Review paper

Immunology of the eye – selected data

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Abstract

The most important elements of the eye in immunity are cornea, aqueous humour, choroid, retina, conjunctiva and lacrimal gland. Among immune reactions in the eye one can enumerate innate, as well as adaptive mechanisms, with the special attention to local immunity systems in the eye, such as conjunctiva-associated lymphoid tissue (CALT), lacrimal drainage-associated lymphoid tissue (LDALT) or eye-associated lymphoid tissue (EALT).

Key words: *eye, immunity, cornea, aqueous humour, choroid, retina, conjunctiva, lacrimal gland.*

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Introduction

Despite the fact that the construction and physiology of the optic organ is well known, there is still little information on its immunity elements that guarantee its specific functions. Among the most specific features, there is production of tears which, due to mucoproteids, show bactericidal properties and constitute an important element of natural immunity [1].

The data on immunity of the eye indicate that special role in this respect belongs to cornea, aqueous humour, choroid, retina, conjunctiva, and among the additional elements of the eye – the lacrimal gland [1, 2].

Cornea

The first element with high impact on shaping the elements of immunity within the optic organ is cornea, by many authors referred to as the "window to the eye's immunity", as it is in a way an "extension" of the mammal brain and contains a high number of elements affecting its immunity, specific for this organ [3, 4]. Cornea is a layer protecting the fibrous capsule against the external environment, forming a physical barrier for the latter. Such a form of protection for this area of the eye is strengthened by the physicochemical barrier created by the layer of specific glycoproteins – mucins, which have the task to protect the eye against adhesion and permeation of pathogens, allergens and against drying [5, 6]. So far, the following mucins have been recorded in cornea: MUC1, MUC4, MUC16, as well as histatins, which form chemical barrier for the eye and affect cell signalling [6, 7]. Specificity of action and the capacity to stimulate immunological response in this part of the eye is affected by the lack of lymphoid cells [5]. Furthermore, the central part of cornea is avascular, which makes it impossible for immune system cells to reach this area, but also prevents permeation of undesired substances [3, 5]. The uniqueness of cornea may be testified to by the fact that it is an organ that is often successfully transplanted without complications [3]. This is due to presence of MHC class I molecules on all cornea layers, namely epithelium, stroma and endothelium, whereas the fewest of them are present in the latter [3]. In turn, cornea features no MHC class II molecules [3]. Cornea also features such elements as FasL, which induces apoptosis of cells with receptor CD95, while its presence contributes to success in allotransplants of cornea [3]. Other factors conditioning cell apoptosis in cornea involve the presence of TRAIL (tumor necrosis factor – related apoptosis inducing ligand) and PD-L1 (programmed cell ligand 1) [3]. As mentioned before [3], endothelium cells of the cornea are rich with HLA-G – MHC class I molecules, inhibiting cytolysis conditioned with NK cells, which as a consequence protects cornea against the attack of NK cells, e.g. after transplantation [3]. It has also been determined [5] that bacterial protein flagellin induces activity of TLR5 receptor in human cornea, which results in activation of local immunity in the eye. Furthermore, in this part of the eye, also the presence of TLR2, TLR3 and TLR4 has been detected, although – which seems to be atypical – they do not induce immunological response to LPS. Moreover, in human and mice

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cornea, the presence of such antibacterial proteins has been determined as β-defensins 1-4, cathelidicin LL37 and collectin, so substances that condition natural immunity, both in the area of antibacterial and antiviral immunity [5].

Aqueous humour

For the purpose of correct functioning of cornea and the lens, aqueous humour is of high importance, which fills the anterior chamber of the eye [2]. It removes harmful products of metabolism and nourishes cornea and lens [2]. It contains, in low concentrations, non-specific factors that have short-term inhibiting effect on immunological responses, which is interpreted that their role in immunity is marginal [8]. Among others, aqueous humour features C-reactive protein – CRP, which has a protective effect on cornea through protection of its cells against cytolysis of immune system cells, mediated with complement [3]. Furthermore, aqueous humour is also rich in such factors as MIF (macrophage migration inhibitory factor) and TGF-β (transforming growth factor β), which are potential inhibitors of cytolysis mediated with NK cells [3]. It was evidenced [8] that aqueous humour also has inhibiting effect on antigens, which impacts on reduced number of immune system cells such as e.g. lymphocytes T in the anterior chamber of the eye.

