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REVIEW ARTICLE

Autophagy: Its Role In Cellular Homeostasis And Various Diseases

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ABSTRACT: Taking out the trash is an important chore, it disposes of the trash overflow in our homes avoiding the attraction of bacteria. In the same manner, our bodies undergo a process called autophagy to effectively cleanse and eliminate debris. Autophagy is a cellular degradation procedure that's essential in maintaining homeostasis by playing a role in maintaining cellular health by contributing to the overall well-being of the cell by removing misfolded proteins, clearing damaged organelles such as mitochondria, endoplasmic reticulum, and peroxides, in addition to eliminating intracellular pathogens. This review highlights the role of autophagy and its effects on certain human diseases. We highlight how autophagy affects different diseases including neurodegenerative diseases and cancer, and why autophagy becomes impaired in patients suffering from these diseases.

KEYWORDS: Cellular and Molecular Biology; Genetics; Autophagy; Diseases; Cellular Homeostasis.

Introduction

Autophagy is a fundamental intracellular degradation process that is used to eliminate debris, protein, and damaged organelles due to faulty folding that is Autophagy takes place in all eukaryotic cells at minimal basal levels, serving to maintain cellular homeostasis by digesting potentially harmful intracellular elements. When we speak about autophagy, the main process refers to the formation and degradation of the membrane within the lysosome. This process is tightly regulated by a group of protein molecules called Autophagy-related proteins (ATGs).[1] Dysregulation in ATG gene function is associated with alterations of cellular homeostasis, cell metabolism, immune responses, and developmental processes.

Figure 1: By clearing out waste debris to maintain cellular health, autophagy can be compared to taking out trash.

There are three types of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy, the major type of autophagy commonly referred to as autophagy, is involved in the formation of double-membrane structures called autophagosomes, which engulf cellular material destined for degradation. These autophagosomes then fuse with lysosomes, forming autolysosomes, where the engulfed contents are broken down by lysosomal enzymes (Figure 3).[2] This type of autophagy plays a crucial role in maintaining cellular homeostasis by removing damaged organelles, misfolded proteins, and intracellular pathogens. Microautophagy, on the other hand, directly involves the engulfment of cytoplasmic components by lysosomes through invagination of the lysosomal membrane. Unlike macroautophagy, which involves the formation of specialized vesicles, microautophagy occurs through direct lysosomal engulfment, making it a more rapid process. Microautophagy is involved in the turnover of small cytoplasmic components

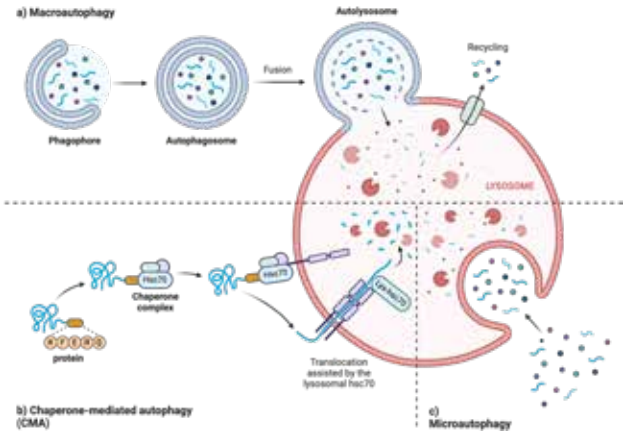

Figure 2: Autophagy involves three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy starts with the formation of a double-membrane structure, engulfing damaged components and forming an autophagosome. The autophagosome then fuses with a lysosome, where its contents are broken down and recycled. Microautophagy involves direct engulfment of small portions of cytoplasm by lysosomes. Here, lysosomes directly engulf and degrade cellular components without the need for an autophagosome. Chaperone-mediated autophagy targets specific proteins for degradation. Chaperone proteins recognize and transport these proteins to lysosomes, where they are unfolded and degraded.

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and is particularly important during nutrient deprivation or stress conditions. CMA is a selective process where specific proteins, containing a recognition motif, are targeted for degradation. It involves the recognition of these proteins by cytosolic chaperones like HSC70, which then transport them to lysosomes. Once inside the lysosomal lumen, the proteins are translocated for degradation. Unlike macroautophagy and microautophagy, CMA focuses on degrading individual proteins rather than entire organelles or cytoplasmic components. This selective protein degradation is crucial for maintaining cellular protein quality control and preventing the accumulation of damaged or misfolded proteins.The 3 processes are shown in figure 2.

