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Alternative cellular disposal pathway-related health issues: A review

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Abstract

Keeping cells in a state of balance and optimal function requires proper cellular waste management. Autophagy and the (ubiquitin-proteasome system) UPS, two well-established routes, have been the subject of substantial research. A growing body of evidence suggests that alternate cellular disposal pathways may play a role in several health problems. This review delves into the inner workings of these alternate routes and how they relate to health and illness. Microautophagy, chaperone-mediated autophagy (CMA), and production of extracellular vesicles (EVs) are our main areas of interest. Our discussion centres on their role in neurodegenerative illnesses, cancer, and metabolic disorders, with an emphasis on possible treatments for these conditions. Novel insights into disease causes and possible treatments can be gained by understanding these pathways. Microautophagy entails direct lysosomal engulfment of cellular material, CMA selectively targets cytosolic proteins for lysosomal degradation, while EV secretion controls waste by exporting it out of the cell. Dysfunction in these pathways can result in pathological diseases, as they are essential for cellular integrity maintenance. This study highlights the significance of potential alternative disposal systems in cellular health and disease management by outlining their functions in different diseases and investigating new treatments that aim to block these pathways.

Keywords: Chaperone-mediated autophagy (CMA); Extracellular vesicles (EV); Micro autophagy; Autophagy-lysosome pathway (ALP)

1. Introduction

Maintaining cellular homeostasis requires proper cellular component remove and recycling. Neurodegenerative illnesses, cancer, and metabolic diseases are among the many conditions that can result from these systems being dysregulated. Alternative pathways do just as important a job as the well-studied and well-characterized autophagy-lysosome pathway (ALP) and ubiquitin-proteasome system (UPS) in keeping cells functioning normally. This review summarizes these other pathways, delves into their workings, and assesses their importance for human health (1).

It is impossible to exaggerate the significance of managing cellular waste. Proteins, lipids, and organelles are cellular components that are continually worn down and damaged. In the absence of efficient and rapid clearance, these damaged components can build up, impair cellular function, and ultimately cause cell death. Protein degradation and organelle turnover are primarily regulated by the UPS and ALP, respectively. Nevertheless, these activities are also significantly impacted by alternate routes, such as microautophagy, chaperone-mediated autophagy (CMA), and extracellular vesicle (EV) secretion (1,2).

Specifically, lysosome-bound cytosolic proteins are the objects of CMA, a kind of selective autophagy. In this process, chaperone proteins act as middlemen by guiding substrate proteins to lysosomal receptors for destruction upon

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recognition of a pentapeptide motif. CMA has a crucial role in cellular stress responses and homeostasis, since it is increased in response to oxidative stress and nutritional deprivation, among other stress situations (3).

In microautophagy, lysosomes directly engulf cytoplasmic debris. Microautophagy engulfs cytoplasmic material by means of invagination or septation of the lysosomal membrane, as opposed to macroautophagy that employs autophagosomes for cargo transport to lysosomes. Important cellular processes including organelle turnover and quality control rely on this pathway. As an essential component of cellular adaptation to environmental changes, it functions both in basal and stress-induced states (4).

Extracellular vesicle secretion is yet another crucial cellular waste removal pathway. Microvesicles and exosomes are two types of extracellular vesicles (EVs) that help cells eliminate waste. These vesicles play a role in the communication between cells and can transport many different types of cargo, including as proteins, lipids, and nucleic acids. By releasing their waste, EVs aid in regulating cellular internal environments and avoiding the buildup of harmful substances (4,5).

Several disorders are linked to the deregulation of these alternate pathways. Defects in CMA and microautophagy exacerbate the development of neurodegenerative illnesses like Alzheimer's and Parkinson's by leading to the buildup of harmful proteins and destroyed organelles. To facilitate their fast proliferation and survival, cancer cells frequently take over these pathways. By influencing the tumor microenvironment, EVs promote tumor growth and spread, and increased CMA activity aids cancer cells in coping with proteotoxic stress (6).

The maintenance of metabolic homeostasis in metabolic diseases relies on the regulation of these pathways. Conditions like obesity and type 2 diabetes can be exacerbated by metabolic imbalances brought on by the buildup of lipid droplets and dysregulation of CMA and microautophagy. The disease causes and possible treatment targets can be better understood with an awareness of these other disposal pathways (7).

The purpose of this study is to shed light on the role of CMA, microautophagy, and EV secretion in maintaining cellular homeostasis and to suggest ways in which these processes could be targeted for the treatment of different disorders. To better understand these pathways and use these discoveries in therapeutic settings, additional study is necessary.

