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High-level of circulating progranulin and its relationship with plasma glycosaminoglycans, as biochemical indicators of proteolytic and oxidative aggrecan modification, in the course of juvenile idiopathic arthritis*

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Związek wysokiego osoczowego stężenia progranuliny ze stężeniem glikozoaminoglikanów, jako biochemicznych wskaźników proteolityczo-prooksydacyjnej modyfikacji agrekanu, w przebiegu młodzieńczego idiopatycznego zapalenia stawów

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Summary

Aim: Progranulin (PGRN) plays an important role in cartilage metabolism. The disturbed interaction between PGRN and glycosaminoglycans (GAGs), as biochemical indicators of aggrecan modification, may contribute to articular damage observed in the course of juvenile idiopathic arthritis (JIA). Hence, the aim of this study was to assess quantitatively the level of progranulin in children with JIA as well as to evaluate the correlation between PGRN and GAGs, MMP-3 (matrix metalloproteinase 3), ADAMTS-4 (a disintegrin and metalloproteinase with thrombospondin motifs 4) as well as the total oxidative status (TOS) and the total antioxidative status (TAS). We have also evaluated interactions between PGRN and inflammatory and anemia indicators, i.e. C-reactive protein (CRP), and hemoglobin (Hb), respectively.

Material/Methods: The PRGN level was measured using the immunoenzymatic method, in blind tested coded plasma samples, obtained from both JIA patients before and after treatment and from healthy children.

Results: Increased ($p<0.001$) plasma progranulin in JIA patients before treatment was observed. Therapy resulted in a decrease in the PRGN level. However, the plasma PRGN level still remained higher ($p<0.05$) than in the controls. In both groups of patients, we have revealed an insignificant correlation between plasma PGRN and GAGs levels. Moreover, a significant correlation between plasma PGRN level and MMP-3, ADAMTS-4, TOS, TAS, CRP and Hb levels, was stated in untreated JIA patients.

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Conclusions: The obtained results may indicate that PGRN has antioxidative properties in the course of JIA, but do not confirm the protective roles of this glycoprotein in respect to the destructive effects of proteolytic factors.

Keywords: **juvenile idiopathic arthritis • progranulin • total oxidative status • total antioxidative status • matrix metalloproteinases**

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most commonly recognized, chronic, systemic disease of the connective tissue with the an autoimmune background diagnosed in children and teenagers younger than 16 years old. The course of the disease, despite the applied therapy, has a progressive character with recurrences leading to the destruction of joint structures of different degrees [2, 6, 10]. Ongoing wearing of the joint cartilage in the course of JIA, which leads to balance disturbances between biological strength, its function and the contact force are linked with aggrecan metabolism disturbances [23]. Aggrecan, which is a large aggregating proteoglycan (PG), is the main component of cartilage extracellular matrix and the molecule that allows the tissue to bear weight by deforming elastically under compressive load. These functions are directly related to chains of glycosaminoglycan (GAG), covalently linked to a core protein of PGs [1, 7, 23]. The profile of GAGs in blood reflects the PGs transformation in tissues [22, 23]. As it was indicated in our previous studies, in the course of JIA the plasma concentration of GAGs decreases, which is likely to account for a significantly intensified degradation of tissue PGs taking place in early, pre-clinical stages of the disease [22]. It seems that at the moment when the clinical symptoms of JIA appear, the overall amount of tissue GAGs is significantly reduced, while the processes of extracellular matrix (ECM) components' synthesis do not compensate for the degradation magnitude of these compounds [22].

