ALZHEIMER DISEASE

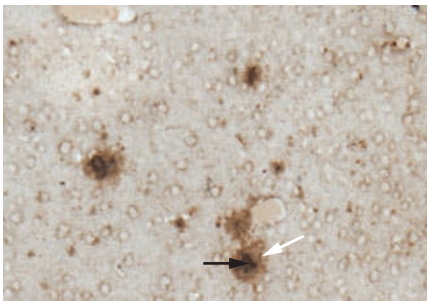
Plasma clusterin predicts degree of pathogenesis in AD

Plasma levels of clusterin, a chaperone protein that regulates amyloid formation and clearance, indicate that blood-based biomarkers could identify individuals at risk of developing Alzheimer disease (AD), according to a study published in *Archives of General Psychiatry*. "The results of this study demonstrate that this protein, which has an established role in several pathways relevant to AD, is closely associated with disease progression," explains lead author Madhav Thambisetty (National Institute on Aging, USA).

AD is a neurodegenerative disease that is associated with profound cognitive deficits, and no disease-modifying therapies are currently available for this condition. "A major hurdle to the development of effective treatments for AD is the lack of inexpensive and noninvasive methods that accurately detect early pathological changes in the brains of individuals who will eventually develop this disease," says Thambisetty. Blood-based biomarkers might represent one means of identifying and monitoring such individuals.

Thambisetty and colleagues used a combined proteomic and neuroimaging approach to identify blood-based biomarkers that could accurately predict disease pathology and clinical progression in AD. The researchers found that the plasma concentration of clusterin is positively associated with atrophy in the hippocampus and entorhinal cortex—two brain regions that are affected in early stages of the disease—in patients with mild cognitive impairment or AD. Furthermore, proteomic analysis in a separate group of patients with AD revealed that clusterin levels were increased in patients deemed to have a faster rate of cognitive decline compared with patients with a slow rate of cognitive decline.

Using PET imaging, the researchers also demonstrated that increased plasma clusterin concentrations were positively associated with fibrillar amyloid-β (Aβ) burden in the entorhinal cortex. This result was confirmed in transgenic mice that had marked cerebral Aβ deposition and cognitive defects: plasma concentrations of clusterin were higher in mice with AD-like symptoms than in wild-type animals. Moreover, in these transgenic animals, cortical Aβ plaques were shown to contain clusterin, and both Aβ burden and clusterin deposition increased with age.



Amyloid plaques in a transgenic mouse overexpressing human amyloid precursor protein and presenilin 1 contain amyloid-β (black arrow) and clusterin (white arrow). Image provided by Dr Madhav Thambisetty.

"We believe that our findings are a significant advance in the field because they identify a strong signal in blood from clusterin that seems to be relevant to both pathology and symptoms in patients with AD," says Thambisetty. However, "although plasma clusterin levels do not seem to be a definitive marker for AD, the results set the stage for further directed studies of other amyloid chaperone proteins like clusterin that might be useful as blood biomarkers for AD."

Nick Jones

Original article Thambisetty, M. *et al*. Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. *Arch. Gen. Psychiatry* **67**, 739–748 (2010)