World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:17, No:06, 2023

IL6/PI3K/mTOR/GFAP Molecular Pathway Role in COVID-19-Induced Neurodegenerative Autophagy, Impacts and Relatives

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Abstract : COVID-19, which began in December 2019, uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter and spread through the cells. ACE2 mRNA is present in almost every organ, including nasopharynx, lung, as well as the brain. Ports of entry of SARS-CoV-2 into the central nervous system (CNS) may include arterial circulation, while viremia is remarkable. However, it is imperious to develop neurological symptoms evaluation CSF analysis in patients with COVID-19, but theoretically, ACE2 receptors are expressed in cerebellar cells and may be a target for SARS-CoV-2 infection in the brain. Recent evidence agrees that SARS-CoV-2 can impact the brain through direct and indirect injury. Two biomarkers for CNS injury, glial fibrillary acidic protein (GFAP) and neurofilament light chain (NFL) detected in the plasma of patients with COVID-19. NFL, an axonal protein expressed in neurons, is related to axonal neurodegeneration, and GFAP is over-expressed in CNS inflammation. GFAP cytoplasmic accumulation causes Schwan cells to misfunction, so affects myelin generation, reduces neuroskeletal support over NfLs during CNS inflammation, and leads to axonal degeneration. Interleukin-6 (IL-6), which extensively over-express due to interleukin storm during COVID-19 inflammation, regulates gene expression, as well as GFAP through STAT molecular pathway. IL-6 also impresses the phosphoinositide 3-kinase (PI3K)/STAT/smads pathway. The PI3K/ protein kinase B (Akt) pathway is the main modulator upstream of the mammalian target of rapamycin (mTOR), and alterations in this pathway are common in neurodegenerative diseases. Most neurodegenerative diseases show a disruption of autophagic function and display an abnormal increase in protein aggregation that promotes cellular death. Therefore, induction of autophagy has been recommended as a rational approach to help neurons clear abnormal protein aggregates and survive. The mTOR is a major regulator of the autophagic process and is regulated by cellular stressors. The mTORC1 pathway and mTORC2, as complementary and important elements in mTORC1 signaling, have become relevant in the regulation of the autophagic process and cellular survival through the extracellular signal-regulated kinase (ERK) pathway.

Keywords : mTORC1, COVID-19, PI3K, autophagy, neurodegeneration
Conference Title : ICNDN 2023 : International Conference on Neurological Disorders and Neurodegeneration
Conference Location : Venice, Italy
Conference Dates : June 15-16, 2023