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Review

Human pathology: role of proteinase's inhibitors

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Abstract Proteinase inhibitors are always involved in protecting the human body. Deficiency of proteinase inhibitors characteristic of patients with Covid-19, colon and stomach cancer, liver cirrhosis. Acute phase of hepatitis B, emphysema, bronchial asthma, flu, acute respiratory infections. An elevated level of a proteinase inhibitor is observed in rhinitis, hepatectomy, psoriasis, benign neoplasms, glomeronephritis in children, rheumatoid arthritis, pulmonary tuberculosis, sarcoidosis of the respiratory system. In the treatment of such patients, it is necessary to correlate the administration of proteinase inhibitors or the proteinases themselves.

Keywords: proteinases, inhibitors, role in pathological processes

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Introduction

Over the past few months, the worldwide attention and efforts of scientists have been riveted to the study of COVID-19. We propose to look at this problem from the angle of consideration of the role of proteinase-inhibitors system and look for common solutions for the most viruses. Coronaviruses still represent a leading source of novel viruses for emergence into the human population [1].

In inflammatory process of this disease a proteinases-inhibitor system plays leading role. Unbalance between proteinases and their inhibitors matters for development of a virus infection contamination.

So, on the SARS-CoV-2 peplomer, a site for cleavage by furin-like serine proteinases was discovered. These proteinases are involved in the activation of a number of toxins and the maturation of viral envelope proteins [2].

Considering the ancient protective mechanisms of the body, we will certainly encounter an inflammatory process in which various proteinase inhibitors participate. They are an integral component of the fibrinolytic blood system.

When we look at the oldest human body protection mechanism we will see inflammation process there and proteinase inhibitors took part in it. It's are inseparable components of bloods fibrinolytic system. At least six inhibitors possess antiplasmin properties:

- α2-antiplasmin,
- α2-macroglobulin,
- α1-antitrypsin,
- antithrombin III,
- C-inactivator and
- inter-α-antitrypsin [3].

In clinical pathology or experiments on animal the level of antiplasmin in blood plasma significantly lowered and most author explain it as antiplasmin's deficit. Such lowering of antiplasmin activity marked in 6 (16,7%) from 36 patients with colon or stomach cancer in age from 50 to

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76 years [3].

Level of α2-antiplasmin in blood plasma significantly decreasing at pathological condition of liver, especially at liver cirrhosis [4]

Blood clots in wounded or surgical sites are dissolving prematurely and bleeding recurs at deficit of α2-antiplasmin and in activator of plasminogen- I [5]. But in case of some other pathologies level of α2-antiplasmin in blood plasma could have no changes. So it was found that with the development of enhanced intravascular coagulation, the levels of plasminogen and α2-antiplasmin in patients with malignant neoplasms and donors did not differ, which indicates the preservation of protective plasma fibrinolytic activity in patients, but α2-macroglobulin is involved in the development of infectious and inflammatory reactions [6].

The prognostic significance of determining the level of α2-macroglobulin in viral and degenerative liver diseases has been established [7]. Thus, in clinical studies patients with the acute phase of hepatitis B, it was found that the onset of the disease was accompanied by a decrease in the level of α2-macroglobulin and that patients with a sufficiently high level of this inhibitor had a better prognosis of the course of the disease. However, other researchers have shown that a high level of α2-macroglobulin is observed at 2-4 weeks of illness in a third of patients with acute hepatitis B virus [8]. In rhinitis, an increase in the level of α2-macroglobulin in blood plasma and in the exudate of the nasal sinuses was observed only in 15% of patients [9].

In patients with destructive pulmonary tuberculosis, several forms of serum were found to have several forms of 2-macroglobulin, the level of which varied during treatment [10]. The F-form of the inhibitor outpaced the decrease in the activity of the total q2-macroglobulin. Based on the results of the studies, the authors proposed to use the definition of the level of S-form alpha-2-macroglobulin as a predictive marker of relapse disease.

Compared with the levels of α2-macroglobulin in the blood serum and plasma of healthy people, the level of this inhibitor increases with some neurological diseases, but does not change (regardless of the duration of the disease) with multiple sclerosis [11].

In an experiment on rats, it was shown that damage to capsaicin-sensitive nerves is accompanied by an increase in α2-macroglobulin 3 days after injection [12].

