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Herpes simplex keratitis

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Abstract

Herpes simplex keratitis (HSK) results from an infection with the herpes simplex virus type 1 (HSV-1) also known as human herpesvirus type 1 (HHV-1). Primary infection may involve an ocular or non-ocular site, following which latency might be established principally in the trigeminal ganglion but also in the cornea. During latency, the virus appears as a circular episome associated with histones with active transcription only from the region encoding the latency-associated transcript (LAT). The LAT region is implicated in neuronal survival, anti-apoptosis, virulence, suppression of transcription, establishment of and reactivation from latency. The initial keratitis may develop after infection through the "front door route" (entry into the ocular surface from droplet spread) or "back door route" (spread to the eye from a non-ocular site, principally the mouth). The initial ocular infection may be mild. Visual morbidity results from recurrent keratitis, which leads to corneal scarring, thinning and neovascularisation. Although, recurrent disease may potentially occur through anterograde axonal spread from the trigeminal ganglion to the cornea, recent evidence suggests that HSV-1 in the cornea may be another source of recurrent disease. The pathogenesis and severity of HSK is largely determined by an interaction between viral genes encoded by the strain of HSV-1 and the make up of the host's immune system. Herpetic stromal disease is due to the immune response to virus within the cornea and the ability of the strain to cause corneal stromal disease is correlated with its ability to induce corneal vascularisation. The pathogenesis of corneal scarring and vascularisation is uncertain but appears to be a complex interaction of various cytokines, chemokines and growth factors either brought in by inflammatory cells or produced locally in response to HSV-1 infection. Evidence now suggests that HSV-1 infection disrupts the normal equilibrium between angiogenic and anti-angiogenic stimuli leading to vascularisation. Thrombospondin 1 and 2, matricellular proteins, involved in wound healing are potent anti-angiogenic factors and appear to be one of the key players. Elucidating their roles in corneal scarring and vascularisation may lead to improved therapies for HSK.

Keywords: Herpes simplex virus; Herpes simplex keratitis; Corneal vascularisation; Latency associated transcripts

Contents

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0. Introduction

Herpes simplex keratitis (HSK) remains a major cause of visual morbidity. The incidence of herpetic ocular surface disease lies between 5.9 and $20.7/10^5$ of the population per year with a prevalence of $149/10^5$ in developed countries (Liesegang, 2001; Norn, 1970). Although there is less information available, the prevalence and incidence of herpetic eye disease in developing countries may be higher, affecting a younger population. The initial (not necessarily primary) sites of herpetic eye involvement usually manifest as a blepharitis, conjunctivitis or corneal epithelial keratitis. In contrast, recurrent disease manifests predominantly as an ulcerative and/or stromal keratitis. It is recurrent disease, however, which has the main impact on vision through corneal scarring, thinning and neovascularisation. Although predominantly unilateral, bilateral disease occurs in 1.3–12% of cases, occurs in a younger age group and tends to be more severe. This may be particularly acute for countries in the developing world, where a younger age group may be affected with more severe disease, compounded by the presence of malnutrition and other diseases as well as the lack of access to treatment. HSK is a result of infection predominantly with the herpes simplex virus type 1 (HSV-1) and reflects the interaction between viral and host factors. Detailed studies on the life cycle of HSV-1 and its behaviour within the host have led and continue to lead to significant advances into the pathogenesis and treatment of HSK.

1. Replication of HSV-1

1.1. Anatomy of HSV-1

HSV-1 is a large double-stranded DNA virus with a genome of approximately 152 kb (Fig. 1). It is an alphaherpesvius and belongs to the human herpesvirus (HHV) family, of which it is the first member, also referred to as HHV type 1 or HHV-1. The HSV-1 virion is 120–300 nm in size. It consists of an electron-opaque core containing the genome, a surrounding capsid, 100 nm in diameter, a tegument and an envelope. Capsid architecture is among the most characteristic feature of the herpesvirus family. It comprises 162 capsomers arranged to form an icosadeltahedron. The tegument is an amorphous structure surrounding the capsid that contains proteins and enzymes such as the important virion host shut-off (VHS) protein. The envelope consists of a lipid bilayer with about 12 embedded glycoproteins, which serve as attachment proteins (gB, gC, gD, gH), fusion proteins (gB), structural proteins and immune escape proteins (gC, gE, gI). Most evidence indicates that HSV-1 acquires its envelope from the host cell. As an enveloped virus, HSV-1 is sensitive to acid, solvents, detergents and drying. The genome is linearly divided into long and short regions of unique sequences, termed UL and US (UL = unique long; US = unique short), bounded by regions of internal and terminal repeats (Fig. 2). It is the variability in the number of these repeat regions, which leads to the variability in the