

## Autophagy in Endocrine-Metabolic Diseases Associated With Aging

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Received: January 06, 2021; Accepted: January 20, 2021; Published: January 27, 2021

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### A Note on Autophagy

Autophagy may be a highly regulated self-degradative process of cytoplasmic cellular constituents usually activated under certain conditions like starvation or other different sorts of cell stress that end in breakdown proteins and other cell components to obtain energy. Autophagy is additionally liable for removing damaged or aged organelles, eliminating different pathogens and misfolded, aggregated, or altered proteins. Autophagy is an evolutionarily biologically conserved process that sequesters and delivers cytoplasmic components to the lysosome for degradation. It is also involved in the removal of cells that have undergone classical apoptosis. Autophagy is usually related to cell survival mechanisms: its dysregulation, however, could also be also related to necrobiosis. In the classical view, consistent with the pathway that cargo follows to succeed in the lysosomal compartment, there are three major sorts of canonical degradative autophagy.

These types are: microautophagy/endosomal microautophagy, chaperone mediated autophagy, and macroautophagy, the last one being characterized by the engulfment of cytoplasmic contents by a double membrane vesicle, named autophagosome. However, other non-canonical types of autophagy have been described. One of these unconventional forms is known as secretory autophagy, a newly recognized process that's becoming of accelerating relevance to elucidate the non-canonical secretion of a series of cytosolic proteins that have critical biological importance.

Disruption of autophagy is related to aging and metabolic and degenerative diseases including cancer. Chaperone-Mediated Autophagy (CMA) represents a major mechanism for degradation of cytosolic proteins. It also plays a significant role in the regulation of lipid and carbohydrate metabolism. Dysregulation of chaperone-mediated autophagy has been found in several models of paralysis agitans, Alzheimer's disease, and Huntington's chorea. Alterations in CMA can also play a task within the pathophysiology of Lateral Amyotrophic Sclerosis and other sorts of condition.

Secretion of some proteins lacking a "signal peptide" (for instance, some cytokines, insulin-degrading enzyme, alpha-Synuclein, etc.) doesn't follow the canonical secretion pathway. Those proteins are secreted following different unconventional processes. One of these routes relies on autophagy; it is autophagy dependent. "Secretory autophagy" may then explain the secretion of some relevant peptides involved in several pathophysiological processes. Some aggregation-prone proteins,

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**Citation:** De Gonzalez M (2021) Autophagy in Endocrine-Metabolic Diseases Associated With Aging. *Endocrinol Metab* Vol. 5 No.1: e156.

like Amyloid beta or alpha-Synuclein are secreted by secretory autophagy. Some pro-inflammatory mediators like interleukin-1 beta also follow this non-canonical secretory process. Alteration in secretory autophagy, as extensively may play a substantial role in degenerative and metabolic diseases and their treatment.

Skeletal muscle atrophy may be a common finding in aging and lots of degenerative diseases. Different degrees of muscle atrophy are often achieved under diverse physiological conditions, exposure to certain drugs, or starvation. Many of the mechanisms associated with muscle atrophy remain obscure.

Hypothalamic arcuate neurons can sense the nutrient status of the organism and accordingly regulate food intake and glucose metabolism. Alterations of this neuronal network can contribute to the pathogenesis of obesity-related diseases like type 2 DM.

Autophagy is an important homeostatic protective mechanism, but, on the other hand, its alterations can be involved in various pathologic processes. Aging can be defined as a time dependent deterioration of cell functioning due to damage accumulation. Autophagic activity has been shown to decrease with age, potentially contributing to the accumulation of damaged molecules and organelles. Thus, to clarify the role of dysfunctional autophagy in establishing the hallmarks of aging could help to define new anti-aging therapeutic strategies and to increase longevity.

The mTORC1 signalling pathway couples energy and nutrient abundance to the execution of cell growth, cellular division and metabolism. Moreover, the activation of mTORC1 inhibits autophagy. The progression of the diabetic disease is related

to a chronic over activation of mTORC1 and consequently with a sustained inhibition of autophagy in pancreatic beta cells. The failure of such a crucial protective mechanism could induce the apoptosis of pancreatic beta cells and therefore the impairment of compensatory insulin secretion that characterize the transition to prediabetes to clinically evident type 2 diabetes.

Cancer is emerging as a posh disease where metabolic alterations and inflammatory processes play a critical role. Autophagy and autophagy related proteins are involved in cancer pathophysiology.

Scientific knowledge in the field of autophagy grew exponentially along the last decade. A more precise characterization of the different forms of autophagy, their molecular mechanisms and potential implications in the pathophysiology of many diseases reflect the magnitude of such advances. However, several gaps in knowledge and unmet needs remain uncovered and involve further research. Identification of molecular targets for pharmacological modulation of autophagy and its translation into clinical practice remains among the more urgent ones. The role of autophagy modulation in therapy of metabolic and degenerative diseases challenges our current knowledge and opens potentially promising avenues for future investigation.