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The impact of herpes simplex virus on the cornea engraftment

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According to the recent WHO data, 39 million people in the world are blind. In developing countries cornea diseases are the second most common cause of blindness. Cornea transplantation remains the only radical method to regain lost vision for many blind people around the world. However, according to literature reports, cadaveric donor corneas pose a potential risk of herpes virus transmission to the recipient during penetrating keratoplasty. It is known that herpes simplex virus-1 persisting in the donor cornea can adversely affect graft survival up to causing the graft failure reaction. The latent herpes simplex virus may be reactivated by a number of factors, most of them occurring with penetrating keratoplasty. One of these factors is immunosuppressive

therapy, an essential element of the pharmacological graft protection. Antiviral agents are strongly recommended in order to inhibit the replicating herpes simplex virus in the cornea graft. The most common antiviral agents are interferons with their inducers and acyclic nucleosides. Viral decontamination during cornea storage would prevent the donor-to-recipient transmission of herpes simplex virus in relation to keratoplasty.

Keywords: herpes simplex virus, herpes simplex keratitis, keratoplasty, cornea preservation, viral decontamination

DNA, deoxyribonucleic acid
HSV, herpes simplex virus
IFN, interferon
PCR, polymerase chain reaction

Introduction

According to the World Health Organization, there are 39 million blind people in the world [1]. Bilateral corneal opacification is the fourth most common cause of vision loss (5.1%) after cataract (47.8%), glaucoma (12.3%) and age-related macular retinal degeneration (8.7%) [2]. According to meta-analysis (2017), 3.4% of blind people in Eastern Europe lost their vision due to bilateral clouding of the cornea [3]. In 23 million people, corneal lesions resulted in unilateral blindness [4]. In developing countries, corneal diseases are the second most prevalent cause of blindness [5], as well as the leading cause of visual impairment [6]. For many blind people around the world, corneal transplantation remains the only way to regain lost vision. It is estimated that about 50% of reported cases of corneal blindness are curable [7].

Characterization and epidemiological features of herpes viruses

According to Russian authors, the leading infectious cause of corneal damage in Russian population is herpes viruses, which are also the main cause of corneal blindness: herpetic keratitis accounts for more than 66% of all corneal pathology and 60% of corneal blindness [8, 9]. Up to 95% of the world's population is infected with herpes viruses [10]. At present, there are 8 types of herpes viruses that are pathognomonic for humans and form a family of human herpes viruses. According to the international classification [11], there are 3 subfamilies of human herpes viruses: alpha, beta and gamma herpes viruses. The alpha subfamily of herpes viruses includes herpes simplex virus (HSV) type 1 (HSV-1), HSV type 2 (HSV-2), chickenpox virus; the beta subfamily of herpes viruses includes human cytomegalovirus, human herpes viruses type 6 (6A and 6B), human herpes virus type 7; the gamma-herpes virus subfamily includes Epstein-Barr virus, as well as the Kaposi's sarcoma-associated human herpes virus type 8. Among the listed human herpes viruses, HSV-1 demands a special attention, since it is most often found in corneal cells [12].

The herpes simplex virus was discovered by German ophthalmologist Wilhelm Grüter in 1912 [13]. HSV-1 is a double-stranded linear deoxyribonucleic acid (DNA) contained in the virus core and surrounded by a capsid and supercapsid, the space between them contains a tegument [14; 15]. Supercapsid is the outer shell represented by a bilipid layer that contains viral glycoproteins protruding outward. The tegument is located between the capsid and supercapsid and is an amorphous protein layer, occupying about 2/3 of the space inside the virion. Capsid is the inner shell of the icosahedral shape with a diameter of 125 nm. Each capsid consists of 161 capsomeres, each being a

structural protein subunit. Capsomeres are subdivided into 150 hexons, which form the edges and faces of the icosahedron, and 11 pentons located at all vertices, except for one, which carries a cylindrical portal protein complex, through which the viral DNA enters or exits the capsid [16]. The most common way of infection transmission is a contact transmission for HSV-1, and sexual intercourse for HSV-2. The entrance gates are the mucous membranes and the skin. After invading the cell, the herpes simplex virus begins to replicate actively, leading to a change in the cell metabolism and to the destruction of the cell membrane, which results in the cell death, and many copies of the virus go outside. Then, nucleocapsids penetrate into neighbouring cells, regional lymph nodes, and circulation; after that, the virus disseminates into organs and tissues, forming the foci of necrosis and inflammatory reactions in them, creating favourable conditions for secondary infections to occur [17].

