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Autophagy and proinflammatory cytokines: Interactions and clinical implications

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ABSTRACT

Autophagy is a ubiquitous cellular process that regulates cell growth, survival, development and death. Its process is closely associated with diverse conditions, such as liver diseases, neurodegenerative diseases, myopathy, heart diseases, cancer, immunization, and inflammatory diseases. Thus, understanding the modulation of autophagy may provide novel insight into potential therapeutic targets. Autophagy is closely intertwined with inflammatory and immune responses, and cytokines may help mediate this interaction. Autophagy has been shown to regulate, and be regulated by, a wide range of proinflammatory cytokines. This review aims to summarize recent progress in elucidating the interplay between autophagy and proinflammatory cytokines, including IFN-γ, TNF-α, IL-17, and cytokines of the IL-1 family (e.g., IL-1α, IL-1β, IL-33, and IL-36).

1. Introduction

In the late 1950s, autophagy was first described as a cellular response to nutrient deprivation that allows removal of damaged organelles [1]. Autophagy is now appreciated as being crucial for cell homeostasis and survival. Generally, the autophagic cascade occurs constitutively at a basal level in various cells and is initiated under stress conditions, such as endoplasmic reticulum stress (ERS), growth factor withdrawal, nutrient deprivation, mitochondrial damage, and inflammation [2–4]. Various subcategories of autophagy have been defined: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy. During CMA, cytosolic target substrate incorporate the chaperone protein which contains a Lys-Phe-Glu-Arg-Gln (KFERQ)-like pentapetide motif via the recognition of heat shock cognate 70 kDa protein (HSC70). Next, HSC70 triggers the delivery of the cargo into the lysosomal lumenin a lysosomal-associated membrane protein 2A (LAMP2A) receptor-dependent manner [1]. Microautophagy refers to the translocation of substrate into lysosome for degradation via either direct protrusion, invagination, or septation of lysosomal. In macroautophagy, the formation of autophagosomes, the double membrane-bound vesicles, which engulf organelles, cytoplasmic proteins, or other materials. The autophagosomes are transported to lysosomes for the form of autolysosomes [3]. In all three types, the target cargos are ultimately degraded by hydrolases. This review focuses on macroautophagy, which is herein termed simply autophagy.

Proinflammatory cytokines have crucial influences on systemic immune and inflammatory responses. These evolutionarily conserved cytokines are generated by innate and adaptive immune cells and regulate their function and survival. The interplay between autophagy and cytokines may be a fundamental mechanism coordinating the activity of the innate and adaptive immune systems [5,6]. Different cytokines can regulate autophagy levels. For example, the proinflammatory cytokine interferon (IFN)-γ triggers autophagy to eliminate invading pathogens, such as *Mycobacteria* and *Chlamydia* [7,8]. Autophagy is also induced by interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-17, and IL-6, whereas the process is blocked by IL-13, IL-33, IL-10, and IL-4. At the same time, autophagy can modulate cytokine production and secretion. Because proinflammatory cytokines and

Abbreviations: ATG, autophagy-related proteins; CMA, chaperone-mediated autophagy; ULK1, Unc-51-like kinase 1; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; PE, phosphatidylethanolamine; IFN-γ, interferon-γ; IL-1, interleukin-1; IL-17, interleukin-17; IL-33, interleukin-33; IL-36, interleukin-36; PRR, pattern recognition receptor; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; NLR, NOD-like receptor; RLR, (RIG-1)-I-like receptor; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; LPS, lipopolysaccharide; APC, antigen presenting cell; MHC, major histocompatibility complex; STAT, signal transducer and activation of transcription; MAPK, mitogen-activated protein kinase; DC, dendritic cell; PBMC, peripheral blood mononuclear cells; JNK, c-Jun amino-terminal kinase; ERK, extracellular signal-regulated kinase; 3-MA, 3-methyladenine; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress

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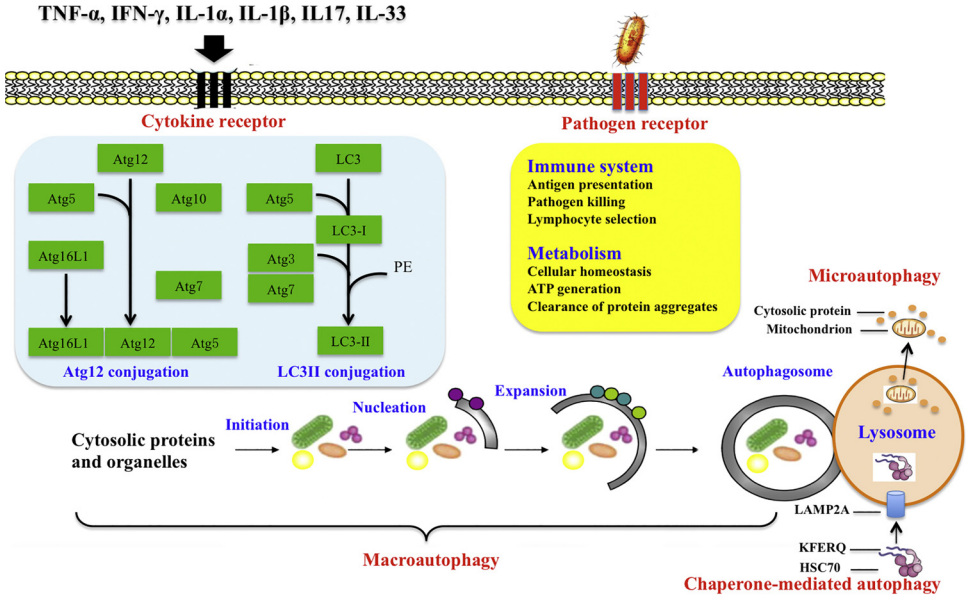

