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Major review

Corneal lymphangiogenesis in herpetic stromal keratitis

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ABSTRACT

Corneal lymphangiogenesis is the extension of lymphatic vessels into the normally alymphatic cornea, a process that compromises the cornea's immune-privileged state and facilitates herpetic stromal keratitis (HSK). HSK results most commonly from infection by herpes simplex virus-1 (HSV-1) and is characterized by immune- and inflammation-mediated damage to the deep layers of the cornea. Current research demonstrates the potential of anti-lymphangiogenic therapy to decrease and prevent herpes-induced lymphangiogenesis.

1. Introduction

Herpes simplex virus 1 (HSV-1) is one of the most prevalent human infectious pathogens, with an estimated global seroprevalence rate between 50% and 90%.[130] Corneal infection by HSV-1 can lead to herpetic stromal keratitis (HSK), the primary cause of infectious blindness in the developed world.[89] HSK is characterized by immuno-inflammatory corneal lesions and neovascularization of the normally avascular cornea, which together create clouding and compromise visual acuity.[4,6,8] The resulting angiogenesis also compromises corneal angiogenic privilege—that is, the cornea's ability to halt the growth

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of new blood vessels after injury.[4,23] Corneal angiogenic privilege is maintained by a delicate balance involving upregulation of anti-angiogenic factors, including angiostatin, endostatin, and soluble vascular endothelial growth factor receptor 1 (sVEGFR1), and downregulation of angiogenic factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2).[42] HSV-1 infection disrupts this equilibrium between angiogenic and anti-angiogenic factors, leading to an angiogenic switch.[68]

Corneal lymphangiogenesis, the extension of lymphatic vessels into the normally alymphatic cornea, is a recently identified significant contributor to HSK.[154] Lymphangiogenesis involves the infiltration of inflammatory mediators and host immune cells, which cause tissue damage with potentially blinding effects. We provide a brief overview of the pathogenesis of HSK and corneal immune privilege and focus on HSK to highlight the lymphangiogenesis that occurs in response to HSV-1 corneal infection, considering both the viral and host immune contributors to this process. In addition to the possible mechanisms leading to HSV-1–induced lymphangiogenesis, we discuss how key insights into this process may aid the discovery and development of potential therapeutics and prophylactics for the treatment and prevention of this vision-threatening disease.

2. HSV-1 background and corneal infection, HSV-1 cell entry, and subsequent pathogenesis of HSK

2.1. *HSV-1 background and corneal infection*

Herpes simplex virus is an enveloped, double-stranded DNA virus and a member of *Alphaherpesvirinae*, a subfamily of Herpesviridae. Of the three members of this subfamily (HSV-1, HSV-2, and varicella zoster virus), HSV-1 has the greatest association with ocular infection.[44] HSV-1 is a regular and spherical-shaped enveloped virion. Apart from the envelope, the other two main structural elements are tegument, which is a proteinaceous region, and the icosahedral-shaped nucleocapsid that houses its genome, which is composed of linear double-stranded DNA. HSV-1 contains 11 viral glycoproteins, four of which are essential for viral entry (gD, gH, gL, and gB). The proteinaceous tegument is also required in the early stages of infection for delivery of viral proteins into the host cell.[3]

HSV-1 is usually acquired from individuals with clinical or subclinical facial, oral mucosal, or genital mucosal manifestations.[88] Less often, HSV-1 is transmitted via corneal transplantation.[117] Primary infection of corneal epithelial cells by HSV-1 rarely leads to HSK. Instead, HSK is more often initiated upon reactivation of HSV-1 virions with life-long latency that lie dormant in the trigeminal ganglion.[112] During reactivation, newly synthesized virion particles migrate along the sensory fibers of the trigeminal nerve and often give rise to orolabial lesions; however, because the sensory fibers from the trigeminal nerve also supply the cornea, occasional reactivation of HSV from its latent state results in the delivery of virion particles to the cornea.[154] The manifestations of this disease in the cornea demonstrate that, although the corneal epithelium may serve as a physical barrier to other infectious microorganisms,[68] viruses such as HSV-1 can still infect the corneal epithelium.[44] Repeated reactivation of dormant HSV-I virions, a process induced by a wide array of stressors, may ultimately lead to chronic inflammation in the corneal stroma, with clinical or subclinical manifestations.[123]

2.2. *HSV-1 cell entry*

HSV-1 infection at a cellular level begins with interactions between viral envelope glycoproteins and their respective host cell receptors.[131] The initial attachment step involves glycoprotein B (gB) and glycoprotein C (gC) interactions with the host cell surface heparan sulfate proteolgycans.[58,124] HSV-1 glycoprotein D (gD) then undergoes conformational changes that allow it to bind to any of its host cell receptors, including nectin-1, herpes virus entry mediator (HVEM),[77] or 3-O-sulfated heparan sulfate (3-OS-HS).[129] These conformational changes of gD represent a critical event that permits the gD-host-cell-receptor complex to associate with the heterodimer complex of glycoprotein H/glycoprotein L (gH/gL). Next, gH/gL binds with gB, allowing viral fusion with the host cell membrane.[41,129] The capsid is then transported to the nuclear pores, DNA is released to the nucleus, and viral replication and transcription begins. Synthesis of proteins from the HSV virion progresses in three rounds, designated as immediate early (IE), early (E), and late (L). The IE products regulate gene expression, the E products are involved in viral DNA synthesis, and the L products include virion structural proteins and viral glycoproteins.[68,73]

2.3. *HSK pathogenesis*

If HSV-1 infection is confined to the corneal epithelium, the resulting pathology is referred to as infectious epithelial keratitis.[36] HSK can either result from a progressive infectious epithelial keratitis or present as a principle manifestation of keratitis.[73] In fact, epithelial keratitis progresses to involve the stroma in approximately 20% of cases.[112] Pathologic findings of HSK include corneal stromal[143] and endothelial damage resulting from both direct viral effects and host immune responses. Two main HSK subtypes exist: non-necrotizing HSK and necrotizing HSK. Non-necrotizing HSK does not include an epithelial defect[151] and does not require active viral replication, whereas necrotizing HSK involves an epithelial defect and active viral replication. Necrotizing HSK induces an immune response from the host, resulting in corneal tissue damage.[59,87]

HSK pathogenesis is frequently performed in the primary disease mouse model. Although the murine corneal model produces herpetic stromal lesions by a different mechanism than occurs in humans,[127,134] the lesions themselves are similar.[15] HSK in the mouse cornea requires viral replication in the corneal tissue as well as chronic inflammation driven by the host immune response, mediated by $CD4^+$ T-cell infiltration and lymph node drainage in the sclera and cornea.[13,22,150] Stromal lesions are absent in animal without T-cells, but way from upon introduction of transferred $CD4^+$ T-cells in these animals.[96,121] Other important players in the host immune response are macrophages,[11] natural killer (NK) cells,[138] corneal Langerhans cells,[97] and polymorphonuclear