Choroid

Within the vascular layer of the eye, namely in the choroid, ciliary body and iris, the presence of receptors important for natural immunity was observed, such as NOD (nucleotide oligomerization domain-like receptors), the role of which is related to regulation of inflammatory processes and apoptosis and involves their impacting on TLR (Toll-like receptors) [9]. The function of such receptors has particularly been observed during inflammations of the vascular layer, and involves increased production of cytokines, for which the signal activating their production is the "impulse" from TLR2 and TLR4 receptors [9]. An important element that is often described when characterising the vascular layer, and which affects "immune privilege" of the eye, is the phenomenon of anterior chamber-associated immune deviation (ACAID) [8, 10]. Anterior chamber-associated immune deviation is understood as specific type of immunological responses, characteristic of the eye, which results from its specific construction [8]. It is worth stating here that lack of effective immune response in the eye may occur in the eye due to its "privilege", and is conditioned with three factors: nature and function of the antigen presenting cells APC, blood-brain barrier, and immune-modulatory nature of the environment of the optic organ [10]. It was evidenced [8] that if the antigen is placed in the anterior chamber of the eye, it remains on the blood flow path, not in the lymphatic system, presented to the immune system via Schlemm's canal. In turn, if immune response occurs in the eye which deviates from the norm, this is a result not of the immunological "ignorance", but also of active immunological regulation comprising inhibition of cellular immunity for the benefit of humoral mechanisms [8]. Hence, it was determined [8] that ACAID comprises immunological phenomena of late type, mechanisms of humoral immunity, and response mediated with cytotoxicity of lymphocytes T. Furthermore, it has been recently evidenced [11] that ACAID reactions also involve natural T regulatory lymphocytes (nTreg), with receptors CD4+CD25+, yet the nature of their functioning in this mechanism in the eye has not been studied in detail.

Retina

Retina features epithelial cells that show immunosuppressive effect by secretion of factors that inhibit immune responses [12]. *In vitro*, it was evidenced [12] that epithelial cells in the retina have suppressive effect on lymphocytes T, by secretion of TGF-β and PD-L1/B7-H1 (programmed cell ligand 1). It was also determined that retina also features natural immunity receptors, namely TLR1-7,9 and TLR10, which participate in fighting bacterial inflammations [13, 14].

Conjunctiva

Cells building lamina priopia of conjunctiva form the type of tissue referred to as CALT (conjunctiva-associated lymphoid tissue), which is a form of structure ensuring local immunity of this part of the eye [5, 15, 16]. Conjunctiva-associated lymphoid tissue's role includes immunological protection of inviolability and privilege of the eye, which is particularly important when blinking and sleeping, as well as distribution of such factors as e.g. sIgA [15, 16]. Among cells forming CALT, one must list lymphocytes with CD8+ receptor, and among them IEL (intraepithelial lymphocytes) and lymphocytes with markers CD45Ro+ and CD25+ [5]. Moreover, in this tissue, mastocytes have been recorded, capable of producing cytokines which increase the effect of white blood cells, mainly in the area of inflammatory reactions [5, 10]. Their number in conjunctiva amounts to 6000/mm^3 and most of them are cells with phenotype MC_{TC} [10]. Moreover, conjunctiva features Langerhans cells (85 ±16 cells/m^2) and lymphocytes with receptor CD3+ (189 ±27 cells/m^2) [10]. It must be added that a specific receptor for Langerhans cells in conjunctiva is receptor CD1+, and not CD6+, which is characteristic of such cells in the skin [10]. In tunica conjunctiva, there are also other dendritic cells, which in many aspects resemble Langerhans cells [17]. It seems to be very important that within conjunctiva, the presence of receptor TLR4 and TLR5 has been recorded, which affect mediation of immune response [13].