Using a number of surgical procedures including castration and hepatectomy it has been shown that the increase in the level of α2-macroglobulin in the liver in response to inflammation is regulated, at least partially, by the testicle through testosterone. Partial hepatectomy caused a tenfold increase in mRNA levels and synthesis of α2-macroglobulin in the liver, and castration caused a moderate increase in the level of α2-macroglobulin. Insufficient synthesis of α2-macroglobulin by the liver after castration can be correlated with preliminary injections of testosterone 6 days before the operation [13].

The hypothesis that the deficiency of 2-macroglobulin can contribute to the proteolytic destruction of arterial tissue and thus α2-macroglobulin is able pattoparticie indirectly in directly in the vascular disease has not been confirmed in studies in patients with arterial aneurysms, as the level of this inhibitor was insignificantly different from that of donors [14]. A study of the level of α2-macroglobulin in the serum of the men with long-term psoriasis cases

showed a significant increase in this indicator in the acute phase of the disease and a decrease in the level to the indications of donors for long periods treatment that allowed the authors to offer α2-macroglobulin as a marker of treatment [15]. Fifty patients have a high level of α2-macroglobulin in blood plasma [16], pleural and abdominal exudates and ascite fluids of benign and malignant tumors [17].

Some authors suggest using the study of the level of α2-macroglobulin as a marker of differential diagnosis of kidney disease in children. The syndrome, as opposed to simple glomerulonephritis, is characterized by a significant increase in the level of α2-macroglobulin in the urine, while in healthy children this inhibitor in the urine is absent [18]. α2-macroglobulin has also been proposed as a diagnostic criterion for rheumatoid arthritis, and monitoring concentrations of α2-macroglobulin with IgG in patients with rheumatoid arthritis can serve predictive criterion of the disease [19].

It is known that level of α1-antitrypsin in blood sera at autoimmune hepatitis, chronic necrotic-inflammatory disease of liver of unknown etiology, characterized by a periportal or more extensive inflammatory process in the liver, remains within the normal values [20].

Also, the level of serum α1- antitrypsin remains within normal values in chronic viral hepatitis - a chronic liver disease caused by hepatitis B, C and D viruses, which develops 6 months after acute viral hepatitis [20].

Within the normal range is the level of serum in patients with multiple sclerosis [21] and in adults with renitis [错误! 未定义书签。].

Increased activity of serum α1-antitrypsin is observed in 90% of cases in pulmonary tuberculosis and respiratory sarcoidosis [20], but in the silicosis of the lungs and in the serum of the electric welders, the content of α1- antitrypsin remains within the norm [21].

There are some diseases, such as some types of liver pathology [22], pulmonary emphysema [23], chronic inflammatory arthritis, which are caused by hereditary deficiency of1-antitrypsin or its gene mutations [24]. Hereditary deficiency of α1-antitrypsin is also caused by the spread of chronic obstructive inflammation [25].

In the emphysema of smokers there is a decrease of activity of α1-antitrypsin blood serum, as a result of disproportionate biochemical processes between elastase and α1-antitrypsin pathological destruction occurs [26].

Deficiency of α1-antitrypsin, which is observed in cirrhosis of the liver, developed after hepatitis C is caused by the homozygous state of allele ZZ, and pathological change of hepatocytes (without necrosis) - homozygous condition allele MM [27].

Individuals with bronchial asthma syndrome also have a reduced content of α1-antitrypsin. In the experiment on rats, exposed to acetic lead inhalation, it was shown that under the influence of this substance there is a destruction of lung tissue, which is accompanied by a decrease in the level of α1-antitrypsin and an increase in the activity of trypsin-like enzymes [28].

In an experiment on mice infected with a lethal dose of influenza A virus, during the period of maximum accumulation of infectious and hemagglutinating activity, there was a sharp decrease in the level of inhibitory activity, up to its complete disappearance, which led to the death of animals. Increased activity of α1- antitrypsin the serum is usually observed in chronic inflammatory processes such as rheumatoid arthritis. Caused by the predominance of M3

allele of this inhibitor [29].

