Regulation of inflammasomes by autophagy

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Inflammasomes detect pathogen-associated molecular patterns to induce inflammatory innate immune responses and play a key role in host defense against infectious agents. However, inflammasomes are often wrongly activated by metabolites, amyloids, and environmental irritants. This induces massive inflammation, causing severe tissue damage, and results in the development of inflammatory diseases. Hence cellular machineries regulating both "activation" and "inactivation" of inflammasomes are definitely important. Recent studies have shown that autophagy, an intracellular degradation system associated with maintenance of cellular homeostasis, plays a key role in inflammasome inactivation. Notably, autophagy deficiency caused by gene mutation disrupts organelle elimination and thus induces aberrant activation of inflammasomes, leading to severe tissue damage. Here we review recent findings regarding the involvement of autophagy in the regulation of inflammasome activation and development of inflammatory disorders. (J Allergy Clin Immunol 2016;138:28-36.)

Key words: *Autophagy, host defense, inflammasome, inflammatory disorders, innate immunity, macrophages, organelle, pattern recognition receptors, reactive oxygen species, signal transduction*

Abbreviations used

AIM2:	Absent in melanoma 2
ASC:	Apoptosis-associated speck-like protein containing caspase recruitment domain
ATG proteins:	Autophagy-related proteins
ER:	Endoplasmic reticulum
NLR:	NOD-like receptor
NLRP3:	NLR family, pyrin domain containing 3
PRR:	Pattern recognition receptor
ROS:	Reactive oxygen species
TLR:	Toll-like receptor

Autophagy is an intracellular degradation system that delivers cytoplasmic constituents into the lysosome.[1,2] Autophagy activity is maintained at relatively low levels under steady-state conditions but is potently induced by various cellular stressors, such as organelle damage and pathogen infection. The autophagosome, a double-membraned organelle, plays an important role in autophagic degradation. Autophagy induction is accompanied by emergence of the isolation membrane, also called the phagophore. Endoplasmic reticulum (ER) and mitochondria, especially mitochondria-associated ER membrane, provide a membrane source for the isolation membrane. The autophagosome, which is formed by elongation and closure of the isolation membrane, engulfs a portion of the cytoplasm and subsequently fuses with the lysosome to form the autolysosome. This leads to degradation of the autolysosome contents, as well as the inner membrane, by lysosomal degradation enzymes (Fig 1).

Accumulating evidence shows that autophagy is involved in various biological processes.[3-5] Steady-state autophagy promotes turnover of the organelles, such as mitochondria, and contributes to maintenance of cellular homeostasis. Autophagy is induced under nutrient-starved conditions and contributes to reuse of cytoplasmic constituents, such as amino acids and lipids. Autophagy is also induced by organelle stress and pathogen infection, contributing to elimination of damaged organelles and pathogens. Additionally, autophagy regulates cell conditions, death, differentiation, and tumorigenesis and is closely associated with high-order cell functions, such as immune response and host defense.

The innate immune system is activated after infection by pathogens and induces inflammation to protect the host.[6] Pattern recognition receptors (PRRs) are key players of the innate immune system, sensing microbial components, such as LPS and flagellin, and play a critical role in induction of inflammatory response. After sensing microbial components, PRRs induce signal transduction pathways that cause activation of transcription factors, such as nuclear factor κB and interferon regulatory factors. These transcription factors induce expression of inflammatory mediators,

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Supported in part by the Japan Society for the Promotion of Science KAKENHI (grant nos. 15H01380, 26111514, and 26713005); the Japan Agency for Medical Research and Development, Core Research for Evolutional Science and Technology; a research grant of the Japan Foundation for Pediatric Research; a research grant of the LOTTE Foundation; a research grant of the Takeda Science Foundation; a research grant of the Mochida Memorial Foundation for Medical and Pharmaceutical Research; a research grant of the Naito Foundation; and a research grant of the Tokyo Biochemical Research Foundation (all to T.S.).