Herpes simplex virus as a cause of graft rejection

Herpes simplex virus type 1 may cause diseases of all the main parts of the eye: eyelids, conjunctiva, cornea, choroid, and retina. HSV damage to the cornea causes various forms of keratitis: from epithelial to deep stromal, and necrotic one [18]. Herpetic keratitis in patients is characterized by a corneal syndrome with abnormal sensitivity of their cornea and the presence of vesicles in it, prone to a fusion in the form of a tree branch [19]. Currently, the main treatment of herpetic keratitis is a conservative therapy, and in case of its inefficacy, and in case of a wall-eye formation or persistent corneal opacity, a surgical treatment of this pathology is possible.

Currently, in order to cope with the corneal pathology sequelae, various keratoplasty options are used all over the world [20], and corneal grafting is the most common type of transplantation [21]. From the first

attempts of keratoplasty operations, there was the search for the factors capable to affect the graft adherence. So, as early as in 1905, after the first successful corneal transplantation from human to human, Dr. Eduard Zirm noted that the engraftment results were strongly influenced by strict following the aseptic rules, minimizing the number of rough mechanical touches to the graft, and the suturing technique [22]. In the well-known book published in 1935 by the Russian ophthalmologist Vladimir P.Filatov, who granted the world a possibility of transplanting preserved cadaveric donor corneas, a considerable attention was paid to the infection control of donors [23]. These works formed the basis of modern transplantology. The development of infection control contributed to determining the role of latent infections in general transplantation [24]. Currently, it is known that the main infectious agent that affects the cornea is HSV-1 [25]. Arkady A.Kasparov, who devoted many of his works to the study of ophthalmic herpes, considered the cornea "a favourite site of HSV location" [15]. Numerous studies have discovered the potential of HSV to exist in the cornea in a latent form [26–28]. These studies defined the HSV latency as its ability to stay for a long time within a host cell without replication or assembling virions. In 1991 [29], a group of scientists led by S.D.Cook paid attention to the intact ability of latent HSV to reactivate, replicate, and activate the immune system even in the absence of a ganglion reactivation. Later it turned out that a high viral load on the cornea by the herpes virus group is able to exert its negative effect on transplantation results. So, in 1994, G.Cleator et al. [30] published the first report on the risks of the transplant rejection reaction development related to HSV transmission through donor material. In 1995, after having evaluated the pathologically altered recipient corneas obtained during transplantation, J.Garweg et al. [31] found that 5 of 6 recipients, in whose corneal tissue culture the HSV was

revealed, developed an episode of herpetic keratitis reactivation in the postoperative period.

A rapidly growing interest in this particular problem in those years prompted scientists to conduct large-scale statistical studies aimed at more accurately investigating the role of HSV in cornea transplantation. So, in 1997, L.Remeijer et al. [32] after a retrospective assessment of 2398 penetrating keratoplasties concluded that postoperative herpetic keratitis may develop even in the patients without a previous history of herpetic diseases. Scientists estimated that herpetic keratitis developed 14.2 times more often after penetrating keratoplasty compared to its incidence rate in the general population. Penetrating keratoplasty is a stimulating factor for HSV reactivation. Meantime, the investigators emphasize that they evaluated only the epithelial form of herpetic keratitis, while there are other manifestations of herpetic infection in the cornea. In the same year, G.C.Cockerham et al. [33] assessed possible causes of three cases of primary graft failure after penetrating keratoplasty. As a result of the study using polymerase chain reaction (PCR), the HSV DNA was detected in two of the three grafts evaluated. According to the study authors, the data obtained were consistent with the observations of G.Cleator [30] and suggested that HSV can cause an early graft failure reaction. In 1998, the group of investigators headed by L.M.Holbach [34] described a case of corneal graft rejection due to viral damage to the endothelium in a patient with a history of severe herpetic recurrent keratitis. The pathologically altered cornea obtained during rekeratoplasty was studied. At a histological examination, numerous inclusion bodies were found in endothelial cells, while HSV-1 virions and antibodies to this virus were detected in stromal keratocytes. The authors suggested that active HSV infection in the corneal graft endothelium results in a graft failure in patients with recurrent herpetic keratitis. In

