Treatment for Alzheimer's Disease by Inhibiting Formation of Platelet Micro-Clots

Technology

The Wisniewski Lab has shown that the chronic progressive vascular disease arthrosclerosis can directly affect Alzheimer's disease (AD) progression and has also demonstrated that inhibiting micro-clot formation can significantly reduce platelet-associated β- amyloid (Aβ) aggregates.

To investigate the possible link between atherosclerosis and AD pathology, the lab subjected an AD mouse model to a high-fat diet (HFD). HFD-treated mice exhibited worse memory deficits accompanied by blood hypercoagulation and chronic platelet activation. Procoagulant platelets with increased surface integrins from HFD-treated triple transgenic mice actively induced the conversion of soluble Aβ40 into fibrillar Aβ aggregates which were observed to obstruct the cerebral blood vessels in these mice. HFD-treated mice exhibited a greater cerebral amyloid angiopathy (CAA) burden and increased cerebral vascular permeability, as well as more extensive neuroinflammation, tau hyperphosphorylation, and neuron loss. Disaggregation of preexisting platelet micro-clots with humanized anti-integrin Antibody (A11) significantly reduced platelet-associated fibrillar Aβ aggregates *in vitro* and improved vascular permeability *in vivo*.

Background

Alzheimer's disease (AD) is the most common cause of dementia among the elderly, affecting approximately 50 million people and with projected to affect ~150 million by 2050. Currently, there were no effective pharmacological means to treat or slow down this progression. AD is characterized by two dominant pathological hallmarks. One is the abnormal deposition of endogenous β-amyloid (Aβ) peptides in the brain parenchyma forming senile plaques and in the walls of cerebral vessels producing cerebral amyloid angiopathy (CAA). The other is the intracellular accumulation of the microtubule-associated protein tau in its hyperphosphorylated form, resulting in neurofibrillary tangles (NFT) in neurons.

Epidemiological studies link atherosclerosis with an increased risk for dementia and AD. However, whether there are direct links between arthrosclerosis to β- amyloid (Aβ) aggregation and tau pathology is uncertain. Atherosclerosis is a chronic progressive vascular disease and is often accompanied by sustained platelet activation, increased platelet numbers, and the formation of platelet thrombi. Platelets contain high concentrations of amyloid precursor protein (APP) found in alpha granules and express all of the enzymes which are required to process APP into Aβ peptides. Moreover, platelet-derived Aβ can pass through the human cerebrovascular endothelial cell layers isolated from the brains of patients with AD, and these secreted Aβ peptides are similar to those found in amyloid plaques of AD patients.

Applications

Humanized anti-integrin Antibody (A11 or other antibodies that can cause disaggregation of pre-existing micro-clots) can be used as treatment for Alzheimer's disease.

Technology ID

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Category

Life Sciences/Neuroscience

Life

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Diseases

Jane Liew

Authors

Thomas Wisniewski, MD

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Advantages

This is a novel target for treatment of Alzheimer's disease by inhibiting formation of platelet micro-clots.

IP Status

Provisional patent application pending