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Role of Connexin and Pannexin containing channels in HIV infection and NeuroAIDS

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Abstract

Neuron-Glia crosstalk is essential for efficient synaptic communication, cell growth and differentiation, neuronal activity, neurotransmitter recycling, and brain immune response. The master regulators of this neuron-glia communication are connexin containing Gap Junctions (GJs) and Hemichannels (HCs) as well as pannexin HCs. However, the role of these channels under pathological conditions, especially in infectious diseases is still in exploratory stages. Human Immunodeficiency Virus-1 (HIV) is one such infectious agent that takes advantage of the host intercellular communication systems, GJs and HCs, to exacerbate viral pathogenesis in the brain in spite of the antiretroviral therapy effectively controlling viral replication in the periphery. Although most infectious agents lead to total “shutdown” of gap junctional communication in parenchymal cells, HIV infection maintains and “hijacks” GJs and HCs to enable few infected cells to spread toxic intracellular agents to neighboring uninfected cells aggravating viral neuropathology even in the absence of viral replication. In this mini-review, we present a comprehensive overview of the role of GJs and HCs in augmenting HIV neuropathogenesis.

Keywords

HIV; Gap junction; Hemichannel; AIDS; Reservoirs

Introduction

After more than three decades of Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) epidemic, the scientific community is still struggling to eradicate the virus from the 36 million HIV-infected individuals. The introduction of antiretroviral therapy (ART) has increased the life expectancy of HIV-infected individuals, but we are still far from a cure [1]. In the current ART scenario, the prevalence of HIV-

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Associated Neurocognitive Disorders (HANDs) in 50–60% of HIV-infected individuals has become a major public health concern [2]. HIV invades the brain early after primary infection and continues to harbor establishing viral reservoirs, despite effective ART and suppression of viral replication in the periphery [3]. Although the extent of HIV infection in the Central Nervous System (CNS) is fairly limited (perivascular macrophages, microglia, and astrocytes), the magnitude of neuropathogenesis observed does not correlate with the viral replication. Instead, it correlates with unidentified amplification systems used by HIV to spread toxicity and apoptosis. We propose that one of the amplification mechanisms employed by HIV is mediated by Gap Junctions (GJs) and Hemichannels (HCs) between HIV-infected cells surviving in the presence of ART and neighboring uninfected brain cells. In this review, we will elaborate on the role of Connexin (Cx) and Pannexin (Panx) containing GJ channels and HCs in HIV neuropathogenesis.

Gap junctions and hemichannels

Gap junctions are the only communication system in multicellular organisms that allows direct exchange of intracellular metabolites and electrical signals between the connected cells. Mammalian GJs are composed of hexameric assemblies of specific membrane proteins (Connexins, Cxs) from adjacent cells that juxtapose each other to form a channel creating a direct exchange hub between the two cells [4]. GJs refer to clusters of these channels in plasma membrane microdomains that result from head-to-head docking of two HCs, each contributed by one participating cell. Unopposed HCs (uHCs) may also open on the cell surface, where they serve to establish communication between the cytoplasm and the extracellular space. Other than Cxs, uHCs may also be composed of another family of proteins, Pannexins (Panxs). In contrast to Cxs, Panxs have only been documented to form uHCs [5]. GJs and uHCs have an internal pore diameter of 12 nm rotation, and allow bi-directional flow of ions (Ca^{2+}), second messengers (ATP, cAMP, inositol triphosphate, IP_3), and small molecules (small RNA, neurotransmitters, glutamate) across the connected cells or between the cytoplasm and the extracellular matrix [4]. Although uHCs are typically closed during the resting state, once open, uHCs release NAD^+, glutamate, ATP, and ions into the extracellular milieu [6].