1999, M.V.Neufeld et al. [35] described a case of herpetic keratitis development in a corneal-scleral disk stored in a donor eye bank at 4° C in Optisol GS preservation medium. A PCR assay of this cornea and culture study using the Vero cell line revealed the presence of HSV-1. According to a group of scientists, this case clearly demonstrates that HSV remains viable even when preserved at 4° C. The pathological effect of the HSV persistence in the cornea on the graft adherence was reported by S.Biswas et al. (2000) [36] who investigated the causes of the graft rejection reaction developed after penetrating keratoplasty in one of the recipients, as well as the appearance of a persistent epithelial defect after corneal transplantation in another recipient. According to laboratory test results (diagnostic PCR, immunohistochemical assay), HSV was found in corneal grafts of both recipients. The authors claim that HSV can cause endothelial destruction during organ cultivation, as well as the rejection reaction and ulcerative keratitis in the postoperative period. By the beginning of the XXI century, scientists had already characterized HSV as an infectious agent that could persist in a latent form in the corneal graft and reactivate in the postoperative period, leading to the graft rejection. At the next stage, the investigators set themselves the task of tracking the HSV transmission through the corneal graft to determine the strains being present in the donor material and the recipient tissues at preoperative stage and in the postoperative period. In this regard, in 2001, Lancet published data from a group of scientists headed by L.Remeijer [37] who were able to document the HSV transmission from a donor to a recipient through a corneal graft, followed by reactivation of the virus. The study was made by means of genotyping the HSV strains of the donor and the recipient using the PCR method based on analysing the differences in the DNA structure. A match of the DNA sequences of the studied strains was found. Scientists focus on the fact that the HSV

transmission to a seronegative recipient poses considerable risks to vision, especially in conditions of immunosuppressive therapy. In the same year, R.DeKesel et al. [38] studied the causes of four cases of early graft failure after penetrating keratoplasty. HSV was detected by PCR in three of the four removed failed grafts. Scientists believe that this study clearly demonstrates the HSV ability to cause early graft failure after penetrating keratoplasty. More and more reports were published further, which also characterized HSV as an infectious agent that can be transmitted from donor to recipient in penetrating keratoplasty and/or lead to the graft rejection [39–50].

Biological effects of herpes virus infection

In order to develop new methods for the prevention of HSV transmission, fundamental studies have been actively conducted in recent years to study the mechanisms of HSV attachment to cells [51]. Five viral glycoproteins: gB, gC, gD, gH, gL are known to be involved in the process of HSV invading the cell [52]. Initial attachment to, or binding, the cells is mediated by the interaction of gC and/or gB with heparan sulfate proteoglycans (HSPGs). F-actin-rich membrane protrusions termed filopodia facilitate the attachment, forming the sites rich in HSPG for initial fixation. After the virus has attached, the process of its penetration into a cell begins, having two possible pathways for the development, depending on the type of cells. The first pathway consists of the fusion of the viral membrane with the plasmatic membrane of the cell, while the second pathway may be activated if it is necessary to merge with an intracellular vesicle. In any case, the membrane fusion requires an obligatory presence of glycoproteins gB, gD, gH, gL. The absence of gC does not stop the attachment process, but reduces the overall binding ability of the virus. Like the attachment process, the

membrane fusion process requires the involvement of cellular receptors. The current widespread model of the membrane fusion suggests that the gD binding to one of its corresponding receptors induces conformational changes in gD and involves the active multi-glycoprotein fusion complex in the process, including gB, gD, gH and gL. The fusion of the viral envelope with the cell membrane leads to the release of viral nucleocapsid proteins and tegument into the host cytoplasm, and their binding to the microtubule-dependent cytoskeletal "engine", dynein. While most of the viral tegument released into the cell is necessary to activate the expression of viral genes and stop the synthesis of the host cell proteins, the remainder is responsible for the dynein-vehicle transfer of nucleocapsids along the microtubules directly to the cell nucleus to release the viral DNA into it. Subsequently, the transcription, replication of the viral DNA, and the assembly of capsids take place inside the host cell nucleus.

