HIV Tat 101-mediated loss of pericytes at the blood-brain barrier involves PDGF-BB

Fang Niu¹, Honghong Yao², Ke Liao¹, Shilpa Buch ¹

¹Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198, USA
²Department of Pharmacology, Medical School of Southeast University, Nanjing, China, 210009

Correspondence: Shilpa J. Buch
E-mail: sbuch@unmc.edu
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Human immunodeficiency virus (HIV), the causative agent of AIDS, is known to enter the CNS within days of infection; however, it is not until years later that the disease manifests in the brain. In the era of combined antiretroviral therapy (cART), although there is successful control of viremia and infected individuals continue to live longer, paradoxically, the lack of cART to enter the CNS and increased longevity of infected individuals, often leads to development of HIV-1-associated neurocognitive disorders (HAND) in almost 30-50% of infected individuals [1]. HAND is pathologically characterized by reversible synaptodendritic injury and inflammation in the CNS [2, 3]. One of the leading mechanism(s) underlying neuroinflammation associated with HAND involves breach of the blood-brain barrier (BBB) resulting in influx of inflammatory cells into the CNS with ensuing cognitive decline and neurological complications.

The cerebrovascular unit comprising of endothelial cells, astrocytes and pericytes, is a highly selective permeability barrier that is impermeable to toxic agents, ions and pathogens. This selective permeability is what maintains the CNS homeostasis with the brain being considered as an immunoprivileged organ [4]. The focus of our study is on the essential but understudied cells of the neurovascular unit, the pericytes that are contractile cells and uniquely positioned within the brain microvascular, playing an integral role in the development and maintenance of blood vessels [5]. Their role...
in HIV is emerging only recently. For example, pericytes have been demonstrated to be activated by inflammatory agents and can also be infected by HIV-1 [6], leading in turn, to transcytosis of HIV-1 virus across the BBB.

Despite the presence of cART, early virus proteins such as HIV-1 Tat continue to lurk in tissues such as the lymph nodes and the CNS. This becomes problematic as HIV Tat is both neuroexcitatory as well as neurotoxic, and has been implicated in the pathogenesis of HAND [7, 8]. Our previous findings have demonstrated that exposure of human brain microvascular pericytes and the pericyte cell line C3H/10T1/2 cells, to HIV-1 Tat101 resulted in increased expression of platelet-derived growth factor (PDGF)-BB that was concomitant with increased migration of these cells [9]. Tat-mediated increased expression of PDGF-BB is in agreement with previous reports demonstrating the same phenomenon in other cell types of the cerebrovascular unit, such as the endothelial cells and astrocytes [10, 11].

PDGF belongs to a family of growth factors that are comprised of four chains (A-D) and play key role in various cellular functions [12]. PDGF-BB plays critical role in pericyte functioning under both physiological as well as pathological conditions [13, 14], and has been shown to increase the migration of retinal microvascular pericytes [15]. Another interesting finding suggests that the PDGF content of the tumor milieu determines the fate of the pericytes [16]. For example, while PDGF is critical for the maintenance of pericytes, high concentrations of PDGF-BB, can in fact, lead to pericyte loss in tumor vessels. Based on this premise we hypothesized that Tat-mediated increased migration of pericytes could, in part, be a mechanism leading to loss of pericyte coverage in the HIV-1 infected brain. Using both in vitro and ex vivo approaches, we confirmed this hypothesis. Our findings demonstrated that HIV Tat101 significantly increased the migration of C3H/10T1/2 cells and Human Brain Microvascular Pericytes (HBVPs) as expected, and that this effect was abolished in cells treated with heated Tat101. Further validation of these findings was demonstrated ex vivo, wherein we observed that higher expression of PDGF-BB correlated with a concomitant
reduction in the expression of NG2 positive pericytes in microvessels isolated from HIV-1 transgenic (Tg) 26 mice. Similar to the observation in HIV-1 Tg26 mice, reduced pericyte coverage was also observed in sections of frontal cortex from brains of individuals with HIV-encephalitis compared with the uninfected controls.

Since HIV Tat accumulates age-dependently in the older Tat Tg 26 mice, we reasoned that there would be increased pericyte loss in the microvessels isolated from older (>1 year) versus younger (< 2 months) mice. Intriguingly, there was increased expression of HIV Tat in the older compared to the younger Tg26 mice and this correlated with increased pericyte loss in the older animals. These findings thus support the role of Tat in mediating loss of pericyte coverage on the brain endothelium. In agreement with these studies, decreased pericyte coverage of BBB has also been reported in HIV-1 infected patients and in an animal model of chronic HIV-1 infection in humanized NSG mice by Hill et al [17].

In our previous study, we also demonstrated a detailed molecular pathway of Tat101-mediated expression of PDGF-BB involved in pericyte migration in vitro (Fig. 1). Briefly, Tat-mediated induction of PDGF-BB expression in pericytes involved activation of ERK and JNK MAPK pathways, with the subsequent activation of NF-κB. Tat-mediated induction of PDGF-BB was further shown to engage and activate PDGFR-β signaling via autocrine regulation, ultimately leading to increased pericyte migration. PDGF-BB was implicated as the key player in Tat-mediated induction of pericyte loss. This brings to light the findings by Hosaka et al, reporting that the concentration of PDGF-BB is what determines the fate of pericytes [16]. Currently we do not have answers as to whether it is the concentration modulation of PDGF-BB by Tat that is mediating the pericyte loss, however, given that Tat-mediates autocrine regulation of PDGF, it can be envisioned that higher concentration of PDGF-BB generated by HIV Tat is driving the pericyte loss. These findings are currently ongoing in the authors’ laboratory.

In summary, mechanisms underlying HIV protein mediated loss of pericytes on the endothelium with breach of BBB are critical for future development of therapeutic strategies aimed at restoring BBB breach in the presence of HIV Tat.

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References


