Nature Reviews Neuroscience | AOP, published online 10 February 2010; doi:10.1038/nrn2812

PRIONS

A protective role for prions

Mutated forms of PrP^C, the endogenous prion protein, are linked to transmissible spongiform encephalopathies, but the normal function of PrP^C has yet to be identified. Bremer *et al*. now show that neuronal expression of PrP^C is necessary for the maintenance of the myelin sheaths around peripheral nerves.

Mice lacking PrP^C are resistant to prion infections but sometimes show peripheral neuropathy. The authors therefore investigated the possible role of PrP^C in peripheral nerves. PrP^C-deficient mice (*prnp*$^{-/-}$ mice) showed demyelinating polyneuropathy in all peripheral nerves by 60 weeks of age, including thinned myelin sheaths and 'onion bulbs', which result from repeated demyelination and remyelination. Signs of neuropathy were evident in 10- and 30-week-old animals, indicating that the pathogenic process starts immediately after the completion of peripheral myelination. There was no myelin degeneration in central nerves.

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Surprisingly, the authors showed that re-expressing PrP^C specifically in neurons of *prnp*$^{-/-}$ mice prevented the polyneuropathy, whereas expressing PrP^C in myelinating Schwann cells did not. Conversely, polyneuropathy was induced by PrP^C depletion in neurons but not by PrP^C depletion in Schwann cells. Thus, neuron-specific expression of PrP^C is required for maintaining peripheral myelin.

As PrP^C can undergo proteolytic cleavage, the authors next investigated whether this process is important for the role of PrP^C in maintaining peripheral myelin. Transgenic mice expressing PrP^C but lacking its membrane anchor showed no proteolytic PrP^C cleavage and had polyneuropathy similar to that of *prnp*$^{-/-}$ mice. Furthermore, sciatic nerves from transgenic mice expressing a PrP^C variant lacking part of the amino-proximal domain were deficient in certain PrP^C cleavage fragments and also showed demyelinating neuropathy, as did mice lacking the hydrophobic core of this domain. This suggests that PrP^C must be capable of undergoing proteolysis to preserve the integrity of peripheral myelin.

The finding that neuronal expression of PrP^C is required for maintaining the myelin sheaths of peripheral nerves suggests that PrP^C might mediate axon–Schwann cell communication; it is possible that PrP^C cleavage products interact with receptors on Schwann cells. Reducing the levels of PrP^C has been suggested as a potential strategy to prevent neurodegeneration in prion diseases, but this study shows that such an approach might have deleterious side effects.

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ORIGINAL RESEARCH PAPER Bremer, J. *et al.* Axonal prion protein is required for peripheral myelin maintenance. *Nature Neurosci.* 24 January 2010 (doi:10.1038/nn.2483)