In turn, the cells have the biological ability to effectively resist the viral invasion, limiting the replication and spread of viruses [53]. The fundamental mechanism of cell protection from viruses is a cell death, which allows the elimination of HSV-infected cells before the assembly of new virions. One of the best-studied forms of a programmed cell death is apoptosis. Apoptosis is known to be necessary for the development and maintenance of tissue homeostasis in multicellular organisms. An apoptotic cell exhibits characteristic morphological features, including vacuolization (blebbing) of the cell membrane, chromatin condensation, fragmentation of intracellular DNA, and the formation of apoptotic bodies [54; 55]. Apoptosis is performed by a specific family of cysteine proteases known as caspases [56]. Necroptosis is an alternative form of controlled cell death, which is activated in case of insufficient caspase activity [57]. Morphologically, this type of cell death is characterized by a

rupture of the cell membrane and edema of organelles. Necroptosis is believed to be initiated by binding the receptor-interacting kinase 3 protein (RIP3 or RIPK3) to the MLKL pseudokinase, which in turn, leads to the destruction of the cell wall. Interferons (IFNs) represent one of the biological intracellular substances that can activate cell apoptosis and necroptosis, leading to the HSV elimination [58–60].

Interferons are the group of proteins that have antiviral effects and are synthesized by the cell in case of a viral invasion or in contact with other non-viral and synthetic substances, as well as bacterial endotoxins [15]. IFN was first described by scientists Alik Isaacs and Jean Lindemann in 1957 [61]. At present, three types of IFN are distinguished, depending on the type of receptor that they rely on for the signal transduction: the IFN-1 type includes IFN-α (12-14 subtypes), IFN-β, IFN-ω, IFN-κ, IFN-ε; the IFN-2 type is represented by IFN-γ; type IFN-3 includes IFN-λ1, IFN-λ2, IFN-λ3. Receptors for the IFN-1 type are present in all body tissues; however, the amount of synthesis varies depending on the type of cells. IFN-2 is produced by antigen-activated T cells, NK cells, and macrophages. IFN-3 is expressed only in individual epithelial cells and binds to a separate receptor formed by the ligand-binding subunit and the signal transducing subunit [62]. The mechanism of the IFN action is not completely studied. It is believed that the IFN expression occurs in response to viral invasion. The synthesized IFNs-1 (IFN-α and IFN-β) spread to neighbouring cells, interacting with located on their membrane specific IFNAR receptors (interferon-α/β receptor), consisting of IFNAR1 and IFNAR2 subunits and bound to tyrosine kinase 2 (TYK2) and JAK kinases. The TYK2 and JAK kinases phosphorylate the tyrosine residues in the IFNAR cytoplasmic domains, creating the attachment sites for the signal transducer family proteins and the activator of transcription (STAT) for further attachment of JAKs to them for

phosphorylation. The phosphorylated STATs (pSTATs) form homodimers or heterodimers and translocate into the nucleus. The pSTAT1 homodimer binds to the gamma-activated sequence (GAS) located in the promoter region of IFN-stimulated genes (ISGs) and initiates the transcription of these target genes, while the homodimer formed by pSTAT3 activates the transcription of genes containing the STAT3 enhancer sequence. Phosphorylated STAT1 and STAT2 form a heterodimer, which leads to the involvement of the IFN-9 regulatory factor (IRF9) and the formation of the IFN-stimulated gene 3 (ISGF3) complex, being the activator of transcription. Then this complex is transferred to the nucleus and binds to IFN-stimulated response elements (ISRE) in the promoter region of IFN-stimulated genes (ISGs) to initiate the transcription of the genes that are essential for creating the antiviral effect of IFN-1 [63; 64].

Antiviral effects of interferon

Type I interferon induces the synthesis of many proteins that restrict the virus replication and stop its spread from cell to cell: 1. IFN-1 induces the 2'-5'-oligoadenylate synthetase (OAS) enzyme that, in turn, activates the latent nuclease RNaseL, which mediates the degradation of viral DNA; 2. Upon the IFN-1 activation of RNA-dependent protein kinase (PKR), the viral RNA translation is blocked; 3. The IFN-1 induction of GTPase enzymes contributes to the viral nucleocapsid localization;

4. The activation of IFN-stimulated gene 15 (ISG15) and TRIM proteins inhibits the release of viral particles; 5. IFN-1-induced APOBEC3 proteins cause the viral DNA hypermutation; 6. To limit the site of infection, IFN-1 is also able to activate the apoptosis mechanism to eliminate virus-infected cells by controlling the Fas (FasL), PDL-1 and

TRAIL ligands; 7. IFN is known for its ability to induce the synthesis of antiviral Myxovirus resistance protein A (MxA), which inhibits the early phases of virus replication [65–67].

