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Herpes simplex virus and neurotrophic factor

Abstract

Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2, respectively) are two highly prevalent neurotrophic human pathogens. Following replication in epithelial cells of the skin or the mucosa the viruses infect free nerve endings (FNE) and establish latency in neurons. Due to stress conditions the viruses reactivate and travel in an anterograde manner to the initial site of infection where they can cause recurrent disease. HSV associated pathologies vary from cold sores to encephalitis or stromal keratitis leading to blindness. Understanding the interaction between HSV and elements of the immune and nervous systems is essential to develop new antiviral strategies and provides relevant knowledge regarding the functioning of these systems. Neurotrophic factors are secreted proteins that play a key role in the nervous system and its interplay with the immune system. Despite their importance in neuronal survival, differentiation, axonal pathfinding, inflammation and induction of pain, the relevance of the interaction between HSV and neurotrophic factors is not well understood. This mini review summarizes the current knowledge and poses relevant questions for future directions.

Keywords: Herpes simplex virus, Neurotrophic factors, Nerve growth factor, Free nerve endings, Neuron

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Abbreviations

HSV, Herpes Simplex Virus; NGF, Nerve Growth Factor; EGF, Epithelial Growth Factor; FNE, Free Nerve Endings; GDNF, Glial Cell-Line Derived Neurotrophic Factor; GFLs, GDNF Family Ligands; TRK, Tropomyosin Kinase Receptor; CBP, CREB Binding Protein

Introduction

The human alpha herpesviruses herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2, respectively) establish latency in sensory neurons of the peripheral and autonomic nervous systems.[1] Infection of the central nervous system, although less frequent, is normally accompanied by severe pathological consequences. HSV-1 and HSV-2 are highly prevalent and cause a variety of diseases such as cold sores, genital herpes, stromal keratitis and encephalitis. HSV-1 preferentially infects orolabial skin and mucosa, while HSV-2 is generally associated to genital infection. The reasons for the different outcomes of infection are not well understood. Initial infection starts in the epithelial cells of the mucosa or the skin. Following lytic replication HSV must infect FNE, dynamic structures able to degenerate and regenerate, in order to infect and establish latency in neurons. The retraction or growth of FNE is dependent on the expression of repellents or neurotrophic factors, respectively. Once latency is established in the soma, several stimuli associated to neuronal stress can induce viral reactivation resulting in the production of viral particles that migrate in an anterograde manner to the mucosa or skin. Colonization of neurons, establishment of latency and reactivation are essential processes for HSV latency and pathogencity. HSV must modulate elements of the immune and nervous systems during initial infection, establishment of latency and reactivation. The viral and cellular factors responsible for establishment of latency in neurons and reactivation are not fully characterized.

Neurotrophic factors were initially defined as secreted proteins that induce neuronal growth. They are required for neuronal survival, growth, development and axonal pathfinding. However, neurotrophic factors are pleitropic molecules that play relevant roles in other processes such as the regulation of the crosstalk between the immune and nervous systems in complex responses like pain and inflammation.[2] There are several families of neurotrophic factors. Among them, the neurotrophins and the glial cell-line derived neurotrophic factor (GDNF) family ligands (GFLs) are probably the best characterized. The former include nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin 3 and neurotrophin 4, that bind and activate tyrosine kinase receptors (Trks). They also interact with p75NTR, a member of the tumor necrosis factor receptor superfamily which has multiple functions.[3] The GFLs include GDNF, neurturin, artemin, and persephin, molecules that bind co-receptors of the GDNF Family Receptor-α protein family, activating tyrosine kinase receptor RET (rearranged during transfection).