2. Mechanisms of Alternative Cellular Disposal Pathways

2.1. Chaperone-Mediated Autophagy (CMA)

CMA specifically breaks down cytosolic proteins within lysosomes. The process includes chaperones such as heat shock cognate 70 (Hsc70) that identify KFERQ-like patterns in substrate proteins and guide them to lysosome-associated membrane protein 2A (LAMP-2A) for transportation into lysosomes (8). This pathway plays a vital role in maintaining cellular quality control, especially during periods of stress. CMA is a distinct type of autophagy that differs from others by not requiring the creation of vesicles. Instead, it directly transports substrate proteins across the lysosomal membrane. The ability to selectively remove oxidized or misfolded proteins is crucial in order to minimize their buildup and potential harm to cells (6).

2.2. Microautophagy

Microautophagy involves the direct engulfment of cytoplasmic material by lysosomes through invagination or septation of the lysosomal membrane. Unlike macroautophagy, which involves the formation of double-membrane vesicles called autophagosomes, microautophagy directly captures small portions of the cytoplasm. This process is less selective than CMA and plays a significant role in the turnover of organelles and protein aggregates. Microautophagy can occur under basal conditions and in response to nutrient deprivation, contributing to cellular adaptation by degrading and recycling intracellular components (9).

2.3. Extracellular Vesicle (EV) Secretion

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3. Implications in Health and Disease

3.1. Neurodegenerative Diseases

Impaired alternative disposal pathways contribute to the accumulation of toxic proteins in neurodegenerative diseases. For instance, defective CMA has been linked to Parkinson's disease (PD) due to inefficient degradation of alpha-synuclein. Accumulation of this protein leads to the formation of Lewy bodies, a hallmark of PD. Similarly, compromised microautophagy and EV secretion are associated with Alzheimer's disease (AD), where abnormal protein aggregates like amyloid-beta and tau proteins accumulate. These aggregates can interfere with neuronal function and lead to cell death. Enhancing the activity of these pathways could potentially ameliorate symptoms or slow disease progression (12).

Despite extensive research over many years, the existing treatments for Parkinson's disease (PD) are not effective in slowing down the progression of the disease by improving the underlying pathology. Cellular proteostasis, also known as protein homeostasis, is crucial for maintaining a stable environment that supports neuronal activity (13). Proteostasis is maintained through many strategies such as controlling protein synthesis, assisting protein folding with chaperones, and utilizing protein breakdown pathways. There is a widely held belief that imbalances in proteostasis are connected to a range of neurodegenerative disorders, such as Parkinson's disease (PD). Although the proteasome is unable to break down big protein clumps, specifically alpha-synuclein (α-SYN) in Parkinson's disease (PD), the activation of autophagy by drugs can effectively eliminate these aggregates and prevent the degeneration of dopaminergic (DA) neurons. Thus, it is crucial to maintain these systems in order to uphold all cellular functions that depend on a properly folded proteome. The associations between endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), which seeks to restore proper protein folding within the secretory route, are widely recognized. Although modest shocks can enhance the function of chaperones, chronic cellular stress or inadequate adaptive response can lead to cell death. Regulating the function of molecular chaperones, like protein disulfide isomerase, which aids in the restructuring of proteins and helps eliminate misfolded proteins, along with their related pathways, could provide a novel strategy for changing the therapy of diseases (14).

3.2. Cancer

Cancer cells exploit alternative disposal pathways to support their rapid growth and survival. Enhanced CMA activity has been observed in several cancers, providing a mechanism for cancer cells to cope with proteotoxic stress. Increased CMA can aid in the degradation of damaged or misfolded proteins, allowing cancer cells to survive under stressful conditions (15). Additionally, EVs are involved in tumor progression by modulating the tumor microenvironment and promoting metastasis. Extracellular vesicles (EVs) generated from cancer cells have the ability to convey oncogenic factors to recipient cells, hence promoting tumor growth and spreading. Targeting these pathways may offer novel approaches for cancer therapy. The cellular defense mechanism against proteotoxicity is known as the integrated stress response. It involves four specific serine/threonine protein kinases that act on the translation initiation factor eIF2α (5). This leads to the phosphorylation of eIF2α at S51, causing cell cycle arrest and a widespread reduction in protein synthesis. Phosphorylation of eIF2α enhances the translation of ATF4 and the activation of ATF4 target genes. This process helps to alleviate proteotoxic stress but can also induce apoptosis. Moreover, it influences the sensitivity and resistance of cells to proteasome inhibitors, which are a novel type of cancer treatments that induce tumor cell death by causing proteotoxic stress (16).

