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## Astrocyte CD38: Links to Neuroinflammation in HAND

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### 1. Introduction

Central nervous system (CNS) HIV-1 infection can lead to encephalitis (HIVE), which compromises brain function and presents clinically as HIV-associated dementia [HAD, (Navia et al., 1986; Price et al., 1988; Wiley and Achim, 1994; Brew et al., 1995; Grant, 2008; Letendre et al., 2008; Price and Spudich, 2008)], the most serious form of HIV-associated neurocognitive disorders [HAND, (Grant, 2008; Letendre et al., 2008)]. HAND is associated with various cognitive, behavioral and motor dysfunctions [for details refer (Ances and Ellis, 2007; Grant, 2008)]. Although initiation of combined antiretroviral therapy (cART) has been linked to cognitive improvement and decreased incidence of HAD (Brodt et al., 1997; Sacktor et al., 1999; Foley et al., 2008), the yearly incidence rates for milder forms of HAND are still as high as 10-25% (Woods et al., 2009), and the prevalence of HAD is on the rise due to longer life expectancy of HIV-1-infected individuals (Lindl et al., 2010).

The neuroinflammatory cascade associated with HAND, beginning with the infiltration of HIV-1-infected macrophages and immune activated microglial cells, likely reaches the endpoint of neurodegeneration via glial activation and changes in glial inflammatory responses (Kaul and Lipton, 2006). Reactive astrogliosis, the recruitment to and proliferation of astroglial cells at injury sites, is commonly observed during HIVE (Gonzales and Davis, 1988; Persidsky et al., 1996; Ridet et al., 1997; Wu and Schwartz, 1998; Petitto et al., 1999). Astrocytes are the most abundant cell type in the CNS; and yet, their specific roles continue to be unraveled. Thus, characterization of molecules/pathways involving the activated astrocytes during HIVE and HAND, is of high interest.

CD38 expression on peripheral T lymphocytes is a marker for disease progression in HIV-1-infected patients (Savarino et al., 2000; Vigano et al., 2000; Kolber, 2008; Sinclair et al., 2008). CD38 is a 45-kD ectoenzyme involved in the synthesis of potent calcium- ( $\text{Ca}^{2+}$ ) mobilizing agents, cyclic ADP ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP+) (Heidemann et al., 2005b; Banerjee et al., 2008). CD38 expression has been detected both in neurons and astrocytes in the cerebral cortex (Mizuguchi et al., 1995; Yamada et al., 1997), while it is primarily expressed by astrocytes in culture (Pawlikowska et al., 1996). Our group has shown that CD38 is one of the most upregulated molecules in IL- $1\beta$ -activated astroglial cells *in vitro* and is also expressed by astrocytes in HIVE brain tissues

(Kou et al., 2009). However, very little is known about the role of CD38 in HAND. In this review, we will explore the possible mechanistic links between, astrocyte-CD38 upregulation, Ca<sup>2+</sup> homeostasis and HIV-1 neuropathogenesis.