The matrix metalloproteinases (MMPs), especially MMP-3 as well as the family of peptidases - a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), especially ADAMTS-4, are thought to be the key enzymes involved in these processes, since they can degrade most components of cartilage in physiological and pathological situations [4, 17, 20, 22, 23, 24]. We previously reported that MMP-3 and ADAMTS-4 were significantly expressed in the plasma of untreated JIA patients [22, 23]. Moreover, it is highly probable that the oxidative balance disturbance of the organism is yet another factor which favors the aggrecan degradation. The reactive oxygen species are the factors capable of degrading both the PG protein fragments and the heteropolysaccharide chains of these compounds. Furthermore, the presence of oxidative stress, which is expressed by the increased activity of free-radicals and by weakening the antioxidative system, was reported by us in JIA patients. It is important that the excessive proteolytic enzymes and reactive oxygen species (ROS) production are key mechanisms by which cartilage matrix destruction occurs during the development of arthritis [4, 17, 20, 22, 23, 24]. Hence, every action which can limit the effect of the destructive factors may inhibit both the development and clinical consequences of JIA. Progranulin (PGRN) appears to be an endogenous factor related to JIA development. PGRN is an autocrine growth factor playing a role in cell cycle progression, neurite outgrowth, wound repair as well as in the modulation of both immune response and inflammation [3, 8, 25]. The factor also functions as an important regulator of cartilage development and degradation [8, 14]. Hence, it is highly probable that the changes of circulating progranulin and the disturbed interaction between this glycoprotein and proteolytic enzymes, may contribute to articular structures damage observed in the course of JIA. Though the role of progranulin in JIA etiopathogenesis is not obvious, it can be assumed that this molecule as a modulator of inflammatory and oxidative processes, may be linked to pathogenetic changes leading to the manifestation of the discussed disease [3, 5, 8, 9, 11, 14, 21, 25].

Hence, the aim of this study was to assess quantitatively the level of progranulin in JIA patients before and after treatment as well as to evaluate of correlation between PGRN and GAGs, MMP-3, ADAMTS-4 as well as total oxidative status (TOS) and total antioxidative status (TAS). We have also evaluated interactions between PGRN and inflammatory and anemia indicators, i.e. C-reactive protein (CRP) and hemoglobin (Hb), respectively.

MATERIALS AND METHODS

The study was carried out on the blood plasma obtained from 30 children of both sexes (19 girls, 11 boys), aged 12-16 years, newly diagnosed with JIA. All patients were diagnosed and classified according to the International League of Associations for Rheumatology criteria as oligoarthritis (17 children) or polyarthritis (13 children). Moderate disease activity was assessed in all patients. We used JADAS (Juvenile Arthritis Disease Activity Score) to assess the JIA activity. This score consist of four variables, i.e. the number of joints with active arthritis (AJC), physician global assessment of disease activity (PGA), parent/child global assessment of well-being (PGE), and erythrocyte sedimentation rate (ESR). Other forms of JIA, as well as any other chronic and autoimmune diseases, traumas or surgical procedures of the locomotor system over the past 3 years, renal or liver diseases, and chronic infections constituted exclusion criteria. Moreover, the accuracy of diagnosis was confirmed by laboratory tests, namely, by determining the indicators of inflammatory responses, i.e. C-reactive protein (CRP, immunonephelometric assay) and ESR (Westergren technique), measuring rheumatoid factor (RF, latex enhanced immunoturbidimetric test), and by determining the titre of antinuclear antibodies (ANA, indirect immunofluorescence assay).

The tests were repeated in the same patients after they had undergone a therapy which modified inflammation, and when clinical improvement was observed, on average, 11.60±0.21 months after the beginning the therapy. Clinical improvement was determined by the ACR Pediatric 30 criteria, which represents improvement by at least 30% from baseline in 3 of any 6 predefined variables, including AJC, number of joints with limited motion (LJC), PGA, PGE, a measure of physical function (CHAQ), and a laboratory measure of inflammation (ESR, CRP). Moreover, no more than 1 of the remaining variables could worsen by >30%. Treatment with stable doses of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), oral glucocorticoids (at a maximum dose of 1 mg of a prednisone equivalent per kilogram per day, with gradual dose reduction) and methotrexate (≤15 mg per square meter of body-surface area once a week) was used. Other disease modifying antirheumatic drugs and biologic agents were not allowed.