Historically, it has been believed that inflammation reduces Cx expression and GJ-mediated communication in parenchymal cells [7]. Consequently, several viral and bacterial infections lead to downregulation of Cx expression and GJ-mediated communication [8]. In astrocytes, GJs and uHCs are reciprocally regulated at the primary site of inflammation, where GJ-mediated communication is reduced while uHC activity is enhanced during acute stages [9]. Enhanced uHC activity has been documented in several cellular stress events such as hypoxia [10], oxidative stress [11], and inflammation [12]. Since the opening of astroglial uHCs has been known to assist in the release of ATP, glutamate, and NAD^+ into the extracellular space, astrocytic dysfunction and enhanced uHC activity would compromise the trophic and metabolic support to neurons enhancing neuronal vulnerability. However, the mechanisms by which GJs and uHCs contribute to disease pathology are still unknown.

Connexin and Pannexin expression and their role in the CNS

The brain is composed of neurons, astrocytes, oligodendrocytes, microglia, ependymal cells and endothelial cells. All of these are connected and coordinated by GJs and uHCs. Table 1 briefly represents the expression of Cx and Panx proteins as well as their role in several of these brain cells types before discussing their involvement in HIV infection and NeuroAIDS.

Role of gap junctions and hemichannels during HIV infection

Only recently, several laboratories including ours have demonstrated that GJs and uHCs play a significant role in HIV life cycle as well as in the pathogenesis of NeuroAIDS. In the following section, we have given a brief introduction of HIV pathogenesis before discussing in detail the role of GJs and uHCs in HIV pathogenesis.

HIV pathogenesis: General introduction

Since its first clinical observation, HIV/AIDS has claimed more than 35 million lives worldwide. Although ART has been highly effective in suppressing systemic HIV replication, persistence of HIV in latent “viral reservoirs” in the human body still poses a challenge for the complete elimination of the virus from the infected individuals [3, 40]. It has been speculated that the human brain acts as a latent reservoir for HIV, as several antiretrovirals have poor penetration across the blood-brain barrier (BBB) [40, 41].

HIV enters the brain via Trojan horse mechanism, hiding inside the blood-borne monocytes [42]. Once inside the brain, HIV-infected monocytes/macrophages promote neuroinflammation by secreting viral proteins and proinflammatory cytokines and chemokines which aid in further recruitment of uninfected and HIV-infected cells into the brain [43]. The cell types harboring HIV infection in the brain are perivascular macrophages, microglia, and a small population of astrocytes (approximately 5%) [44, 45]. Since astrocytes are the most abundant brain cell type, even limited HIV infection in these cells correspond to a significant viral reservoir [40]. Moreover, amplification of HIV neuropathogenesis by intercellular communication systems involving GJs and uHCs exacerbate the pathology of CNS HIV infection several folds.

Role of Panx1 uHCs in HIV infection and replication

Recent work on the role of Panx1 uHCs and purinergic receptors during HIV infection has revealed novel and exciting results [46–48]. HIV infection in $CD4^+$ T-lymphocytes and peripheral blood mononuclear cells leads to opening of Panx1 uHCs and release of ATP [48]. Extracellular ATP then activates purinergic receptors (P2Y) and allows downstream signaling cascade involving Proline-rich tyrosine kinase-2 (Pyk2), and membrane depolarization to facilitate the early steps of HIV infection [49]. Interestingly, Panx1 uHC activity has also been found to be indispensable for HIV replication in $CD4^+$ T-lymphocytes [48]. We propose that HIV-induced Panx1 uHC opening results in increased intracellular Ca^{2+} levels and rearrangement of the actin cytoskeleton that assists in successful fusion of HIV virions with the host cell membrane (Figure 1A) [46, 47].

The role of Panx1 uHCs in NeuroAIDS is further strengthened by the observation that pharmacological inhibition of Panx1 uHCs by probenecid has been shown to reduce the efflux of antiretrovirals from the infected cells (Figure 1B). More importantly, probenecid has been utilized extensively with Tenofovir and Zidovudine during the early HIV epidemic to increase their antiviral effects [50]. Thus, Panx1 uHCs play a crucial role in HIV infection, viral replication, and maintenance of clinically effective concentration of antiretrovirals in the infected cells.