## 2. Neuroinflammation during HIVE and astrocytes

HIV-1 enters the brain early, after systemic infection of circulating T cells and macrophages, by crossing the blood brain barrier [BBB (Bell et al., 1998; Bell, 2004)]. Neurons are rarely infected by the virus (Price et al., 1988; Kaul et al., 2001; Ellis et al., 2007), thus most neuronal damage is due to indirect toxicity mediated by activated astrocytes and virus-infected and/or activated mononuclear phagocytes (MP, macrophage/microglia). However, viral proteins like HIV-1 Tat and gp120 released by infected MP may show direct neurotoxicity (Mauermann et al., 2008; Li et al., 2009). Pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$  and IL-6, have been implicated in HIV-1 neuropathogenesis (Dickson et al., 1991; Sebire et al., 1993; Gendelman and Tardieu, 1994; Persidsky et al., 1999). Indeed, IL-1 $\beta$  production is one of the first responses observed upon activation of immune cells including MP (Pellegrini et al., 1996). This suggests that immune cell activation during peripheral HIV-1 infection may provide soluble IL-1 $\beta$  that penetrates the BBB (Vitkovic et al., 2000a; Vitkovic et al., 2000b). Brain tissue and cerebrospinal fluid from HIVE patients (Gallo et al., 1991; Tyor et al., 1993; Vitkovic et al., 1995; Boven et al., 1999), as well as brain tissue from simian immunodeficiency virus infected rhesus monkeys (Lane et al., 1996), demonstrated elevated IL-1 $\beta$  levels. Various studies have shown links between IL-1 $\beta$  and astrocyte activation during HIVE (Blumberg et al., 1994; Kaul and Lipton, 2006; Peng et al., 2006). IL-1 $\beta$  is also known to stimulate release of neurotoxic molecules like reactive oxygen species and inducible nitric oxide synthase by astrocytes (Jana et al., 2005; Sharma et al., 2007). Our previous work showed IL-1 $\beta$ -mediated astrocyte Fas ligand expression and subsequent caspase activation in surrounding neurons *in vitro* (Deshpande et al., 2005). We have also shown the effects of IL-1 $\beta$  and HIV-1 gp120, leading to CD38 upregulation in primary astrocyte cultures (Banerjee et al., 2008) and increased CD38 mRNA and protein expression in HIVE brain (Kou et al., 2009). IL-1 $\beta$ -activated astrocytes are known to release cytokines like IL-6 and chemokines like CCL2, CXCL8 and RANTES (Lee and Aarhus, 1993; Zhao and Brinton, 2004; Sharma et al., 2007). Our work showed that CD38 is a partial regulator of chemokine and cytokine signaling by IL-1 $\beta$ -activated astrocytes, thus affecting the inflammatory milieu during HIVE (Kou et al., 2009). IL-1 $\beta$  has also been shown to mediate activation of mitogen activated protein kinases (MAPKs) in primary astrocyte cultures (Parker et al., 2002; Zhao et al., 2004). MAPKs belong to a family of serine threonine kinases [for details refer (Davis, 1995; Chang and Karin, 2001)]. These kinases are involved in inflammation, cell proliferation and differentiation in astrocytes (Rajan and McKay, 1998; Hua et al., 2002; Morita et al., 2003). It is also well established, that the prolonged activation of MAPKs and nuclear factor (NF)- $\kappa$ B may mediate inflammatory conditions during HIVE (Yi et al., 2004; Kaul and Lipton, 2006). Our studies have shown direct involvement of MAPK and NF- $\kappa$ B in the regulation of CD38 expression and signaling in primary astrocytes, thus indicating that CD38 may be a major molecule in astrocyte-mediated inflammatory signaling in HIVE brain (Mamik et al., In Press).

### 3. Calcium in glial biological functions and HAND

Astrocytes can sense, respond to, and modulate neuronal activity (Cotrina and Nedergaard, 2005; Heidemann et al., 2005a). They provide crucial support for neurons and the other CNS cells through diverse functions, ranging from the production of neurotrophic factors to the elimination of neurotoxins (Ransom et al., 2003). Their ability to respond vigorously to diverse neural insults is commonly referred to as reactive astrogliosis, astrocytosis or astrocyte activation (Eng and Ghirnikar, 1994). Astrogliosis is associated with HAND and also observed in HIV-1 gp120 transgenic mice (Kaul et al., 2001). Since astrocytes are not electrically excitable, they sense changes in the microenvironment through receptors on their plasma membranes. Activation of these transmembrane receptors or ion channels and intracellular endoplasmic reticulum (ER) receptors, as well as mitochondrial  $\text{Na}^+/\text{Ca}^{2+}$  exchangers, increases intracellular calcium concentration ( $[\text{Ca}^{2+}]_i$ ) [for details review (Cotrina and Nedergaard, 2005; Reyes and Parpura, 2009)]. Depending on the amplitude, spatial resolution and duration of  $\text{Ca}^{2+}$  response, genes are up or downregulated (Berridge et al., 2003). Change in free  $[\text{Ca}^{2+}]_i$  also results in secretion of glutamate and other neuro-active compounds (peptides, eicosanoids, neurotrophins) into the microenvironment. These substances modulate the activity of juxtaposed neurons and other astrocytes (Cotrina and Nedergaard, 2005). In addition,  $\text{Ca}^{2+}$  waves are also used for long-distance communication between astrocytes via gap junction proteins, which in turn can be modulated by IL-1 $\beta$  (John et al., 1999).

