Identification of a novel pathway with relevance in Alzheimer's disease

The study conducted at DBT's National Institute of Immunology (NII), New Delhi showed that E3 ubiquitin ligase Itch, which primes proteins for destruction, is a major regulator of CRNA. Team also elucidated the mechanism which regulates this process. Neurotoxic amyloid peptide A_{42}-which is over produced in AD and causes toxicity- treated neurons or neurons from an AD transgenic mouse model (TgAD) exhibited aberrant activation of the JNK signaling pathway which resulted in the abnormal phosphorylation of Itch.

The phosphorylation of Itch primes is for self-ubiquitination which is necessary for its activation. These post-translational modifications of Itch facilitate its interaction with transcription factor TAp73 resulting in its degradation. These series of events are critical for Itch-mediated CRNA and its phosphorylation and self-ubiquitination site mutants reversed this process and prevented neuronal death. These studies unravel a novel pathway via which neurodegeneration in AD and possibly other related disorders may be regulated by aberrant regulation of the neuronal cell cycle.

The β-neurons are terminally differentiated cells which cannot divide. Therefore, it is critical for the neuronal cell cycle to remain suppressed in terminally differentiated neurons as its activation results in aberrant cell cycle re-entry that causes neuronal apoptosis (CRNA), which has been observed in several neurodegenerative disorders like Alzheimer's disease (AD).

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