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The possibilities of using the inhibitors of matrix metalloproteinases for keratoplasty

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Abstract

The review is devoted to the actual problem of treating patients with keratolysis. The role of matrix metalloproteinases in the pathogenesis of cornea and corneal graft melting is discussed as well as the practical experience of using synthetic metalloproteinase inhibitors in various branches of medicine and in ophthalmology, in particular. In the field of eye diseases, the search for effective methods for the treatment of corneal injuries of various origins, as well as its post-transplant complications, has been underway for a long time. Recent studies have shown that local imbalance of matrix metalloproteinases and their inhibitors system, as well as the immune system status, may play the main role in the outcome of urgent keratoplasty, and the use of synthetic metalloproteinase inhibitors can significantly improve the biological result of the donor cornea transplant. The role of platelets in the regulation of the proteolytic system has not been fully studied. However, some literature data on the platelet-associated inhibitor of metalloproteinases and the use of platelet-rich plasma to correct the collagenolytic activity of enzymes are of great

interest to ophthalmologists, due to therapeutic efficacy and simple method of producing its production the autologous platelet-rich plasma.

The present brief literature review covers the pathogenesis and clinical features of keratolysis, factors which can affect the outcome of urgent keratoplasty, describes the features of matrix metalloproteinases, their inhibitors, and the platelet-rich plasma as a potential endogenous source of a tissue inhibitor of matrix metalloproteinases.

Aim. *To evaluate the possibility of using inhibitors of matrix metalloproteinases for keratoplasty based on a literature review.*

Material and methods. *To write the review article, we have made the search in the homeland eLibrary.RU database and in the PubMed resource database to select the articles on the topic published in the period from 1985 to 2022.*

Keywords: cornea, keratoplasty, matrix metalloproteinases, synthetic inhibitors of metalloproteinases, platelets, aprotinin

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ELISA, enzyme immunoassay
IL, interleukin
MMP, matrix metalloproteinases
PRP, platelet rich plasma
TIMP, tissue inhibitor of matrix metalloproteinases
TNF-α, tumor necrosis factor alpha

Introduction

Human visual acuity significantly depends on the status of the eye optical media, mainly the cornea, which provides 2/3 of the optical power

of the visual analyzer. Corneal blindness is a significant social and economic problem, as it affects the working-age population to a greater extent. According to the World Health Organization data for 2014, blindness as a result of corneal pathology ranks 4th (5.1%) after cataract, glaucoma, and age-related macular degeneration. In the Russian Federation, corneal blindness accounts for 5.9% of blind and visually impaired patients, and 9% in the structure of visual disability [1].

Over the recent decades, progress has been made in the treatment of the eye anterior segment pathology. Layer-by-layer corneal transplantation techniques are becoming more widespread; however, penetrating keratoplasty remains the main, and sometimes the only, method of treating corneal pathology [2].

Often, complications may develop after emergency keratoplasty: flaccid eithelialization, erosion and ulcers, which can lead to corneal graft lysis [2] and require various interventions in the anterior segment of the eye: the use of therapeutic soft contact lenses, conjunctival autoplasty, amniotic membrane transplantation, blepharorrhaphy [3]. However, all these measures do not affect the pathogenetic component of the process, they are symptomatic treatment, and the results are not always satisfactory.

In this regard, the continuation of research in order to find new ways to prevent and treat corneal graft lysis remains an urgent task in ophthalmology. In our opinion, a pathogenetically substantiated approach to its solution is to study the local proteolytic status, as well as the parameters of the immune system in the pre- and post-transplantation period.

The literature describes the significance of tear enzymes [4, 5], as well as systemic immunity parameters in local processes in the anterior segment of the eye [6]. In 1962, the investigators J. Gross and C. Lapierre

discovered a new class of enzymes called matrix metalloproteinases (MMPs). Since then, more than 20 enzymes of this family have been characterized and their functions have been described in detail [7]. The role of MMPs and their inhibitors in the development of autoimmune diseases [8], glaucoma [9], uveal melanoma [10], oncology [11, 12], etc. has been studied in various fields of medicine. The efficacy of synthetic MMP inhibitors has been demonstrated in trauma surgery and orthopedics [13, 14], cardiology [15], in ophthalmology for the treatment of posterior blepharitis [16], as well as after the fistulizing antiglaucoma surgery [9].