After a physiological task is completed, the cytosolic  $\text{Ca}^{2+}$  levels return to normal by extrusion of  $\text{Ca}^{2+}$  either via  $\text{Na}^+/\text{Ca}^{2+}$  exchangers or plasma membrane  $\text{Ca}^{2+}$ -ATPases (Rojas et al., 2004; Rojas et al., 2007), while  $\text{Ca}^{2+}$  mobilized from internal stores return to normal via sarco/ER  $\text{Ca}^{2+}$ -ATPase (Bers, 2002; Wang et al., 2006; Liu et al., 2007). Some recent reports show that mitochondrial  $\text{Ca}^{2+}$  uniporter may also act as a sink to trap off the excess  $[\text{Ca}^{2+}]_i$  (Reyes and Parpura, 2008, 2009). Thus, the physiological levels of free  $[\text{Ca}^{2+}]_i$  are tightly controlled. However,  $\text{Ca}^{2+}$  overload triggered by excessive influx through plasma membrane voltage and receptor-operated channels, by metabotropic receptors or  $\text{Ca}^{2+}$  released from intracellular pools, may lead to HIV-1-induced neurotoxicity (Nath and Geiger, 1998; Holden et al., 1999). Mobilization of intracellular  $\text{Ca}^{2+}$  pools is an important modulator of apoptosis in various cells, including T cells, ventricular myocytes, and cerebellar granule cells (Khan et al., 1996; Jayaraman and Marks, 1997; Lin and Leonard, 1997; Felzen et al., 1998; Herbein et al., 1998). Furthermore, it has been associated with HIV-1 gp120-induced neuronal cell death *in vitro* (Meucci et al., 1998).

### 4. CD38 function and $\text{Ca}^{2+}$ homeostasis

It has been suggested that there is more than one substrate for the enzymatic activity of CD38, including nicotinamide adenine dinucleotide (NAD $^+$ ) and nicotinamide adenine dinucleotide phosphate (NADP) in astrocytes (Bertheliet al., 1998; Deaglio et al., 2001; Antonelli and Ferrannini, 2004; De Flora et al., 2004; Heidemann et al., 2005a). The CD38-catalyzed cleavage of the nicotinamide-ribose bond eventually leads to the production of cADPR (Bertheliet al., 1998). Despite the fact that CD38 is a very inefficient cyclase because ADPR produced by hydrolysis of cADPR is the major end product (Lee and Aarhus, 1993), it has been demonstrated that this small amount of cADPR is still biologically relevant (Partida-Sanchez et al., 2003).

