The Effect of gp120 on Furin Cleavage of pro-BDNF in HIV-1 Clade B & C Leading to HIV Associated Neurocognitive Disorders (HAND)

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HAND remains an unsolved problem in the Clinical management of HIV-1 carriers, because existing therapies do not prevent neurocognitive impairment such as Memory loss and Learning difficulty. Some viral proteins, including gp120, has been proposed as contributors to HAND, because it is shed by infected cells and find its way across the blood-brain barrier. Further, the use of antibodies revealed the presence of gp120 in CSF shed by defective proviruses. Interestingly, HIV-1 subtypes contribute to HAND differently, for instance Clade B, which is primarily found in North America and Europe, has a higher propensity for developing HAND then clade C, which is found elsewhere. This difference was attributed to the response of cellular factors such as BDNF. Brain-derived neurotrophic factor (BDNF) is essential for neuronal plasticity and is usually found in abundance in healthy adult brains. Gp120 has been shown to reduce the expression of BDNF, and this could contribute to the development of HAND. However, samples prepared from cells treated with HIV-1 gp120 clade B displayed a reduction of BDNF that is not as significant as in clade C. These results indicate that the reduction of BDNF is not the primary driver for the development of HAND. An active BDNF protein is normally cleaved from pro-BDNF by the protease Furin. While BDNF is associated with neuronal protection and healthy neurons, pro-BDNF elicit the opposite effect. Gp120 has shown to reduce Furin levels without the reduction in mRNA levels pointing to a post transcriptional reduction in Furin activity. Here we set out to explore the link between gp120 and its role in reducing Furin activity, as well as explore the differences in rate of HAND development between clades. Using this data, we can start to establish a link between Furin, BDNF, and synaptic plasticity in relation to memory

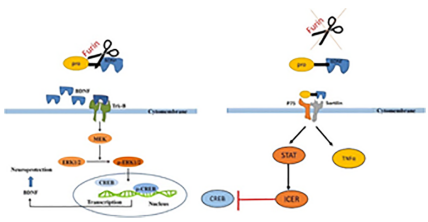

Figure 1: In healthy neurons pro-BDNF gets cleaved and activates the CREB signaling pathway through TrkB, however in HIV gp-120 pro-BDNF does not get cleaved and this inhibits CREB signaling through the activation of ICER

Biography

Charles Nathan S Allen, a third year PhD student at Temple University, he has worked in Bassel E. Sawaya's lab for the past 7 months researching HIV-1's effect on HIV associated neurocognitive disorders (HAND). Prior to joining Temple University, he received his B.S. in Cellular and molecular biology with minors in biochemistry and chemistry from the Towson University. While at Towson University Charles researched novel opening reading frames of small proteins in E. coli under Mathew Hemm's lab.

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