NEURODEGENERATIVE DISEASES

Simple amyloids to provide protection in MS?

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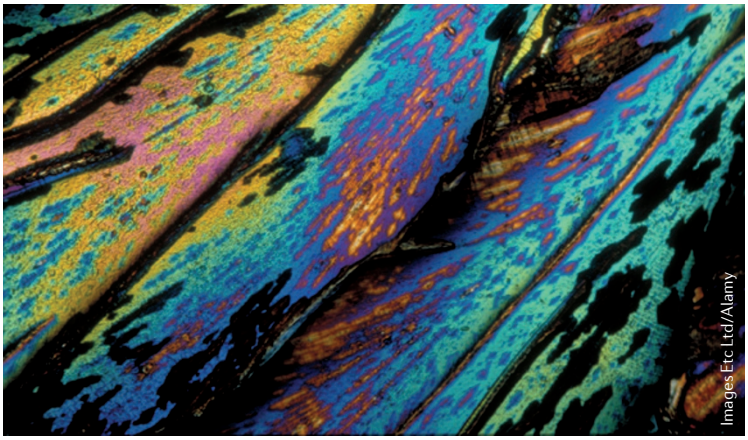
The accumulation of amyloids, which are insoluble fibrous aggregates of misfolded proteins, has long been associated with neuropathology. However, evidence has been emerging that amyloid fibrils can also have a protective function in a range of conditions. Now, reporting in *Science Translational Medicine*, Kurnellas *et al.* show that simplified amyloidogenic hexapeptides are effective therapeutics in a mouse model of multiple sclerosis (MS).

The work was based on the observation that some amyloid-forming proteins can act as anti-inflammatory agents in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, as well as in models of stroke and brain trauma. Moreover, it had been shown that the genetic deletion of several amyloid-forming proteins, including amyloid-β (Aβ) A4 and tau (both better known for their role in Alzheimer's disease), leads to disease exacerbation in mice with EAE.

The protective mechanism of these amyloid-forming proteins had previously been ascribed to their ability to act as molecular chaperones and bind pro-inflammatory mediators. Even short peptides derived from amyloid-forming proteins were found to have potential chaperone function, an activity that correlated with the ability of these peptides to form amyloid fibrils. Other studies showed that peptides composed of only six amino acids could fold into amyloid fibrils — with the structural unit of amyloid fibrils being simple β-strands.

Building on these observations, the authors used a previously published algorithm to identify hexapeptides that are likely to form amyloid fibrils within the sequences of the amyloid-forming proteins Aβ, heat shock protein β5 (HSPB5), tau, major prion protein PrP, amylin as well as insulin A and B chains. As controls, the authors used peptides that contained the same amino acids as the hexapeptides identified, but with a shuffled sequence.



Mice with EAE were treated with daily intraperitoneal injections of the peptides at the onset of hindlimb weakness. Treatment with all but one of ten different amyloid-forming hexapeptides reduced paralysis compared to treatment with the control peptide, with worsening of paralysis after withdrawal of the treatment. There was no apparent toxicity.

Further *in vitro* experiments showed that the ability of the hexapeptides to form fibrils correlated with their ability to function as chaperones. Importantly, the authors found no evidence that the hexapeptides can seed the pathogenic forms of amyloid fibrils (ascribed to their capacity to poke holes in biological membranes), which require more complex secondary structures than those formed by the hexapeptides. Using plasma from patients with MS, the authors showed that the hexapeptides, when aggregated as fibrils, were able to precipitate a number of proteins that predominantly belonged to the acute-phase, complement or coagulation pathways, which all have an important role in inflammation.

Together, these results show that simple amyloid-forming hexapeptides can have therapeutic properties — that are likely to reside in their ability to bind pro-inflammatory mediators — which might provide the basis for a completely novel class of drugs for the treatment of neuroinflammatory diseases.

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ORIGINAL RESEARCH PAPER Kurnellas M. P. *et al.* Amyloid fibrils composed of hexameric peptides attenuate neuroinflammation. *Sci. Transl. Med.* **5**, 179ra42 (2013)