The use of blood preparations: whole autologous blood, packed white cells and platelets, various forms of platelet-rich plasma (PRP) has been shown to be promising in the treatment of corneal diseases [17, 18]. According to the literature, α-granules of human platelets, in addition to growth factors, contain tissue inhibitor of metalloproteinases-1 (TIMP-1), which was confirmed by immunohistochemical staining [19, 20]; however, the use of PRP to correct local proteolytic status has not yet found its application in ophthalmology.

Thus, MMPs and their inhibitors have not been sufficiently studied, and the possibilities of using synthetic MMP inhibitors in the treatment of eye diseases and ophthalmic transplantation are under investigation.

Clinical and pathogenetic features of keratolysis

Keratolysis is a multifactorial process of damage to the corneal tissue or a corneal graft with melting and defibration of the stroma, which is caused by the combined action of enzymes of the local proteolytic system, the activation of immunocompetent cells, and the toxins of microorganisms [2].

The causes of corneal graft melting can be a delayed epithelialization and a long-term persistent ulcer defect in the postoperative period, recurrent infection, neurotrophic and immunological disorders, dry eye syndrome, persistent ophthalmohypertension, comorbidities, primarily autoimmune diseases, as well as an increased aggression of proteolytic tear enzymes [21].

The main indications to emergency corneal transplantation are: descemetocele, corneal perforation, corneal graft melting. In conditions of urgent surgery, due to the shortage of donor material, preserved cornea is used. Despite the fact that such a material has less immunogenicity due to a decrease in the content of lymphocytes and antigen-presenting cells in it, emergency patients who belong to the high-risk group undergo 2-3 or more rekeratoplasties, often without a satisfactory result and with graft lysis [22]. With a high risk of epithelialization disorders and the associated dry eye syndrome that accompanies autoimmune diseases, urgent keratoplasty is combined with cornea coverage with conjunctiva, amnion, blepharorrhaphy; however, this does not always contribute to the uneventful course of the postoperative period [2].

Comprehensive consideration of these factors in the context of keratolysis is a pathogenetically substantiated research vector in ophthalmic transplantation and will contribute to the improvement of treatment outcomes.

Etiological factors affecting the keratoplasty outcome

The outcomes of corneal transplantation depend on the presence of the risk factors in a patient, such as neovascularization of the bed, inflammation, infections, repeated keratoplasty, allosensitization during transplantation of other solid organs, glaucoma, allergic and systemic

diseases of the recipient, pregnancy, previous history of eye surgery [23, 24].

Neovascularization is the most significant factor determining the keratoplasty outcome. The blood and lymphatic vessels, while penetrating into the corneal graft, play a critical role in the transfer of foreign antigens to the host and delivery of effector immune cells, aggravating the course of the postoperative period [23, 24]. According to the literature, the 5-year graft survival in surgery on an avascular bed with local immunosuppressive therapy can reach about 90% [24, 25]; the results are noticeably worse in urgent keratoplasty on an inflamed, vascularized bed and, according to various sources, the 5-year survival rates make only 35–70 % [24, 26]. The high percentage of keratoplasty favorable outcome in patients of the “low” risk group, despite the absence of HLA-typing, is explained by the immune privilege of the organ of vision, namely, anterior chamber-associated immune deviation (ACAID), immunosuppressive components of aqueous humour, factors involved in maintaining corneal avascularity, membrane-associated immunologically active molecules of corneal endothelial cells [27].