In addition to activating the cell antiviral system, IFN-1 is also capable to localize the viral infection by regulating the innate immunity systems. IFN-1 directly activates NK cells to enhance their cytotoxicity, which helps to eliminate infected cells and localize infection. However, the complete elimination of intracellular infection requires the activation of the acquired immune response system, and IFN-1 plays a key role in this process. IFN-1 promotes the maturation of dendritic cells (DCs) that are involved in the differentiation of $CD4^+$ T cells into Th1 or Th2 cells [68–70]. Studies have shown that IFN-1 of experimental antigen-presenting cells is able to cross-present and stimulate native $CD8^+$ T cells, leading to their clonal accumulation and proliferation. IFN-1 in experimental dendritic cells increased the expression of chemokines that attracted NK, T, and B cells to the infection site, as well as IL-15 that was important for maintaining cellular memory of NK and $CD8^+$. These intracellular and extracellular effects of IFN-1 prepare the immune system for an effective cellular antiviral response.

Pharmacological protection of corneal graft

In addition to IFN, numerous nucleoside analogues are actively used as therapeutic agents for herpetic lesions of the cornea. Among the drugs of this pharmacological group, acyclovir has been the most widespread in clinical practice [71]. Acyclovir is a synthetic analogue of acyclic purine nucleoside, which, when entering the infected cells, is phosphorylated to acyclovir triphosphate and builds into the chain of viral DNA, blocking its synthesis by competitive inhibition of viral DNA polymerase. In the course of laboratory studies, IFN and acyclovir

demonstrated an identical antiherpetic activity [72]. A widespread use of acyclovir in the late XX, early XXI centuries led to the emergence of acyclovir-resistant HSV strains capable of causing severe forms of herpetic keratitis [73, 74]. To date, it is known that the combination of nucleoside analogues with the drugs of the IFN pharmacological group and IFN inducers has a synergistic effect [75]. According to the meta-analysis, the combination of IFN with anomalous nucleosides, can significantly improve the therapeutic effect compared to the therapy with anomalous nucleosides alone [76], and, according to the Cochrane Library database [77], also accelerates the healing process. It was also found that the combined use of IFN-α, -β and -γ also had a synergistic effect, providing 1000 times more effective antiherpetic effect on cells than the use of IFN-α alone [78].

An integral part of the pharmacological protection of the corneal graft in the postoperative period is the use of immunosuppressive therapy with glucocorticosteroids [79]. Herpes virus is considered an opportunistic infection that is activated in conditions of compromised immunity [17]. There are reports showing that glucocorticosteroid therapy can induce the activation of even latent HSV [39, 44] and lead to the graft rejection if used during active herpetic infection of the cornea [49].

The above listed antiviral drugs are used at various stages of the treatment for herpetic lesions of the cornea. Viral decontamination of donor corneas at preservation stage can be used to prevent the HSV transmission during corneal transplantation [80, 81]. The IFN inducer-containing preparation developed according to this technology as designated for the preservation of donor corneas demonstrated an antiviral (antiherpetic) effect in a pilot trial.

Conclusion

Herpes viruses constitute the leading infectious cause of corneal damage in the Russian Federation population. The only radical treatment of herpes-originated corneal opacification is penetrating keratoplasty. Numerous studies have demonstrated that after corneal transplantation, there is a risk of the graft rejection that may be caused by the herpes simplex virus, being in a latent form in the donor material. The transition of the herpes simplex virus to its active form in this case is facilitated by a postoperative immunosuppressive therapy, as well as surgical trauma and many other factors. Currently, the search for new ways to fight the herpes simplex virus at various stages of treatment is underway. Undertaking the viral decontamination of donor corneas at preservation stage would prevent the donor-to-recipient transmission of herpes simplex virus during corneal transplantation.

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