Lacrimal gland

In the upper-lateral part of the orbital cavity, there is lacrimal gland secreting tears, which have the task of clear-

ing the surface of the eye of dirt and of moisturising it. Tears form an important element of local immunity of the eye, as being a sterile liquid, they form one of the first, earliest elements of natural immunity. Furthermore, tears contain electrolytes, aminoacids, enzymes, prealbumins, immunoglobulin class A, G, M, and E, as well as tryptase, histamine, lysozyme, lactoferrin, plasmin and ceruloplasmin, and a number of other substances affecting immunological response [10]. Such a composition of tears also results in their cidal effect on bacteria, viruses and fungi. Moreover, among the cells with immunological function in the lacrimal gland, there are plasmatic cells, which are present in much higher numbers than intraepithelial lymphocytes (IEL) and lymphocytes T with receptor CD4+ [15]. In turn, within the lacrimal gland, there is lacrimal drainage-associated lymphoid tissue (LDALT) [15].

Immunity related to mucosal membranes in the eye

When describing immunity related to mucosal membranes in the eye, one must mention mucosa-associated lymphoid tissue (MALT), which conditions correct functioning of mucous membranes' defence system in mammals [1, 18, 19]. Within MALT, there are elements related to various parts of the body, which within such tissue form specific systems, namely gut-associated lymphoid tissue (GALT) [20], nosopharynx/nose-associated lymphoid tissue (NALT), bronchus-associated lymphoid tissue (BALT), genitourinary-associated lymphoid tissue (GUALT), mammary gland-associated lymphoid tissue (MGALT), and Eustachian tube-associated lymphoid tissue (TALT), as well as saliva-associated lymphoid tissue (SALT) [1, 19]. In turn, within the optic organ, there is eye-associated lymphoid tissue (EALT), the task of which is to guard immunological inviolability of the eye by implementation of mechanisms of natural and acquired immunity [5, 21]. Within EALT, one can differentiate a small group of cells in the conjunctiva forming the aforementioned CALT and LDALT. The existence of lymphoid tissue condensed as LDALT exactly within the lacrimal gland seems to be the most appropriate place due to the fact that it is the flow of tears via the gland that can cause the presence of alien material there, including various pathogens [22]. The contact of such pathogens with conjunctiva within the lacrimal gland may be prolonged in time, particularly within the lacrimal sac, due to its build, and such a situation promotes contact between the immune system and pathogens [22]. One of the fundamental functions of LDALT is to produce IgA, which permeate into tears in the secretion form sIgA, and which participate in opsonisation and agglutination of bacteria [21, 23]. Also, very important functions of sIgA within LDALT include bacteriostatic effect, prevention of microorganisms' adhesion to the epithelium, and thus of their permeation inside the mucosa, as well as neutralisation of bacterial toxins [18, 21]. Among important elements of LDALT, there are TLR receptors and antibacterial peptides, as well as cells capable of phagocytosis, such as macrophages, which not only phagocytise, but also present antigens [5]. Among antibacterial substances, the role of which has been confirmed in the immunity of the eye, there are lysozyme capable of lysis of the bacterial cellular wall, lactoferrin, which by binding to iron distorts the growth and development of microorganisms, lipocalin which affects bacterial metabolism, and angiogenin with antibacterial effect [24].

In turn, within EALT, the key role also belongs to immune system cells, namely granulocytes, including neutrophilic, which form an integral component of such immunity, as they launch within EALT e.g. the processes of intracellular killing within the process of phagocytosis [5]. Mastocytes, which are also present in EALT, have an important role, because their number in the eye is estimated at over 50 million, and they show high involvement in allergic reactions within the eye [5, 10]. Another important element within EALT involves lymphocytes, the activation, proliferation and differentiation of which, as a result of attack of microorganisms, leads to their transformation into effector cells that can react within the entire optic organ [24].

Conclusion

Undoubtedly, the eye is a very important and at the same time complex organ. Its structure, including the "immune privilege", causes the immune responses within the eye to have a different course than in other organs. At present, it is known that the functioning of the eye is affected by both its anatomical components, and by elements of the immune system, such as ACAID system, TLR and NOD receptors, as well as antibacterial proteins, which create local immunity systems within the eye, such as CALT, LDALT, or EALT.

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