Disclosure of potential conflict of interest: T. Saitoh has received research support from the Japan Society for the Promotion of Science KAKENHI (grant nos. 15H01380, 26111514, and 26713005), the Japan Agency for Medical Research and Development, Core Research for Evolutional Science and Technology, the Japan Foundation for Pediatric Research, the LOTTE Foundation, the Takeda Science Foundation, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, the Naito Foundation, the Tokyo Biochemical Research Foundation, Eisai, and Ono Pharmaceutical. S. Akira has received research support from the Japan Society for the Promotion of Science KAKENHI (grant no. 15H05704) and the National Institutes of Health (PO1 Project).

Received for publication May 3, 2016; revised May 17, 2016; accepted for publication May 18, 2016.

Available online May 24, 2016.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.05.009

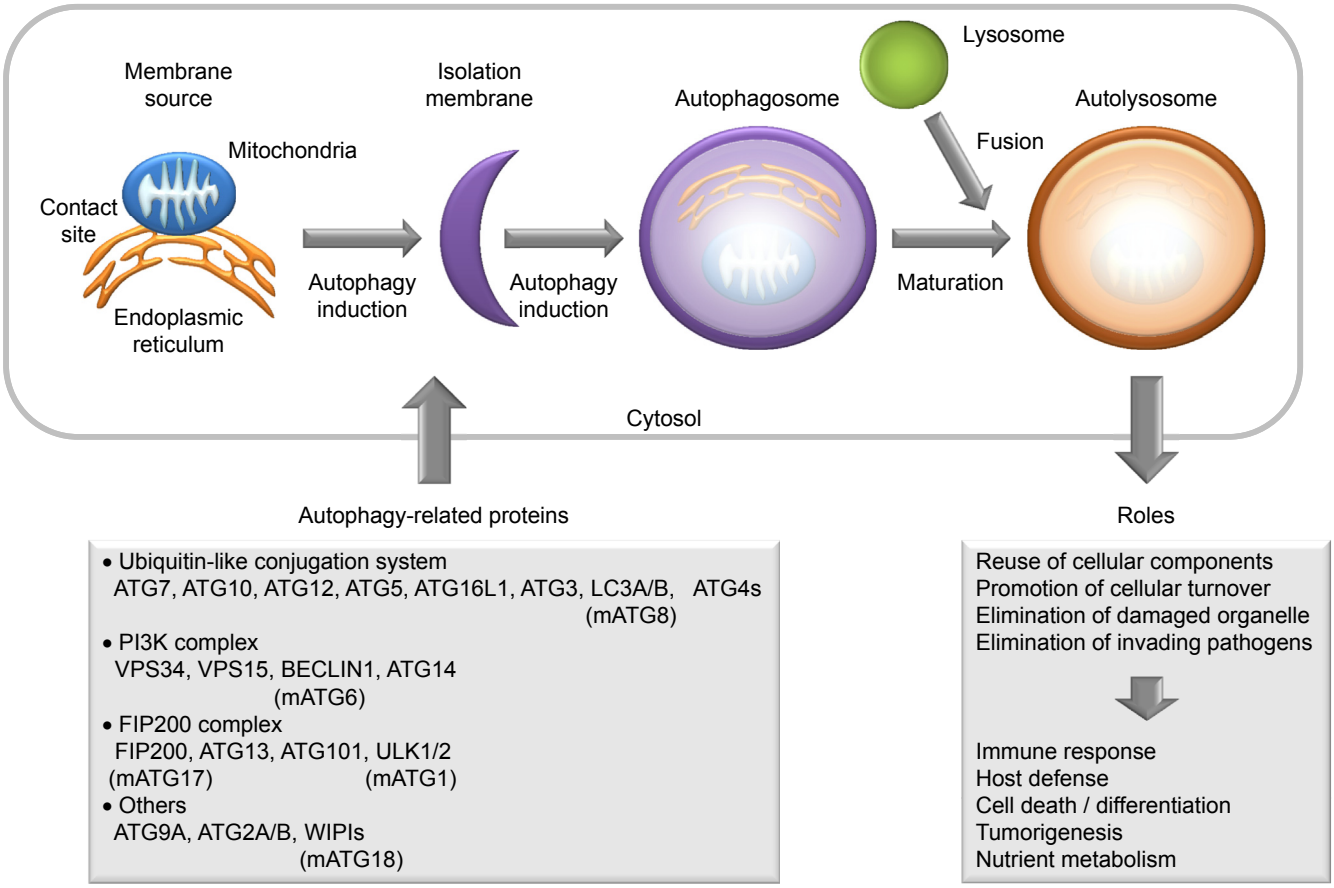

FIG 1. Autophagy. The isolation membrane appears after exposure to stressors. The ER-mitochondria contact site is a membrane source for the isolation membrane. The isolation membrane elongates and engulfs cytosolic constituents to form the autophagosome, which fuses with lysosomes to form the autolysosome, resulting in degradation of the engulfed constituents. Autophagy promotes reuse of cellular components, turnover of old organelles, and elimination of unfavorable materials, thus playing a vital role in maintenance of cellular homeostasis and disease prevention. ATG proteins drive membrane trafficking necessary for the generation of isolation membrane and autophagosomes.

such as cytokines, chemokines, and type I interferons. PRRs also induce activation of inflammatory proteases, leading to production of processed mature cytokines. Although inflammation is essential for host defense, wrongly induced inflammation often causes the development of inflammatory diseases, such as septic shock, autoimmune diseases, and metabolic diseases.