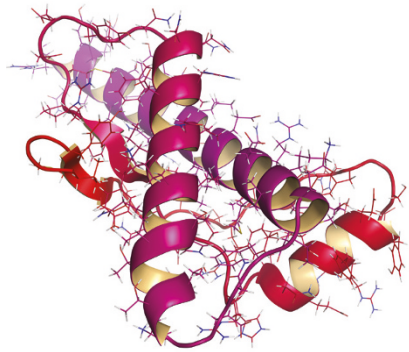
Protecting neurons from misfolded prion proteins

Prion disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia and amyotrophic lateral sclerosis all share a common etiology: neurodegeneration linked to the misfolding and aggregation of a specific protein. But the causes of neuronal death in these diseases are still poorly understood, impeding the development of strategies to prevent neurodegeneration. To fill this knowledge gap, Corinne Lasmézas (The Scripps Research Institute, Jupiter, FL) and her collaborators study neurodegeneration in prion disease using a highly toxic misfolded monomeric form of prion protein (TPrP).

They recently reported that TPrP induces neuronal death by depleting nicotinamide adenine dinucleotide (NAD^+) in neurons. They also showed that neuronal death could be rescued *in vitro* and *in vivo* by replenishing NAD^+ (*Brain* doi:10.1093/brain/awv002; published online 11 February 2015). "What we found is that if you replenish NAD in these neurons, it completely protects them against the injury caused by misfolded prion protein," Lasmézas told Jon Hamilton of *National Public Radio* (http://www.npr.org/blogs/health/2015/03/09/390980364/mad-cow-research-hints-at-ways-to-halt-alzheimers-parkinsons). The results suggest that neurodegeneration in prion disease is reversible, raising hopes for new treatment strategies for these and other diseases associated with protein misfolding and aggregation.

The researchers first examined the effects of TPrP on cultured neurons. Exposure to TPrP caused cell death and markedly reduced intracellular levels of NAD^+, but restoring normal levels of NAD^+ rescued the neurons. They subsequently assessed the effects of TPrP and NAD^+ *in vivo* in C57BL/6 mice. TPrP induced extensive neuronal damage in the hippocampus, which was prevented by co-administration of NAD^+. Finally, the researchers sought to determine whether NAD^+ had similar neuroprotective effects in a mouse model of prion disease. Mice were given daily doses of NAD^+ beginning either at the onset of the clinical phase or after symptoms had developed (117 d or 130 d after inoculation with prions, respectively). In both cases, NAD^+ treatment slowed disease progression, improved activity and motor skills and delayed severe motor impairment and paralysis. NAD^+ treatment did not prolong survival, however.



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The study identifies NAD^+ depletion as a cause of neurodegeneration induced by a misfolded protein. Moreover, the results show that neuronal death induced by NAD^+ depletion is reversible and that NAD^+ replenishment can alleviate neurodegeneration and preserve motor function in mice with prion disease. If it has similar effects in people with prion disease, NAD^+ treatment could offer a way to improve their quality of life.

Monica Harrington

TRACKING DOWN SYSTEMIC VIRAL INFECTIONS

Many viral infections occupy organs and tissues throughout the body, but *in vivo* assessments frequently estimate viral loads based on plasma samples or select tissue biopsies. These indirect measurements can guide clinical management of systemic infections, but they might inaccurately represent the distribution and intensity of virus replication in different tissues. Once an infection is successfully subdued, these common measurements can yield negative results for viral presence while replication and evolution still occur in un-monitored viral reservoirs.

Modern techniques in medical imaging now permit researchers to monitor systemic conditions on a large, even whole-body scale. In combination with antibody therapy, positron emission tomography (PET) scans can provide repeatable, *in vivo* visualizations of radioactively labeled features. When targeting a virus, immunoPET methods can help detect, localize and monitor systemic infection across multiple tissues over time.

To this end, researchers lead by Francois Villinger (Emory University, Atlanta, GA) developed an immunoPET probe that targets the simian immunodeficiency virus (SIV) in infected rhesus macaques, which closely model humans with SIV's human cognate, HIV. Villinger's team joined a detectable radiotracer to antibodies that target the glycoprotein Gp120, which occurs on the surface of the viral envelope of SIV. They then introduced this antibody to chronically infected macaques and to 'elite controllers'—individuals that are infected but naturally manage the virus below detectable levels without treatment (*Nat. Methods* doi:10.1038/nmeth.3320; published online 9 March 2015). Using immunoPET, they tracked the uptake of this antibody in different tissues and compared the localization of infected tissues between control macaques, elite controllers and chronically infected macaques (before and during anti-retroviral therapy).

Among the expected results, the authors were surprised to find discrete areas of virus replication in nasal tissues and the male reproductive tract of macaques, even after anti-retroviral therapy. These reservoirs are important both because they were unanticipated and because they are otherwise difficult to sample in live animals.

These new findings emphasize the need for care and caution when interpreting biopsies and plasma samples, as these measurements can inaccurately represent the virus load across different tissues. The authors anticipate that this methodology should be translatable to humans, where it could reveal how infection takes hold and lingers, dormant, during successful repression. It might even inform site-specific treatments to eradicate such reservoirs and prevent reactivation of successfully managed infections.

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