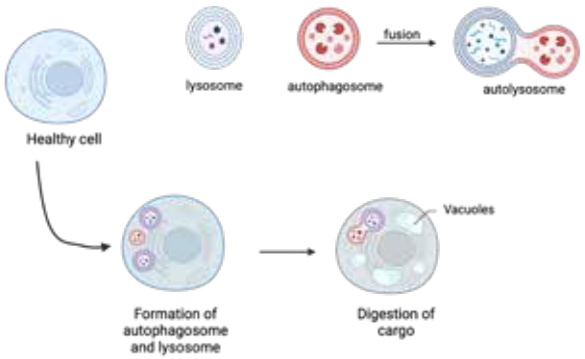

Figure 3: Macroautophagy starts with the formation of a membrane around damaged components, creating an autophagosome. This fuses with a lysosome for breakdown and recycling.

Autophagy's Crucial Role:

Autophagy plays a crucial role in a variety of human diseases, such as cancer where it fuels cellular metabolism and clears damaged substrates.[3] It is well-known for overcoming carcinogenic, infectious, degenerative, and deleterious agents to maintain the homeostasis of body systems; therefore, its dysregulation is recognized to cause many human diseases.[4]

The word autophagy comes from the Greek words auto for "self" and phagy for "eating". In times of nutrient scarcity or stress, autophagy takes center stage, providing a source of energy by breaking down cellular components and clearing cellular waste making it critically important in homeostasis.[5] Autophagy becomes a survival strategy, allowing the cell to adapt to challenging conditions. It can be selective or non-selective, depending on whether it targets specific intracellular entities. Selectivity is achieved through specific autophagic receptors (SARs) characterized by ubiquitin-binding and LC3-interacting regions, acting as adaptors between cargo and autophagosome membranes.[6]

Different types of selective macroautophagy are named based on what they degrade such as mitophagy which is responsible for the bulk degradation of the mitochondria and xenophagy which is in charge of degrading foreign microorganisms such as bacteria.[7]

Macroautophagy is induced when a stress signal is received by the cell which causes ATP levels to decrease since energy prohibits autophagy. As ATP levels decrease, AMP levels increase and this transition would be sensed by molecular sensors (AMPK or mTOR). This in turn activates ULK1 which is derived from the endoplasmic reticulum and causes a cascade of reactions that ultimately generates PI3K on the isolation membrane to recruit factors necessary for elongation.[8,9] This is now called the phagophore which extends further to elongate the cargo to be digested. The membrane-bound cargo is now called the autophagosome which fuses with the lysosome to form an autolysosome and the proteases from the lysosomes can now digest the cargo and release nutrients and metabolites.[10]

Research performed on mice deficient in particular ATG genes has resulted in conceptual discoveries within the field. The concept of "intracellular quality control" has been formulated through the examination of mice featuring neuron-specific and liver-specific deletion of Atg5 or Atg7.In mouse models, when autophagy, a cellular process responsible for removing damaged components, is lacking in the brain and liver, there is an accumulation of certain types of proteins (ubiquitinated), impaired organelles, and specific substrates related to autophagy, like SQSTM1/p62.[11] These findings suggest that autophagy plays a critical role in preventing the harmful buildup of damaged proteins and organelles in mammals. It acts as a quality control mechanism, ensuring the proper removal of cellular debris to maintain overall cellular health and function.

Autophagy and diseases:

As previously mentioned, autophagy plays a role in overcoming carcinogenic, infectious, degenerative, and deleterious agents to maintain the cellular homeostasis of the human body systems. Growing evidence indicates that the dysregulation of autophagy leads to the buildup of abnormal proteins and/or damaged organelles, a phenomenon commonly observed in neurodegenerative diseases like Alzheimer's (AD), Huntington's, and Parkinson's disease (PD).[12]l

Alzheimer's disease:

Alzheimer's disease is a progressive neurodegenerative disorder, related to memory and cognitive deficits. AD is intricately linked to the process of autophagy, where cellular components are recycled. Central to this connection are enzymes called β-secretase, γ-secretase, and α-secretase.[13,14] β-secretase cleaves amyloid precursor protein (APP), leading to the formation of amyloid-β (Aβ) peptides, which are toxic and form plaques in the brain.[15] In a healthy human central nervous system, Aβ peptide production typically occurs at a rate lower than their clearance, with percentages of 7.6 and 8.3 per hour, respectively.[16]

Studies have shown that enhancing autophagy can help alleviate Alzheimer's pathology and improve cognitive function.[17] Various pharmacological and genetic approaches aimed at boosting autophagy have been investigated as potential therapeutic strategies for Alzheimer's disease. For example, rapamycin, a drug that activates autophagy, has been shown to reduce amyloid-beta levels and improve cognitive function in mouse models of Alzheimer's disease.[18] Similarly, small molecules known as autophagy enhancers have demonstrated the ability to promote the clearance of protein aggregates and improve neuronal survival in preclinical studies.[19]

