IN Volvement of the Notch-1 Pathway in PDGF-BB-Mediated Astrocyte Activation: Implications for HIV-Associated Neurocognitive Diseases (HAND)

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Abstract: HIV-associated neurocognitive disorders (HAND) affect more than 50% of infected patients on antiretroviral therapy (ART) and the incidence is expected to rise with increasing longevity of HIV-infected individuals. Glial activation rather than viral load has been shown to be correlated with HAND severity, thus identifying key molecular mechanisms involved in glial activation is of paramount importance. We have previously shown that HIV and HIV protein Tat upregulate platelet-derived growth factor-BB (PDGF-BB), a potent blood brain barrier permeant and inducer of monocyte chemoattractant protein-1 (MCP-1). The aim of this study was to determine the autocrine effect of increased PDGF-BB expression on astrocytes. To explore the role of the PDGF/PDGF-R axis in astroglial function, human astrocytes were treated with PDGF-BB, and proliferation and activation via GFAP upregulation were assessed. Exposure of astrocytes to PDGF-BB increased GFAP levels in a time and concentration-dependent manner. MTT cell viability assays also revealed an increase in astrocyte proliferation in response to PDGF-BB. We previously identified that PDGF-BB is a novel target gene of the Notch pathway in endothelial cells, but whether PDGF-BB can regulate the Notch pathway is unclear. Since the Notch pathway is known to play a key role in astrocyte development, we hypothesized that this pathway may be involved in PDGF-BB-mediated activation and proliferation of astrocytes. Exposure of human astrocytes to PDGF-BB resulted in activation of the Notch pathway. Furthermore, pharmacological inhibition of the Notch pathway ameliorated PDGF-BB-mediated increase of GFAP expression as well as proliferation. These results revealed a significant role of the Notch pathway in astrocyte activation and proliferation, as well as highlight this pathway as a potential therapeutic target of HAND.

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