The proteasome as a key player in the progression of ageing and age-related diseases

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Ageing is a physiological process that represents a high-risk factor for the progression of age-related diseases. Several molecular pathways deteriorate with ageing or the progression of age-associated proteinopathies, including the proteasome system. Proteasomes are constituents of the proteostasis network responsible for the proteolysis of normal and abnormal proteins. Using the replicative senescence model of human primary fibroblasts and the multicellular nematode *Caenorhabditis elegans*, we have shown that proteasome activation (either through genetic means or through natural or synthetic compounds), results in lifespan extension. More importantly, the lifespan extension is accompanied by healthspan (time period free of diseases) improvement. With regard to the progression of the Alzheimer's disease (AD) phenotype, elevated proteasome function confers lower paralysis rate in various AD nematode models accompanied by decreased Aβ deposits, thus ultimately decelerating the progression of the disease. Similar positive results were also obtained when primary murine cortical neurons were co-treated with proteasome activators and increased concentrations of various Aβ forms. More recently, we have shown that proteasome activation in the nervous system can enhance the proteasome activity in the muscle of *C. elegans*, thus revealing a cell non-autonomous communication. Mechanistically, this communication depends on Small Clear Vesicles (SCVs), with glutamate as one of the neurotransmitters required for the distal regulation. The identified distal communication may have serious implications in the design of therapeutic strategies based on tissue-specific proteasome manipulation.