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γ-secretase then cleaves these peptides, generating shorter, more toxic forms.[20] α-secretase, however, cleaves APP within the Aβ domain, producing non-toxic fragments.21 Mutations in presenilin genes (PSEN1 and PSEN2), components of the γ-secretase complex, increase cleavage and activity, promoting Aβ production.22 Dysregulation of autophagy further exacerbates Alzheimer's pathology by failing to clear these toxic Aβ peptides, leading to their accumulation and subsequent neuronal damage.[23] Thus, understanding the intricate interplay between autophagy, secretase enzymes, and genetic mutations is crucial for unraveling the mechanisms underlying Alzheimer's disease and developing effective therapeutic strategies.
In those who do not have AD, autophagy prevents its development. However, in individuals who already have AD, autophagy becomes dysregulated, leading to impaired clearance of protein aggregates and compromised neuronal function.[24] This is because several factors impair the autophagy-lysosomal pathway such as Aβ plaques, genetic mutations, and tau tangles. The aggregation of Aβ plaques and tau tangles can obstruct autophagosome formation and its fusion with lysosomes, causing the accumulation of damaged proteins and organelles that should be degraded. In addition,mutations and changes in genes related to the autophagy pathway, along with persistent cellular stress and inflammation, add to the dysfunction of autophagy. Consequently, the compromised autophagy worsens neuronal harm and speeds up the advancement of Alzheimer's disease, establishing a harmful cycle of cellular deterioration and neurodegeneration.[25]

In conclusion, autophagy plays a critical role in maintaining neuronal health and preventing the accumulation of toxic protein aggregates associated with Alzheimer's disease. Strategies aimed at enhancing autophagy hold promise as potential therapeutic interventions for Alzheimer's disease, offering hope for effectively treating this devastating neurodegenerative disorder. Lifestyle factors such as fasting and exercise, known to stimulate autophagy, have been associated with a reduced risk of Alzheimer's disease. Fasting triggers autophagy by depleting cellular energy stores, leading to the breakdown of cellular components for energy production.[26] Exercise, on the other hand, enhances autophagy by increasing cellular energy demand and promoting the clearance of damaged proteins and organelles.[27]

Huntington's disease:

Huntington's disease is a genetic disorder that affects the brain and is caused by a mutation in the huntingtin gene (HTT), leading to the production of a mutated form of the huntingtin protein (mHTT). This abnormal protein damages nerve cells in the brain, particularly in areas associated with movement, cognition, and emotions and tends to aggregate in neurons. The mHTT aggregates interfere with the formation of the autophagosome and the fusion of the lysosome with the autophagosome. The disruption prevents autophagy from occurring, leading to the accumulation of mHTT within neurons which is the cause of neurodegeneration.[28,29]

The disease typically manifests in adulthood and progresses over time. Symptoms include involuntary movements, changes in personality, and cognitive decline. As the condition advances, individuals with Huntington's disease may experience difficulties in coordination, balance, and daily activities.[30] Huntington's disease is inherited in an autosomal dominant manner, meaning that a person only needs to inherit one copy of the mutated gene from either parent to develop the disorder. Genetic testing can identify individuals at risk, allowing for proactive management and counseling. Unfortunately, there is currently no cure for Huntington's disease, but supportive treatments and therapies can help manage symptoms and improve the quality of life for affected individuals.[31]

Researchers collected skin cell samples from patients with Huntington's disease at various ages, comparing those with and without symptoms. They discovered that neurons reprogrammed from older patients exhibited elevated levels of a microRNA called miR-29b-3p, which is a small amount of nucleotides that sabotage gene expression, leading to impaired autophagy and cell death.[32,33] Reducing this microRNA or enhancing autophagy can be done using a compound called G2-protected neurons.[34]

G2, initially identified for liver disease, may be a candidate for preventing neurodegeneration in Huntington's and other diseases involving misfolded proteins. The study also revealed that even in healthy aging, neurons gradually produce low levels of the harmful microRNA, potentially contributing to cognitive decline.[35]

Parkinson's disease:

Parkinson's disease is a chronic neurodegenerative condition first described in 1817 by Dr. James Parkinson. It affects both motor and nonmotor functions, causing both progressive degeneration in mobility and muscle control. PD is characterized by motor symptoms like resting tremor, bradykinesia, and muscular rigidity, attributed to the loss of striatal dopaminergic neurons. Research indicates that pathophysiological changes may precede motor symptoms, emphasizing the importance of preventive therapies.PD is prevalent, with approximately 145,000 people in the UK alone affected.[36] Although more common in the elderly, PD can develop in individuals in their 30s and 40s. PD's progression, variable but impactful, can lead to serious complications and increased mortality.

