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Review Article

A Comprehensive Review on the Role of Autophagy in Immunity

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Abstract

Autophagy, a cellular degradation process, is a key regulator of immune function, interacting with the major histocompatibility complex (MHC) and human leukocyte antigen (HLA) systems, and the NF-κB pathway. It encompasses three main types: macroautophagic, micro autophagy, and chaperone-mediated autophagy (CMA). Autophagy plays a crucial role in both innate and adaptive immunity, contributing to pathogen clearance, antigen presentation, and immune cell homeostasis. Dysregulation of autophagy has been implicated in autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (MS). Understanding the complex interplay between autophagy and immunity offers potential therapeutic targets for immunomodulation, paving the way for novel treatments for immune-related disorders. Further research is needed to unravel the intricate mechanisms of autophagy and its impact on immune cell function, ultimately leading to the development of effective therapies for autoimmune and inflammatory diseases.

INTRODUCTION

Autoimmune diseases present a significant and escalating health issue globally, characterized by the immune system's abnormal reaction against the body's own tissues [1]. Maladies like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) showcase the adverse impacts of an excessively active immune response, resulting in persistent inflammation, tissue harm, and an array of incapacitating symptoms. Grasping the fundamental mechanisms contributing to these conditions is essential for the development of efficacious treatments. One such mechanism is autophagy, a cellular degradation process that has emerged as a pivotal regulator of immune function [2].

Autophagy, originating from the Greek terms "auto" (self) and "phagy" (eating), is an intracellular degradation system that transports cytoplasmic components to the lysosome. This mechanism is indispensable for preserving cellular equilibrium by eliminating impaired organelles, misfolded proteins, and invading pathogens [3]. Initially perceived as a reaction to nutrient deficiency, autophagy has now been acknowledged for its diverse roles in cellular physiology, encompassing development, differentiation, and immune system regulation. Particularly, autophagy intersects with the major histocompatibility complex (MHC) and human leukocyte antigen (HLA) systems, which play a pivotal role in antigen presentation and immune identification [5]. Autophagy aids in the processing and display of antigens via MHC class I and II molecules, impacting the immune system's ability to differentiate self from non-self. Additionally, the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, responsible for regulating the expression of various immune and inflammatory genes, is influenced by autophagy, thereby impacting the overall immune response [6]. This paper aims to deliver a comprehensive summary of the current comprehension of autophagy within the realm of immunity, highlighting its intricate mechanisms and their consequences for health and disease.

TYPES OF AUTOPHAGY

Autophagy, a tightly regulated cellular process, encompasses several distinct types, each serving specific functions and responding to different cellular and environmental cues. Autophagy is divided into 3 types as shown in Figure 1.

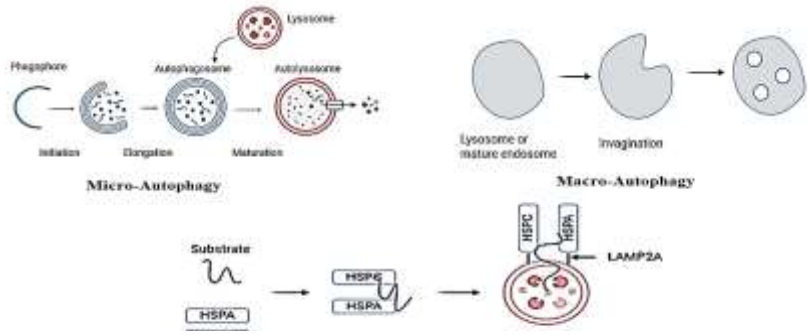

Figure 1 Types of Autophagy with their mechanism.

Macroautophagy:

Macroautophagy, commonly referred to as autophagy, is the most extensively studied and well-characterized form of autophagy. It involves the formation of double-membraned vesicles called autophagosomes, which engulf cytoplasmic components, including organelles, protein aggregates, and intracellular pathogens. Autophagosomes then fuse with lysosomes, forming autolysosomes, where the sequestered contents are degraded by lysosomal hydrolases. Macroautophagy plays a crucial role in cellular homeostasis, nutrient recycling, quality control, and response to stress conditions [7].

Microautophagy:

Micro autophagy involves the direct engulfment of cytoplasmic components by invaginations or protrusions of the lysosomal membrane. Unlike macroautophagy, which relies on the formation of autophagosomes, microautophagy directly delivers cytoplasmic cargo into the lysosomal lumen for degradation. Microautophagy can target various cellular constituents, including proteins, lipids, and organelles, and contributes to cellular remodeling, nutrient recycling, and organelle turnover [8].

