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Physiology of autophagy

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Abstract
The process of intracellular components being broken down by lysosomes is known as autophagy. By destroying intracellular components and giving cells breakdown products, autophagy plays a crucial part in preserving and regulating cell homeostasis [1]. The most recent studies have demonstrated that autophagy serves a variety of physiological and pathological functions, some of which are intricate. There are fewer autophagic vacuoles and poorer lysosome fusion as autophagy decreases with age. The innate immune system is strengthened by activating the autophagic pathway, which has also been shown to be helpful in avoiding different foreign infections. Tau and synuclein protein accumulation result from a decrease in autophagic protein clearance in neurodegenerative diseases. Similar to this, lysosomal lipid accumulation results from autophagic failure. Tumors are first suppressed by autophagy, but they are subsequently immune system-protected. Muscle and cardiac issues are favourably and negatively regulated by autophagy, respectively.

Keywords: Autophagy, autophagosome, types, immune autophagy, ageing, cancer

Introduction
The word "autophagy," which is taken from the Greek for "eating oneself," was first used more than 40 years ago by Christian de Duve [2]. Observations of the oxidation of mitochondria and other intracellular components in the lysosomes of rat liver perfused with the pancreatic hormone glucagon served as the main source of inspiration for him. The molecular basis of glucagon-induced autophagy in the liver is currently poorly understood, however it requires cyclic AMP-induced activation of protein kinase-A and is very tissue-specific. The scientific community "rediscovered" autophagy in recent years, and numerous laboratories have made substantial contributions to our understanding of the molecular basis of this process as well as our knowledge of its physiological significance. For his work on autophagy, molecular biologist Yoshinori Ohsumi [3] was awarded the 2016 Nobel Prize in Physiology or Medicine. Despite the fact that the importance of autophagy in mammalian systems is well known, yeast has made significant fundamental progress in identifying how autophagy is regulated and carried out at the molecular level [4] (Saccharomyces cerevisiae). 32 distinct autophagy-related genes [5] (Atg) have so far been identified by genetically screening yeast. Notably, a large number of these genes are preserved throughout phylogenies and are found in slime mould, plants, worms, flies, and mammals, demonstrating the importance of the autophagic process in starving responses. Today, it is recognised that autophagy is a critical procedure for quality assurance and a method for controlling metabolism within the cell. Essentially, autophagy happens when a specific region of the cytosol is enveloped by two membranes, forming the so-called autophagosome [6]. A number of catabolic enzymes work with the lysosomes, the cell's digestive organelles, to break down the cargo and enable the recycling of the metabolites created. General metabolic signals like famine or very particular cues that assist eliminate defective or unnecessary proteins or organelles to preserve cellular homeostasis can both trigger autophagy.

Types of Autophagy
The proteolytic breakdown of cytosolic components at the lysosome is promoted by all three of the recognised kinds of autophagy: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy [7].To carry cytoplasmic cargo to the lysosome, macro autophagy uses a double membrane-bound vesicle called an autophagosome, which joins with the lysosome to form an autolysosome. By invagination of the lysosomal membrane, the lysosome itself directly absorbs cytosolic components during micro-autophagy.

Both macro- and micro-autophagy are capable of ingesting large objects via selective and non-selective methods. In chaperone-mediated autophagy (CMA), targeted proteins are transported across the lysosomal membrane in a combination with chaperone proteins (such as Hsc-70) that are recognised by the lysosomal membrane receptor lysosomal-associated membrane protein 2A (LAMP-2A).

The Basic Autophagy Apparatus

Although the exact origin of the phagophore in mammalian cells is unclear, the process of autophagy begins with the formation of an isolation membrane, or phagophore, which is most likely made from a lipid bilayer supplied by the endoplasmic reticulum (ER), trans-Golgi, and/or endosomes. This phagophore enlarges to sequester internal cargo, such as protein aggregates, organelles, and ribosomes, in a double-membraned autophagosome. Lysosomal acid proteases are prodded to break down the autophagosomal contents as the loaded autophagosome expands by fusing with the lysosome. Lysosomal permeases and transporters transfer amino acids and other degradation byproducts back to the cytoplasm so they can be employed once again for the synthesis of macromolecules and for metabolism. As a result, autophagy can be seen of as a cellular "recycling factory" [8] that promotes energy efficiency by creating ATP and aids in damage control by getting rid of proteins and organelles that are no longer needed.

Immune autophagy

Research shows autophagy regulates immunity and inflammation. Autophagy regulates immunity. In innate immunity, xenophagy [9] removes intracellular pathogens such bacteria (S. pyogenes, S. flexneri, M. tuberculosis, S. typhimurium, and L. monocytogenes), parasites (T. gondii), and viruses (Herpes simplex virus). Autophagy protects plants and mice from infections. LC3- and ubiquitin-binding NDP52 [10] and p62 attract intracellular ubiquitin-coated pathogens to autophagy. Innate defence regulator-1, an antimicrobial peptide that reduces infection and inflammation, targets p62, emphasising its role in innate immunity. Pathogens resist autophagy. Pathogens impede autophagy, which is essential to innate immunity. Herpes simplex virus ICP34.5 [11] blocks autophagy by binding to host. Nef and Beclin-1 suppress HIV breakdown by inhibiting autophagosome maturation. Bcl-2-like proteins or mTOR signalling decrease autophagy in gamma-herpes and human cytomegalovirus. Autophagy aids adaptive immunity. It controls T- and B-cell survival, differentiation, and Paneth cell homeostasis. Autophagy displays MHC class I/II antigens. Autophagosomes load endosomal MHC class I and II molecules with proteolytically processed antigens. Autophagy distributes HSV-1 antigens on MHC class I molecules, preventing CD4+ T-cell priming in Atg5-deficient dendritic cells. Autophagic cell immunisation enhances antigen-specific CD8+ T-cell cross-priming. Autophagy delivers cytoplasmic viral nucleic acids to endosomal TLRs, inducing type I IFN and IFN-dependent immune responses. Ultimately, autophagy affects mouse thymus T-cell selection and self-tolerance. Atg5 [12] deficient thymic epithelium causes colitis and multi-organ lymphoid infiltration.

