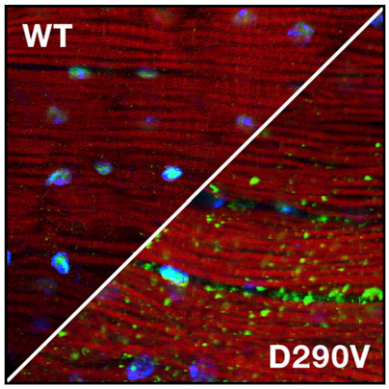
Cell

Prion Progress

Although disease-causing prions are an extreme pathogenic aberration in protein behavior, emerging evidence places them at the end of a broad spectrum of ordered protein aggregates with diverse biological roles. This Select highlights recent findings on prions, including mutations that push proteins with prion-like domains over the threshold to pathogenicity in degenerative disorders, a vertebrate model of prion disease with the fastest known incubation time, and a system to examine how cytoplasmic prions are transmitted between cells. A unique therapeutic perspective is also offered by a recent study that suggests potential beneficial effects of prion-like amyloid fibrils in neuroinflammatory diseases, such as multiple sclerosis.



In the muscle of flies expressing human hnRNPA2, wild-type protein is nuclear, whereas the mutant form is found in cytoplasmic inclusions. Image courtesy of H. Kim.

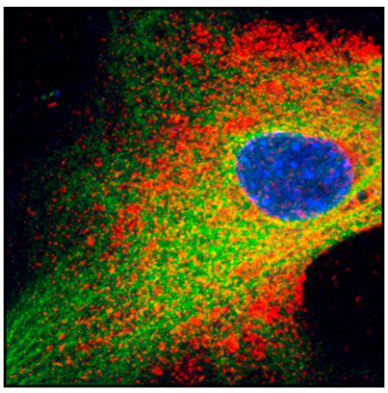
Living on the Edge of Bad Behavior

Proteins with prion-like domains are likely a rich source for the discovery of degenerative disease-causing mutations in humans. This is the take-home message of a recent landmark study by Paul Taylor and colleagues (Kim et al., 2013), who, by examining familial cases of multisystem proteinopathy and amyotrophic lateral sclerosis, identify pathogenic mutations in prion-like domains of the RNA-binding proteins hnRNPA2B1 and hnRNPA1. The prion-like domains correspond to ''low-complexity sequences,'' a feature of many RNA-binding proteins, which underlies their capacity to form ordered RNA granules. The authors show that both stress granule formation and fibrillization are enhanced by the pathogenic mutations, and in muscle biopsies from individuals with the mutations, cytoplasmic inclusions are observed for the normally nuclear proteins. The mutations likely strengthen the ''steric zipper'' motif (wherein two layers of a β sheet interdigitate) pushing the already aggregation-prone proteins down the road to more pathogenic prion-like behavior. What are the steps from here? A first will be further investigation of hnRNPA2B1 and hnRNPA1 in other familial and sporadic cases of proteinopathy to get a sense of the frequency of their involvement. From there, the door is cast wide open to examine the roles of other proteins that contain prion-like domains, estimated at around 250 in humans, as potential instigators or collaborators in degenerative disease.

Kim, H.J., et al. (2013). Nature 495, 467–473.

Aggregates Unbound

The prion precursor protein (PrP) in mammals is membrane anchored, and thus its mode of transmission from cell to cell may differ from that of cytosolic aggregates, such as the amyloids that are observed in numerous neurodegenerative diseases. To examine the life cycle of cytosolic aggregates in mammalian cells, Hofmann et al. (2013) establish coculture models that take advantage of a well-studied cytosolic yeast prion, the N-terminal and middle (NM) domain of Sup35. Growing cells with NM-hemagglutinin-tagged aggregates with cells expressing soluble NM-green fluorescent protein leads to the efficient induction of aggregate formation in the latter. This effect is shown to depend on cell-to-cell contact and is observed in permanent cell lines, cultured astrocytes, granule cell neurons, and hippocampal slices, suggesting that the transmission mechanism is cell type independent. How then is the prion transmitted? It appears to be direct exchange of aggregates between donor and recipient cells, and although the exact mode of transfer awaits further characterization, the authors propose the interesting possibility that aggregates might cross via filopodial bridges. If so, in what circumstances, in addition to the transfer of aggregates, do neighboring cells directly connect their cytoplasms, and what factors promote the interchange?



