CYTOSKELETON

Neurodegenerative polyglutamylation

> interference with microtubule deglutamylation … impairs intracellular transport and causes neuronal degeneration

Microtubules are subject to various post-translational modifications that modulate their properties and functions. Microtubule polyglutamylation — which is particularly prominent in neurons — involves the addition of a variable number of glutamate residues on tubulin by the tubulin–tyrosine-ligase-like (TTLL) family of proteins and their removal by cytosolic carboxypeptidases (CCPs). In mice, *Ccp1* loss causes neurodegeneration, most prominently affecting motor function-coordinating Purkinje cells of the cerebellum (referred to as the Purkinje cell degeneration (*pcd*) mouse model). Three studies now reveal that neuronal degeneration associated with the loss of deglutamylating enzymes can be explained by impaired microtubule-based transport and that these aberrations are relevant to human neuropathology.

Magiera et al. generated conditional Purkinje-cell-specific *Ccp1*-knockout mice and observed Purkinje cell loss and similar neurological phenotypes to those reported for *pcd* mice. Thus, degeneration of Purkinje cells in the absence of CCP1 occurs cell-autonomously. Co-deletion of *Ccp1* and a major brain polyglutamylase, *Ttll1*, prevented Purkinje cell degeneration. α-Tubulin was the key target of TTLL1-driven polyglutamylation in the cerebellum, collectively indicating that aberrant microtubule polyglutamylation is the cause of Purkinje cell degeneration.

Pcd mice do not show neurodegeneration in brain regions such as the cerebral cortex or hippocampus, which could be due to compensation by other CCPs, including CCP6, for CCP1 loss. Indeed, $Ccp1^{-/-}Ccp6^{-/-}$ mice showed elevated tubulin polyglutamylation in the cerebral cortex and the hippocampus, which was associated with a progressive reduction in cortical thickness, neuronal loss and increased numbers of reactive brain glia, indicative of neurodegeneration.

Transmission electron microscopy of the cerebral cortex from $Ccp1^{-/-}Ccp6^{-/-}$ mice revealed axonal swellings and accumulation of organelles in axonal processes, suggesting that intracellular transport of organelles was defective. Indeed, overall mitochondrial motility was reduced in cultured neurons from $Ccp1^{-/-}Ccp6^{-/-}$ mice.

Gilmore-Hall et al. also reported defects in mitochondrial dynamics upon interference with microtubule deglutamylation. They showed that in CCP1-deficient retinal pigment epithelial cells (a cell type that contributes to retinal degeneration in *pcd* mice) as well as in primary cerebellar neurons from *pcd* mice, polyglutamylation of α-tubulin was increased. Analysis of mitochondrial dynamics in cerebellar granule neurons (another cerebellar neuronal population that undergoes degeneration in *pcd* mice) revealed that loss of *Ccp1* prolonged mitochondrial stalling during both retrograde and anterograde movement, similar to what was observed by Magiera et al. Interestingly, this movement defect correlated with impaired mitochondrial fusion, and cells lacking CCP1 were characterized by an increased number of small, circular mitochondria. These data collectively indicate that interference with tubulin deglutamylation and consequent microtubule hyperglutamylation hamper the intracellular transport of some cargoes, such as mitochondria, which has profound consequences for organelle dynamics.

Shashi et al. carried out genomic analysis of 13 individuals who presented with genetically unresolved childhood-onset, progressive neurodegeneration. They found biallelic alterations in *CCP1* in all cases, including six loss-of-function variants and six missense variants with single amino acid changes that abrogated CCP1 catalytic activity, resulting in functional nulls. Thus, *CCP1* loss can be recognized as a cause of severe neurodegeneration in humans.

In summary, interference with microtubule deglutamylation leads to unopposed polyglutamylation, which impairs intracellular transport and causes neuronal degeneration. It is likely that even small changes in microtubule deglutamylation efficiency could be detrimental, as polyglutamylation may progressively accumulate over time, potentially leading to late-onset neurodegenerative disorders. Thus, modulation of enzymes involved in microtubule polyglutamylation could open up new avenues for the treatment of neurodegenerative diseases.

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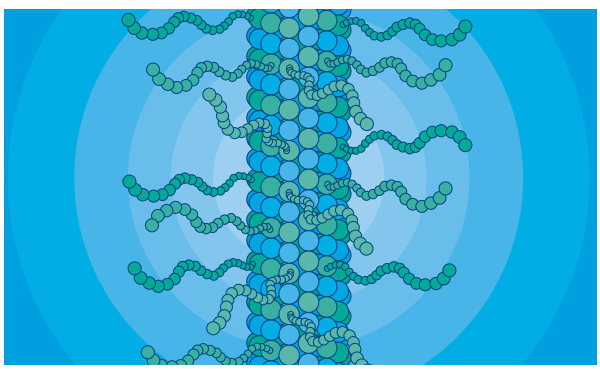

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ORIGINAL ARTICLES Magiera, M. M. et al. Excessive tubulin polyglutamylation causes neurodegeneration and perturbs neuronal transport. *EMBO J.* https://doi.org/10.15252/embj.2018100440 (2018) | Gilmore-Hall, S. et al. CCP1 promotes mitochondrial fusion and motility to prevent Purkinje cell neuron loss in *pcd* mice. *J. Cell Biol.* https://doi.org/10.1083/jcb.201709028 (2018) | Shashi, V. et al. Loss of tubulin deglutamylase CCP1 causes infantile-onset neurodegeneration. *EMBO J.* https://doi.org/10.15252/embj.2018100540 (2018)