Blood samples obtained from 30 age and body mass index-matched healthy individuals were used as controls. The healthy children who were included in our study did not suffer from any diseases which required hospitalization and did not undergo surgical procedures during the previous year. What is more, they were not treated pharmacologically just before the studies, and their results of routine laboratory tests, i.e. blood cell morphology, blood levels of cholesterol, glucose and creatinine, as well as urine levels of protein and glucose were normal for this age group. The clinical data of healthy individuals and JIA patients enrolled in our study is shown in Table 1.

The plasma obtained both from healthy individuals and JIA patients were divided into portions and stored at –80 ºC till the initiation of the study. The determination of one parameter was completed within one day; consequently, the inter-assay variation was insignificant. The PathozymeElisaSure Kit (ref OD707, Omega Diagnostics Ltd, Scotland, UK) was used to control linearity and precision of a microplate reader (Infinite M200, Tecan, Schweiz), as well as the efficiency and reproducibility of the HydroxFlex microplate washer (HydroFlex, Tecan, Schweiz), and the precision of automatic pipettes.

Informed consent was obtained from teenage participants under the age of 16 according to the ethical guidelines of the Helsinki Declaration. In cases of all under-aged patients, parents or legal guardians signed the informed consent. The Local Ethics Committee of Medical University of Silesia approved the research protocol used in this study.

No conflicts of interest have occurred during implementation and completion of the study.

The assay of the concentration of progranulin in plasma samples

The PGRN level was measured using blind-tested coded plasma samples, in duplicate. The tested compound was quantitatively measured using a human Progranulin ELISA Kit from Mediagnost GmbH (Reutlingen, Germany) according to the manufacturer's protocol. This assay utilizes specific monoclonal antibodies of high affinity for human progranulin. The analytical sensitivity of the assay yields 0.018 ng/mL. The intra-assay CV that quantified variation in the assay technique itself was less than 7%.

Statistical analysis

A statistical analysis was carried out using Statistica 10.0 package (StatSoft, Cracow, Poland). The normality of distribution was verified with the Shapiro-Wilk test. The clinical data obtained from healthy individuals and JIA patients were expressed as mean values and standard deviation. Since the variables were normally distributed, the parametric Student's t-test was used to evaluate the differences between untied variables. To compare the

Table 1. Clinical characteristics of control subjects and JIA' disease patients

Parameter	Control subjects (n=30)	Untreated JIA (n=30)	JIA' disease after attainment of clinical improvement (n=30)
Age (years)	8.67±4.12	7.27±4.49	8.21±4.01
Sex, female/male	17/13	19/11	19/11
JADAS-27	-	18±8.56	4±2.52
WBC (10^3/µl)	7.32±2.19	10.04±4.03[a]	7.14±2.31[b]
RBC (10^6/µl)	4.95±0.35	4.48±0.41[a]	4.62±0.36
Hb (g/dl)	13.85±0.94	11.58±1.38[a]	12.97±1.16[a,b]
Ht (%)	40.96±3.18	35.35±3.61[a]	37.17±7.39[a,b]
PLT (10^3/µl)	283.47±73.83	405.47±129.10[a]	351.20±93.78[b]
Total cholesterol (mM)	4.12±0.87	4.61±1.42[a]	4.25±1.65[b]
Glucose (mM)	4.56±0.38	4.11±1.16	4.40±0.98[b]
Creatinine (µM)	80.01±12.66	52.97±10.23[a]	64.54±15.47[a,b]
CRP (mg/l)	1.24±1.59	20.25±24.00[a]	2.76±0.57[b]
ESR (mm/h)	10.50±7.03	42.00±27.02[a]	13.11±7.21[b]
ANA	-	56% (positive)	56% (positive)
RF	-	100% (negative)	100% (negative)
*Plasma GAGs (hexuronic acids, mg/L)	156.06±19.84	119.73±22.33[b]	128.86±23.02[a,b]
*MMP-3 (ng/mL)	0.26±0.13	2.25±1.36[a]	0.55±0.25[a,b]
#ADAMTS-4 (ng/mL)	15.55±6.70	26.71±15.17[a]	13.26±8.10[b]
*TOS (mmol/L)	0.44±0.17	1.05±0.48[b]	0.49±0.26[b]
*TAS (mmol/L)	0.20±0.06	0.14±0.04[b]	0.17±0.05[a,b]