Maintenance of CNS GJ communication during HIV infection

As mentioned in the preceding section, inflammation decreases Cx43 expression; however, we have observed that during HIV infection, expression of Cx43 is enhanced in HIV-infected human fetal astrocytes (HIV-p24-positive) [51]. This results in the maintenance of GJ-mediated communication which contributes to bystander apoptosis of uninfected astrocytes by transferring toxic/apoptotic signals from few HIV-infected astrocytes to the uninfected cells (Figure 2). Cx43 expression was also found to be elevated in astrocytes in post-mortem brain tissue from individuals with HIV-Encephalitis (HIV-E) as compared to CNS tissue sections from uninfected individuals [52].

Our studies have demonstrated that HIV-Tat, the transactivating protein of HIV, is responsible for the maintenance of GJ-mediated communication during HIV infection [52]. HIV-Tat exposure leads to enhanced expression of Cx43 at both mRNA and protein levels by directly binding to the Cx43 promoter [52]. Since the current antiretroviral treatments have no effect on HIV-Tat production, which continues even in the absence of viral replication [53], it is imperative to consider the role of HIV-Tat in amplification of HIV neuropathogenesis via GJ channels.

Gap junctions, hemichannels, and astrocyte/neuronal compromise

As mentioned earlier, GJs contribute to the amplification of HIV neuropathogenesis by enabling the diffusion of toxic metabolites from few HIV-infected astrocytes (HIV-p24-positive cells) to surrounding uninfected astrocytes leading to apoptosis of uninfected cells [51, 54]. We have also observed mitochondrial dysfunction in HIV-infected astrocytes that lead to an uncontrolled release of cytochrome *c* by a Ca^{2+} and IP_3-mediated mechanism [55]. We have proposed that IP_3 and Ca^{2+} present in HIV-infected astrocytes diffuse, via GJ channels, into the uninfected cells leading to their apoptosis since blocking either GJ crosstalk or cytochrome *c*/IP_3 signaling abolished bystander apoptosis [55]. However, HIV-infected astrocytes do not succumb to apoptosis even after direct intracellular microinjection of cytochrome *c*, which suggests unique HIV-mediated mechanisms of cellular protection that possibly contribute to the establishment of viral reservoirs [55]. These HIV-mediated mechanisms of infected cell survival are under active investigation in our laboratory.

HIV infection also induces the opening of astroglial Cx43 uHCs enhancing the secretion of Dickkopf-1 (DKK1) protein, a soluble Wnt pathway inhibitor, which leads to the compromise of neuronal processes [56]. The role of astroglial uHCs in HIV neuropathogenesis is further strengthened by observations of increased DKK1 expression in astrocytes and endothelial cells in brain tissue sections from HIV-E cases [56]. Enhanced

DKK1 levels have already been linked to amyloid-β-mediated synaptic loss [57]. Since compromised neuronal processes and synaptic loss subsequently lead to cognitive impairment, uHCs may be contributing to cognitive decline in HAND patients by mediating DKK1 release. In conclusion, HIV successfully “hijacks” GJs and uHCs to promote infection, invasion of the virus into the CNS, and neurotoxicity. GJs and uHCs participate in the survival of HIV reservoirs and play a fundamental role in the viral neuropathogenesis observed in at least half of the HIV-infected population.

Discussion

The success of ART has transformed HIV/AIDS into a chronic disease with immune reconstitution and activation, ART-associated toxicities, accelerated aging, and persistence of the virus in latent reservoirs such as the brain. The exploitation of the host intercellular communication systems (especially GJs and uHCs) by HIV has allowed the virus to disseminate infection and associated inflammation leading to aggravated HIV neuropathogenesis [58]. Comprehensive evaluation of the functions of GJs and uHCs as well as other modalities of cell-cell communication (tunneling nanotubes and exosomes) is required to gain deeper insights into HIV pathology and development of NeuroAIDS.

The involvement of Panx1 uHCs and purinergic receptors in HIV life cycle has not been fully explored. Along with adenosine, ADP, and ATP, purinergic receptors and Panx1 uHCs are important regulators of various cellular events, and unlocking their critical relationship could hold the key to understanding several pathological conditions. The deeper understanding of these mechanisms will provide a unique opportunity towards the discovery of novel therapeutics for prevention and cure of HIV and NeuroAIDS.