Similarly to both AD and HD, autophagy is impaired in patients suffering from PD. This leads to the accumulation of α-synuclein aggregates, and since autophagy clears out damaged organelles, dysfunctional mitochondria builds up within the neurons. Because mitochondria produces adenosine triphosphate (ATP), which is the energy used by the cells, energy levels will decrease. The energy deficit impairs neuronal function and neurotransmitter release, promoting neuronal death and causing trembles.[37]

The current approach to treatment primarily addresses symptom management, with a recommended emphasis on a multidisciplinary care strategy. Various risk factors, including oxidative stress and environmental toxins, are associated with PD.[38] Limited genetic associations exist, and intriguingly, an inverse relationship is observed between cigarette smoking, caffeine intake, and PD risk. Worldwide prevalence variations suggest a complex interplay of genetic, environmental, and ethnic factors in disease development. Ongoing biomedical

research aims to uncover additional risk factors and inform future prevention and treatment strategies for PD.[39]

Cancer:

Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body.[40] These abnormal cells can form tumors, interfere with the normal function of organs, and eventually spread to other parts of the body, a process known as metastasis.[41] Cancer can develop in virtually any part of the body and can arise from various factors, including genetic mutations, environmental exposures, and lifestyle choices.[42] It is a major global health concern, with significant impacts on individuals, families, and healthcare systems worldwide. Despite advances in detection, treatment, and prevention, cancer remains a leading cause of death globally, emphasizing the ongoing need for research, innovation, and comprehensive approaches to cancer care.

Multiple studies discovered that autophagy plays a significant role in cell survival and cell death regarding tumor initiation and progression as it is regulated under anticancer therapy.[43,44] Research performed on autophagy-deficient mouse models suggests that the primary levels of autophagy can inhibit tumor growth at the initial stages.[45] Nonetheless, autophagy could also facilitate cancer advancements in several cancers.

Autophagy-related genes mostly play roles in autophagy-related functions but some may play roles in non-autophagy functions in addition to their usual roles. FIP200 (Focal Adhesion Kinase Family Interacting Protein of 200 kDa) is an autophagy-related protein that interacts with ATG 13 and triggers autophagy.[46] Research has disclosed that the loss of autophagy-related genes increased the rapid growth of HER2 (Human Epidermal Growth Factor Receptor 2)-positive breast cancer proving that autophagy plays a pivotal in maintaining the overall homeostasis of the body.[47]

Summary

In this article, we have summarized the role of autophagy in cellular homeostasis and the relationship between autophagy and human diseases. Autophagy is a fundamental intracellular degradation process that serves as the cell's maintenance crew, eliminating debris, damaged proteins, and organelles under stressful conditions like starvation, hypoxia, or exposure to drugs. It operates in all eukaryotic cells and is tightly regulated by a group of proteins called Autophagy-related proteins (ATGs).

Autophagy plays a pivotal role in a variety of human diseases, including cancer and neurodegenerative diseases like Alzheimer's, Huntington's, and Parkinson's disease (PD). In Alzheimer's disease, for instance, abnormal protein aggregates, such as beta-amyloid plaques and tau tangles, accumulate in the brain, leading to neuronal dysfunction and cognitive decline. Autophagy acts as a cellular janitor, clearing away these toxic protein aggregates and dysfunctional organelles, thus protecting neurons from damage and degeneration. In Huntington's disease, dysregulated autophagy leads to the accumulation of abnormal proteins, contributing to neuron death. Similarly, in Parkinson's disease, disruption of autophagy leads to the accumulation of α-Synuclein aggregates, impairing neuronal function.

Autophagy's role in cancer is complex, with basal levels suppressing tumor initiation but promoting progression in many cancers. Understanding the intricate interplay between autophagy and disease mechanisms is crucial for developing effective therapeutic strategies. Various pharmacological and genetic approaches aimed at enhancing autophagy have been investigated as potential treatments for neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's. Lifestyle factors such as fasting and exercise, known to stimulate autophagy, have also shown promise in reducing the risk of Alzheimer's disease. In conclusion, autophagy is a vital cellular process involved in maintaining homeostasis and preventing the accumulation of toxic proteins and organelles associated with various diseases. Harnessing the potential of autophagy holds promise for the development of novel therapeutic interventions for a wide range of human disorders, offering hope for improved treatment outcomes and better quality of life for affected individuals.

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