In most cases, with pathological conditions, a decrease of antithrombin III is observed. In cancer patients, compared with healthy patients, is found a decrease of level of antithrombin III (1.4 times). Therefore, in response to increased intravascular coagulation, consumption of own inhibitors of thrombin and other active serine proteinases is increased. Also, depression of level of an antithrombin III (in 1,3 times for 3-6 days after operation) in the postoperative period at the patients of control group, who were not receiving preventive therapy [30]. has been taped. At the same time at the patients receiving low molecular heparins (Clexane and fraxiparine), the maintenance of an antithrombin III practically did not differ from initial indexes that testifies to conservation of natural inhibitors of thrombin and protection of an organism against a thrombosis.

Main inhibitory activity in relation to plasmin (in euglobulin precipitate) has c1-antiactator. C1-antiactivator contains 43.7% carbohydrates, and sialic acid is 14-15 percent [31]. C1-antiactivator inhibits urokinase activity, is able to inhibit the vascular (tissue) plasminogen activator, but does not inhibit streptokinase activity. The fibrinolytic activity of the euglobulin fraction of plasma is partially dependent on the fluctuations in the content of C1-antioxidant in the blood [32].

Conclusion

1. Inhibytors proteolytic enzymes act as regulators of the constant level of the corresponding enzymes in the body, being with them in a constant dynamic equilibrium.

2. Disruption of the enzyme-inhibitor system leads to the development of diseases such as: gastrointestinal cancer, cirrhosis of the liver, tuberculosis, tumors, glomerulonephritis, influenza, asthma, myocardial infarction.

3. Inhibitors block the process of splitting viral influenza proteins by suppressing cellular proteins.

4. A method of obtaining an antiviral drug against influenza, a trypsin-like protein inhibitor, has been developed and patented.

Conflicts Of Interest

None

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References

1. Belouzard, S., Chu, V. C., & Whittaker, G. R Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proceedings of the National Academy of Sciences, . 2009; 106(14): 5871-5876.
2. Kopitar-Jerala, N. The role of cysteine proteinases and their inhibitors in the host-pathogen cross talk. Current Protein and Peptide Science,.2012; 13(8):767-775.
3. Lysikova M. , M. Wald, Z. Masinovsky . The mechanism of inflammatory reactions and the effect on them using proteolytic enzymes / M. Lysikova // Cytokines and inflammation .—2004; 3(3):48-53.
4. Vorobiev P.A., A.N. Shilova, S.A. Khodorenko Clinical and economic analysis of the prophylactic use of unfractionated and low molecular weight heparins in the surgical treatment of cancer patients. Communication 1. Efficiency criteria (and others) . Modern Oncology .—2002; 4 (. 2):67-72.
5. Aoki N. Yamanaka T. The alpha2-plasmin inhibitor levels in liver diseases. Clin. Acta.—1978;1(84):99-105.
6. Lampl L., Helm M., Specht A. et al. Blood coagulation parameters as prognostic factors in multiple traumas: can clinical values be an early diagnostic aid? Zentralbl Chir. 1994; 119 (10): 683-689.