Chaperone-Mediated Autophagy (CMA):

Chaperone-mediated autophagy (CMA) is a selective form of autophagy that specifically targets soluble cytosolic proteins for lysosomal degradation. CMA relies on a specific recognition motif, the KFERQ-like motif, present in target proteins. These proteins are recognized by a cytosolic chaperone, Hsc70 (heat shock cognate protein of 70 kDa), which facilitates their translocation to the lysosomal membrane. At the lysosomal membrane, the target proteins are recognized by lysosome-associated membrane protein type 2A (LAMP-2A), which forms a translocation complex allowing the substrate to enter the lysosomal lumen. Once inside the lysosome, the substrate is degraded by lysosomal proteases. CMA plays a crucial role in maintaining protein homeostasis, particularly during periods of cellular stress and metabolic demand [9].

MOLECULAR PATHWAY OF AUTOPHAGY

Autophagy is a tightly regulated cellular process essential for maintaining cellular homeostasis and responding to various stress conditions. The core mechanism involves the formation of autophagosomes, double-membraned vesicles that engulf cytoplasmic components, followed by their fusion with lysosomes where the contents are degraded and recycled. The regulation and execution of autophagy involve a complex network of signaling pathways and autophagy-related genes (ATGs) [10].

The initiation of autophagy begins with the activation of the ULK1 (Unc-51 Like Autophagy Activating Kinase 1) complex, a critical regulator of autophagy induction. This complex comprises ULK1/2, ATG13, FIP200, and ATG101. Nutrient status and energy levels tightly regulate the ULK1 complex through mTOR and AMPK pathways. Under nutrient-rich conditions, active mTOR inhibits the ULK1 complex, preventing autophagy. Conversely, nutrient deprivation activates AMPK, promoting autophagy initiation by inhibiting mTOR and directly activating the ULK1 complex [11].

The nucleation step involves the recruitment of the class III PI3K complex, crucial for phagophore formation. This complex includes VPS34, Beclin-1, p150, and ATG14L, generating PI3P at the

nascent phagophore to recruit downstream effectors for membrane expansion. Elongation and maturation of the autophagosome involve two ubiquitin-like conjugation systems: the ATG12–ATG5–ATG16L1 complex and LC3 conjugation. LC3-I is conjugated to PE to form LC3-II, essential for membrane expansion and closure [12].

The completed autophagosome fuses with a lysosome to form an autolysosome, mediated by SNARE proteins, the HOPS complex, and Rab7. This fusion exposes the inner membrane and contents to lysosomal hydrolases, leading to degradation. Signaling pathways like mTOR, AMPK, NF-κB, PI3K/Akt, and p53 integrate various cues to regulate autophagy, balancing cellular responses to growth factors, energy status, and stress [11,12].

ROLE OF AUTOPHAGY IN IMMUNITY

Autophagy, a fundamental cellular process, plays a critical role in regulating immunity by influencing various aspects of both innate and adaptive immune responses. In innate immunity, autophagy serves as a frontline defense mechanism against microbial pathogens. Through a process known as xenophagy, autophagy selectively engulfs and degrades intracellular pathogens, such as bacteria, viruses, and parasites, within specialized vesicles called autophagosomes. This clearance of pathogens helps to prevent the replication and spread of infections, thereby bolstering the host's innate immune defenses and promoting microbial clearance. Moreover, autophagy contributes to the regulation of inflammation by modulating the production of pro-inflammatory cytokines and dampening excessive immune responses. By maintaining immune homeostasis, autophagy helps to prevent immunopathology and ensures an appropriate balance between protective immunity and tissue damage [13].

Autophagy in Innate Immunity:

Autophagy plays a pivotal role in innate immunity by interacting with pattern recognition receptor (PRR) signaling pathways, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which detect microbial components. By modulating the intensity and duration of PRR signaling, autophagy influences the production of inflammatory cytokines and interferons. Additionally, autophagy targets and degrades inflammasome components, suppressing excessive activation and subsequent release of pro-inflammatory cytokines like IL-1β and IL-18. Furthermore, autophagy influences the production and secretion of antimicrobial peptides (AMPs) by immune cells, contributing to innate defense mechanisms [14].

Autophagy in Adaptive Immunity:

Autophagy plays a pivotal role in cross-presentation, where antigens from extracellular sources are presented on MHC class I molecules to CD8+ T cells, critical for activating CTL responses against viruses and tumors. Autophagy also regulates the differentiation of naïve T cells into subsets like Th1, Th2, Th17, and Tregs by influencing metabolic reprogramming and signaling pathways, impacting the balance between pro-inflammatory and anti-inflammatory responses. Furthermore, autophagy is essential for the survival and maintenance of memory T cells, crucial for long-term immunity against reinfection [15].