NM prions in astrocytes (red). Image by J. Hofmann.

Hofmann, J.P., et al. (2013). PNAS. Published online March 18, 2013. http://dx.doi.org/10.1073/pnas.1217321110.

A bank vole from the breeding colony at the Istituto Superiore di Sanità. Image courtesy of M.A. Di Bari.

Take It to the Bank (Vole)

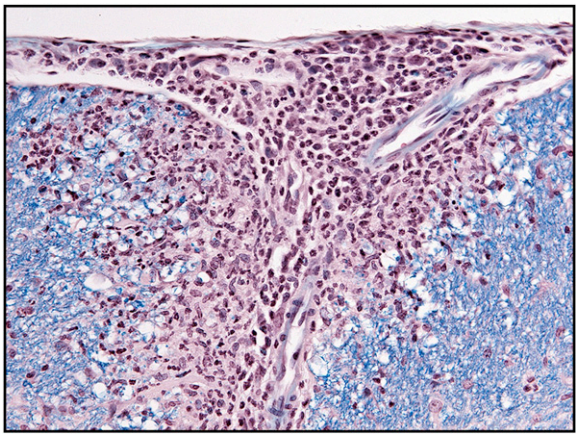
Most prion diseases have long incubation periods; for example, Creutzfeld-Jacob disease in humans often lies in wait for decades. At the other end of the spectrum, Di Bari et al. (2013) report an astonishingly short incubation period in an experimental model of chronic wasting disease (CWD), an ailment that afflicts wild and captive populations of deer, elk, and moose. They show that CWD isolates from these species, when adapted to the bank vole (Bv^{109I}CWD), a small rodent native to Eurasia, have an incubation time of 25–28 days culminating in a mean survival time of only 35 days. Besides this incredibly fast time course, which provides a helpful tool for laboratory research on CWD pathogenesis, the study raises a broader question about how host and prion factors impact incubation periods for prion disease. What contributes to the exceptionally short incubation period in bank voles? A clue is provided by Watts et al. (2012), who generated mice that overexpress the bank vole prion protein precursor, BVPrP, including the same variant explored by Di Bari et al. with isoleucine at codon 109. These mice spontaneously develop prion disease, and if brain isolates are then reinnoculated back into the BVPrP transgenic mice, their survival time is only 35 days, similar to that seen for vole-adapted Bv^{109I}CWD generated by Di Bari et al. This contrasts with transgenic mice overexpressing the methionine codon 109 variant of vole PrP, which do not spontaneously exhibit prion disease, suggesting that isoleucine at that position is critical for the vole PrP's enhanced pathogenic propensity.

Di Bari, M.A., et al. (2013). PLoS Pathogens 9, e1003219.
Watts, J.C., et al. (2012) PNAS 109, 3498–3503.

Putting a Hex on Inflammation

Proteins that are prone to aggregation are not just a cause of disease; they can have positive roles as well. Kurnellas et al. (2013) demonstrate this using a variety of hexapeptides that form amyloid fibrils, including segments of PrP, tau, and amyloid precursor protein. Mice injected with the hexapeptides exhibit reduced symptoms in experimental autoimmune encephalomyelitis (EAE), which recapitulates features of multiple sclerosis in humans. How these peptides have this effect in vivo is not yet clear, but in vitro experiments indicate that the ability of the peptides to form fibrils correlates with their capacity to act as chaperones in the inhibition of insulin aggregation. Additionally, hexamers derived from tau (amino acids 623–628) precipitate serum proteins, suggesting another route by which the fibrils might alter the extracellular milieu to impact inflammatory cytokine production. Regardless of the mechanism of action, which will undoubtedly be explored in future work, the findings add a therapeutic perspective on the growing literature on the native and beneficial functions of amyloids.

Kurnellas, M.P., et al. (2013). Sci. Transl. Med. 5, 179ra42.



Histology of mouse experimental autoimmune encephalomyelitis. Image courtesy of L. Steinman.

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