilin-1 interacting chitinase-like protein (SI-CLP) is up-regulated in alternatively activated macrophages and secreted via lysosomal pathway. Blood. 2006 Apr 15; 107(8): 3221–8. doi: 10.1182/blood-2005-07-2843.

10. *Kzhyshkowska J., Yin S., Liu T., Riabov V., Mitrofanova I.* Role of chitinase-like proteins in cancer. Biol Chem. 2016 Mar; 397(3): 231–47. doi: 10.1515/hsz-2015-0269. doi: 10.1515/hsz-2015-0269.

11. *Ranok A., Wongsantichon J., Robinson R.C., Suginta W.* Structural and thermodynamic insights into chitooligosaccharide binding to human cartilage chitinase 3-like protein 2 (CHI3L2 or YKL-39). J Biol Chem. 2015 Jan 30; 290(5): 2617–29. doi: 10.1074/jbc.M114.588905.

12. *Schimpl M., Rush C.L., Betou M., Eggleston I.M., Recklies A.D., van Aalten D.M.* Human YKL-39 is a pseudo-chitinase with retained chitooligosaccharide-binding properties. Biochem J. 2012 Aug 15; 446(1): 149–57. doi: 10.1042/BJ20120377.

13. *Bigg H.F., Wait R., Rowan A.D., Cawston T.E.* The mammalian chitinase-like lectin, YKL-40, binds specifically to type I collagen and modulates the rate of type I collagen fibril formation. J Biol Chem. 2006 Jul 28; 281(30): 21082–95. doi: 10.1074/jbc.M601153200.

14. *Fusetti F., Pijning T., Kalk K.H., Bos E., Dijkstra B.W.* Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. J Biol Chem. 2003 Sep 26; 278(39): 37753-60. doi: 10.1074/jbc.M303137200.

15. *Renkema G.H., Boot R.G., Au F.L., Donker-Koopman W.E., Strijland A., Muijsers A.O., Hrebicek M., Aerts J.M.* 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. Eur J Biochem. 1998 Jan 15; 251(1-2): 504–9.

16. *Nishikawa K.C., Millis A.J.* gp38k (CHI3L1) is a novel adhesion and migration factor for vascular cells. Exp Cell Res. 2003 Jul 1; 287(1): 79–87.

17. *Meng G., Zhao Y., Bai X., Liu Y., Green T.J., Luo M., Zheng X.* Structure of human stabilin-1 interacting chitinase-like protein (SI-CLP) reveals a saccharide-binding cleft with lower sugar-binding selectivity. J Biol Chem. 2010 Dec 17; 285(51): 39898–904. doi: 10.1074/jbc.M110.130781.

18. *Chang N.C., Hung S.I., Hwa K.Y., Kato I., Chen J.E., Liu C.H., Chang A.C.* A macrophage protein, Ym1, transiently expressed during inflammation is a novel mammalian lectin. J Biol Chem. 2001 May 18; 276(20): 17497–506. doi: 10.1074/jbc.M010417200.

19. *Sekine T., Masuko-Hongo K., Matsui T., Asahara H., Takigawa M., Nishioka K., Kato T.* Recognition of YKL-39, a human cartilage related protein, as a target antigen in patients with rheumatoid arthritis. Ann Rheum Dis. 2001 Jan; 60(1): 49–54.

20. *Shao R.* Secreted glycoprotein YKL-40: A potential cancer biomarker and therapeutic target. Integr Cancer Sci Therap. 2018; 5(1): 1–1. doi: 10.15761/ICST.1000268.

21. *Johansen J.S.* Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. Dan Med Bull. 2006 May; 53(2): 172–209.

22. *Rathcke C.N., Vestergaard H.* YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res. 2006 Jun; 55(6): 221-7. doi: 10.1007/s00011-006-0076-y.

23. *Johansen J.S., Jensen B.V., Roslind A., Nielsen D., Price P.A.* Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev. 2006 Feb; 15(2): 194–202. doi: 10.1158/1055-9965.EPI-05-0011.