Repeated keratoplasty aggravates the course of the postoperative period. The probable causes for this are presensitization, immunological memory and, of course, an inflamed, often infected environment and neoangiogenesis from previous operations, which result in increased production of pro-inflammatory cytokines: IL-1, IL6, tumor necrosis factor-alpha (TNF-α), chemokines, including MIP-1α, MIP-1β, MIP-2. At the same time, donor corneal antigen-presenting cells become more efficient in alloantigen presentation and in the transition of T cells to Th1 effectors [24, 28]. According to world studies, with an intact bed before surgery, a 4-year mean survival rate of full-thickness corneal grafts was

85%, compared with 58% for the group with pre-transplant inflammation of the recipient bed [23].

The presence of systemic, mainly autoimmune and allergic diseases in the recipient (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, Lyell's disease, etc.) is an important factor determining an unfavorable course of the postoperative period after urgent keratoplasty. On the one hand, the complications in such patients occur due to the peculiarities of the immunological status, namely, excessive production of IL-1, IL-6, TNF-α, as well as synergistic inhibition of IL-4, IL-10 [29]. On the other hand, the level of these pro-inflammatory cytokines, being in direct correlation with MMP activity, enhances the proteolytic ability of tears, which negatively affects the graft acceptance process, and often leads to its melting [30].

Matrix metalloproteinases: general characteristics and clinical significance in the development of various diseases

Matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes that are capable of degrading native collagen and other extracellular matrix proteins. These proteins are involved in the protein metabolism of connective tissue, in the processes of normal development and remodeling of the cell matrix, embryogenesis, tissue repair, neoangiogenesis, as well as in the processes of tumor transformation and metastasis [5, 7]. MMPs are secreted by keratinocytes, fibroblasts, monocytes, tissue macrophages, polymorphonuclear leukocytes, and malignant cells [8].

To date, 28 MMP enzymes are known, which are classified into 5 subfamilies: collagenases, gelatinases, stromelysins, mitrilysins, and membrane-bound MMPs (MB-MMPs), while insufficiently studied ones are referred to the “other enzymes” subfamily [30].

For ophthalmology, MMP-2 and MMP-9 (a subfamily of gelatinases) are of greatest interest, exhibiting substrate activity towards laminin and type IV collagen being the main components of basement membranes. MMP-2 and MMP-9 are produced by corneal epithelial cells, as well as by stromal fibroblasts [31]. The MMP level is regulated by the activators IL-1, IL-2, IL-8, TNF-α, plasmin, and inhibitors TIMP-1,2,3,4, α2-macroglobulin, IL-4, IL-6, IL-10, IFN-β. It has been proven that when tissues are damaged, proinflammatory cytokines are released, plasmin activity increases, which leads to an increased secretion of MMPs and the appearance of an imbalance between MMPs and their tissue inhibitors (TIMPs), which ultimately triggers the process of tissue remodeling and denaturation, closing a vicious circle [4].

In 2013 R. Sambursky et al. in a large group of patients (n=206), including 143 patients having Sjögren's syndrome, by using the InflammaDry detector, found an increased MMP-9 activity in the tear and on the surface of the eye, which led to desquamation of the corneal epithelium and determined the clinical presentation and severity of the disease [32].

In 2014 M. Xue et al. identified the activity of MMP-2 and MMP-9 on the surface of synovial fibroblasts isolated from 7 patients with rheumatoid arthritis and 8 patients with osteoarthritis after knee replacement, and proved that MMP-2 and MMP-9 are expressed on the surface of cells, promote survival, proliferation, migration and invasion of synovial fibroblasts in rheumatoid arthritis, stimulate the cartilage inflammation and degradation [33].

In 2015, on the base of the Glaucoma Department in the Helmholtz National Medical Research Center for Eye Diseases, M.U. Arapiev et al. conducted a study of 60 patients with confirmed or suspected glaucoma. The analysis showed an increase in the systemic production of MMP-9 in

patients with primary open-angle glaucoma due to changes in the structure of the extracellular matrix components, a decrease in the cornea elastic properties, which ultimately affected the outflow of intraocular fluid through the drainage zone and created the conditions for compression damage to the axons of retinal ganglion cells [34].

