Identification of a β -amyloid-binding plasma protein, LRP1: implications for biomarker research and therapy in Alzheimer's disease

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Evaluation of Sagare A, Deane R, Bell RD *et al.*: Clearance of amyloid- β by circulating lipoprotein receptors. *Nat. Med.* (2007) (Epub ahead of print) [1].

Sagare and coworkers have identified a major amyloid- β (A β)-binding protein in plasma low-density lipoprotein receptor-related protein-1 (LRP1). This protein may bind 70–90% of the A β that circulates in peripheral blood and seems to function as a peripheral sink for Alzheimer's disease (AD) causing brain A β . Using a mouse model of AD, the authors demonstrate that boosting the capacity of the sink by administering a recombinant form of soluble LRP1 (sLRP1) reduces brain amyloid plaque load and improves learning and memory. They extend these results by demonstrating that patients with AD have depressed plasma sLRP1 levels. Their data suggest that exogenously administered, recombinant sLRP1 may provide a novel approach to reduce or reverse the AD-related build up of A β in the brain. Furthermore, it would be interesting to explore the possibility that reduced sLRP1 levels in plasma may be a specific biochemical sign of incipient AD.

Amyloid- β (A β) clearance may be of profound importance in the pathogenesis of sporadic Alzheimer's disease (AD) [1], which is the most common form of dementia, accounting for 50–60% of approximately 20–30 million dementia cases around the world [2]. Clinical signs of AD are characterized by progressive cognitive deterioration, together with neuropsychiatric symptoms or behavioral changes. The pathological hallmarks of AD are the presence of intracellular neurofibrillary tangles of hyperphosphorylated protein tau and extracellular deposits of A β -protein in senile plaques in the cerebral cortex. Although these brain lesions may also be observed in aged nondemented individuals, the accumulation of A β in the brain is believed by many to represent the earliest event in the disease process [2].

A β is generated from amyloid precursor protein, a membrane-spanning protein expressed by most cells in the body, by enzymatic digestion involving β - and γ -secretase activities. Once formed, A β can undergo degradation by the many proteases that are present in the brain interstitial fluid [3], stabilization in monomeric forms by binding to cerebrospinal fluid (CSF) apolipoprotein E and other chaperone-like amyloid-binding proteins, such as β -trace protein [4], or aggregation to synaptotoxic oligomers. A β may also be cleared across the blood–brain barrier to the blood by low-density lipoprotein receptor-related protein-1 (LRP1) [5].

The amyloid cascade hypothesis holds that an imbalance between the production and clearance of A β is the primary alteration in the AD

process [6]. Although still somewhat controversial, the hypothesis has survived many attempts of falsification and has already translated into a series of advanced therapeutic approaches that are in different stages of clinical trial. The main focuses are to inhibit brain A β production (e.g., by the use of β - or γ -secretase inhibitors and inhibitors of amyloid precursor protein mRNA translation) and aggregation (e.g., by the use of A β oligomerization inhibitors), and to increase A β clearance from the brain (e.g., by active or passive A β immunotherapy) [7]. These types of drugs are likely to have the best efficacy in the early or even preclinical stage of the disease, when the synaptic and neuronal loss has not become too widespread. Therefore, there is a great need for biomarkers that identify AD preclinically, or in the mild cognitive impairment stage of the disease.

One of the most promising biomarkers for AD is the A β peptide *per se*. A wealth of evidence shows that reduced levels of the 42 amino acid form of A β , A β 42, in CSF is a reliable biochemical sign of AD, especially when interpreted together with CSF levels of tau proteins [3]. However, despite the known safety of lumbar punctures [8], many researchers and clinicians are trying to find AD biomarkers in peripheral blood.

Several studies have examined plasma levels of A β in AD but the findings are contradictory. Some groups report high concentrations of either A β 42 or A β 40 in plasma of AD patients, although with a broad overlap between patients

Keywords: amyloid- β ,
Alzheimer's disease,
biomarker, pathogenesis,
plasma

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and controls, whereas most groups find no change [9]. Apart from disease-related factors, the opposing data may be due to the fact that A β 42 is notoriously difficult to measure in plasma. The peptide is very hydrophobic and binds not only to certain test tube walls, but also to several plasma proteins, including albumin [10] and cystatin C [11].

Results

In a very recent and potentially groundbreaking investigation, Sagare and coworkers present data that may be of relevance both to the treatment and diagnosis of AD in the future [1]. They show that, in addition to mediating A β transport across the blood–brain barrier, a soluble circulating variant of LRP1 (sLRP1) functions as a major A β -binding protein in peripheral blood. As much as 70–90% of total A β in plasma may be bound to this protein. This may explain the phenomenon, known by many AD biomarker researchers but rarely publicized, that addition of increasing amounts of detergent to their plasma A β assays will increase the signal up to a certain threshold value when the antibody affinity is lost. In addition, Sagare and colleagues show that AD patients have approximately 30% lower sLRP1 levels in plasma [1]. Finally, they show that administration of a recombinant form of sLRP1 to amyloid precursor protein-transgenic mice diminished amyloid plaque pathology in brain tissue and improved their memory. The treatment removed both vascular and

parenchymal amyloid, and increased plasma A β , approximately half of which was associated with the LRP1 analogue.

Significance of the results & future perspective

AD is a very common disease against which there is still no effective therapy. The result that peripheral sLRP1 can mobilize neurotoxic A β from the brain in a transgenic mouse model of AD lends support to the view that passive immunization using infusion of anti-A β antibodies in the peripheral blood in humans may work in a similar manner. However, given the fact that there are more than 40 different treatments that cure transgenic AD mice but have little or no effect in humans [2], the next important step will be to test the therapeutic potential of recombinant sLRP1 administration in humans. Furthermore, it will be worthwhile to test the possibility that a reduction in plasma sLRP1 may be an early and specific biochemical sign of incipient AD.

Financial & competing interests disclosure

Work in the author's group is supported by the Swedish Research Council, the Swedish Council for Working Life and Social Research, the EU project cNEUPRO and the Alzheimer Foundation. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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