ABSTRACT

Alzheimer's disease (AD) and related dementia are the primary cause of dependency and disability among the elderly. The related social, psychological, physical, and healthcare-related economic concerns on society are enormous. Out of the various causes of neurodegeneration in sporadic AD, neuroinflammation provoked by protein misfolding plays a very important role. In AD, Amyloid β and tau can fold improperly or self-aggregate to form dimers, toxic oligomers, plaques, NFTs of higher-order magnitude, which can direct the cellular immune system to act leading to inflammatory responses. Microglial cells are non-neuronal cells of the CNS responsible for innate immune reactions. Aβ has been shown to modulate the microglial response overexpressing NLRP3 inflammasome cascade, ultimately leading to interleukin-18 (IL-18) & interleukin-1β (IL-1β) secretion. The tau- hexapeptide fragment, ^{306}VQIVYK^{311} (PHF6), was used in this research to assess the effect on microglial neuroinflammation. The fibrillary aggregates of acetylated PHF6 (Ac-^{306}VQIVYK^{311}-NH_2), as characterized by ThT assay, circular dichroism spectroscopy, fluorescence microscopy & turbidity assay, were found to polarize the HMC3 cells towards neuroprotective M2 state in a time-dependent fashion. This study revealed the overwhelming of NLRP3-inflammasome components by aggregated tau-PHF6 in a time and concentration-dependent fashion. Further, the aggregated PHF6 was also found to modulate the autophagy process of microglial cells in a time-dependent fashion. Since autophagy, microglial polarization and inflammsome cascade are closely related, this study could be an initial stepping stone in the field of aggregated PHF6-induced neuroinflammation in microglia. Future research on anti-inflammatory or autophagy promoting drugs along the line of this research could serve as a therapeutic opportunity.