A novel avenue to explore in the treatment of dementia

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6 September 2024

A collaborative project between the University of South Florida and The Healthy Aging Company is exploring how a new biological entity called ALF5755 could be a candidate drug for the treatment of dementia and Alzheimer's disease

Aging is the major common risk factor for death from all adult diseases. Death rates increase logarithmically with advancing age for all diseases associated with aging, including heart disease, cancer, stroke, type 2 diabetes mellitus (T2DM), and Alzheimer's disease.

In this context, Alzheimer's disease has emerged as a major health concern. Despite some improvement in the therapy, the overall prognosis of AD is still poor. With the current lack of treatments, any type of symptom alleviation will have a beneficial impact on the lives of patients and their caregivers.

The pathogenesis of Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the deposition of extracellular senile plaques, neurofibrillary tangles (NFTs), and neurodegeneration, leading to memory impairment and dementia. In addition, cellular changes are observed, such as mitochondrial and synaptic abnormalities, oxidative stress, and neuronal loss. Adding to this, a growing body of evidence suggests a link between gut dysbiosis and the aggregation of amyloid plaques, hyperphosphorylated tau, and the occurrence of neuroinflammation and oxidative stress associated with AD. Although several studies have shown that oxidative stress, mitochondrial malfunction, metabolism dysregulation, and gut dysbiosis are early pathological events in AD, no effective drugs/agents are available that target these aspects of AD pathogenesis.

Oxidative stress and neurodegeneration

REG3A, a 149 amino acid protein, also known as Hepatocarcinoma-Intestine-Pancreas/Pancreatic Associated Protein (HIP/PAP), is a scavenger protein for reactive oxygen species (ROS) that belongs to a calcium-dependent family of C-type lectin superfamily. Overexpression of REG3A is observed in response to injury in various pathological settings, i.e., acute pancreatitis, Crohn's disease, hepatocellular carcinoma, cystic fibrosis, Alzheimer's disease, and after peripheral injury, in sensory neurons and motoneurons. REG3A is a potent tissue repair (mitogen and anti-apoptosis) and anti-inflammatory protein. It is also an antimicrobial peptide that is active in the gut intestine and restores a healthy microbiome. The mechanisms of action have now been deciphered. REG3A yields a direct scavenging activity, allowing it to directly capture ROS.

ALF-5755 is a new biological entity, which is a recombinant protein derived from the human protein REG3A/HIP/ PAP. Now, The Healthy Aging Company (THAC) and the University of South Florida have obtained very stimulating pre-clinical data on cognitive improvements in the context of AD with ALF5755. REG3A/ALF5755 represents a novel class of antioxidants that can cross the blood-brain barrier and target several pathways of oxidative stress, offering a broader action and the potential for higher efficacy.

Oxidative stress (OS) is the result of an imbalance between the production and elimination of free radicals (reactive oxygen species – ROS- or reactive nitrogen forms). OS is detrimental to the proper functioning of the brain because high concentrations of free radicals significantly reduce long-term synaptic enhancement (LTP), synaptic signaling, and synaptic plasticity and contribute to neurodegeneration. Additionally, the formation of pro- inflammatory cytokines is induced in response to oxidative stress, which enhances the inflammatory response, a hallmark of neurodegenerative diseases. In fact, oxidative imbalance and a substantial increase in its by-products have been repeatedly reported in AD. Numerous studies have documented mitochondrial dysfunction through the abnormal processing of ROS as an essential factor in AD pathogenesis.

Despite increasing evidence showing the role of oxidative stress in neurodegenerative diseases, no therapeutic treatment has been approved. This is in part because most antioxidants have permeability limitations, owing to which they are unable to cross the blood-brain barrier. In addition, the majority of antioxidants are limited to single pathway activity, resulting in lower efficacy and the necessity of combining several molecules to reach significant improvement.

REG3A: targeting several antioxidative pathways

REG3A, as opposed to classic antioxidants, combines beneficial effects on several pathways of oxidative stress. Relevant to ALF5755 is the scavenging activity of REG3A, which can directly capture ROS. The attenuation of the oxidative damage by ALF5755 results from its scavenging activity against two deleterious ROS, namely, the superoxide and hydroxyl free radicals, which are abundantly generated during the numerous cell death processes activated during acute liver failure. REG3A also activates antioxidant enzymes, such as Superoxide dismutase 1 (SOD-1) and Heme oxygenase (HO-1), and preserves the integrity of the extracellular matrix.

ALF5755/REG3A is a novel candidate drug for the treatment of dementia

REG3A was first identified in the digestive system for its protective properties against cell death and oxidative stress in pancreatic and liver cells. Only recently has it been reported to be expressed in the brain and shown to promote neuronal survival and plasticity as well as prevent astrocytosis and microgliosis. Neurodegeneration, inflammation, and oxidative stress are hallmarks of AD. Hence, we hypothesized that increased levels of REG3A in the brain could be beneficial in the context of AD.

The scientists at the University of South Florida have demonstrated significant rescue in learning and memory in a mouse model of amyloidosis following overexpression of REG3A in the brain. This improvement in cognition was not associated with a decrease in amyloid pathology in the brain. However, an increase in the levels of antioxidant enzymes in the hippocampus was observed. Moreover, there is now solid evidence of blood-brain barrier penetration of ALF5755/REG3A and endogenous REG3A and recombinant ALF-5755 following intravenous and subcutaneous administration.

Given the lack of efficiency of therapies aiming at reducing amyloidosis, there is an immediate need for alternative therapies. Improving cognition by reducing oxidative stress caused by inflammation and amyloidosis in the brain represents an additional therapeutic avenue to explore. Given the antioxidant properties of both endogenous REG3A and recombinant ALF5755, we believe ALF5755 will be a great candidate for direct translational application in patients with Alzheimer's disease and maybe other types of dementia.

Thus, THAC is now ready to initiate a proof-of-concept, phase 1/2a clinical study to develop ALF5755 as a candidate drug for the treatment of Alzheimer's disease.

Safety has been established in previous phases 1 and 2 clinical studies in patients with acute liver diseases based on a short-term intravenous administration of the molecule (clinical trial number NCT01318525). Alzheimer's disease is a neurodegenerative disease with slow progression that requires treatment over a longer period of time.

Therefore, the effects of ALF5755 administration will be studied over a period of 18 months by daily subcutaneous administration.

Overall, this project offers a novel avenue to explore in the treatment of dementia, and in particular Alzheimer's disease, with the repurposing of a drug approved by the Europe Medical Agency and the US FDA.

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