Fig. 1. Autophagic pathways in eukaryotic cells and their roles in cellular survival (e.g., homeostasis, metabolism, and the immune system) and cell death.
Generally, autophagy is classified into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Inmacroautophagy, cytoplasmic material is sequestered into a pre-autophagosomal membrane structure called the phagophore, in the presence of an autophagic inducer (e.g., cytoplasmic material, cytokines). The phagophore membrane then expands and encloses its cargo to form a double-membrane vesicle, the autophagosome. The autophagosome fuses with a lysosome (or, in yeast, a vacuole) to form an autolysosome. In microautophagy, cytoplasmic materials are trafficked to lysosome via direct protrusion or invagination at the lysosomal membrane. In CMA, the cytosolic target substrate binds to Lys-Phe-Glu-Arg-Gln (KFERQ)-like pentapetide motif dependent on the recognition of heat shock cognate 70 kDa protein (HSC70) and then was delivered into lysosomes via lysosomal-associated membrane protein 2A (LAMP2A) receptor. In all three forms of autophagy, their cargos are degraded by acid hydrolases in the end. After the resulting macromolecules are transported back into the cytosol through membrane permeases, they can either be used to synthesize proteins or oxidized by the mitochondria to generate ATP for cell survival. However, when autophagy occurs at excessive levels or under certain physiological conditions, it can lead to type II programmed cell death (PCD). See the text for additional details.

autophagy play key roles in the pathophysiology of disease, crosstalk between them has become a key research topic and an area of substantial progress.

2. Overview of the autophagic pathway

In autophagy, lysosomal proteolysis disposes of aged or aberrant organelles and proteins. Double-membrane vesicles, called autophagosomes or autophagic vacuoles, target and engulf denatured proteins or damaged organelles [9–11] via a multi-step process involving initiation, vesicle nucleation, vesicle expansion and completion, which have been extensively studied (Fig. 1). At least 30 autophagy-related genes (Atgs) have been identified in yeast, and mammalian orthologs of various Atgs have been shown to modulate autophagy [12,13].

In the initial stages of autophagy, the Atg1 complex is activated. In yeast, the Atg1 complex is composed of the Atg17-Atg31-Atg29 subcomplex, Atg1, and Atg13. In mammals, this complex, also known as the Unc-51-like kinase (ULK) complex, refers to the mammalian Atg1 homolog ULK1 or ULK2, mammalian autophagy -related13 homolog (Atg13, a putative counterpart of yeast Atg17), RB1-inducible coiled-coil 1 (RB1CC1), and Atg101 [14,15]. During the vesicle nucleation stage, a phosphatidylinositol 3-kinase (PI3K) complex composed of vacuolar protein sorting 34 (Vps34), Beclin-1, and Atg14 must be activated. The primary function of this complex is to recruit Atg proteins to the phagophore assembly site (PAS). For vesicle expansion and completion, the isolation membrane elongates as the PAS expands via the actions of two ubiquitin-like (UbI) conjugation systems: the conjugate of Atg12-Atg5-Atg16L1, and the conjugate of phosphatidylethanolamine (PE)-microtubule-associated protein 1 light chain 3 (LC3, also known as Atg8). In the final stages of autophagy, the mature autophagosome fuses with the lysosome to form the autolysosome, in which the cargo is degraded by hydrolases. The end products are released back into the cytosol [16,17].

3. Interactions of autophagy with immunity and inflammation

3.1. Autophagy and immunity

Autophagy may be a primordial form of eukaryotic innate immunity [18]. Currently, autophagy is believed to be important for clearing pathogens via autolysosome-dependent degradation and for modulating innate as well as adaptive immunity.

Adaptive immunity depends on the recognition of extra- or intracellular peptide epitopes presented by major histocompatibility complex (MHC) class I and II molecules, which are identified by $CD4^+$ and $CD8^+$ T cells [19–22]. As a result of this recognition, autophagy promotes the trafficking of extracellular antigens (e.g., microbial antigens) to endosomes, where they are loaded onto MHC class II molecules and subsequently transported to the plasma membrane, and presented as antigens to $CD4^+$ T cells [23]. Meanwhile, autophagy accelerates antigen loading onto MHC class I molecules, which prime antigen-specific $CD8^+$ T cells. This promotes antigen "cross-presentation", which is crucial for activating T cell response [24,25]. In this way, autophagy can regulate lymphocyte development and functional diversification. In fact, autophagy plays multiple roles in the immune system, and activation of autophagy can facilitate pathogen clearance.

3.2. Autophagy and inflammation

Autophagy and inflammation are two crucial biological processes associated with physiological and pathophysiological states. Notably, autophagy is essential for regulating the inflammatory response [26,27]. Sufficient pathogen recognition can drive the inflammatory response, leading to recruitment of immune cells. Production of chemo- and cytokines recruits other immune cells and simultaneously activates dendritic cells (DCs) involved in the adaptive immune response [28,29]. Pathogen-associated molecular patterns (PAMPs) may improve autophagic activation by triggering signaling pathways involving the mammalian target of rapamycin (mTOR) and adenosine monophosphate-activated protein kinase (AMPK).

Toll-like receptors (TLRs) trigger pathways that induce autophagy in macrophages as well as other cell types [30]. For example, TLR4 activation leads to the ubiquitination of TNF receptor-associated factor 6 (TRAF6)/BECN1/Beclin-1. TRAF6 also activates the upstream autophagic activator ULK1. In addition to TLRs, nucleotide-binding oligomerization domain2 (NOD2) can induce autophagy in DCs and target Atg16 L1 to the plasma membrane at the site of bacterial entry [31,32].

Autophagy is critical for a well-balanced inflammatory response,