In 2019, on the base of the Mariinsky Hospital, I.V. Brezhskaya et al. conducted a study that included 81 patients with aseptic corneal ulcers of various origins. In addition to surgical treatment, the proteolytic status of tears was assessed and, if necessary, corrected. As a result, the authors showed that the collagenolytic activity of the conjunctival fluid of the eye having an aseptic corneal ulcer is a mean of 150–340% higher than in healthy people. The severity of enzymatic aggressiveness depended on the depth of the developed corneal ulcer and its etiology, and was higher in patients with autoimmune pathology [5].

Platelets as an endogenous source of tissue inhibitors of matrix metalloproteinases

The expression of MMPs is strictly controlled by their tissue inhibitors, i.e. TIMPs. These regulatory molecules are secreted by fibroblasts, macrophages, endothelial cells, smooth muscle cells, scar tissue, synovial membranes, and platelets [35–37]. Platelets contain numerous α-granules with biologically active substances.

In 1985 T.W. Cooper et al. conducted a study investigating a tissue inhibitor of platelet-derived collagenases. Collagenase inhibitors that are functionally and immunologically identical to the inhibitors secreted by human dermal fibroblasts have been identified in a number of human connective tissues, amniotic fluid, and blood serum. The authors examined cell lysates of purified platelets, mononuclear cells, granulocytes and erythrocytes for the presence of immunoreactive protein

by using enzyme immunoassay (ELISA) to detect human collagenase inhibitor. It turned out that only the platelet lysate contained a collagenase inhibitor in the amount of 225 ng/mg of cellular protein; other cell lysates did not contain measurable amounts of the inhibitor. It was shown that the content of the inhibitor in plasma mad 46% of its value in blood serum, and the blood coagulation process led to a 2-fold increase in the blood serum concentration of the inhibitor compared to plasma, which was associated with its release from platelet α-granules. An ELISA was also performed on a lysate of megakaryocytes (platelet precursors) / with the addition of megakaryocyte lysate (platelet precursors), and as it turned out, it contained the inhibitor in an amount of 140 ng/mL. Thus, it was shown that the platelet-associated inhibitor is produced endogenously. The authors noted that various pathological processes can occur with the participation of a platelet-derived collagenase inhibitor. For example, in fibrotic diseases, atherosclerosis, the platelet inhibitor action can lead to the collagen accumulation, thereby contributing to the occurrence of these complex and multifactorial diseases [20].

In 1997 T. Murate et al. studied the possible role of platelet and megakaryocytic TIMPs in the development of bone marrow fibrosis. They quantified serum TIMP-1 and TIMP-2 in healthy subjects and in patients with low or high platelet counts. Serum levels of TIMP-1 and TIMP-2 in healthy volunteers were 101.1±13.3 ng/mL and 82.7±26.3 ng/mL, respectively. In patients with elevated platelet counts, such as those with essential thrombocytosis, polycythemia vera, and myelofibrosis, serum levels of TIMP-1 and TIMP-2 were 351.6±200.9 ng/mL and 148.9±84.0 ng/mL, respectively. Serum levels of TIMP-1 and TIMP-2 in patients with low platelets, such as in aplastic anemia and idiopathic thrombocytopenic purpura, were 57.2±25.8 ng/mL and 19.7±7.68 ng/mL, respectively. According to the authors, the serum level

of TIMP-1 statistically significantly correlated with the platelet counts in all cases, the relationship between the blood serum level of TIMP-2 and the platelet counts was not so strong. Immunohistochemical analysis revealed the presence of TIMP-1 and TIMP-2 on megakaryocytes and platelets, confirming that they are rich sources of TIMP. The authors suggested that TIMPs released from megakaryocytes and platelets, along with transforming growth factor beta (TGF-b) and platelet-derived growth factor (PDGF), can stimulate the proliferation of bone marrow fibroblasts and play an important role in the processes of bone marrow fibrosis [19].

