P0245 / #2096

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

PROSPECTIVE INVESTIGATION OF 3AB, A POTENT SMALL MOLECULE AGAINST PARP1 MEDIATED NECROSIS AS A THERAPEUTIC APPROACH FOR CONTUSION SPINAL CORD INJURY.

Khaviyaa Chandramohan [1], Preeja Chandran [2], Krithika Iyer [2], Felicia Mary Michael [2], Sankar Venkatachalam [2]

[1] *ANDAMAN AND NICOBAR ISLANDS INSTITUTE OF MEDICAL SCIENCES, Anatomy, PORT BLAIR, India*
[2] *University of Madras, Department Of Anatomy, Chennai, India*

Spinal cord injury (SCI) is a major cause of paralysis, among the several forms of injury, contusion SCI is the most prevalent. After SCI, immediate cell death occurs near the epicenter, and the delayed cell death process begins in the penumbra. These subsequent cell deaths were caused by apoptotic and necrotic processes. Necrosis, unlike apoptosis, is more debilitating due to the direct release of cellular debris into the extracellular space, affecting neighboring uninjured cells. As a result, preventing the development of necrosis has considerable therapeutic benefits. PARP1 is a DNA repair enzyme that becomes overactivated as a result of the substantial DNA damage that can occur after SCI. Overactivation of PARP1 is harmful since it results in ATP depletion, which leads to necrosis due to energy failure. Chemical compounds such as 3-amino benzamide have been proposed to inhibit PARP1 activation. Such PARP1 inhibitor-based therapy methods have been developed for other disorders such as stroke and cardiovascular disease; however, research testing the role of such inhibitors in SCI is uncommon. The present work aims to explore the prospects of suppressing PARP1 by 3-AB in producing functional recovery and conserving tissue from injury in long term after contusion SCI. A rodent model of contusion spinal cord injury in rats was created using the MASCIS method and the objectives were pursued using 3AB as the PARP1 inhibitor and analyzed through behavioral, histological, and Immunofluorescence parameters. 3AB, when delivered systemically, did not result in functional recovery and looked to be a modest histological neuroprotector. It was also shown that systemically administering 3-AB to mimic a therapeutically realistic strategy was useful. In the case of PARP-1 inhibition, the gap between histological and functional results demonstrates a tight line between functional loss and neuronal preservation, demonstrating that maintaining motor neurons is inadequate to ensure locomotion persistence.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.250

P0246 / #3311

Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

RNA-SEQ ANALYSIS REVEALS THE IMPLICATION OF AMYLOID PRECURSOR PROTEIN (APP) IN CELL FATE SPECIFICATION OF HUMAN NEURAL STEM CELLS BY SEVERAL SIGNALING PATHWAYS

Raquel Coronel [1], Andreea Rosca [1], Rosa González-Sastre [2], Patricia Mateos-Martínez [1], Marta Gallego [3], Isabel Liste [1], Victoria López Alonso [2]

[1] *Instituto de Salud Carlos III, Unidad De Regeneración Neural, Majadahonda - Madrid, Spain*
[2] *Instituto de Salud Carlos III, Unidad De Biología Computacional, Majadahonda, Spain*
[3] *Instituto de Salud Carlos III, Unidad De Histología, Madrid, Spain*

Numerous studies have focused on the pathophysiological role of amyloid precursor protein (APP) in Alzheimer's disease (AD), being the aggregation of β-amyloid (Aβ) peptide a central event. However, many authors consider that alterations in physiological functions of APP are likely to play a key role in AD pathogenesis. APP is a glycoprotein expressed ubiquitously in a wide variety of tissues, being especially abundant in the brain. The APP expression is detected at early stages of nervous system development, as well as in adult brain, suggesting that this protein plays a key and important role at various stages of life. Previous studies in our laboratory revealed that APP playing an important role on differentiation of human neural stem cells (hNSCs), favoring glial differentiation (gliogenesis), and preventing the differentiation of them towards neuronal phenotype (neurogenesis). In that case, we proposed to the APP/AICD/GSK-3β system as a possible molecular mechanism involved in the observed effects. However, given the multifunctionality of APP, we think that other molecular mechanisms could also be implicated. In the present study, we have evaluated the effects of APP overexpression in hNSCs at a global level by a transcriptomic analysis using the massive RNA sequencing (RNA-seq) technology. Specifically, we have focused on differentially expressed genes (DEGs) that are related to neuronal and glial differentiation processes, as well as on groups of DEGs associated with different signaling pathways, to find a possible interaction between them and APP. Our data indicate a differential expression in genes related to gliogenesis and neurogenesis processes, as well as in the pathways of Notch signaling, Wnt signaling, PI3K-AKT signaling, and JAK-STAT signaling, among other. The knowledge of physiological functions of APP, as well as the possible signaling pathways that could be implicated, are essential to advance the understanding of the pathogenesis of AD.

Declaration of Interest Statement: None

https://doi.org/10.1016/j.ibneur.2023.08.251