24. *Suzuki T., Hashimoto S., Toyoda N., Nagai S., Yamazaki N., Dong H.Y., Sakai J., Yamashita T., Nukiwa T., Matsushima K.* Comprehensive gene expression profile of LPS-stimulated human monocytes by SAGE. Blood 2000; 96: 2584–91.

25. *Liu T., Larionova I., Litviakov N., Riabov V., Zavyalova M., Tsyganov M., Buldakov M., Song B., Moganti K., Kazantseva P., Slonimskaya E., Kremmer E., Flatley A., Klüter H., Cherdyntseva N., Kzhyshkowska J.* Tumor-associated macrophages in human breast cancer produce new monocyte attracting and pro-angiogenic factor YKL-39 indicative for increased metastasis after neoadjuvant chemotherapy. Oncoimmunology. 2018 Mar 13; 7(6): e1436922. doi: 10.1080/2162402X.2018.1436922

26. *Shao R., Hamel K., Petersen L., Cao Q.J., Arenas R.B., Bigelow C., Bentley B., Yan W.* YKL-40, a secreted glycoprotein, promotes tumor angiogenesis. Oncogene. 2009 Dec 17; 28(50): 4456–68. doi: 10.1038/onc.2009.292.

27. *Francescone R.A., Scully S., Faibish M., Taylor S.L., Oh D., Moral L., Yan W., Bentley B., Shao R.* Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. J Biol Chem. 2011 Apr 29; 286(17): 15332–43. doi: 10.1074/jbc.M110.212514.

28. *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: 742–51. doi: 10.1158/1535-7163.MCT-10-0868.

29. *Salamon J., Hoffmann T., Elies E., Peldschus K., Johansen J.S., Lüers G., Schumacher U., Wicklein D.* Antibody directed against human YKL-40 increases tumor volume in a human melanoma xenograft model in scid mice. PLoS One. 2014 Apr 21; 9(4): e95822. doi: 10.1371/journal.pone.0095822.

30. *Wan G., Xiang L., Sun X., Wang X., Li H., Ge W., Cao F.* Elevated YKL-40 expression is associated with a poor prognosis in breast cancer patients. Oncotarget. 2017 Jan 17; 8(3): 5382–5391. doi: 10.18632/oncotarget.14280.

31. *Saidi A., Javerzat S., Bellahcène A., De Vos J., Bello L., Castronovo V., Deprez M., Loiseau H., Bikfalvi A., Hagedorn M.* Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. Int J Cancer. 2008 May 15; 122(10): 2187-98. doi: 10.1002/ijc.23313.

32. *Nio J., Fujimoto W., Konno A., Kon Y., Owhashi M., Iwanaga T.* Cellular expression of murine Ym1 and Ym2, chitinase family proteins, as revealed by in situ hybridization and immunohistochemistry. Histochem Cell Biol. 2004 Jun; 121(6): 473–82. doi: 10.1007/s00418-004-0654-4.

33. *Kawada M., Seno H., Kanda K., Nakanishi Y., Akitake R., Komekado H., Kawada K., Sakai Y., Mizoguchi E., Chiba T.* Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer. Oncogene. 2012 Jun 28; 31(26): 3111–23. doi: 10.1038/onc.2011.498.

34. *Tang H., Sun Y., Shi Z., Huang H., Fang Z., Chen J., Xiu Q., Li B.* YKL-40 induces IL-8 expression from bronchial epithelium via MAPK (JNK and ERK) and NF-κB pathways, causing bronchial smooth muscle proliferation and migration. J Immunol. 2013 Jan 1; 190(1): 438–46. doi: 10.4049/jimmunol.1201827.

35. *Jefri M., Huang Y.N., Huang W.C., Tai C.S., Chen W.L.* YKL-40 regulated epithelial-mesenchymal transition and migration/invasion enhancement in non-small cell lung cancer. BMC Cancer. 2015 Aug 15; 15: 590. doi: 10.1186/s12885-015-1592-3.

36. *Schultz N.A., Johansen J.S.* YKL-40-A Protein in the Field of Translational Medicine: A Role as a Biomarker in Cancer Patients? Cancers (Basel). 2010 Jul 12; 2(3): 1453-91. doi: 10.3390/cancers2031453.