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Highlights

- HIV hijacks gap junctions and hemichannels to enhance viral neuropathogenesis.
- Gap junctions contribute to bystander apoptosis of uninfected astrocytes.
- Gap junctions disrupt blood-brain barrier facilitating HIV neuroinvasion.
- Pannexin1 hemichannels play a crucial role in HIV infection and replication.

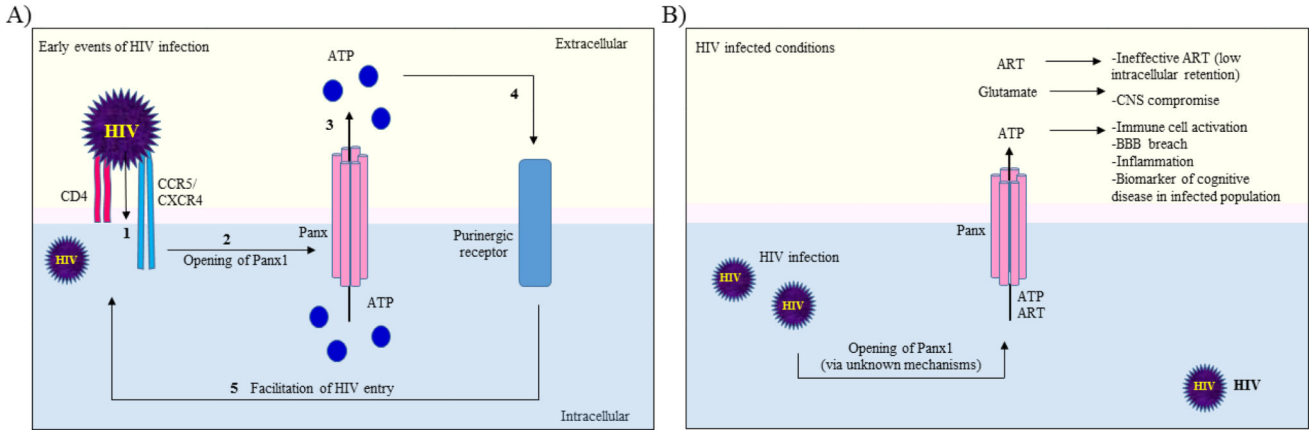

Figure 1. Role of Panx1 uHCs in HIV neuropathogenesis

(A) Binding of HIV to host CD4 receptor and CCR5/CXCR4 co-receptors in $CD4^+$ T-lymphocytes and monocytes **(1)** leads to opening of Panx1 uHCs **(2)**. As a result, ATP is released through the Panx1 uHCs **(3)**, which then activates purinergic receptors **(4)**. Downstream signaling through purinergic receptors leads to membrane depolarization and actin rearrangement which facilitates the entry of HIV virions into the cells **(5)**. **(B)** At later stages, ATP released from HIV infected cells via Panx1 uHCs also leads to inflammation and contributes to BBB disruption. We propose that circulating ATP levels may be considered as a biomarker for cognitive disease in the HIV-infected population. Furthermore, as a consequence of Panx1 uHC opening, there is efflux of ART from the cells leading to a lower intracellular concentration of antiretrovirals which may be ineffective against the virus. Glutamate, which is also released from the Panx1 uHCs is a prime mediator of CNS compromise. Hence, it is imperative to decipher the role of Panx1 uHCs in HIV neuropathogenesis.

