PP24

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

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Aging is associated with decline of proteostasis and accumulation of damaged macromolecules. The proteasome is the major cellular protease implicated in the removal of both normal and damaged proteins, having an impaired function during aging. In previous reports using human cells, we demonstrated that proteasome activation through overexpression of proteasome subunits confers lifespan extension and resistance to oxidative stress. In this study, we sought to investigate the impact of enhanced proteasome degradation on a multicellular organism and employed *Caenorhabditis elegans* as an established model of organismal aging. We found enhanced proteasome activity upon overexpression of a single core proteasome subunit in wild type worms. We explored the effects of proteasome activation on lifespan and on animal survival under proteotoxic conditions. Finally, we examined the impact of enhanced proteasome activity on age-associated pathologies by exploiting established models of neurodegeneration. Understanding the mechanism by which restoration of proteostasis via increased proteasome function, decelerates the aging process may lead to new therapeutic and anti-aging interventions.

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PP25

Mitochondria-related effects and epigenetic changes induced by incretins and humanin in pancreatic mouse beta cells

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Background: Glucose-dependent insulinotropic peptide (GIP) and Glukagon-like peptide-1 (GLP-1) are incretin hormones targeting pancreatic β-cells, where they enhance insulin secretion in a glucose depended manner. Recent studies reported that excess of GLP-1 exerted other beneficial effects, including antiapoptotic and proliferative effects on β-cells. Humanin, the mitochondrial DNA derived 24-amino acid peptide is reported to act by suppressing apoptosis as well as exerting anti-inflammatory properties, in which some mechanism improving mitochondrial bioactivity could be involved. We investigated the effects of incretins and humanin on β-cells function and survival under cytokine-induced stress. Methods: The mouse line of pancreatic beta-cells BTC6 were preincubated with humanin HNG or GIP/GLP-before the challenge with TNF-α for the following 24h. Apoptosis was measured using Annexin V /propidinum iodine staining by flow cytometry, as well as caspases activity. The mitochondrial membrane potential was measured by JC-1 fluorescence by flow-cytometry. Oxygen consumption in intact cells was measured using high resolution respirometry and ATP-generation was monitored. Glucose-stimulated insulin secretion, central to normal control of metabolic fuel homeostasis, was also studied. Epigenetic changes were studied measuring global DNA methylation using MethylFlash Methylated DNA Quantification Kit. Results: In the TNF-α induced model of apoptosis, prevention of especially late apoptosis of BTC6 cells by GIP as well as by humanin, was observed. Caspase-9 and caspase-8 activity together with mitochondrial membrane potential changes revealed the pathway of apoptosis. Humanin was also found to enhance DNA methylation. GLP-1 potentiated GSIS, also in presence of TNF-α. Conclusions: These results suggest that humanin exert some beneficial effects promoting β-cells survival under cytokine-induced stress. Incretins (GIP and GLP-1) prevent β-cells dysfunction and consistently insulin secretion, partially through the mitochondria-related pathways. Different mechanism may be involved in these protective effects, including epigenetic modification –methylation of DNA.

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PP26

Stimulation of insulin-like action in 3T3-L1 cells exposed to mild dose of lipopolysaccharide

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Excessive differentiation of adipocytes lead to obesity and this phenomenon has been linked to oxidative stress and chronic low grade inflammation. Studies using murine preadipocytes (3T3-L1 cell line) have demonstrated that lipopolysaccharide (LPS) stimulate adipose tissue-derived cytokines involved in differentiation and inflammation. In this study, the effects of LPS (Escherichia coli [055:B5]) on 3T3-L1 preadipocyte differentiation and the expression of glutathione peroxidise (GPx3), lipogenesis markers and inflammatory cytokines were investigated. Fully differentiated adipocytes were treated with various concentrations of LPS for 3 days and the lipid accumulation was measured using Oil Red O staining. The RNA was extracted and the expression of markers was quantified using Real-Time Taqman-PCR. Insulin was used as a positive control. LPS treated adipocytes stimulated lipogenesis at lower concentrations (0.001- 0.01μg/ml) but inhibited lipogenesis at higher concentrations (0.1- 10μg/ml). Peroxisome proliferator activated-receptor-gamma, sterol regulatory binding protein-1c, lipoprotein lipase, adiponectin, glucose transporter-1 and glucose transporter-4 were up-regulated in 0.001 μg/ml and 0.01 μg/ml LPS treated adipocytes (similar to insulin effect) however, the effect was more enhanced at a lower dose (0.001μg/ml). The expression of anti-inflammatory cytokine, interleukin 10 (IL-10)