A conformational transition of the cellular prion protein (PrP<sup>C</sup>) into an aberrantly folded isoform designated scrapie prion protein (PrP<sup>Sc</sup>) is the hallmark of a variety of neurodegenerative disorders collectively called prion diseases. They include Creutzfeldt-Jakob disease and Gerstmann-Stäussler-Scheinker syndrome in humans, scrapie in sheep, bovine spongiform encephalopathy (BSE) in cattle and chronic wasting disease (CWD) in free-ranging deer. In contrast to the deadly properties of misfolded PrP, PrP<sup>C</sup> seems to possess a neuroprotective activity. Moreover, animal models indicated that the stress-protective activity of PrP<sup>C</sup> and the neurotoxic effects of PrP<sup>Sc</sup> are somehow interconnected.

In this special issue of Current Issues in Molecular Biology we have assembled a set of reviews from some leading scientists in the field to highlight the apparently incongruous activities of different PrP conformers. The articles will outline current research on cellular pathways implicated in the formation and signaling of neurotoxic and physiological PrP isoforms and delineate future research direction.

Vilma Martins comments on our current understanding about the physiological activity of PrP<sup>C</sup> and its possible role as a neurotrophic factor. The observation that aberrant PrP conformers can cause neurodegeneration in the absence of infectious prion propagation is an expanding field highlighted by David Harris. Giovanna Mallucci expands on this topic and reports on the intriguing finding that the GPI anchor of PrP<sup>C</sup> is required to mediate neurotoxic effects of scrapie prions. To follow up this track, Konstanze Winklhofer and I specifically concentrate on pathways implicated in the formation and neurotoxic properties of cytosolically localized PrP. Neena Singh illustrates that metal ions can have a significant impact on the processing of PrP. Finally, Hermann Schätzl provides insight into the role of autophagy in the propagation and clearance of PrP<sup>Sc</sup>.

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