37. *Shao R., Cao Q.J., Arenas R.B., Bigelow C., Bentley B., Yan W.* Breast cancer expression of YKL-40 correlates with tumour grade, poor differentiation, and other cancer markers. Br J Cancer. 2011 Oct 11; 105(8): 1203–9. doi: 10.1038/bjc.2011.347.

38. *Litviakov N., Tsyganov M., Larionova I., Ibragimova M., Deryusheva I., Kazantseva P., Slonimskaya E., Frolova I., Choinzonov E., Cherdyntseva N., Kzhyshkowska J.* Expression of M2 macrophage markers YKL-39 and CCL18 in breast cancer is associated with the effect of neoadjuvant chemotherapy. Cancer Chemother Pharmacol. 2018 Jul; 82(1): 99–109. doi: 10.1007/s00280-018-3594-8.

39. *Kavsan V.M., Baklaushev V.P., Balynska O.V., Iershov A.V., Areshkov P.O., Yusubalieva G.M., Grinenko N.P., Victorov I.V., Rymar V.I., Sanson M., Chekhonin V.P.* Gene Encoding Chitinase 3-Like 1 Protein (CHI3L1) is a Putative Oncogene. Int J Biomed Sci. 2011 Sep; 7(3): 230–7.

40. *Itik V., Kemik O., Kemik A., Dulger A.C., Sümer A., Soyoral Y.U., Begenik H., Purisa S., Kotan C.* Serum YKL-40 Levels in Patients with Gastric Cancer. Biomark Cancer. 2011 May 4; 3: 25–30. doi: 10.4137/BIC.S7154.

41. *Dupont J., Tanwar M.K., Thaler H.T., Fleisher M., Kauff N., Hensley M.L., Sabbatini P., Anderson S., Aghajanian C., Holland E.C., Spriggs D.R.* Early detection and prognosis of ovarian cancer using serum YKL-40. J Clin Oncol 2004; 22: 3330–9. doi: 10.1200/JCO.2004.09.112.

42. *Yasar O., Akcay T., Obek C., Turegun F.A.* Diagnostic potential of YKL-40 in bladder cancer. Urol Oncol. 2016 Jun; 34(6): 257.e19-24. doi: 10.1016/j.urolonc.2016.02.003.

43. *Bi J., Lau S.H., Lv Z.L., Xie D., Li W., Lai Y.R., Zhong J.M., Wu H.Q., Su Q., He Y.L., Zhan W.H., Wen J.M., Guan X.Y.* Overexpression of YKL-40 is an independent prognostic marker in gastric cancer. Hum Pathol. 2009 Dec; 40(12): 1790–7. doi: 10.1016/j.humpath.2009.07.005.

44. *Johansen J.S., Drivsholm L., Price P.A., Christensen I.J.* High serum YKL-40 level in patients with small cell lung cancer is related to early death. Lung Cancer. 2004; 46: 333–340. doi: 10.1016/j.lungcan.2004.05.010.

45. *Cintin C., Johansen J.S., Christensen I.J., Price P.A., Sørensen S., Nielsen H.J.* High serum YKL-40 level after surgery for colorectal carcinoma is related to short survival. Cancer. 2002; 95: 267–274. doi: 10.1002/cncr.10644.

46. *Johansen J.S., Bojesen S.E., Mylin A.K., Frikke-Schmidt R., Price P.A., Nordestgaard B.G.* Elevated plasma YKL-40 predicts increased risk of gastrointestinal cancer and decreased survival after any cancer diagnosis in the general population. J Clin Oncol. 2009 Feb 1; 27(4): 572–8. doi: 10.1200/JCO.2008.18.8367.

47. *Chang S.T., Zahn J.M., Horecka J., Kunz P.L., Ford J.M., Fisher G.A., Le Q.T., Chang D.T., Ji H., Koong A.C.* Identification of a biomarker panel using a multiplex proximity ligation assay improves accuracy of pancreatic cancer diagnosis. J Transl Med. 2009 Dec 11; 7: 105. doi: 10.1186/1479-5876-7-105.

Received 29.07.18
Accepted 14.08.18

Funding

The study was supported by the Russian Science Foundation (№14-15-00350 project) and Competitiveness Improvement Program of Tomsk State University.