Results are expressed as mean ± SD; ap<0.05 compared to control group; bp<0.05 compared to untreated JIA patients; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; PLT, platelet; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor; GAGs, glycosaminoglycans; MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloprotease with thrombospondin motifs; TOS, total oxidative status; TAS, total antioxidative status; * results reported in [23]; # results reported in [22]

same parameters in each patient, before the treatment and after the restoration of clinical improvement, the paired Student's t-test was used. The Pearson's correlation coefficient was employed for the statistical analysis of correlations between two variables. p-Values of less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Inflammatory state in untreated JIA patients caused significantly elevated levels of plasma progranulin (55.79 ng/mL ±18.26; mean ±standard deviation). The patients had a 35% higher (p<0.001) level of this parameter than the controls (41.38±10.34). Achieving clinical improvement was accompanied by a statistically significant (p=0.005) decrease in PRGN level, vs. pre-treatment situation. However, treated JIA patients (47.15±8.62) still had a markedly (p=0.011) higher plasma concentration of the above-mentioned parameter than the control subjects. Compared to the control values, the mean increase in PRGN was by 14%. The correlations between plasma levels of PGRN and GAGs, MMP-3, ADAMTS-4, TOS, TAS, CRP as well as Hb are shown in Table 2. We cannot compare our results with those obtained by other researchers, since the plasma PRGN has not been estimated in children with JIA so far. However, it should be mentioned that a high level of PRGN was recorded in rheumatoid arthritis, many types of cancer, and neurodegenerative diseases [5, 8, 9, 14, 15, 18, 19, 26]. Both anti- and pro-inflammatory effects of PRGN have been detected in the above-mentioned pathologies. This is probably due to the fact that, during inflammation, neutrophils and macrophages release serine proteases that digest PGRN into individual 6 kDa granulin units, which are actually pro-inflammatory and can neutralize the anti-inflammatory effects of intact PGRN [11, 14, 21]. These observations suggest that a carefully maintained equilibrium between PGRN and granulin peptides may be important for cartilage homeostasis. The trend of changes in the progranulin level, which is observed during JIA, can be a sign of the body's defense against destructive oxidative and inflammatory processes. Thus, a protective effect of progranulin

Table 2. Correlation analysis between plasma PGRN and: GAGs, MMP-3, ADAMT-4, TOS, TAS, CRP and Hb (Pearson's correlation coefficients, r)

Parameter	Non-treated JIA patients (n=30)	JIA patients after treatment and attainment of clinical improvement (n=30)
	r (p)	r (p)
GAGs	-0.03 (0.866)	0.24 (0.222)
MMP-3	0.49 (0.006)	0.27 (0.148)
ADAMTS-4	0.46 (0.011)	0.188 (0.317)
TOS	0.38 (0.042)	0.45 (0.054)
TAS	-0.56 (0.012)	0.51 (0.004)
CRP	0.47 (0.008)	0.431 (0.172)
Hb	-0.53 (0.002)	-0.47 (0.008)

GAGs, glycosaminoglycans; PGRN, progranulin; MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; TOS, total oxidative status; TAS, total antioxidative status; CRP, C-reactive protein; Hb, hemoglobin.

