SUN-519
Endoplasmic reticulum-associated degradation controls the levels of amyloid precursor protein

C. Yefi, A. Gonzalez, V. Cavieres, H. Bustamante, G. Mardones, P. Burgos
Universidad Austral de Chile, Valdivia, Chile

Alzheimer's disease (AD) is characterized by the overproduction of pathogenic amyloid-b peptide (Ab), which is generated by proteolytic cleavage of the b-amyloid precursor protein (APP). The action of b-secretase on APP produces a C-terminal fragment (C99) that is subsequently processed by g-secretase to release Ab. It has been proposed that substrate availability contributes to Ab production, and that this may in turn be affected by the rate of APP/C99 turnover. We have demonstrated that the degradation of C99 can be triggered at the ER in an ubiquitin- and proteasome-dependent manner. In this study we investigated the contribution of the ER-associated degradation (ERAD) machinery on APP/C99 endogenous levels. It is known that misfolded glycoproteins that fail to attain their correct conformation at the ER are recruited by the ER Degradation Enhancer Mannosidase alpha like 1 (EDEM1) from the calnexin/calreticulin folding cycle, and are directed to the dislocation channel for cytosolic degradation by ERAD. This last step relies on the hexameric ATPase p97/VCP, and on a small p97/VCP-interacting protein (SVIP) that functions as an inhibitor of the ERAD pathway. The aim of this study was to investigate the outcome of ERAD inhibition on APP and C99 levels by either stable expression of an EDEM1 shRNA, transient overexpression of SVIP, or pharmacological inhibition of p97/VCP. Our results support a model in which the levels of APP and C99 are highly controlled at the ER. Funded by FONDECYT 1130929, Beca CONICYT 21110499 and DID-UACh.
Keywords: APP, ER, ERAD.

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Enhanced proteasome degradation extends *Caenorhabditis elegans* lifespan and ameliorates neurodegeneration

K. Georgila[1], N. Chondrogianni[1], N. Kourtis[2], N. Tavernarakis[2], E. S. Gonos[1]
[1]Institute of Biology, Medicinal Chemistry & Biotechnology, National Hellenic Research Foundation, Athens, [2]Institute of Molecular Biology and Biotechnology, Foundation of Research and Technology-Hellas, Heraklion, Greece

Aging and various age-related diseases are associated with progressive decline in proteostasis and accumulation of damaged macromolecules. The proteasome is the major cellular protease implicated in the disposal of normal and damaged proteins, having an impaired function during aging. In previous reports, using human primary cells, we demonstrated that proteasome activation through overexpression of proteasome subunits confers extension of replicative senescence and resistance to oxidative stress. 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 single core proteasome subunit in wild type worms enhanced proteasome content, assembly and function. The activation of the proteasome extended animal lifespan, healthspan and survival under proteotoxic conditions. The longevity prolonging effect of the ectopic expression of the core proteasome subunit was found to depend on the FOXO transcription factor DAF-16 and was associated with its elevated transcriptional activity. Finally, we have unveiled 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, whereas knockdown of a key component of the proteasome exaggerated the disease phenotypes. Similar results were obtained by using a temperature inducible model of Amyloid beta (Aβ) –induced toxicity mimicking Alzheimer's disease. Collectively, our findings demonstrate that enhanced proteasome function alleviates proteotoxicity and promotes longevity in synergy with other key 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 lead to new therapeutic and anti-aging interventions.
Keywords: aggregation-related pathologies, longevity, proteasome activation.

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Expression of SUMO negatively regulates interferon signaling

G. Maarifi, M. A. Maroui, S. Nisole, M. K. Chelbi-Alix
INSERM, Paris, France

Interferons (IFNs) exhibit pleitropic functions including antiviral, growth inhibitory and apoptotic activities. IFNs activate the JAK/STAT pathways to trigger the transcription of IFN-inducible genes (ISGs) whose products mediate their biological functions. It has been established that ubiquitin or ubiquitin-like modifiers such as SUMO or ISG15 modify many ISGs or key regulators of IFN signaling. However, little is known on the role of SUMO in IFN signaling, cell regulation and antiviral response.

Here, we report that stable expression of each of the SUMO paralog in different human cell lines altered type II IFN signaling. SUMO1, SUMO2 or SUMO3 stable expression led to a lower STAT1 phosphorylation and binding to DNA in response to IFNγ, resulting in a selective inhibition of IFNγ-induced transcriptional activity. Indeed, the expression of SUMO did not affect the increase of IRF1 mRNA in response to IFNγ whereas it blocked IP10 mRNA expression. Importantly, enhanced SUMOylation reduced the capacity of IFNγ to inhibit cell growth and to protect cells from viral infection, a finding that implicates SUMO as a negative regulator of IFNγ responses.

Taken together, these results identify SUMOylation as a mechanism that attenuates cell sensitivity to IFNγ by decreasing STAT1 activation and its binding to DNA, preventing hyperresponsiveness to this cytokine, thus adding the SUMO-mediated inhibition as part of other negative IFN signaling pathways known to date.
Keywords: interferon, STAT1, SUMO.

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Functional and structural studies of the BiP chaperon protein and his role in protein translocation

C. A. Wilson, M. Vega, A. Tapia
Bioquímica y Biología Molecular, Universidad de Chile, Santiago, Chile

BiP (Binding inmmunoglobulin protein) also known as Kar2p in yeast, is a Chaperon involved on protein translocation from the citoplasm to the endoplasmatic reticulum (ER), the first step on protein trafficking. BiP helps to the correct folding of various

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