As life expectancy increases, understanding challenges related to the processes of aging are more relevant than ever. Common age-related diseases progress as consequences of accumulative protein damage and protein aggregates. PA28αβ has previously demonstrated protective effects against proteinopathy and is involved in removal of protein damage early in mammalian embryonic development. In this thesis project, female and male mice overexpressing PA28αβ have been followed and analyzed throughout their lifespan to investigate the molecular function of PA28αβ and what physiological and behavioral effects its overexpression induces.

Herein, the finding of a chaperone-like function of PA28αβ is demonstrated by enhanced aggregation prevention in hippocampal extracts from mice overexpressing PA28αβ. This function correlates to enhanced cognitive capacities represented as improved learning and memory in young adults and as exploratory activity in aging mice, the latter a strong behavioral marker of aging. Thus, we have found a previously unprecedented role of PA28αβ in neuronal protein homeostasis, which improves cognitive behavior in mice, but with altered behavioral outcomes in young and old mice.

The neuronal role of PA28αβ and its cognitive effects combined with PA28αβ's molecular mechanism of preventing protein aggregation, highlight a therapeutical potential of PA28αβ in combating proteinopathies, especially neurogenerative diseases.

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