for bone and articular structures is related to an anti-oxidative, anti-inflammatory and chondroprotective effect of this glycoprotein [3, 8, 11, 19, 21]. Although such actions do not appear to be directly linked with GAGs changes in JIA children, which is proven by the reported lack of relation between the mentioned variables, they still take place by indirect mechanisms. In our analysis, plasma PGRN concentration was significantly positively correlated with TOS and negatively correlated with TAS levels in untreated patients. The obtained results may indicate that ROS are factors stimulating the synthesis of PGRN [16], which, in turn, has an antioxidant function in the course of JIA. It is known that the discussed growth factor reduces reactive oxygen species production by immune complex-activated neutrophils through the suppression of nuclear factor-κB (NF-κB) activation, and ameliorates inflammation via the NF-κB pathway [3, 5]. On the other hand, PGRN protects cells from death induced by high concentrations of H_2O_2 in extracellular-signal-regulated kinases 1/2 (Erk1/2)-dependent manner [16]. Although similar mechanisms have not been detected in JIA patients, their presence cannot be excluded. PGRN exerts its anti-inflammatory effects mainly by interacting with the tumor necrosis factor receptors, especially TNFR2, and, thereby, it inhibits downstream pro-inflammatory TNF-αsignaling cascades [3, 12, 14, 15, 21, 25, 26]. Thus, for example, progranulin attenuates the release of TNF-α-induced inflammatory and catabolic mediators, including IL-8, MMP-13, runt-related transcription factor 2 (RUNX2), cyclooxygenase-2 (COX-2) as well as inducible nitric oxide synthase (iNOS) in human osteoarthritis chondrocytes [3, 12, 19]. It was shown that progranulin, or a synthetic progranulin fragment, had a therapeutic effect in an arthritis model, essentially acting as an endogenous TNF-α antagonist [3]. Meanwhile, PGRN also has a function in limiting the intensity of inflammation by controlling the production of anti-inflammatory cytokines, such as IL-10 [8].

In many ways, PGRN is also an important regulator of chondrogenesis and cartilage matrix integrity [8, 12, 14]. On the one hand, progranulin increases the proliferation of chondrocytes by interacting with a cartilage oligomeric matrix protein (COMP), i.e. a glycoprotein essential for cartilage matrix stability [12, 14, 19]. On the other hand, PGRN also prevents the degradation of COMP and other extracellular matrix cartilage components by inhibiting the TNF-α induced increase in ADAMTS-7 and ADAMTS-12 expression [8, 14, 21]. So far, the relationship between progranulin and other enzymes, including ADAMTS-4 and MMP-3, has not been evaluated. These mentioned proteinases are strongly involved in the degradation of aggrecan in the course of JIA [20, 21, 22, 23, 24]. Whereas, the relationship between high PRGN levels and the concentration of ADAMTS-4 and MMP-3 in children with untreated JIA, which we revealed in the study, shed a different light on the role of PGRN in JIA. It seems that progranulin is not a protecting factor against articular cartilage proteolysis catalyzed by these enzymes, but we cannot eliminate such a possibility.

The protective effects of PGRN preventing the development of JIA may also be complicated by the fact that a pro-inflammatory granulin (GRN) is a cleavage product of PGRN [3, 5, 14, 25]. This process is catalyzed by various proteases, including elastases, especially released during infection. Hence, progranulin might be a favorable factor for JIA progress due to its ability to modify the resistance to infectious diseases by PGRN/GRN. This hypothesis is based on the fact that the development of JIA is linked to infection and a post-infectious period [6, 10]. In the course of JIA, the balance between anti- and pro-inflammatory activities of PGRN is disturbed. It has been suggested that the analyzed growth factor could promote an inflammatory response by both potentiate monocyte recruitment as well as by increasing the secretion of pro-inflammatory factors, including IL-6, IL-4, IL-5 [8, 15, 18]. The induction of IL-6 *via* PGRN is a

possible explanation for the fact that progranulin levels are correlated with anemia [18]. In patients with JIA we observed a negative correlation between PGRN and hemoglobin levels, which could confirm the above thesis. One possible explanation for this finding relates to hepcidin, which is produced by the liver in response to IL-6 [13]. Hepcidin exerts a dual effect in that it interferes with the release of iron from macrophages and interferes with iron absorption, leading to anemia of chronic diseases [13, 18].

