ALZHEIMER DISEASE

Fibrinogen links amyloid with vascular dysfunction

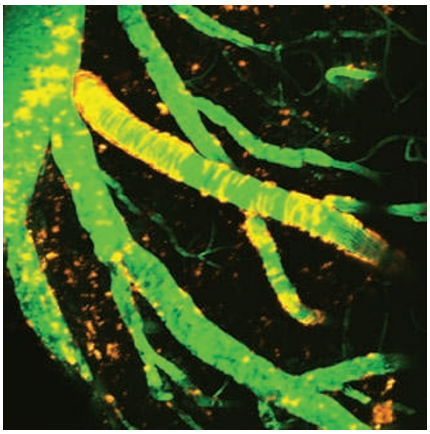
Amyloid-β (Aβ) deposition and vascular pathology have both been strongly implicated in the etiology of Alzheimer disease (AD), but have tended to be studied largely as separate entities. Now, however, researchers at The Rockefeller University, New York have proposed a new model of AD pathogenesis that brings these two processes together, with the blood-clotting factor fibrinogen providing the 'missing link'.

In a transgenic mouse model of AD, the team studied blood clotting behavior in the presence of Aβ. They focused on fibrinogen, which, during clotting, is cleaved by thrombin to form the insoluble protein fibrin. "An increase in fibrinogen levels has previously been reported to be associated with an increased risk of AD, and fibrinogen deposition in the brain has been described in AD patients and mouse models of the disease," explains lead author Marta Cortes-Canteli. "To analyze clot formation and degradation, we used *in vitro* and *in vivo* approaches that complement each other." The researchers also analyzed postmortem tissue samples from patients with AD.

Cortes-Canteli *et al.* showed that fibrinogen colocalized with Aβ in and around blood vessels, thereby contributing to the prothrombotic environment that is present in AD. The fibrin clots formed in the presence of Aβ were found to be structurally abnormal and unusually resistant to degradation. The authors propose that fibrinogen could trap Aβ, thereby creating a self-perpetuating cycle that results in obstruction of blood flow and neuronal damage.

To further study the role of fibrinogen in AD pathogenesis, Cortes-Canteli *et al.* used pharmacological and genetic approaches to deplete this protein from the blood of AD transgenic mice. These interventions not only reduced the amount of cerebral amyloid angiopathy in the brains of the mice, but also improved their performance on memory tasks, indicating a direct link between cognitive deficits and impaired fibrin degradation in these animals.

In addition to providing new insights into AD pathogenesis, the findings of this study suggest a potential new therapeutic approach for AD. "A drug that could interfere with the effects of Aβ on fibrin clot formation would, in theory, normalize any blood clots formed in the brain and increase their lysis, hence improving cerebral blood flow and neuronal function and survival," says Cortes-Canteli. "Such a drug would have little effect on general clotting in locations where Aβ levels are low, and could have significant therapeutic benefit for the treatment of AD."



Vasculature of an Alzheimer disease mouse showing blood flow (green) and amyloid deposition (red); ring-like structures surrounding blood vessels represent cerebral amyloid angiopathy. Image provided by Dr Marta Cortes-Canteli.

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Original article Cortes-Canteli, M. *et al.* Fibrinogen and β-amyloid association alters thrombosis and fibrinolysis: a possible contributing factor to Alzheimer's disease. *Neuron* **66**, 695–709 (2010)