NEURODEGENERATIVE DISEASE

Draining SAP to target Alzheimer's disease

The formation of insoluble deposits of tangled proteins is a characteristic of several neurodegenerative diseases, including Alzheimer's disease, although its contribution to pathogenesis remains controversial. Serum amyloid P (SAP) has previously been shown to bind to amyloid deposits and protect them from proteolytic degradation, suggesting that inhibiting or reducing the levels of this glycoprotein might be an effective strategy to promote the degradation of these protein aggregates and potentially combat Alzheimer's disease.

SAP levels in the serum correlate with amyloidogenesis in animal models. Several studies have suggested that SAP could also have direct neurotoxic effects, as it induces apoptosis in neurons and can trigger the release of proinflammatory cytokines from microglia. In 2002, Pepys and colleagues developed a novel small synthetic compound, CPHPC, that depletes SAP levels in the circulation of patients with amyloidoses. Now, they shed further light on the compound's action in a pilot proof-of-concept study in patients with Alzheimer's disease, providing support for conducting larger, long-term efficacy studies in patients with neurodegenerative diseases associated with deposition of SAP in the brain.

In this study, which involved 5 patients with Alzheimer's disease, injection of CPHPC 3 times a day for 12 weeks dramatically reduced the levels of SAP in both the serum and cerebrospinal fluid. These effects were observed within 1 week of treatment and were maintained throughout treatment, with levels of SAP returning to baseline 4 weeks after drug discontinuation. The compound was well tolerated, and there was no cognitive deterioration or structural changes in the patients' brains, as assessed by magnetic resonance imaging, supporting the safety and tolerability of CPHPC and of systemic and cerebral SAP depletion.

To gain further insight into the mechanism of action of CPHPC, the authors determined the three-dimensional structure of SAP complexed with CPHPC in solution. They found that CPHPC induces the crosslinking of pairs of SAP molecules. In mice, such complexes with radiolabelled SAP were eliminated from the circulation 20 minutes after CPHPC injection, indicating that the dimerization of SAP is sufficient to trigger rapid clearance from the plasma. The authors also found that, in the presence of calcium, SAP binds to phosphothreonine, a putative ligand on hyperphosphorylated tau, which is a hallmark of Alzheimer's disease. The structure of this complex shows that native SAP pentamers bind to phosphothreonine, suggesting that multivalent SAP binding could promote the stabilization of tau aggregates.

Although the precise mechanisms by which SAP stabilizes protein aggregates and the CPHPC–SAP complexes are eliminated remain to be determined, the potential therapeutic effects of CPHPC warrant further investigation of this compound as a new strategy to treat Alzheimer's disease and other amyloidoses.

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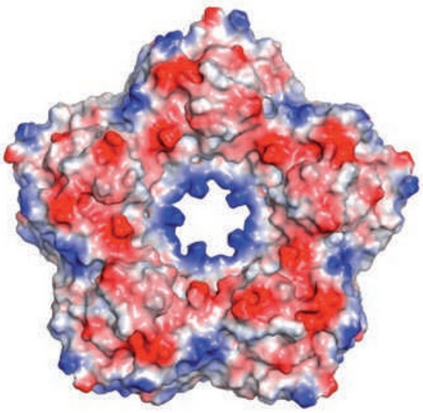

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