Paths of transformations of PGRN in the course of JIA are complex, which has been proven by the lack of normalization of plasma PGRN levels in children who achieved clinical improvement. The progranulin alterations are probably related not only to inflammatory processes (demonstrated by positive correlations with CRP) but also to the autoimmune background of the disease. In antinuclear antibodies (ANA) positive patients, higher levels of PGRN were recorded. It is likely that induction of IL-6 by PGRN could be a mechanism by which PGRN is connected with the production of these autoantibodies [18]. It is a fact that IL-6 acts as a stimulator of both B and T cell functions and also promotes the proliferation of plasmablasts during their final stages of maturation into immunoglobulin producing plasma cells [13].

CONCLUSIONS

We postulate that the quantitative changes of plasma PGRN in JIA patients are probably the expression of a defense response to free radical damage underlying this pathology. The obtained results may indicate that progranulin has antioxidative properties in the course of JIA, but they do not confirm the protective role of this glycoprotein in respect to the destructive effects of proteolytic factors. Although we have not indicated the direct link between PGRN and the level of GAGs plasma, the presented data does not allow us to exclude its influence on the aggrecan transformations in JIA children.

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REFERENCES

[1] Aspberg A.: The different roles of aggrecan interaction domains. J. Histochem. Cytochem., 2012; 60: 987-996

[2] Beena J.P.: Juvenile idiopathic arthritis: Review of the literature and case report. J. Dent. Child., 2013; 80: 25-30

[3] Cenik B., Sephton C.F., Kutluk Cenik B., Herz J., Yu G.: Progranulin: A proteolytically processed protein at the crossroads of inflammation and neurodegeneration. J. Biol. Chem., 2012; 287: 32298-32306

[4] Del Carlo M., Schwartz D., Erickson E.A., Loeser R.F.: Endogenous production of reactive oxygen species is required for stimulation of human articular chondrocyte matrix metalloproteinase production by fibronectin fragments. Free Radic. Biol. Med., 2007; 42: 1350-1358

[5] Egashira Y., Suzuki Y., Azuma Y., Takagi T., Mishiro K., Sugitani S., Tsuruma K., Shimazawa M., Yoshimura S., Kashimata M., Iwama T., Hara H.: The growth factor progranulin attenuates neuronal injury induced by cerebral ischemia-reperfusion through the suppression of neutrophil recruitment. J. Neuroinflammation, 2013; 10: 105

[6] Ellis J.A., Munro J.E., Ponsonby A.L.: Possible environmental determinants of juvenile idiopathic arthritis. Rheumatology, 2010; 49: 411-425

[7] Hanyecz A., Olasz K., Tarjanyi O., Nemeth P., Mikecz K., Glant T.T., Boldizsar F.: Proteoglycan aggrecan conducting T cell activation and apoptosis in a murine model of rheumatoid arthritis. Biomed. Res. Int., 2014; 2014: 942148

[8] Jian J., Hettinghouse A., Liu C.J.: Progranulin acts as a shared chaperone and regulates multiple lysosomal enzymes. Genes Dis., 2017; 4: 125-126

[9] Jian J., Konopka J., Liu C.J.: Insights into the role of progranulin in immunity, infection, and inflammation. J. Leukoc. Biol., 2013; 93: 199-208

[10] Kalinina Ayuso V., Makhotkina N., van Tent-Hoeve M., de Groot-Mijnes J.D., Wulffraat N.M., Rothova A., de Boer J.H.: Pathogenesis of juvenile idiopathic arthritis associated uveitis: the known and unknown. Surv. Ophthalmol., 2014; 59: 517-531