NADP<sup>+</sup>, the major alternate substrate to NAD<sup>+</sup>, leads to the formation of NAADP<sup>+</sup> by CD38 primarily in acidic conditions (Heidemann et al., 2005b). While some recent reports have shown that hydrolysis of NAD<sup>+</sup> to adenosine may increase [Ca<sup>2+</sup>]<sub>i</sub> in astrocytes (Doengi et al., 2008; Okuda et al., 2010), both cADPR and NAADP<sup>+</sup> are potent Ca<sup>2+</sup> mobilizing metabolites (Lee, 2001; Antonelli and Ferrannini, 2004; De Flora et al., 2004; Heidemann et al., 2005a). These secondary messengers generated by CD38 lead to intracellular Ca<sup>2+</sup> release by various mechanisms. NAADP<sup>+</sup> has been shown to mobilize Ca<sup>2+</sup> from inositol 1,4,5 trisphosphate (IP<sub>3</sub>) receptors (IP<sub>3</sub>R) in astrocytes (Heidemann et al., 2005b), ryanodine (Ry) receptors (RyR) in T cells (Dammermann and Guse, 2005; Steen et al., 2007), or from other uncharacterized intracellular Ca<sup>2+</sup> stores (Mandi and Bak, 2008). However, cADPR is primarily involved in release of intracellular Ca<sup>2+</sup> through RyRs in various cell types including myocytes, fibroblasts, smooth muscle cells, T cells, neuronal cells and astrocytes (Bruzzone et al., 2003; Partida-Sanchez et al., 2003; Kunerth et al., 2004; Hashii et al., 2005; Fliegert et al., 2007; Jude et al., 2008). cADPR can also be involved in the extracellular Ca<sup>2+</sup> influx in T cells and neuroblastoma-derived neuronal cells (Partida-Sanchez et al., 2001; Amina et al., 2010). These evidences suggest that CD38 is a primary regulator of Ca<sup>2+</sup> signaling in various cell types, including astrocytes.

## 5. Astrocyte glutamate production vs. glutamate uptake in HAND

Astrocytes are known to regulate glutamate homeostasis in CNS [for details review (Hamilton and Attwell, 2010)]. In the HIV-1-infected brain, multiple factors may impair astrocyte regulation of Ca<sup>2+</sup> and glutamate levels. Gendelman and co-workers first reported high levels of arachidonic acid and cytokines such as TNF- $\alpha$  and IL-1 $\beta$ , in HIVE brain tissue (Gendelman et al., 1994), which likely lead to reduced glutamate uptake and increased Ca<sup>2+</sup>-mediated release of glutamate by astrocytes (Parpura et al., 1994; Bezzi et al., 1998). It has also been shown that HIV-1 gp120 may indirectly contribute to impaired astrocyte-glutamate uptake *in vitro* (Schneider-Schaulies et al., 1992; Benos et al., 1994). Thus, in addition to glutamate release, dysregulation of [Ca<sup>2+</sup>]<sub>i</sub> in astrocytes may also contribute to HIV neuropathogenesis through impaired glutamate uptake. Impaired glutamate uptake can lead to further increases in the extracellular glutamate levels. Enhanced glutamate levels in turn activate N-methyl-D-aspartic acid (NMDA) receptors causing increased levels of intracellular Ca<sup>2+</sup> in neurons as shown both in cultured neurons and acute brain slices (Kaul et al., 2001), and can eventually lead to neuronal apoptosis or necrosis. Excess glutamate may also lead to lipid peroxidation and eventually affect both astrocyte and neuronal viability (Visalli et al., 2007).

Under normal physiological conditions, astrocytes selectively regulate extracellular levels of glutamate to maintain homeostasis in the neuronal microenvironment mainly through glutamate transporters (Rothstein et al., 1996). Previous work on primary human astrocytes has shown downregulation of excitatory amino acid transporter 2 (EAAT2) upon activation of astrocytes with HIV-1 gp120, leading to reduction in glutamate uptake (Wang et al., 2003). Glutamate transporter activity and inhibition of glutamate uptake can also be mediated by MAPKs and NF- $\kappa$ B in astrocytes (Abe and Saito, 2001; Jayakumar et al., 2006). Our laboratory showed that CD38 expression and function in astrocytes, is primarily regulated by NF- $\kappa$ B and MAPKs (Mamik et al., In Press). Thus, it is relevant to propose that CD38 levels may affect astrocyte-mediated glutamate homeostasis during neuroinflammatory conditions.