Antigen Presentation by Autophagy:

Autophagy orchestrates antigen presentation by contributing to the turnover

of self-proteins for presentation on MHC class I molecules and by facilitating the delivery of exogenous antigens to lysosomes for processing and subsequent loading onto MHC class II molecules. These pathways are essential for immune surveillance against transformed cells and adaptive responses against extracellular pathogens, respectively [16].

Modulation of Inflammation by Autophagy:

Autophagy modulates inflammation by suppressing excessive inflammation through the degradation of signaling molecules involved in inflammatory pathways, while also contributing to the resolution of inflammation by clearing cellular debris and damaged organelles [17].

Maintenance of Immune Cell Homeostasis:

Autophagy plays critical roles in macrophage polarization and function, influencing the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophages. It also regulates dendritic cell maturation and antigen presentation, essential steps in initiating adaptive immune responses. Additionally, in lymphocytes, autophagy maintains energy homeostasis, supports cell survival, and regulates the differentiation and effector functions of B and T cells. Overall, autophagy is indispensable for the proper functioning of the immune system, impacting various cellular processes essential for immune responses and maintaining immune homeostasis [18].

AUTOPHAGY DYSREGULATION IN AUTOIMMUNE DISEASE

Autophagy, the cellular process of self-eating and recycling, plays a complex and multifaceted role in autoimmune diseases. While it's essential for maintaining immune balance, its dysregulation can contribute to the development and progression of these conditions.

Mechanisms of Autophagy Dysregulation [19]:

a) Genetic Factors:

Genetic variations in autophagy-related genes (ATGs) can significantly impact the autophagic process, predisposing individuals to autoimmune diseases. For instance, polymorphisms in ATG5 have been associated with systemic lupus erythematosus (SLE), altering autophagic flux and immune cell homeostasis. Similarly, variations in other ATGs, such as ATG16L1 and IRGM, have been linked to inflammatory bowel diseases (IBD), affecting autophagy-mediated defense mechanisms against intracellular pathogens in the gut.

b) Environmental Triggers:

Environmental factors play a crucial role in modulating autophagy and can contribute to its dysregulation in autoimmune diseases. Various triggers, including microbial infections, exposure to environmental toxins, and psychological stress, can disrupt autophagic processes. For example, viral infections can impair autophagosome formation or maturation, leading to the accumulation of viral particles and triggering autoimmunity through molecular mimicry or bystander activation. Additionally, exposure to environmental toxins, such as cigarette smoke or air pollutants, can induce oxidative stress and inflammation, compromising autophagic function and exacerbating autoimmune responses. Moreover, psychological stressors can activate the hypothalamic-

pituitary-adrenal (HPA) axis and sympathetic nervous system, which may dysregulate autophagy through altered signaling pathways, further contributing to autoimmune pathogenesis.

c) Immune Cell-Specific Dysregulation:

Autophagy dysregulation in specific immune cell populations can have profound consequences for immune responses and autoimmune diseases. Immune cells, including dendritic cells (DCs), macrophages, and lymphocytes, rely on autophagy for various functions, such as antigen presentation, cytokine production, and cell survival. Dysfunctional autophagy in DCs can impair antigen processing and presentation, leading to defective immune tolerance and enhanced autoimmune responses. Similarly, defective autophagy in macrophages may compromise their antimicrobial activity and promote inflammation, contributing to autoimmune tissue damage. Moreover, dysregulated autophagy in lymphocytes can disrupt immune cell homeostasis, favoring the expansion of autoreactive T and B cell populations and exacerbating autoimmune pathologies.

Consequences of Autophagy Dysregulation [20]:

Autophagy plays a critical role in the clearance of apoptotic cells, a process known as efferocytosis, which is essential for maintaining tissue homeostasis and preventing the release of self-antigens. When autophagy is dysregulated, it can impair efferocytosis, leading to the accumulation of apoptotic debris and the exposure of self-antigens to the immune system. This aberrant presentation of self-antigens can trigger autoimmune responses, contributing to the development and progression of autoimmune diseases. Additionally, autophagy is intricately involved in antigen processing and presentation, influencing immune responses and self-tolerance. Dysregulated autophagy can disrupt the proper processing of self-antigens, leading to altered peptide presentation on major histocompatibility complex (MHC) molecules. This altered antigen presentation may activate autoreactive T cells, initiating autoimmune attacks against self-tissues. Furthermore, dysregulated autophagy can affect the presentation of microbial antigens, potentially leading to inappropriate immune responses and autoimmunity.

