Role of CHIP E3 ligase in neurodegenerative diseases and cancer

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The C-terminus of Hsc70-interacting protein (CHIP), encoded by STUB1, is an E3 ubiquitin ligase and co-chaperone that safeguards neuronal proteostasis by targeting misfolded or unstable proteins for refolding or degradation. While CHIP's neuroprotective role is well recognised, the specific mechanisms by which it maintains neuronal structure and signalling, particularly in disorders such as Alzheimer's, Parkinson's, and Huntington's disease, have remained incompletely understood.

This thesis demonstrates that loss of CHIP disrupts axonal homeostasis, destabilises neurofilament architecture, and impairs key signalling pathways in a neuronal context. Using CRISPR/Cas9-engineered CHIP-knockout SH-SY5Y neuroblastoma cells, deep quantitative proteomics identified a core network of CHIP-sensitive proteins, including NEFL, NEFM, INA, TAU, DPYSL2 (CRMP2), ELAVL3, VGF, NPY, and netrin-1, that support axonal scaffolds, cytoskeletal dynamics, and synaptic transmission. In the absence of CHIP, this network was markedly down-regulated, leading to reduced expression of neurofilament proteins, impaired axon-guidance signals (notably the netrin–CRMP2 axis), and broad suppression of G - protein - and PKC-dependent neurotransmitter pathways. Ingenuity Pathway Analysis revealed widespread inhibition of GPCR cascades, glutamatergic signalling, and vesicular transport, alongside a modest but reproducible activation of the Ras/MAPK axis.

These proteomic changes recapitulate molecular signatures seen in multiple neurodegenerative diseases, offering mechanistic insight into how pathogenic STUB1 variants cause conditions such as spinocerebellar ataxia and early-onset dementia. Simultaneously, the up-regulation of Ras/MAPK signalling and dysregulation of proteostasis observed here mirror oncogenic processes, highlighting CHIP's dual role as both tumour suppressor and tumour facilitator in a context-dependent manner. This work thus establishes CHIP as a molecular bridge between neurodegeneration and cancer; two biological domains traditionally viewed as distinct.

Building on these findings, this thesis proposes CHIP as a potential early-life biomarker for neurodegenerative susceptibility. Newborn genomic screening for deleterious STUB1 variants could enable identification of at-risk individuals, offering opportunities for targeted neuroprotective strategies. Overall, this work positions CHIP as a master regulator of neuronal integrity and a clinically relevant node at the intersection of proteostasis, neurodegeneration, and cancer biology.