In 2002 M.N. Holten-Andersen et al. reported that cancer patients who received blood transfusions during surgery for solid tumors had higher rates of disease recurrence and mortality. They suggested that the cause is tissue TIMP-1 present in high amounts in platelets, which stimulates cell growth and inhibits apoptosis and, therefore, can be considered as a factor influencing tumor progression. The authors measured the levels of TIMP-1 in various blood products and in packed platelets. The mean levels of TIMP-1 in whole blood and platelet-rich plasma were 41.6 and 139.8 μg/L, respectively. TIMP-1 could not be detected in the blood products with a platelet content reduced by more than 99%. In addition, the level of TIMP-1 significantly increased during long-term storage of preparations containing platelets, which, apparently, is associated with their breakdown and release of TIMP-1 from α-granules [38, 39].

Experience of using synthetic inhibitors of matrix metalloproteinases in various fields of medicine

In the course of studying the MMP–TIMP system and understanding the important role of its imbalance in the development of

many diseases of the human body, scientists from various fields of medicine began to develop synthetic MMP inhibitors. The most famous of them and used in clinical practice include aprotinin, doxycycline, azithromycin, etc.

The action of doxycycline as an MMP inhibitor has been demonstrated in an experimental study in a model of glaucoma in rabbits undergoing trabeculectomy. In the postoperative period, the drug was administered subconjunctivally and in the form of instillations. According to the results of immunohistochemical analysis, an increase in the level of TIMP-1 and a decrease in MMP-9 were found, which solved the problem of excessive fibrosis of the filtration bleb and determined the success of the operation. The authors emphasize that topical application of doxycycline can be considered as an alternative to mitomycin-C in antiglaucoma surgery [9].

In 2010 D. Li et al. conducted an *in vitro* study and showed that in cultured human corneal epithelial cells, azithromycin suppresses the expression of pro-inflammatory cytokines and MMP-1,3,9 in a dose-dependent manner [40]. In 2015 L. Zhang et al. found that topical application of 1% azithromycin in patients with dry eye syndrome reduced MMP-9 expression to normal after 4 weeks [41].

Aprotinin is an inhibitor of the proteolytic enzymes, such as plasmin, trypsin, chymotrypsin, kallikrein. This drug is a strong MMP inhibitor, suppressing the metalloproteinase activation pathways by plasmin. In 1996 E. Lee, D.E. Vaughan found that plasminogen induced the MMP secretion in cultured vascular smooth muscle cells, while aprotinin inhibited it [42].

In 2008 J. Orchard et al. published the results of a clinical study in which aprotinin was administered peritendonally to 430 subjects with tendopathies of the Achilles tendon and patella. According to the survey,

patients who had previously received cortisol injections reported better clinical outcomes from aprotinin therapy. Meantime, the condition of 76% of patients improved, 22% reported no changes, and only 2% noted a negative trend [14].

In 2018 N. Ryosuke et al. conducted a study in vitro, where they investigated a series of chondral, meniscus, and synovial tissue cultures from patients with osteoarthritis. The samples were treated with cytokines (IL-1, TNF-α), lipopolysaccharide (endotoxin, which is an inflammatory mediator), and aprotinin. The results of the performed zymography showed higher levels of MMP-2 and MMP-9 in samples treated with cytokines and lipopolysaccharide. The authors concluded that the molecular structure of the endotoxin signaling cascade was similar to that of IL-1; that is why lipopolysaccharide induced the expression of MMP-2 and MMP-9. On the contrary, the use of aprotinin contributed to a decrease in the secretion of MMP-2 and MMP-9 in culture tissues [43].

Conclusion

Keratoplasty is the surgery of choice for emergencies such as corneal perforation or threatened perforation. Despite the fact that penetrating keratoplasty is a common operation in the clinical practice of an ophthalmologist, post-transplant complications ranging from delayed epithelialization to keratolysis occur in every third emergency patient.

An analysis of the literature shows that matrix metalloproteinases can play a significant role in the processes of cornea and graft lysis, but the parameters of the immune system in patients with keratolysis have been studied incompletely.

The use of aprotinin, a synthetic inhibitor of matrix metalloproteinase, and platelet-rich plasma lysate, a source of tissue inhibitor of matrix metalloproteinase-1 in high concentrations, can be

considered a pathogenetically substantiated method for the prevention and treatment of corneal graft melting in urgent surgery.

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