[11] Kao A.W., McKay A., Singh P.P., Brunet A., Huang E.J.: Progranulin, lysosomal regulation and neurodegenerative disease. Nat. Rev. Neurosci., 2017; 18: 325-333

[12] Konopka J., Richbourgh B., Liu C.: The role of PGRN in musculoskeletal development and disease. Front. Biosci., 2014; 19: 662-671

[13] Lipsky P.E.: Interleukin-6 and rheumatic diseases. Arthritis Res. Ther., 2006; 8 (Suppl. 2): S4

[14] Liu C.J.: Progranulin: A promising therapeutic target for rheumatoid arthritis. FEBS Lett., 2011; 585: 3675-3680

[15] Nguyen A.D., Nguyen T.A., Martens L.H., Mitic L.L., Farese R.V. Jr.: Progranulin: at the interface of neurodegenerative and metabolic diseases. Trends Endocrinol. Metab., 2013; 24: 597-606

[16] Sato K., Yamanaka Y., Ishii M., Ishibashi K., Ogura Y., Ohtani-Kaneko R., Nishihara M., Nedachi T.: Dual cell protective mechanisms activated by differing levels of oxidative stress in HT22 murine hippocampal cells. Biosci. Biotechnol. Biochem., 2014; 78: 1495-1503

[17] Sun S., Bay-Jensen A.C., Karsdal M.A., Siebuhr A.S., Zheng Q., Maksymowych W.P., Christiansen T.G., Henriksen K.: The active form of MMP-3 is a marker of synovial inflammation and cartilage turnover in inflammatory joint diseases. BMC Musculoskelet. Disord., 2014; 15: 93

[18] Tanaka A., Tsukamoto H., Mitoma H., Kiyohara C., Ueda N., Ayano M., Ohta S., Inoue Y., Arinobu Y., Niiro H., Horiuchi T., Akashi K.: Serum progranulin levels are elevated in patients with systemic lupus erythematosus, reflecting disease activity. Arthritis Res. Ther., 2012; 14: R244

[19] Toh H., Chitramuthu B.P., Bennett H.P., Bateman A.: Structure, function, and mechanism of progranulin; the brain and beyond. J. Mol. Neurosci., 2011; 45: 538-548

[20] Troeberg L., Nagase H.: Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim. Biophys. Acta, 2012; 1824: 133-145

[21] Wei J., Hettinghouse A., Liu C.: The role of progranulin in arthritis. Ann. N Y Acad. Sci., 2016; 1383: 5-20

[22] Winsz-Szczotka K., Komosińska-Vassev K., Kuźnik-Trocha K., Gruenpeter A., Lachór-Motyka I., Olczyk K.: Influence of proteolytic-antiproteolytic enzymes and prooxidative-antioxidative factors on proteoglycan alterations in children with juvenile idiopathic arthritis. Clin. Biochem., 2014; 47: 829-834

[23] Winsz-Szczotka K., Komosińska-Vassev K., Kuźnik-Trocha K., Siwiec A., Żegleń B., Olczyk K.: Circulating keratan sulfate as a marker of metabolic changes of cartilage proteoglycan in juvenile idiopathic arthritis; influence of growth factors as well as proteolytic and prooxidative agents on aggrecan alterations. Clin. Chem. Lab. Med., 2015; 53: 291-297

[24] Wojdasiewicz P., Poniatowski Ł.A., Szukiewicz D.: The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm., 2014; 2014: 561459

[25] Wu H., Siegel R.M.: Progranulin resolves inflammation. Science, 2011; 332: 427-428

[26] Yamamoto Y., Takemura M., Serrero G., Hayashi J., Yue B., Tsuboi A., Kubo H., Mitsuhashi T., Mannami K., Sato M., Matsunami H., Matuo Y., Saito K.: Increased serum GP88 (Progranulin) concentrations in rheumatoid arthritis. Inflammation, 2014; 37: 1806-1813

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