Role of autophagy in immune regulation

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Abstract

Autophagy is a highly conserved protein degradation pathway responsible for removal of damaged organelles, malformed proteins during biosynthesis, and nonfunctional long-lived proteins by lysosome. Autophagy has been divided into three general types depending on the mechanism by which intracellular materials are delivered into lysosome for degradation that is, microautophagy, chaperone mediated autophagy (CMA), and macroautophagy. Numerous studies reveal autophagy and autophagy related proteins also participate in immune regulation. in this review we summarized current understanding of the roles of autophagy and autophagy proteins in immune regulation.

Introduction

1.1. Autophagy pathways

Autophagy is the only known conserved protein degradation pathway other than the ubiquitin-proteasome system (UPS). There are three major types of autophagy: 1) macroautophagy (referred as autophagy in general), 2) chaperone mediated autophagy (CMA), and 3) microautophagy.

1.2. Microautophagy

Microautophagy involves direct lysosomal engulfment of cytoplasmic cargo without forming autophagosomes, which is essential for cell survival when cells are under stress such as nutrient starvation, microautophagy has been shown to regulate synaptic protein turnover in neurons and thus defects in microautophagy may result in accumulation of dysfunctional proteins and cause neurodegenerative disorders ***(Uytterhoeven et al, 2015).***

1.3. Macroautophagy

Macroautophagy involves phagophore formation, autophagosome formation, and fusion of autophagosomes and lysosomes to form autolysosomes for protein degradation.Phagophore is an isolation membrane, which may derive from the endoplasmic reticulum (ER) or mitochondria. Phagophore can recruit and enclose cytoplasmic components selectively or non-selectively to form a double layer membrane vesicle called autophagosome. Autophagosome later fuses with the lysosome and forms the autolysosome where degradative enzymes break down cytoplasmic components. The formation of the double membrane vesicle is a complex process involving 16 autophagy-related proteins (Atg proteins) **(Badadani, *2012*)**.

1.4. Chaperone-mediated autophagy

Chaperone-mediated autophagy (CMA) is another type of autophagy that does not involve the formation of autophagosomes. CMA involves several steps including 1) substrate recognition and lysosomal targeting, 2) substrate binding and unfolding, 3) substrate translocation and substrate degradation in CMA proteins flagged with pentapeptide motif (KFERQ) were selectively degraded through direct translocation into lysosome ***(Cuervo and Wong, 2014***)

2. Autophagy in the immune system

Autophagy plays four principle roles in the immune system including 1) removal of intracellular pathogens,

2) secretory pathway, 3) lymphocyte development, and 4) pro-inflammatory signaling ***(Deretic et al., 2013)***.

2.1. Intracellular pathogens removal

Autophagy remove intracellular pathogens through two pathways. The first is xenophagy that includes formation of double-membrane autophagosomes that engulf intracellular pathogens. The second is LC3-associated phagocytosis (LAP) that is characterized by formation of single membrane phagosomes decorated with LC3 that enclose pathogens. Those vesicles then fuse with lysosomes to form autolysosomes or autophagolysosomes for degradation of intercellular pathogens ***(Klionsky et al., 2014)***.

2.2. Role of autophagy in secretory pathway

Phagocytosis like secretory pathway in vesicle trafficking and membrane fusion. Therefore,the autophagy pathway/autophagy proteins that play roles in phagocytosis also participate in secretory pathways. For instance, mice deficient in autophagy-related protein 5 (ATG5fl/fl LysM Cre+) present high level of IL-1α secreted by macrophages in vitro and in vivo, which lead to excessive inflammatory responses [33]. Furthermore, Inhibition of autophagy in antigen presenting cells also leads to elevated IL-23 secretion as a consequential event of increased IL-1 β level ***(Peral et al, 2012)***.

2.3. Lymphocyte development and autophagy

Lymphocytes including T cells and B cells are important for adaptive immunity. Lymphocyte development requires proper activation, and defective activation may result in autoimmunity. Proper T cell activation requires antigen presentation via the major histocompatibility complex (MHC) molecules I, II that reside on the cell surface to display antigens. MHC class I are found on all nucleated cells and MHC class II are found in antigen presenting cells (APCs) including macrophages, dendritic cells and B cells. To enable proper presentation of antigens, peptides derived from intracellular or extracellular proteins need to be digested or processed via degradation pathways including the ubiquitin proteasome
system and autophagy ***(Cooney et al., 2010).***

B cells can differentiate into plasma cells that are responsible for generating autoantibodies and are critical for autoimmunity. It was previously shown that ATG5 is required for B cell survival during development and for the maintenance of B cell subset (B-1a) in the periphery and plasma cells require autophagy for sustainable immunoglobulin production Defective or overactive autophagy modulates B cell development and function and therefore contributes to autoimmunity ***(Pengo et al., 2013).***

2.4. Autophagy in pro-inflammatory signaling

Autophagy can modulate survival and pro-inflammatory signaling via many pathways including NF-κB activation in many cell types. Since autophagy plays multiple roles in the immune system, disturbances in autophagic activity are likely to affect the development of autoimmunity ***(Kanayama et al., 2015)***.

3. Conclusion

Autophagy is a conserved cellular degradation pathway. Recent evidence ranging from genome-wide association studies to basic in vivo and in vitro research have linked the autophagy pathways and/or autophagy-related proteins to autoimmunity. Crosstalk between autophagy and immune system includes removal of intracellular pathogens, secretory

pathway, lymphocytes development, and pro inflammatory signaling. Distinguishing the autophagy-related protein's roles in autophagy or other cellular mechanisms in autoimmune disease pathologies remains to be a challenge.

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