[7] Therefore rigorous control of the innate immune system is required to prevent insufficient or excessive inflammatory responses. A growing body of evidence has shown that intracellular degradation systems play an important role in this regulation, in which autophagy has been recognized as critically involved in innate immune responses mediated by Toll-like receptors (TLRs), retinoic acid–inducible gene I–like receptor, cyclic guanosine monophosphate–adenosine monophosphate synthase, and inflammasomes.[4,8-18] In this review we discuss recent advances in the understanding of autophagy and the inflammatory innate immune response, especially inflammasome activation.

IDENTIFICATION AND FUNCTION OF AUTOPHAGY-RELATED PROTEINS

Autophagic structures were first reported through electron microscopy studies in the 1950s, and contributors to autophagosome formation were identified by means of yeast genetic screening in the 1990s.[19-22] Essential components of autophagosome formation are called autophagy-related proteins (ATG proteins). At present, 38 ATG proteins have been identified in yeast. Core ATG proteins are phylogenetically highly conserved. Mammalian counterparts, such as ULK1 (mammalian ATG1), ATG3, ATG4s, ATG5, BECLIN1 (mammalian ATG6), ATG7, LC3A/B (mammalian ATG8), ATG9A, ATG10, ATG12, ATG13, ATG14, ATG16L1, FIP200 (mammalian ATG17), and WIPIs (mammalian ATG18), have been identified. Hence autophagy is an evolutionarily conserved machinery for maintenance of cellular homeostasis.

Core ATG proteins are classified into several functional units, such as the FIP200 complex; the class III phosphoinositide 3-kinase complex; and the ATG7-mediated, ubiquitin-like conjugation system (Fig 1). The coordinated action of functional ATG protein units induces the membrane-trafficking events responsible for isolation membrane formation and subsequent autophagosome formation. Mice lacking ATG3, ATG5, ATG7, or ATG16L1 have been observed to die shortly after birth because of poor nutrition and energy depletion; therefore autophagy-dependent maintenance of cellular homeostasis is required for survival. On the other hand, mice lacking BECLIN1 and FIP200 show early embryonic lethality. Thus ATG proteins have additional functions beyond simply inducing autophagosome formation.