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AMYLOID DISEASES

A therapeutic knockout of SAP

Many different approaches are being tried in the attempt to disrupt the insoluble deposits of tangled proteins that characterize so many diseases, including type 2 diabetes, Alzheimer's disease and systemic amyloidosis. Now, Pepys *et al.*, writing in *Nature*, report the use of a small-molecule drug in patients with human amyloidosis that reduces the circulating levels of serum amyloid P (SAP), a glycoprotein component of all amyloid deposits. As SAP is known to protect amyloid deposits from proteolytic degradation, reducing SAP levels is hoped to promote the breakdown of these aggregates, which have long proved intractable to therapy.

Circulating SAP is thought to be in dynamic equilibrium with that found in amyloid deposits, and plasma SAP concentrations have been shown to correlate with amyloidogenesis in animal models. Almost 20 years ago, the authors suggested that promoting the dissociation of SAP from amyloid deposits might be an effective therapeutic strategy, and more recently, they have shown that deleting the *Sap* gene in mice slows the onset of experimentally induced amyloidosis. The search was on

for a drug that would, ideally, decrease the levels of SAP in plasma, as well as its binding to amyloid deposits.

Screening the Roche compound library against amyloid- β fibrils that were immobilized in microtitre plates initially revealed two inhibitors of SAP binding. The dimer of one of these was found to be a more potent inhibitor than the monomer, and was selected for further synthetic development, which led eventually to the selection of a dimerized form of proline — known as CPHPC — for

taking forward into clinical trials. The molecule has limited oral bioavailability, and is excreted rapidly from the body without being metabolized.

However, intravenous injection of CPHPC into eight patients with amyloidosis for 48 hours resulted in almost complete clearance of circulating SAP, apparently through hepatic elimination. Furthermore, although SAP levels rapidly returned to normal after withdrawing the drug in individuals with little or no amyloid, they remained reduced for much longer in those with

a greater degree of amyloidosis, which implies that the 48-hour infusion had achieved the goal of significantly depleting the amyloid-associated SAP pool.

Preliminary results are also reported from an open-label study of 19 patients with systemic amyloidosis, predominantly with end-stage disease, who received CPHPC by injection for up to 9.5 months. Plasma SAP levels fell to a mean of 5% of pretreatment levels, and although most of the patients are reported to have remained clinically stable, autopsy samples from one patient who died showed that the SAP content of the amyloid deposits was much lower than normally found. On the evidence so far, long-term CPHPC treatment therefore seems to be an effective route to whittling down the SAP content of amyloid deposits in systemic amyloidosis, which could well be extendable to other amyloidogenic diseases. As the drug might be able to exert its positive effects via circulating SAP, and not directly at the site of the amyloid deposits, CPHPC might not need to gain access to affected tissues in order to work.

Adam Smith

References and links

ORIGINAL RESEARCH PAPER Pepys, M. B. *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* **417**, 254–259 (2002)

FURTHER READING Botto, M. *et al.* Amyloid deposition is delayed in mice with targeted deletion of the serum amyloid P component gene. *Nature Med.* **3**, 855–859 (1997)

WEB SITES Pepys' laboratory:
<http://www.ucl.ac.uk/medicine/amyloidosis/staff/mbp.html>