NEURODEGENERATIVE DISEASES

Clearing up A β

The aggregation and deposition of amyloid- β (A β) peptides in the brain are thought to underlie the pathogenesis of Alzheimer's disease, and so therapeutic strategies to reduce A β levels are being intensively pursued. Two recent studies highlight how modulation of pathways involved in the regulation of A β levels can lead to enhanced degradation and clearance of A β from the brain.

In the first paper, published in *Proceedings of the National Academy of Sciences*, Jacobsen and colleagues investigated the role of plasmin — a protease that is generated from the cleavage of plasminogen by tissue plasminogen activator (tPA) — in the breakdown of A β . By screening a compound library, the authors identified PAZ-417 as a potent and selective inhibitor of plasminogen activator inhibitor-1 (PAI-1), a known inhibitor of the plasmin cascade. *In vitro* assays revealed that PAZ-417 augmented tPA, which led to plasmin generation and induced the cleavage of synthetic monomeric and oligomeric A β . In a transgenic mouse model

of Alzheimer's disease, PAI-1 inhibition led to a twofold increase in hippocampal tPA activity. Next, clearance of plasma and brain A β was measured in two mouse models (plaque- and non-plaque-bearing ages), in which a single oral dose of PAZ-417 resulted in reduced plasma and brain A β levels in both mouse types.

Administration of PAZ-417 to mice 24 hours before hippocampal slice preparation reversed the deficits in long-term potentiation that are associated with models of Alzheimer's disease, without altering neuronal function. Last, in a mouse model of hippocampal learning and memory, PAZ-417 reduced cognitive deficits, with complete reversal when given 24 hours before memory training.

The second study by Jiang and colleagues, reported in *Neuron*, looked at the mechanism by which the lipidation of apolipoprotein E (ApoE) affects A β homeostasis. The authors first established that microglia are responsible for the uptake and degradation of soluble A β , and co-incubation of purified human ApoE resulted in stimulation of A β clearance from microglia, as a consequence of enhanced degradation. Treatment with an agonist of the liver X receptor (LXR), a nuclear receptor that has a key role in lipid

metabolism, caused an increase of lipidated ApoE, resulting in enhanced degradation and lower levels of A β . The combination of an LXR agonist and exogenous high-density apolipoproteins led to further reduction of A β levels.

Next, it was shown that the lipidation status of ApoE influences its ability to promote A β degradation, and influences the capacity of insulin-degrading enzyme to degrade A β . In a transgenic mouse model of Alzheimer's disease, oral treatment with an LXR agonist for 4 months led to 50% fewer plaques and a reduction in plaque load, without altering amyloid precursor protein levels. Mice treated for 6 days with an LXR agonist had significantly improved contextual memory scores.

Together, these papers demonstrate that targeting two pathways that regulate A β levels — ApoE lipidation or the plasmin cascade — with an LXR agonist or PAI-1 inhibitor, respectively — might have therapeutic potential in the treatment of Alzheimer's disease.

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ORIGINAL RESEARCH PAPERS Jacobsen, J. S. et al. Enhanced clearance of A β in brain by sustaining the plasmin proteolysis cascade. *Proc. Natl Acad. Sci. USA* **105**, 8754–8759 (2008) | Jiang, Q. et al. ApoE promotes the proteolytic degradation of A β . *Neuron* **58**, 681–693 (2008)