Conflict of interest

The authors declare that they have no conflict of interest.

ABOUT THE AUTHORS

Irina V. Larionova, Junior Researcher of Laboratory of Translational Cellular and Molecular Biomedicine, Tomsk State University; Postgraduate, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia). Researcher ID (WOS): R-2391-2017. Author ID (Scopus): 57201182530. ORCID: 0000-0001-5758-7330.

Tatyana N. Sevastyanova, Scientific Researcher of Laboratory of Translational Cellular and Molecular Biomedicine, Tomsk State University; Postgraduate of of Department of Innate Immunity and Tolerance, Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, University of Heidelberg (Mannheim, Germany). ORCID: 0000-0002-6236-6556.

Apollinariya A. Rakina, Engineer, National Research Tomsk Polytechnic University (Tomsk, Russia). Researcher ID (WOS): O-6297-2018. ORCID: 0000-0002-9347-7806.

Nadezhda V. Cherdyntseva, DSc, Professor, Corresponding member of Russian Academy of Sciences, the Head of the Laboratory of Molecular oncology and immunology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences; senior researcher of Laboratory of translational cellular and molecular biomedicine, Tomsk State University (Tomsk, Russia). Researcher ID (WOS): C-7943-2012. Author ID (Scopus): 6603911744. ORCID: 0000-0003-1526-9013.

Julia V. Kzhyshkowska, DSc, Professor, the Head of the Laboratory of translational cellular and molecular biomedicine, Tomsk State University (Tomsk, Russia); Head of Department of Innate Immunity and Tolerance, Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, University of Heidelberg (Mannheim, Germany). Researcher ID (WOS): J-5835-2016. Author ID (Scopus): 6603091281. ORCID: 0000-0003-0898-3075.

СВЕДЕНИЯ ОБ АВТОРАХ

Ларионова Ирина Валерьевна, младший научный сотрудник лаборатории трансляционной клеточной и молекулярной биомедицины, Национальный исследовательский Томский государственный университет; аспирант, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук (г. Томск, Россия). SPIN-код: 6272-8422. Researcher ID (WOS): R-2391-2017. Author ID (Scopus): 57201182530. ORCID: 0000-0001-5758-7330.

Севастьянова Татьяна Николаевна, научный сотрудник, Национальный исследовательский Томский государственный университет; аспирант, Институт Трансфузионной Медицины и Иммунологии, Медицинский факультет, Маннхайм, Университет Гейдельберга (г. Маннхайм, Германия). ORCID 0000-0002-6236-6556.

Ракина Аполлинария Александровна, инженер, Национальный исследовательский Томский политехнический университет (г. Томск, Россия). SPIN-код: 2569-1297. Researcher ID (WOS): O-6297-2018. ORCID: 0000-0002-9347-7806.

Чердынцева Надежда Викторовна, доктор биологических наук, профессор, член-корреспондент РАН, заведующая лабораторией молекулярной онкологии и иммунологии, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук; ведущий научный сотрудник, Национальный исследовательский Томский государственный университет (г. Томск, Россия). SPIN-код: 5344-0990. Researcher ID (WOS): C-7943-2012. Author ID (Scopus): 6603911744. ORCID 0000-0003-1526-9013.

Кжышковска Юлия Георгиевна, доктор биологических наук, профессор, заведующая лабораторией трансляционной клеточной и молекулярной биомедицины, Национальный исследовательский Томский государственный университет (г.Томск, Россия); заведующая отделом врожденного иммунитета и толерантности, Институт трансфузионной медицины и иммунологии, Медицинский факультет, Университет Гейдельберга (г. Маннхайм, Германия). SPIN-код: 2465-2280. Researcher ID (WOS): J-5835-2016. Author ID (Scopus): 6603091281. ORCID: 0000-0003-0898-3075.

Финансирование

Работа поддержана грантом Российского научного фонда №14-15-00350 и программой повышения конкурентоспособности Томского государственного университета.

Конфликт интересов

Авторы объявляют, что у них нет конфликта интересов.

Поступила 29.07.18
Принята в печать 14.08.18