

HIV Associated Eye Diseases: Existing Cognitive and Possible Mechanisms

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ABSTRACT

The Human Immunodeficiency Virus-1 (HIV-1) envelope protein gp120 is the major contributor to the pathogenesis of retinopathy and uveitis in HIV-1-related eye diseases. Disruption of the structure and function of the Blood-Retina Barrier (BRB) is the major contributor of HIV-1-related eye diseases and the molecular mechanism remains unknown. Our mini review revealed that retinopathy and uveitis are required for gp120-induced inflammation and epigenetic changes and suggest that gp120 regulate tight junction protein.

Keywords: GP120; Function; Retinopathy; Uveitis

INTRODUCTION

HIV-1-related eye diseases have become a great challenge for patients of HAART treatment all over the world. Approximately 70% of HIV-1 infected patients acquire ocular opportunistic infections and manifest eye disorders during the course of their illness [1]. A single-center, retrospective study in Tokyo, of the 1,515 study patients, HIV retinopathy (HIV-R) was diagnosed in 127 (8%) patients [2].

Severe retinopathy and uveitis are the main untreatable causes of blindness in these patients, since the molecular mechanism has remained unclear until now. In this Review, we present an overview of the existing cognitive and possible mechanisms for retinopathy and uveitis in HIV-1-related eye diseases [3-6].

HIV ASSOCIATED EYE DISEASES

At present, existing knowledge has believed that disruption of the structure and function of the blood-retina barrier (BRB) is the major contributor of HIV-1-related eye diseases. The BRB include the neurons, pigment epithelium, vascular cells and microglia or resident macrophages that are organized into distinct layers [7,8]. Both the vascular endothelium and retinal pigment epithelial possess a well-developed tight junction complex to form the BRB, which give a stringent control of solute and fluid permeability and maintains the autologous microenvironment for a functional retina.

Pathways by which HIV-1 enters various tissues across the epithelium have been covered, containing transcytosis, direct infection, diffusive percolation and sequestration. Some studies revealed that direct interaction of HIV-1 with the endothelium, which share tight junction structures in common with the epithelium, could lead to the disruption of endothelial integrity and subsequent increased HIV leakage across the endothelium [9].

It has been confirmed that gp120 has many functions, for example, apoptosis, HIV-associated B cell dysfunction, inflammation and so on. HIV-1 envelope glycoprotein gp120 mediates viral entry by binding to receptors-CD4 glycoprotein on host cells [10]. Gp120 and Tat protein have been associated with the disruption of tight junctions in the endothelium.

Notably, gp120 can induce the degradation of tight junction proteins in endothelial cells and has been associated with increased permeability of the BRB during progressive HIV-1-associated retinopathy and uveitis. The enhanced BRB permeability induced by HIV-1 gp120 has also been observed in transgenic mice. Treatment with HIV-1 gp120 down-regulated the expression of tight junction proteins in human RPE cells and led to increased monolayer permeability and consequent translocation of HIV-1 and bacteria across the epithelium. However, the molecular mechanism of gp120 down regulating tight junction protein is still elusive.

These tight junction proteins comprise of F-actin and zonula occludens-1(ZO-1) which coordinates with various signaling

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proteins, such as symplekin, ZO-2, ZO-3, and cingulin, and link the cell membrane to the actin cytoskeleton [11]. Multiple studies confirmed that inflammation and immune dysregulation play a major role in HIV-induced endothelial dysfunction. There are research found that gp120 could bind to DC-SIGN molecules expressed on the surface of human RPE cells. The binding then triggers cellular NF- κ B signaling for the induction of MMPs. The MMPs can then mediate the degradation of tight junction proteins, resulting in the disruption of BRB integrity. HIV-1 causes endothelial dysfunction impairment by mechanisms involving inflammation, cytokine, and IFN signaling in endothelial cells, actually. Among the process of inflammation, the direct effect of TNF- α on disruption of epithelial tight junction and increased permeability has been extensively characterized. TNF-induced raise in permeability of cells is known to be mediated by NF- κ B activation that downregulates ZO-1 protein expression. The disruption of tight junctions following HIV-1 exposure likely composed of two stages: initially there may be a displacement of ZO-1 that leads to disruption of tight junction integrity followed by marked reduction in the amount of ZO-1 and other tight junction proteins due to decreased transcription. Thus, TNF- α produced by the epithelium in response to gp120 could induce NF- κ B activation and subsequent downregulation of tight junction proteins, including ZO-1.

In addition, previous research shown that gp120 and Tat proteins with epithelial cells substantially reduced E-cadherin expression and activated vimentin and N-cadherin expression, which are well-known mesenchymal markers [12]. Gp120 and Tat proteins induce epithelial-mesenchymal transition (EMT) in epithelia via activation of TGF- β and MAPK signaling. EMT is an epigenetic process leading to the disruption of mucosal epithelia and allowing the paracellular spread of viral and other pathogens. So gp120 and Tat proteins induce EMT may be also is the potential mechanism for disruption of the structure and function of the BRB.

The blood-retinal barrier has a similar nature to the Blood-Brain Barrier (BBB) and is derived from the same embryonic primordium. Gp120 can disrupt the integrity of the BBB and cause HIV-associated neurocognitive disorders of research and plentiful literatures appear.

DISCUSSION

There is substantial additional data to suggest that gp120 affects ER and mitochondrial function, albeit much of it coming from cortical neuron studies rather than work on Dorsal Root Ganglion (DRG) or peripheral nervous tissue [13]. Mitochondria play an essential role in axonal transport and calcium homeostasis. Gp120 has been shown to affect intracellular calcium levels in rat retinal cultures and mitochondrial genetic information. I Suppose that gp120 by cross-talk of intermediate phenotype of ER, mitochondrion, and other organelles is related to cell apoptosis, autophagy, vesicle transport, inflammation, disrupt the integrity of the BRB and ultimately the outcome for retinopathy and uveitis.

On the other hand, gp120 can increase oxidative stress and promote production of inflammatory cytokines, and increased

expression of pro-inflammatory cytokines, including IL-6, IL-8, and CCL5, was observed in astrocytes upon exposure to gp120. Exposure to gp120 results in increased oxidative stress in astrocytes, including decreased GSH/GSSG ratios and reduced levels of glutathione peroxidase and glutathione reductase [14]. It has certain reference significance to gp120 could increase the production of IL-8, CCL-2 and TNF- α , and these pro-inflammatory cytokines may also play a role in the breakdown of the BRB.

CONCLUSION

Finally gp120 and Tat is the most studied HIV protein in the context of HIV-1-cell damage. Nef and Vpr have also been studied for their cytotoxicity in endothelial cells. So I think, the urgent demand for research of gp120 or/with other HIV proteins work together using theory or experiment together based on existing research. We will hope to confirm that central-control by the retinopathy and uveitis regulates the upstream and downstream molecular mechanisms. We will obtain a wider knowledge and a deeper understanding.

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