Neurotrophic factors orchestrate the development of the peripheral nervous system.[4] and neurotrophic dependency defines the different identity of the sensory and autonomic neuronal subpopulation.[5] Anatomically, the more exposed neurons to HSV are the sensory neurons innervating the outer layers of skin and mucosa. Many of these neurons are NGF-dependent, which has driven most researchers to investigate NGF-HSV interaction. Several groups have investigated the role of NGF during HSV initial infection and establishment of latency, both *in vitro* and *in vivo*. NGF has the capacity of inhibiting HSV-1 and HSV-2 infection.[6] Application of NGF reduced the clinical and laboratory keratitis parameters in rabbits whereas an anti-NGF antibody had opposite results.[7] The molecular mechanism beneath NGF effect is not well understood and it could be related to the effect of NGF on the immune system.[8-10] However, another report observed that NGF/fibroblast growth factor-dependent signaling pathways enhanced HSV gene expression and yield.[11]

NGF plays a role in the establishment and maintenance of HSV latency.[12] Indeed, HSV establishes latency in neurons that depend on NGF and incubation with NGF and epidermal growth factor delays HSV reactivation.[13-17] Moreover, blocking of NGF with antibodies or depletion of NGF results in HSV reactivation *in vitro*, *ex vivo* and in animal models.[17-23] An explanation for this could be the trigger of caspase 3-dependent apoptosis following NGF depletion.[23-25] However, the molecular mechanisms leading to reactivation seem to differ when apoptosis is triggered in the presence of NGF.[26] This result together

with the fact that viral reactivation due to NGF removal is not strictly dependent on caspase-dependent apoptosis.[22] suggests that induction of apoptosis is not the sole trigger of reactivation following NGF removal. Recent work indicates a role for STAT3 and p300/CBP in the control of HSV-1 reactivation since inactivation of STAT3 induces HSV reactivation even in the presence of NGF and EGF.[23] Activation of p300/CBP induced HSV reactivation in mouse trigeminal ganglia while inhibition of this transcriptional co-activator had the opposite effect. On the contrary, impairment of STAT3 activity resulted in HSV-1 reactivation. In both cases, these events took place despite the presence of NGF or EGF in the culture.[23] As mentioned above, HSV establishes latency in neurons that require NGF for survival. This may be related to the fact that NGF induced signaling through TrkA leads to the activation of PI3-kinase p110a isoform and Akt is required to maintain latency in sympathetic neurons.[22] Interestingly, despite the fact that other growth factors activate the same signaling cascade not all of them can regulate HSV-1 latency indicating that other characteristics such as the kinetic of signaling may be relevant for this phenomenon.[22]

Discussion

All previous cited reports address the role of neurotrophic factors on HSV biology. However, due to the relevance of neurotrophic factors in the interplay between the immune and nervous system and the ability of HSV to modulate host factors it is plausible to speculate that HSV could modify their activity. Also, the expression of particular neurotrophic factors or their receptors could influence HSV neurotropism. Observations obtained with mouse neurons point to the relevance of the differential expression of neurotrophic factor receptors in different neurons and its effect on the establishment of HSV latency.[22] Indeed, the differential expression of neurotrophic factor receptor and other neuronal markers in mouse neurons seems to be linked to the preference of HSV-1 or HSV-2 to establish latency in distinct subpopulations of mouse sensory neurons.[27,28] In particular, NGF dependent neurons seem to support HSV-2 productive infection, but not latency, whereas the contrary is true for HSV-1.[27] These results obtained in mice do not explain the fact that the presence of latent HSV-1 in post-mortem human trigeminal ganglia does not seem to correlate with the expression of a particular cellular marker.[29] clearly indicating the need to perform more research in this field. The use of neurons from different species, different antibodies to detect the receptors and the time post-infection when the neurons are examined may be responsible for some the differences observed.

Conclusion

Neurotrophic factors, in particular NGF, play relevant roles in HSV primary infection, establishment of latency and reactivation. Future research should address the possible modulation of neurotrophic factors by HSV and the relevance of neurotrophic factors other than NGF and their receptors on HSV biology in more detail.

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Conflicts of interest

None.

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