UNIVERSITY GRADUATE SCHOOL BULLETIN ANNOUNCEMENT

Florida International University
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Doctoral Dissertation Defense

Abstract

Serpin-Derived Novel Peptide for the Treatment Against HIV in the Central Nervous System

by

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In the brain, HIV predominantly infects microglia/macrophages and astrocytes to a lesser extent. These cells form virus reservoirs with low levels of infection that are very hard to eradicate. Even though the use of cART increases survival rate in HIV patients, the virus persists as a chronic condition. cART is not able to effectively cross the BBB, control HIV replication, or attenuate inflammation in brain reservoirs. Therefore, the virus still causes neuronal dysfunction, pain-related pathology, and ultimately HAND.

In this study, we decided to test the hypothesis that a serpin-derived small peptide, SP16, can serve as an anti-viral, anti-inflammatory, pro-survival, and neuro-protective agent for the treatment of HIV in brain reservoirs. SP16 was developed by Serpin Pharma and was derived from the pentapeptide "FVFLM" sequence of the serpin AAT. The SP16 peptide sequence was subsequently modified to improve the stability, bioavailability, efficacy and binding to the LRP-1 receptor. LRP-1 functions as a scavenger regulatory receptor that internalizes ligands in order to induces anti- viral, anti-inflammatory and pro-survival signals.

Using brain cells (microglia and astrocytes) infected with HIV, we showed that (i) SP16 attenuated viral-induced secretion of pro-inflammatory molecules, and (ii) SP16 attenuated viral replication. Moreover, SP16 stimulated neuronal growth in stressed neurons exposed to serum-free media. Using an artificial 3D BBB, we showed that (i) SP16 transmigrated across the BBB, and (ii) SP16 restored the integrity of the BBB compromised by HIV. Mechanistically, we showed that SP16 interacted with LRP-1 and binding leads to (i) down-regulation in the expression levels of NF-kB and (ii) up-regulation in the expression levels of Akt. Using an *in vivo* mouse mode, we showed that (i) SP16 transmigrated the BBB after intranasal delivery, while animals infected with EcoHIV undergo a reduction (i) in viral replication and (ii) in viral secreted inflammatory molecules after exposure to SP16 and cART. Overall, these studies demonstrated the potential efficacy of SP16 for the treatment of HIV in the brain.

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