3.3. Metabolic Disorders

Alternative pathways also play roles in metabolic regulation. For example, CMA activity influences lipid metabolism, and its dysfunction is linked to obesity and type 2 diabetes. During fasting, CMA is upregulated to degrade lipid-droplet-associated proteins, mobilizing stored fats (17). Dysregulation of this process can lead to lipid accumulation and metabolic imbalances. Microautophagy helps maintain lipid homeostasis by degrading lipid droplets and other organelles involved in lipid metabolism. Defects in this pathway can contribute to metabolic disorders by disrupting lipid turnover and storage. Unwholesome sources of lipids, highly processed foods including added sugars, and a sedentary way of life increase the vulnerability of persons to becoming overweight and obesity (18). Lipids are an important part of the body. However, when there is too much lipid accumulation that exceeds the capacity of lipid droplets, it disrupts the composition of fatty acids inside cells and releases harmful lipid species. This leads to a condition called lipotoxicity, which is a pathological state. This disease leads to endoplasmic reticulum stress, mitochondrial malfunction, inflammatory responses, and cell death. Recent advancements in omics technologies and analytical methodologies, as well as clinical research, have yielded new understandings of the mechanisms behind lipotoxicity (19). These include gut dysbiosis, epigenetic and epi transcriptomic modifications, dysfunction of lipid droplets, post-translational modifications, and changes in membrane lipid composition. This review examines the current understanding of the mechanisms involved in the development of lipotoxicity and lipotoxic cardiometabolic illness in obesity, with a specific emphasis on lipotoxic and diabetic cardiomyopathy (20).

3.4. Therapeutic Interventions

Targeting alternative cellular disposal pathways offers potential therapeutic strategies. Modulating CMA activity, for example, could enhance the clearance of pathological proteins in neurodegenerative diseases or reduce proteotoxic stress in cancer. Similarly, influencing EV biogenesis and release could impact cancer progression and metabolic diseases. Autophagy is a cellular process that involves the breakdown of proteins and organelles through lysosomes. It plays a crucial role in encouraging cell survival, and development, and maintaining a stable internal environment (21). The process of autophagosome synthesis and fusion with lysosomes involves multiple steps. Genetic studies have successfully discovered numerous proteins that play a role in this process, as well as various signaling factors that are involved in the regulation of autophagy. Autophagy serves as a cellular defence mechanism and its malfunction is associated with various diseases, including neurodegeneration, liver, heart and muscle disorders, cancer, inflammation, and aging (22).

3.5. Pharmacological Modulation

Small molecules that enhance CMA, such as AR7 and spermidine, have shown promise in preclinical models of neurodegenerative diseases. These compounds can increase the degradation of harmful proteins, potentially mitigating disease symptoms. Inhibitors of EV release, like GW4869, are being explored for their potential to disrupt tumor-promoting communication. By preventing the release of EVs, these inhibitors may reduce the spread of oncogenic factors and slow tumor progression. There is a tremendous need to improve the condition of PD patients through the development of novel pharmaceutical techniques that can slow the disease's progression and enhance brain function. One challenge in delivering PD treatments into the brain has been the inadequate penetrance of the blood-brain barrier (BBB), a problem that is common among many brain illnesses (23). Considering EVs' inherent capabilities to transfer biomolecules intercellularly, shield their contents, and traverse the brain capillary endothelial cells or the BBB, they provide a promising platform for transporting mRNAs, miRNAs, medications, or proteins to the central nervous system . In light of these considerations, research into the potential of induced pluripotent stem (iPS) cells and other EVs produced from stem or progenitor cells to restore or revitalize brain function has been conducted (24).

3.5.1. Gene Therapy

Gene therapy approaches aim to correct defects in alternative disposal pathways. For example, upregulating LAMP-2A expression to boost CMA activity has potential therapeutic benefits in diseases characterized by protein aggregation. Enhancing the expression of key proteins involved in microautophagy and EV biogenesis could also be explored as a strategy to restore normal cellular function in various diseases. Researchers examine the role of genes in health or disease and for therapeutic development (6). Biology offers numerous strategies to change gene expression. A gene's expression can be elevated (as in gene therapy), reduced (as in RNAi or ASO), or eliminated (as in a permanent manner) using several methods. Other knock-out techniques, including as microRNAs, transcription activator-like effector nucleases (TALEN), and CRISPR-Cas9, are primarily used in the latter instance. The alternate pathway (AP) of the complement system is the intended target of these novel medicines (25). Additional gene-targeted therapy development for complement-mediated disease treatment will be possible if progress and clinical breakthroughs in treating rare or monogenetic disorders have been achieved.

4. Conclusion

Alternative cellular disposal pathways are integral to maintaining cellular homeostasis and are implicated in various diseases. Understanding these pathways provides insights into disease mechanisms and reveals novel therapeutic targets. Further research is needed to fully elucidate these pathways and translate findings into clinical applications. By continuing to explore and manipulate these pathways, we can develop new treatments for neurodegenerative diseases, cancer, and metabolic disorders, improving patient outcomes and quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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