Both RyR and IP3R blockers can reduce excess glutamate release by astrocytes (Hua et al., 2004; Reyes and Parpura, 2009). This suggests that perhaps both IP3R and RyR may be involved in the increase in  $[Ca^{2+}]_i$ , an event that plays a major role in glutamate release. We have previously reported CD38-cADPR-mediated increase in  $[Ca^{2+}]_i$  in activated astrocytes. Our data suggests that elevated CD38 level leads to production of excess cADPR, which may eventually result in higher  $Ca^{2+}$  in activated astrocytes during HIVE (Banerjee et al., 2008). As previously reported by De Flora's group, this rise in  $[Ca^{2+}]_i$  by CD38 may lead to increased release of glutamate by astrocytes (Verderio et al., 2001). Studies by Bezzi and co-workers showed that cultured astrocytes may trigger  $[Ca^{2+}]_i$ -dependent release of

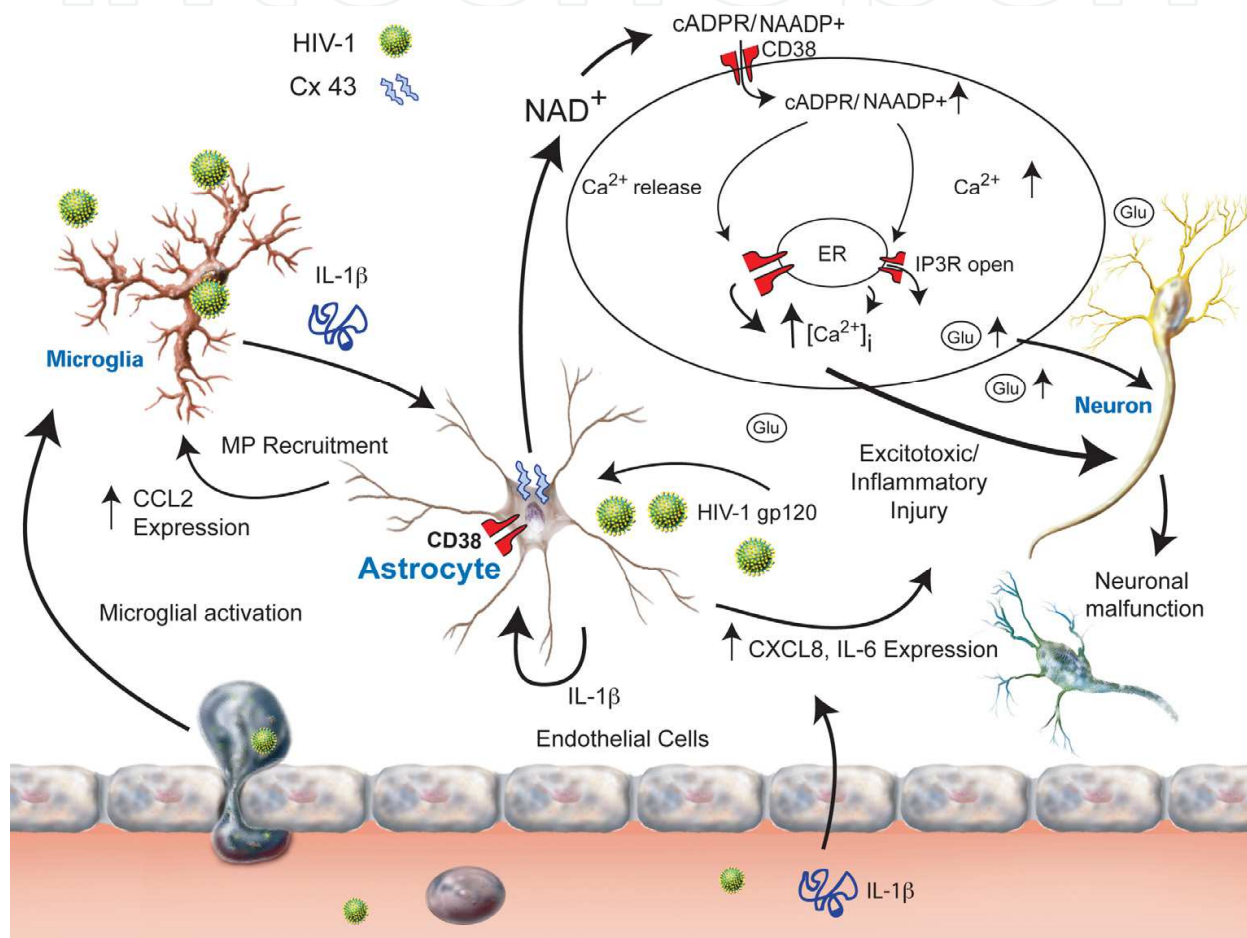


Fig. 1. Schematic representation of CD38-mediated astrocyte-neuron interactions. In HIVE, virus-infected macrophages cross the blood-brain barrier and initiate inflammatory processes in the brain including microglial activation. Activated macrophages and microglia produce IL-1 $\beta$ , which along with viral protein HIV-1 gp120 leads to activation of astrocytes. Inflammatory responses of activated astrocytes may include upregulation of molecules detrimental to neural homeostasis. One of these pathways includes CD38 upregulation, which produces Ca<sup>2+</sup>-mobilizing metabolites like NAD<sup>+</sup>. NAD<sup>+</sup> upon release through Connexin 43 (Cx 43) hemichannels is hydrolyzed and transported back into the cell as cADPR by membrane bound CD38. cADPR and NAADP<sup>+</sup> may regulate release of  $[Ca^{2+}]_i$ . Astrocyte-mediated release of glutamate and other inflammatory mediators (IL-6 and CXCL8) into the synapse may ultimately lead to excitotoxic neuronal injury.

