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## PROSAAS AND NEURODEGENERATIVE DISEASES: A REVIEW ESSAY

By Cydney Battle

**ABSTRACT**– Neurodegenerative diseases such as Alzheimer’s disease, prion diseases, Huntington’s disease, and Parkinson’s disease undeniably wreak havoc on the system of the body. The catastrophic effects of neurodegenerative diseases are felt by the reality of being incurable and the resulting effect of the progressive degeneration of the individual’s physical and mental stature. Through continuous research, experimentation, and an understanding of how neurodegenerative diseases develop and function, scientific tactics against the development and progression of these diseases will be uncovered. The abnormal aggregation of proteins is largely attributed to the development of neurodegenerative diseases. In the instance of abnormal protein aggregation, the study of proSAAS, an anti-aggregate chaperone protein, is newfound and viewed as profound in the scientific community.

Diseases in the realm of neurodegenerative decay stem from a common denominator: the abnormal aggregation of proteins. Abnormal protein aggregation commonly characterized by neurodegenerative diseases involves fibers consisting of misfolded proteins with amyloids, also known as a beta-sheet conformation (Ross and Poirier, 2004). In the instance of the aggregation of misfolded proteins, the pathogenesis of neurodegenerative diseases is imminent; however, the body’s way of preventing the accretion of diseased proteins transforming into amyloid-regions is by means of chaperone proteins. Chaperone proteins are collectively active participants in proteostasis — a conglomerate of cellular processes including the synthesis — turnover, oligomerization, and folding of proteins (Lindberg et al., 2015). The efforts asserted by chaperone proteins ensures the legitimacy and efficacy of protein development. For unknown specific reasons thus far, with the exception of scientific theories alluding to genetic and environmental susceptibilities, chaperone proteins are unable to halt the aggregation and misfolding of proteins. The aggregation of misfolding proteins induces neurotoxic and cytotoxic events that inevitably lead to the development of neurodegenerative diseases. Regarding the aggregation of

amyloid proteins, the anti-aggregate chaperone protein, proSAAS, is at the forefront of scientific research on neurodegenerative diseases.

ProSAAS is most often associated as a neuroendocrine peptide found commonly in the brain's neuronal pathways and in other physiological pathways. In the scientific study, "A novel function for proSAAS as an amyloid anti-aggregant in Alzheimer's disease," the anti-aggregate chaperone protein, proSAAS, is discussed in terms of neurodegenerative diseases. More specifically, the study aims to discuss and study a novel function for proSAAS, relative to the protein's evident abundance and presence in amyloid pathology. Respectively, the researchers in the conducted study hypothesized that proSAAS serves as a potential anti-aggregant in Alzheimer's disease.

The conducted study used models of mice displaying Alzheimer's disease, as well as post-mortem brain tissue of human individuals diagnosed with Alzheimer's disease. To associate the connection between proSAAS and neurodegenerative diseases, the researchers examined a hippocampal tissue sample from a 73-year-old human diagnosed with Alzheimer's disease. For the animal model of the study, 12-month-old male mice were chosen for brain examination of potential amyloid plaques. The key marker used in this proportion of the experiment was the cerebrospinal fluid,  $A\beta_{1-42}$ , which is a key indicator of Alzheimer's disease.

Through the examination of both species in relation to the neurodegenerative disease, Alzheimer's disease, it was found that proSAAS was co-localized with amyloid deposits in both the human and the animal brain specimens (Hoshino et al., 2013). To further strengthen the researcher's theory of a novel function for proSAAS in neurodegenerative diseases, the researchers set up a control of a healthy individual not displaying symptoms of Alzheimer's disease. The results of the control experiment displayed proSAAS levels in the brain but no  $A\beta_{1-42}$  immunoreactivity. Definitively speaking, the founding of proSAAS in the highly-plaqueted amyloid regions of the brain in the Alzheimer specimens indicates a physiological role of proSAAS in Alzheimer's disease pathology (Hoshino et al., 2013).

To further their study on proSAAS effects on neurodegenerative diseases, the researchers conducted a study on proSAAS's effect on  $\beta$ -sheet fibrils – fibers often found in the misfolded protein aggregates of neurodegenerative diseases. Described in Figure 4, the researchers found that when recombinants of proSAAS were introduced into the equation,  $A\beta_{1-42}$  fibrillation was prevented. The caveat of their experiment was that the efficacy of the recombinant proSAAS against fibrillation was dose-dependent, time-dependent, and proSAAS was not able to deaggregate fibrils that were already formed (Hoshino et al., 2013). Through the process of this phase, the researchers also aimed to discover which region of proSAAS is responsible for the prevention of fibrillation. While using different sequence homologies of proSAAS on fibrils, the conclusion was formed that the N-domain portion of proSAAS served as the anti-aggregation function.

At the completion of the study, the researchers concluded that proSAAS does not operate under the normal chaperone protein facade of refolding but rather by blocking the formation of protein aggregation (Hoshino et al., 2013). The research collected in this study suggest the high likelihood of proSAAS function in the pathogenesis of neurodegenerative diseases and supports the concept of future applications for proSAAS. Due to the functions of proSAAS still being discovered and uncovered, there is a possibility of proSAAS potentially curing or slowing the progression of various neurodegenerative diseases.

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