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YOUNG INVESTIGATORS AWARDS SYMPOSIUM

YIA-1

Circadian modulation of proteasome activities and removal of carbonylated proteins

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The circadian clock generates rhythms with a periodicity of 24 hours of various biochemical and physiological processes. Recent data suggest a mutual influence between the circadian clock and the cell cycle, and provide a functional connection between the circadian clock, cancer and ageing. In addition, the established link between the circadian clock and anti-oxidative defence suggests that elements of the redox homeostasis, including oxidized protein degradation pathways such as the proteasome, could be modulated by the circadian clock. Using HEK cells synchronized by a serum shock as an initial cellular model for studying the circadian influence on protein maintenance, we have shown that the level of carbonylated protein varies rhythmically following a 24 hours period as well as the level of ROS. The proteasome also exhibits circadian rhythmicity in either its expression levels or activities. The rhythms match the circadian oscillations observed for protein oxidative damage.

Moreover, adaptation to a Nrf2-dependent oxidative stress has been associated with an increase in the cellular capacity to degrade oxidized proteins that is attributable to an increased expression of the 20 S proteasome and its activator Pa28αβ. Therefore, using our synchronized cellular models to investigate more precisely the modulation of proteasome function mediated by the circadian clock, we have shown that both Nrf2 and Pa28αβ exhibit a circadian expression. Interestingly, the circadian variation in ROS precedes the Nrf2 protein level and the transcript level of proteasome catalytic subunits and activators. If as we envisage, circadian rhythmicity is involved in damaged protein degradation, the age-associated alteration of the circadian system may therefore contribute to the accumulation of oxidized proteins and the decline of intracellular protein maintenance. Hence, strategies that could restore this vital function may be effective in slowing ageing and the onset of diseases for which a defect in the protein homeostasis has been proposed to play a key role.

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YIA-2

Enhanced proteasome degradation extends *Caenorhabditis elegans* lifespan and alleviates aggregation-related pathologies

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Collapse of proteostasis and accumulation of damaged macromolecules have been recognized as hallmarks of aging and age-related diseases. The proteasome is the major cellular protease responsible for intracellular protein degradation, having an impaired function during aging. We have previously shown that proteasome activation through overexpression of β5 proteasome subunit delays replicative senescence and confers resistance to oxidative stress in primary fibroblasts. Herein, we have investigated the impact of enhanced proteasome function on organismal longevity and aggregation-related pathologies by employing *Caenorhabditis elegans* as a model system. We have found that overexpression of a core 20 S proteasome subunit in wild type worms extends lifespan, healthspan and survival under proteotoxic conditions. The longevity prolonging effect of the proteasome subunit overexpression was found to depend on the FOXO transcription factor DAF-16 and was associated with its elevated transcriptional activity. We have also uncovered a major role of enhanced proteasome activity in aggregation-related pathologies underlying neurodegenerative diseases. Genetic activation of the proteasome minimized the detrimental effect of polyglutamine-induced toxicity mimicking Huntington's disease, whereas knock-down of the proteasome component exaggerated the disease phenotypes. Similar results were obtained by using a *C.elegans* model of Amyloid beta (Aβ) –induced toxicity mimicking Alzheimer's disease. Collectively, these findings demonstrate that enhanced proteasome function alleviates proteotoxicity and promotes longevity in synergy with other nodes of lifespan regulation in *C.elegans*. Understanding the mechanism by which preservation of proteostasis via enhancement of proteasome function, decelerates the aging process and alleviates age-related pathologies may assist in the rational design of therapeutic and anti-aging interventions.

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