Molecular Biology of Prion Infections

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(1) The integrity of peripheral nerves relies on messaging between axons and Schwann cells. The axonal signals ensuring myelin maintenance are distinct from those instructing myelination, and are largely unknown. Here we show that ablation of the prion protein, PrPC, triggers a chronic demyelinating polyneuropathy (CDP) in four independently targeted mouse strains. Ablation of the neighboring Prnd locus, or inbreeding to four distinct mouse strains, did not modulate the CDP. CDP was triggered by neuron-specific, but not by Schwann cell-specific, PrPC depletion and was suppressed by neuronal, but not by Schwann cell-restricted, PrPC expression. CDP was prevented by PrPC variants undergoing proteolytic amino proximal cleavage, but not by variants nonpermissive for cleavage, including secreted PrPC lacking its glycolipid membrane anchor. These results indicate that neuronal expression and regulated proteolysis of PrPC is essential for myelin maintenance.

(2) Alzheimer´s disease (AD), the most common neurodegenerative disorder, goes along with extracellular amyloid-ß (Aß)deposits. The cognitive decline observed during AD progression correlates with damaged spines, dendrites, and synapses in hippocampus and cortex. Numerous studies have shown that Aß oligomers, both synthetic and derived from cultures and AD brains, potently impair synaptic structure and functions. The cellular prion protein (PrPC) was proposed to mediate this effect. We report that secretion of a soluble PrPC variant reduced the impairment of hippocampal synaptic plasticity in a transgenic model of AD, whereas ablation of PrPC had no effect. Rather than supporting a role for PrPC as a toxicity mediator, these findings suggest that PrPC may sequester and detoxify Ab species.

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