7. Somonova O.V. Outbreak Diagnostics hemostasis and principles of their correction thrombotic complications oncologists: Abstract. Dis. Doc. Med. Sciences: 14.00.14., 14.00.46. Rossiysky oncologists. Scientific Center N. N. Blokhina RAMS Moscow, 2008; 50 c .
8. Pedrazzini A., Wuhrmann F. Prognostic importance of albumins and alpha-2-Mglobulins in viral and degenerative liver diseases Epatologia. 1969; 15(6) : 389-392.
9. Meliconi R., Parracino O., Facchini A. et al. Serum protease inhibitors in acute viral hepatitis . Ric Clin Lab. 1987; 17(1):53-59.
10. Hamaguchi Y., Ohi M., Ukai K. et al. Proteolytic activity and serum protease inhibitors in nasal secretions from adult patients with common colds . Rhinology. 1986; 24(2):125-132.
11. Esmedliaeva D.S., Titarenko O.T., Skvortsova L.A. et al. The activity of alpha2-macroglobulin and its forms in patients with destructive pulmonary tuberculosis . Probl Tuberk Bolezn Legk. 2004; 6(11) : 40-43.
12. Bollengie F., Mahler A., Clinet G. Measles antibodies, anti-proteinase and plasminogen distribution in serum and plasma from patients affected with multiple sclerosis and patients affected with non6neurological diseases. J Clin. Chem Clin Biochem. 1984;22(10):653-659.
13. Tolochko Z.S. Spiridonov V.K. Alternative changes of activity of alpha2-macroglobulin and alpha16antitrypsin in rat blood following damage in capsaicin6sensitive nerves . Ross Fiziol Zh Im I M Sechenova.. 2006;. 92(9):1078-1084.
14. Lui W. Y., Cheng Y. H., Mruk D. D. et al. Alpha2-macroglobulin expression in the liver in response to inflammation is mediated by the testis. J Endocrinol. --2005;185(3):497-505.
15. Konrad C., Langer C., Muller G. A. et al. Protease inhibitors in spontaneous -cervical artery dissections . Stroke. 2005; 36(1): 9-13.
16. Chodorowska G., D. Wojnowska, M.Juszkiewicz Borowiec C-reactive protein and alpha2-macroglobulin plasma activity in medium-severe and severe psoriasis . J Eur Acad Dermatol Venereol. 2004; 18(2)P:180-183.
17. Alexandrakis M.G, Moschandrea J., Kyriakou D.S. et al. Use of a variety of biological parameters in distinguishing cirrhotic from malignant ascites. Int J Biol Markers. – 2001;16(1.):45-49.
18. Alexandrakis M. G., Kyriakou D.S., Bouros D. et al. Interleukin66 and its relationships to acute phase proteins in serous effusion differentiation. Oncol Rep. 2001; 8(2): 415-420.
19. Lubec G., Weissenbacher G., Balzar E. Alpha2-macroglobulin in children with glomerular diseases . Wien Klin Wochenschr. 1977; 89(1): 49-53.
20. 20. Van Gool J. Profiles of acute-phase reactants and clinical significance of alfa-2-macroglobulin in acute hepatitis B.Inflammation. 1983;7(3):277-289.
21. 21.Rundle A.T. ,Atkin J. Serum alfa-2-macroglobulin levels in tuberose sclerosis. J Ment Defic Res. 1976;20 (4):231-236.
22. Zorina V.N., Trofimenko N.A., Archipova S.V. et al. Alpha2-macroglobulin, its complexes with IgG and some several factors of humoral immunization theta for rheumatoid arthritis . Scientific - rheumatol. - 2006.;1:22-27.
23. Popov E.V. Clinical comparison manifestations of systemic inflammation in patients with small forms of tutuberculosis and sarcoidosis organs respiration: abstract Dis. Cand. honey.sciences. Central Research Institute of Tuberculosis RAMS.2008; 21 p.
24. Gola A., Ga˙nzka Z., Tychowski K. Alpha 1-antitrypsin level and the state of the respiratory tract in arc welders .Med Pr. 1980; 31(1): 41-44.
25. Otte, J. B., de B. Hemptine, D. Moulin et al. Liver transplantation in children . Chir Pediatr. 1985; 26(5): 261-273.
26. Ulmer W.T., Schmidt E.W., Schwabl U. et al. Pulmonary emphysema. Clinical aspects and open questions // FortschrMed. 1989; 107(9):201-204.
27. Loche F., Tremeau-Martinage C., Laplanche G. et al. Panniculitis revealing qualitative alpha 1 antitrypsine deficiency (MS variant) . Eur. J. Dermatol. 1999; 9(7):565-567.
28. Dzyublik A.Ya., Mukhin A.A., Bialik E.I. Chronic Obstructive Disease lungs modern concept pathogenesis, approaches to therapy. Clinic. immunology. Allergology. Infectology. 2007; (6):98 – 102.
29. Hug G., Chuck G., Bowles B. Alpha 16antitrypsin phenotype: transient cathodal shift in serum of infant girl with urinary cytomegalovirus and fatty liver . Pediatr Res. 1982;16(3): 192-198.
30. Zhukova E.N. Deficiency of a protease-A1-antitrypsin inhibitor in the development and exacerbation of various clinical forms of chronic pancreatitis . Russian Gastroenterological Journal . —1998;(2):128-132
31. Likholat, E.A., T.V. Ananyeva , S.V. Antoniuk et al. Proteolytic system in lungs upon inhalation exposure to low

doses of lead salts . Ukr. Biokhim.J.- 2000;72(6):84-87.

32. Divocha VA . Influenza virus and cell enzymes . Experimental and clinical medicine. – 1999; (2):100-105.