Autophagy and Ageing

ATG proteins and other autophagy-triggering proteins like Sirtuin [13] decrease in aged tissues, according to several studies. Sirtuin1, Atg5, Atg7, and Beclin 1 are downregulated in osteoarthritis, insulin resistance, metabolic syndrome, and brain ageing. With age-related neurological illnesses like Alzheimer's and heart hypertrophy, IP3 receptor [14] activation is increased, suggesting that autophagy may have decreased. These data are phenomenological and correlative, but they show that autophagic response enfeeblement may contribute to the phenotype of ageing.

Autophagy and Cancer

Due to its role in cell survival in challenging environments, autophagy shields cancer cells from cellular and metabolic harm. Tumours may potentially be prevented by autophagy. Autophagy appears to have two functions in cancer. In addition to preventing malignant transformation and cancer advancement, autophagy also has a pro-survival role in non-optimal growth settings, giving established tumours an adaptive mechanism that aids in their survival. Autophagy-modulating cancer therapies are challenging because of this ostensible dual role. In situations with low levels of nutrients and oxygen, autophagy encourages the growth of tumours. In fact, autophagy increases cell survival in cells that lack growth factors, amino acids, and serum. Current research indicates autophagy is essential for both tumour development and survival. By preserving mitochondrial metabolic activity and energy levels, autophagy aids Ras-mediated carcinogenesis [15]. It is also necessary for the tumorigenic growth of pancreatic cancer, maybe through limiting oxidative damage and maintaining metabolic balance. After being released from the extracellular matrix, autophagy prevents cells from going into anoikis [16] pointing to a potential role in metastasis. The majority of anticancer medications encourage autophagy in tumour cells to combat cellular damage and therapeutic stress. Autophagy suppression may occasionally enhance anticancer treatment.

Autophagy and Other Disorders

Because autophagy is involved in many biological processes, signalling defects may cause numerous illnesses. Neurological illnesses, liver, heart, infectious, cancer, diabetes type II, cystic fibrosis, and more are linked to autophagy. Mutated proteins cause several of these diseases. Autophagosomes break protein clumps. Autophagy failure harms them. Autophagy inhibits neurodegeneration. Autophagy protects against aggregation-prone mutant proteins in spinocerebellar ataxia, Parkinson's disease, Huntington's disease, tau mutations that cause frontotemporal dementia, pathogenic intraneuronal amyloid beta in Alzheimer's brain, and polyglucosan inclusion bodies in Lafora disease. Lower Beclin-1 [17] levels may impair autophagic clearance in most neurodegenerative diseases. Aging reduced brain function. Beclin-1 expression Caspases cleaved Beclin-1 in Alzheimer's brain tissues.

In CF lung epithelia, transmembrane conductance regulator mutations impair autophagy and protein aggregation. ROS-induced TG2-dependent crosslinking of Beclin-1 and PIK3C3 [18] complex sequestration in perinuclear aggregates hinder autophagy.

Certain myopathies decrease autophagic clearance of aggregation-prone proteins or damaged organelles. Due to autophagy stimulation, collagen VI deficiency induces organelle dysfunction and spontaneous muscle fibre loss. Bethlem myopathy and Ullrich congenital muscular dystrophy muscle samples have reduced Beclin-1 and BNIP3 levels. Genetic, dietary, and pharmacological autophagy activation enhanced myofiber survival and dystrophic phenotype in collagen VI-knockout rats. Pompe and Danon illnesses produce muscle autophagosome accumulation due to LAMP-2 and acid alpha-glucosidase deficits. X-linked myopathy patients' skeletal muscles autophagy more.

Autophagy may cause cardiac disease. LAMP-2 [19] - efficient animals suffer cardiomyopathy, and cardiac-specific Atg5 deficiency increases polyubiquitinated proteins, ER stress, and apoptosis. Autophagy protects failing hearts from hemodynamic stress. Autophagy and cell death can damage the heart during ischemia/reperfusion.

Liver diseases are prevented by autophagy. Alpha 1 anti-trypsin deficiency promotes liver inflammation and malignancy. Autophagy destroys alpha 1 anti-Z trypsin's mutation-induced protein misfolding, polymerization, and intrahepatic inclusions. Carbamazepine reduces hepatic fibrosis and clears alpha 1 anti-trypsin inclusions in rats by stimulating autophagy. Finally, autophagy is associated to Crohn's disease (CD), a serious chronic inflammatory bowel illness. Atg16L1 [20] and IRGM1 are autophagy-related CD susceptibility genes.

Conclusion

The autophagic mechanism has become more well understood in recent years. Many autophagy-related proteins have been found and functionally identified in both yeast and humans. Also, we are starting to comprehend how autophagy affects our bodies physiologically. Nonetheless, despite these recent improvements, many issues remain essentially unresolved. The mechanisms underlying autophagy, its functions in numerous biological processes, and the signalling routes that control its activation should all be the subject of future study. This knowledge is essential for demonstrating that autophagy can be used as a therapeutic target for a variety of diseases, including cancer.

Conflict of Interest

Not available

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