13th International Conference on

Alzheimers Disease and Dementia

November 25-26, 2019 | Frankfurt, Germany

Role of HIF-1α/lncRNA BACE1-AS axis in HIV-1 Tat-mediated astrocytic amyloidogenesis: Implications of Alzheimer's like pathology in HIV

Shilpa Buch
University of Nebraska Medical Center, USA

Increased life expectancy of HIV+ patients in the current era of effective treatment is unfortunately accompanied with the continued prevalence of HIV-associated neurological disorders & risk of age-associated comorbidities such as Alzheimer's Disease (AD). In the current study we sought to assess the contribution of non-neuronal cells such as the astrocytes in HIV-Tat-mediated amyloidogenesis. Findings in SIV-infected macaques/ HIV+ subjects with differential cognitive status demonstrated brain region specific upregulation of the amyloid precursor protein (APP), Aβ1-42 & Aβ 1-40, in astrocytes. Along these lines, in the in vitro studies involving human primary astrocytes (HPA) exposed to HIV protein That there was increased expression of AD markers such as β-site cleaving enzyme (BACE1) enzyme, APP, Aβ 1-42 & Aβ 1-40. These findings were also validated by increased expression of cellular BACE-1 activity & Aβ-42 in the supernatant fluids of Tat-exposed astrocytes. Molecular mechanism(s) involved upregulation of the hypoxia inducible factor (HIF-1α), its translocation & binding to the lncRNA BACE-1AS in the nucleus, resulting in the formation of the BACE-1AS/BACE1 RNA complex, which increased the expression of BACE-1 involving transcriptional, post transcriptional & translational mechanisms, as well as increased activity, leading, in turn, to generation of Aβ-42 protein via cleavage of APP. Gene silencing approaches confirmed the regulatory role of HIF-1α in BACE-1AS/ BACE-1 in Tat-mediated amyloidogenesis. This is the first report implicating the role of HIF-1α-lncRNA BACE1-AS in Tat-mediated induction of astrocytic amyloidogenesis. Strategies aimed at targeting the HIF-1α-lncRNA BACE1-AS complex could be developed as adjunctive therapies for HAND-associated comorbidity of AD.

Biography

Shilpa Buch, Phd is currently a Professor & Vice Chair for Research and the Director of the Nebraska Center for Substance Abuse research at the University of Nebraska. She received my PhD in 1982 in Microbiology from Maharaja Sayajirao University in Baroda, India and moved to Canada for postdoctoral training. She began her independent research career as an Assistant Professor at the Hospital for Sick Kids, Toronto, following which, she moved to Kansas University and embarked on a research area focused on understanding how addictive drugs co-operate with HIV-1 to exacerbate neurological complications. she rose through the ranks at Kansas and in 2007, made a move as a full Professor to University of Nebraska in Omaha. Research approaches used in my lab involve a multipronged approach comprising of a variety of complementary model systems ranging from cell cultures to rodent models to the higher more relevant macaque model of SIV pathogenesis. More recently, her research interest is centered on exploring how exosomes act as conduits to transport key signaling mediators (small noncoding RNAs/microRNAs) to distant recipient cells as a means to regulate gene expression and cellular cross talk. She lead an active research program involving collaborations both nationally and internationally, with over 160 peer-reviewed publications. She have consistently held NIH funding throughout my career and continue to serve on NIH study sections.

e: sbuch@unmc.edu

Notes: