CHAPTER 25

GENETICS

Doctoral Theses

01. AGGARWAL (Prerna)
Investigating the Molecular Mechanism of Toll-Signalling Cascade in Pathogenesis and Mitigation of Human Tauopathies and Exploring Tau-Mediated Glial Response in Drosophila.
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Abstract

Human neuronal tauopathies, exemplified by Alzheimer's disease and Frontotemporal dementia are neurodegenerative conditions characterized by toxic deposition of hyperphosphorylated tau protein. Chronic, glial-driven immune response, predominantly via Toll-signalling in the CNS has emerged to aggravate neurodegeneration. However, the role of altered neuron-specific Toll-receptor expression and contribution of glial response in these brain illnesses remains poorly understood, highlighting the need for further investigation. My PhD work was aimed to delineate the dynamics, efficacy, and molecular mechanisms of neuronal Toll-signalling cascade in mitigating human tauopathies, and to examine the impact of tau-induced neurodegeneration on glial response in Drosophila disease models. The first part of the study established an upregulated status of Toll-pathway in Drosophila neurons as a potential contributor of disease etiology. Its suppression was found to alleviate tau pathogenesis. Mechanistically, Toll-pathway restricted disease-associated tau hyperphosphorylation, primarily by restoring the physiological activity of tau kinases, including Gsk-3β, JNK, and ERK-1/2. The rescue was additionally found to manifest in suppression of several consequential and interlinked pathophysiological hallmarks, the oxidative stress, impaired autophagy, and formation of neurotoxic aggregates, potentiating both inherent and acquired non-immune functions of Toll-pathway genes in neurons. The second part of the thesis investigated the response of glial cells upon neuron-specific expression of pathogenic tau. Glial cells were found to display over-proliferation, increased motility, altered morphology and behaviour. An altered JNK signalling emerged as a modulator of glial response. These proof-of-concept observations provide an experimental foundation to further delineate the intricacies and fate of glial response in tauopathies. Collectively, this work for the first time deciphers the mechanistic in-depths of the Toll-pathway in tau pathogenesis, and suggests JNK-mediated glial response in tauopathy disease background. Together, these findings could prove instrumental in developing novel Toll-pathway specific, and glial-targeted therapeutic interventions for efficient management of these devastating brain disorders.

Contents

1. Introduction 2. Materials and Methods 3. Human tau aberrantly activates Toll–NF-κB signalling, and its downregulation mitigates disease pathogenesis and phenotypic manifestations in Drosophila disease models.4. Tau-mediated neuronal apoptosis incites glial response in larval eye imaginal disc and adult brain tissue in a JNK-dependent manner References and Appendices. Summary and References.