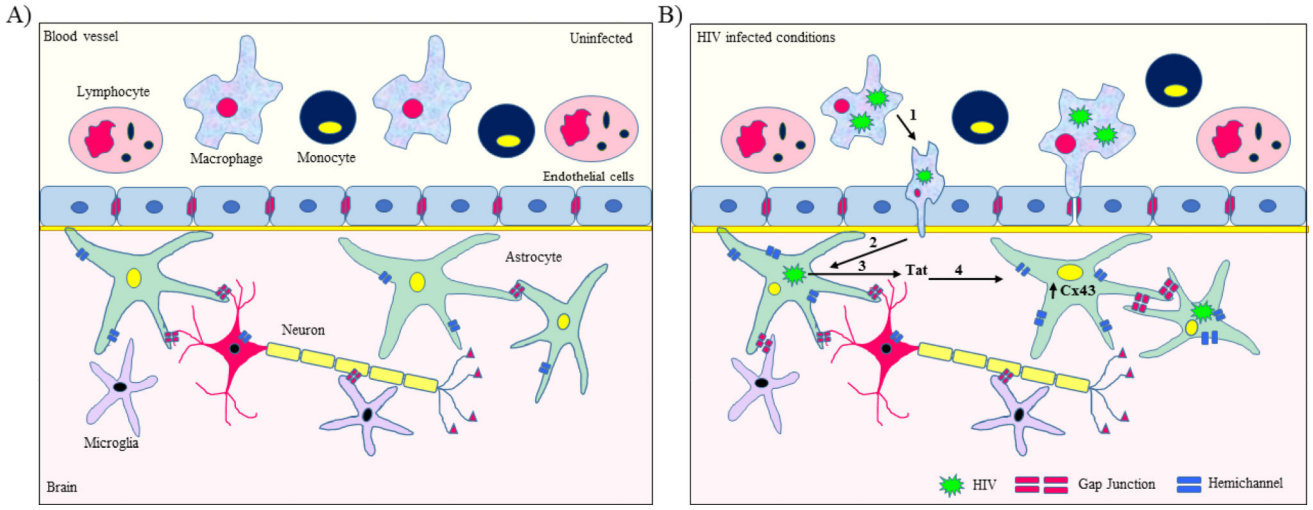

Figure 2. HIV infection increases Cx43 expression in human astrocytes

(A) During physiological conditions, Cx containing GJs mediate neuron-glia crosstalk and coordinate several essential cellular functions. **(B)** HIV infection leads to upregulation of Cx expression and maintenance of GJ-mediated communication. During HIV infection, BBB disruption leads to infiltration of infected monocytes and macrophages into the brain **(1)**. As HIV infects resident brain cells such as astrocytes and microglia **(2)**, infected cells release several proinflammatory cytokines and HIV protein, Tat **(3)**. HIV infection, as well as HIV-Tat exposure, leads to upregulation of Cx43 expression in astrocytes. HIV infection also leads to opening of Cx43 uHCs in astrocytes. Although HIV infection in astrocytes is restricted, diffusion of toxic metabolites from HIV-infected cells to uninfected cells contributes in amplification of HIV neuropathogenesis

Table 1

Expression of Cx and Panx proteins and their role in CNS cells.

Cell type	Connexin/Pannexin expression	Functions	
Astrocytes	Cx26[13], Cx30[14], Cx43[14]	Cx GJs	Adult neurogenesis[15], Glutamate transport[16], Glucose trafficking[17], Regulation of K^+[18] and Na^+[19] concentration
	Panx1[20]	Cx/Panx uHCs	Neurotoxicity[21]
Neurons	Cx36[14], Cx45[22], Cx50[23], Cx57[24]	Cx GJs	Electric and metabolic coupling[25], Spatial memory[26]
	Panx1[20], Panx2[20]	CX/Panx uHCs	Electrical coupling[20], Neuronal development, adult neurogenesis[27], Synaptic plasticity[28]
Microglia	Cx32[29], Cx36[30], Cx43[31]	Cx GJs	Do not express GJs under resting conditions
	Panx1[32]	Cx/Panx uHCs	Glutamate release[29], Neurotoxicity[33], Inflammation[34]
Oligodendrocytes	Cx29[35], Cx32[35], Cx45[36], Cx47[35]	Cx GJs	Maintenance of ionic homeostasis[37], Myelination[38]
	Panx1[39]	Cx/Panx uHCs	Formation of uHCs has not been reported