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Spermidine-Induced Autophagy, the Key to Extend Lifespan?

Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. **Nat Med 2016;22:1428-8. http://doi.org/f3t5hg**

Aging is associated with increased risk of cardiovascular disease, which reaches epidemic proportions in the elderly population and becomes the leading cause of death worldwide. Human aging is accompanied by the hypertrophic remodeling of the heart and progressive diastolic function impairment. Lack of adequate treatment increases the progression to symptomatic heart failure in a high proportion of these patients. Possibly, the limited understanding of the ultrastructure and function of the heart in elderly patients hampers better therapeutic opportunities.

In the last years, autophagy has been shown to minimize the functional damage of aging cardiomyocytes through the recycling of old proteins and cytoplasmic components or damaged organelles, as mitochondria. The accumulation of dysfunctional mitochondria increases the deleterious effects of oxidative stress by increasing the production of free radicals with catastrophic consequences for cellular function and survival. Cells which depend on a high level of oxidative metabolism have a great potential to develop autophagy of damaged mitochondria, a process known as mitophagy. Therefore, the stimulation of autophagy induces cytoprotective effects opposing the structural and functional impairment of the aging heart.

In the work commented here, the authors of different laboratories in various countries performed a very interesting study on how the administration of oral spermidine supplement is able to prolong the lifetime of mice by increasing cardiomyocyte autophagy. Longer survival was associated to a cardioprotective effect, reducing cardiac hypertrophy and diastolic ventricular dysfunction in old mice. These benefits were attributed to a series of mechanisms studied by the authors, as increased autophagy and mitophagy resulting in enhanced mitochondrial respiration. Increased titin (a key protein in the mechanical properties of the heart) phosphorylation and reduced inflammatory response resulted in improved ventricular elastic properties. Conversely, transgenic inhibition of autophagy blocked all these beneficial effects. Similar effects were observed in a model of heart failure in hypertensive rats which presented low blood pressure levels, reduced myocardial hypertrophy, increased titin phosphorylation and delayed left ventricular dysfunction. Interestingly, in a study in elderly patients, these authors also found a correlation between those declaring greater spermidine consumption in their usual diet and lower blood pressure levels and reduced incidence of cardiovascular events.

Autophagy is a very specialized catabolic process that works as a qualitative control system of eucariotic cells. The cells can break and recycle molecules and other cytoplasmic contents as excess or dysfunctional organelles through the formation of autophagic vacuoles. This makes it a very efficient system to save energy and for cellular adaptation in moments of great organic stress, as diseases, prolonged fasting and aging. Autophagy started to be studied in detail only in the 90s. Since then, its interest has grown due to its involvement in numerous physiological and pathological cellular processes. Proof of this is the 2016 Nobel Prize in Medicine awarded to Yoshinori Ohsumi for his contributions on the study of the mechanisms of autophagy.

Spermidine, a polyamide described in the composition of semen, is also abundantly found in a variety of foods, especially in vegetables and dairy products. Its beneficial properties have been well demonstrated in the adequate functioning of several organs, as the brain, and experimentally it has been shown to prolong lifespan. Eisenberg et al. were the first to associate this spermidine effect of life prolongation with cardioprotective effects in aging, through the induction of autophagy in cardiomyocytes. This opens the pathway for future investigations in the search of a novel therapeutic option for heart failure in the growing group of population suffering from this disease.