Update on the Pathophysiology of Prion Diseases

**Summary**

- Prion diseases are characterised by the accumulation of misfolded prion protein (PrP\(^{\text{Sc}}\)) and widespread neuronal loss throughout the brain. Recent work has elucidated a major mechanism by which misfolded PrP\(^{\text{Sc}}\) induces neurodegeneration in prion disease.
- Rising levels of misfolded PrP\(^{\text{Sc}}\) lead to sustained dysregulation of an endogenous cellular pathway, the unfolded protein response (UPR), which regulates protein synthesis at the level of translation initiation.
- This results in the sustained reduction in global protein synthesis rates in neurons, leading to loss of critical proteins, resulting in synaptic failure and neuronal death.
- Genetic and pharmacological manipulation of this pathway to restore protein synthesis prevents neuronal loss, reverses cognitive deficits and abrogates clinical disease.
- The same branch of the UPR is over-activated in other protein misfolding disorders, including Alzheimer’s and Parkinson’s diseases, ALS and PSP. Further, it is a key pathway in learning and memory. Therefore, UPR modulation to restore protein synthesis levels in neurons is potentially an important new therapeutic strategy for neurodegenerative disease.

**Background**

Prion diseases are rare neurodegenerative disorders that belong to the emerging group of protein misfolding diseases, which includes Alzheimer’s and Parkinson’s diseases. In each case, the accumulation of a disease specific protein is associated with a relatively stereotyped clinicopathological syndrome. How neuronal loss occurs in these disorders is not clear, but recent work has revealed the mechanism by which protein misfolding leads to neurodegeneration in prion disease.

The central pathogenic process in prion disorders is the formation and accumulation of an aberrantly folded conformer (PrP\(^{\text{Sc}}\)) of the host-encoded cellular prion protein (PrP\(^{\text{C}}\)). PrP\(^{\text{Sc}}\) is generated from PrP\(^{\text{C}}\) through an autocatalytic post-translational change in secondary structure (Figure 1). The misfolded protein aggregates and accumulates throughout the brain, is accompanied by astrocytosis, spongiform change and extensive neuronal cell loss. Whilst PrP\(^{\text{Sc}}\) is associated with infectivity (prion diseases are transmissible), there is extensive evidence that it is not in itself neurotoxic. Sub-clinical states of prion disease have been identified in which extensive accumulation of PrP\(^{\text{Sc}}\) is dissociated from neurotoxicity. PrP\(^{\text{Sc}}\) is harmless to cells devoid of PrP\(^{\text{C}}\), and therapeutic agents targeting PrP\(^{\text{Sc}}\) have very limited efficacy and do not prevent neuronal loss. PrP\(^{\text{Sc}}\) is absolutely required for susceptibility to prion neurotoxicity: PrP-null mice are resistant to prion disease\(^1\) and depleting PrP\(^{\text{Sc}}\) in neurons of prion infected mice cures disease, as conversion can no longer occur. Thus, the process of prion protein misfolding is central to neurotoxicity. Recent work has shown that neuronal death results from dysregulation of the cellular response to unfolded proteins triggered by the process of prion protein misfolding.\(^6\)

**The Unfolded Protein Response**

All cells need correctly folded proteins for normal functioning. The build up of unfolded proteins within the endoplasmic reticulum (ER) constitutes a form of cellular stress that elicits a protective signalling cascade, the Unfolded Protein Response (UPR), which maintains protein-folding homeostasis, “proteostasis”. Rising levels of misfolded proteins in the ER are detected by Binding immunoglobulin protein (BiP), which results in activation of the three branches of the UPR to increase protein folding through chaperone expression (via ATF6 and IRE1 branches) and to transiently reduce protein levels by inhibiting protein synthesis (PERK branch). This occurs via the phosphorylation first of PERK and then of the alpha subunit of eIF2\(\alpha\)P, which is needed for formation of ternary complex and initiation of translation. Activation of the UPR is usually a transient event that terminates when eIF2\(\alpha\)P is dephosphorylated by GADD34, rapidly restoring protein translation.\(^7\)

**The UPR in prion disease**

Recent work in prion diseased mice revealed that rising levels of misfolded prion protein caused and sustained increase in the phosphorylation of PERK and eIF2\(\alpha\)P in neurons.\(^7\) The effect of this is the sustained reduction in global protein synthesis rates in neurons, causing catastrophic decline in levels of key proteins including synaptic proteins vital for healthy functioning and neuronal survival. The result is neurodegeneration. Genetic manipulation of the pathway to reduce levels of eIF2\(\alpha\)P restored vital protein synthesis rates and was profoundly
neuroprotective (Figure 2). This was true for upstream (knockdown of PrP levels) or downstream (by lentivirally mediated overexpression of the elf2α-P phosphatase GADD34) interventions that reduced elf2α-P levels. The resultant rescue of protein synthesis rates prevented decreases in synaptic protein levels, maintained synapse number and synaptic function, preventing behavioural and cognitive deficits, and resulted in extensive neuroprotection. Most importantly, there was a significant increase in survival. Notably, inhibiting the dephosphorylation of elf2α-P with the small molecule salubrinal, had the opposite effect, exacerbating the decrease in protein synthesis and accelerating disease. Critically, this rescue occurs downstream of prion replication and independently of it. PrPα levels are unaffected.

Pharmacological modulation of the UPR in prion disease

These data led to the prediction that pharmacological inhibition of PERK-elf2α-P signalling would be similarly neuroprotective. GSK2606414, a highly selective PERK inhibitor,1 was orally administered to prion-infected mice daily from points both before and after the onset of behavioural deficits.2 PERK inhibition by GSK2606414 similarly prevented elevated levels of elf2α-P and decline in protein synthesis rates and resulted in extensive neuroprotection throughout the brain. Encouragingly treatment that was started even after the emergence of cognitive deficits had the same beneficial effects as treatment from earlier time-points. This work was the first description of a small molecule able to prevent neuronal loss and clinical disease in vivo.

Wider relevance

There is increasing evidence that UPR dysregulation is a central process in protein misfolding neurodegenerative diseases, and that maintaining translation levels is essential for neuronal health. Increased PERK-P and elf2α-P have been reported in post-mortem analyses of brains of patients with AD, PD, ALS, and the tauopathy progressive supranuclear palsy (PSP), as well as prion disease.3 Genetic polymorphisms in PERK pre-dispose to PSP.4 The pathway is also implicated in learning and memory; manipulation of elf2α-P levels boost cognition in wild type mice and restore memory deficits in AD mouse models. Thus, it would appear that targeting UPR dysregulation that occurs downstream of misfolded protein replication, be this prion, amyloid beta, tau, α-synuclein or TDP-43 may hold promise for new treatments for neurodegenerative disorders more broadly.

REFERENCES

9. Aster JC et al. Discovery of 7-methyl-5-(1...