glutamate, which may lead to NMDA receptor-mediated increased  $\text{Ca}^{2+}$  levels in neurons (Bezzi et al., 1998). The above evidences suggest that the initial release of glutamate due to increase in  $[\text{Ca}^{2+}]_i$  by astrocytes, may be influencing the prolonged higher  $\text{Ca}^{2+}$  levels in neurons during HAND. Taken together, CD38/cADPR-mediated rise of  $[\text{Ca}^{2+}]_i$  in activated astrocytes (Banerjee et al., 2008) may contribute to increased extracellular glutamate levels, resulting in neuronal excitotoxicity during HAND.

## 6. Conclusion

### 6.1 Role of astrocyte-CD38 in HAND: Possible mechanisms

Astrocytes are capable of generating complex changes in  $[\text{Ca}^{2+}]_i$ , allowing them to communicate with each other and with neighboring neuronal cells. The CD38/cADPR system is involved in regulating  $[\text{Ca}^{2+}]_i$  homeostasis in astrocytes (Banerjee et al., 2008). A paracrine model of interaction has been suggested, involving NAADP<sup>+</sup> and cADPR, leading to glutamate-release by astrocytes, affecting neurons (Verderio et al., 2001; De Flora et al., 2004). Our previous data demonstrate that in HIV-1 CNS disease, astrocytes express elevated levels of CD38 (Kou et al., 2009), thus activating these paracrine pathways. The possible connections between HIV-1 infection, neuroinflammation and astrocyte activation, which result in CD38 upregulation and dysregulation of  $\text{Ca}^{2+}$ /glutamate homeostasis and culminate in neuronal injury (Fig. 1).

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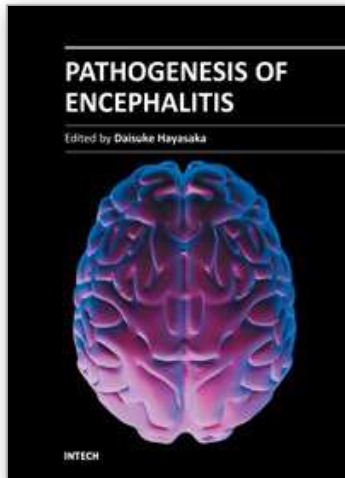
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## **Pathogenesis of Encephalitis**

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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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