Autophagy also plays a crucial role in maintaining T cell homeostasis by regulating T cell survival, differentiation, and function. Dysregulated autophagy can perturb T cell homeostasis, leading to the dysregulation of immune responses and the development of autoimmune diseases. For example, impaired autophagy may disrupt the balance between regulatory T cells (Tregs) and effector T cells, favoring the expansion of autoreactive T cell subsets and promoting autoimmunity. Additionally, dysregulated autophagy can compromise T cell survival and function, contributing to immune dysregulation and autoimmune pathogenesis. Moreover, autophagy dysfunction can result in the accumulation of damaged cellular components and the activation of inflammatory pathways, leading to increased production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). These cytokines can promote inflammation and tissue damage, exacerbating autoimmune diseases. Dysregulated autophagy can also impair the

clearance of pro-inflammatory cytokines, further perpetuating inflammation and contributing to autoimmune pathogenesis.

Autoimmune Diseases Associated with Autophagy Dysregulation

Autophagy dysregulation has been implicated in various autoimmune diseases, significantly impacting their pathogenesis through altered immune responses and inflammation. Systemic Lupus Erythematosus (SLE) is marked by dysregulated immune responses against self-antigens, leading to widespread inflammation and tissue damage. Impaired autophagy in SLE is linked to genetic variations in autophagy-related genes such as ATG5, resulting in decreased autophagic activity in lymphocytes and monocytes. This impairment contributes to the accumulation of cellular debris and self-antigens, promoting autoimmune responses and inflammation. Similarly, in Rheumatoid Arthritis (RA), autophagy dysregulation in synovial fibroblasts and T cells plays a critical role. Impaired autophagy in synovial fibroblasts can lead to increased production of pro-inflammatory cytokines and resistance to apoptosis, contributing to synovial hyperplasia and joint inflammation. Dysregulated autophagy in T cells further exacerbates inflammatory responses and tissue damage in RA [20,21].

Inflammatory Bowel Disease (IBD), including Crohn's disease and ulcerative colitis, is characterized by chronic inflammation of the gastrointestinal tract, with autophagy playing a crucial role in maintaining intestinal homeostasis. Dysregulation of autophagy in IBD has been linked to genetic variations in autophagy-related genes such as ATG16L1, increasing the risk of Crohn's disease. Impaired autophagy in intestinal epithelial cells can disrupt mucosal barrier function and immune regulation, contributing to intestinal inflammation and tissue damage. In Multiple Sclerosis (MS), autophagy dysregulation in T cells and microglia, the resident immune cells of the central nervous system (CNS), has been implicated in the disease's development. Impaired autophagy in T cells can lead to increased T cell survival and pro-inflammatory responses within the CNS, contributing to neuroinflammation and tissue damage. Similarly, dysregulated autophagy in microglia impairs their ability to clear cellular debris and regulate immune responses, exacerbating inflammation and neuronal injury in MS [20,21].

THERAPEUTIC IMPLICATION AND FUTURE DIRECTION

The therapeutic implications of autophagy in immunity are substantial, offering potential treatments for a range of diseases. Inducing autophagy can enhance the clearance of intracellular pathogens, making it a promising strategy for combating infectious diseases. For autoimmune disorders, drugs like rapamycin that promote autophagy can help degrade autoreactive immune cells, thereby reducing disease severity in conditions such as systemic lupus erythematosus. Conversely, inhibiting autophagy can be advantageous in certain cancers where tumor cells use this process for survival, allowing for more effective cancer therapies.

Future directions in therapeutic research should focus on developing specific autophagy modulators with minimal side effects. Exploring combination therapies that integrate autophagy modulation with

other immune-targeting treatments could enhance their efficacy. Additionally, a deeper understanding of the molecular mechanisms by which autophagy influences immunity will aid in designing targeted therapies, potentially leading to significant clinical benefits across various immune-related conditions.

CONCLUSION

Autophagy is crucial for immune homeostasis, pathogen clearance, and antigen presentation, with its dysregulation linked to autoimmune diseases like SLE, RA, IBD, and MS. Understanding its role offers insights into disease mechanisms and potential therapeutic targets. However, the complexity of autophagy pathways poses challenges, necessitating further research to unravel these mechanisms and develop effective treatments. Future directions include developing non-invasive biomarkers, identifying therapeutic targets, and understanding role of autophagy in immune cells. Collaboration across disciplines, ethical considerations, and patient advocacy are vital for advancing autophagy-targeted therapies and improving patient care.

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