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Review

The role of autophagy in the pathogenesis of systemic lupus erythematosus

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ABSTRACT

Autophagy is a highly conserved catabolic process, whereby unwanted cytoplasmic contents are enclosed by the double-membrane autophagosomes and delivered to the lysosomes for degradation. It is responsible for the recycling of nutrients and cellular components, thus playing a pivotal role in maintaining cellular homeostasis as well as cell survival during stress conditions. Perturbations in autophagy are implicated in multiple diseases, such as cancers and neuro-degeneration diseases. Recent studies demonstrate that autophagy may participate in almost every step of immune responses, including pathogen recognition, antigen processing and presentation, immune cell development and function, and immunoregulation. The pathogenesis of some autoimmune diseases, such as multiple sclerosis and Crohn's disease, has been reported to be associated with dysregulated autophagy. Systemic lupus erythematosus (SLE) is a chronic, potentially fatal autoimmune disease, characterized by dysregulation of immune cells and production of autoantibodies that cause widespread tissue and organ damage. The pathogenesis of SLE remains unclear. With several single nucleotide polymorphisms (SNPs) in autophagy-related gene5 (ATG5) being linked to SLE susceptibility, more and more lines of evidence from animal model, cell biology, immunology, and genetics studies show that autophagy contributes to the occurrence, development, and severity of SLE.

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1. Introduction

Autophagy is a highly conserved catabolic process mediated by lysosomes. It can remove unwanted cytoplasmic components, such as long-lived and/or misfolded proteins, damaged and/or effete organelles [1], playing an essential role in maintaining cellular homeostasis and cell survival in stress conditions, such as nutrient deprivation and hypoxia [2]. Recently, such process is implicated in nearly all steps of both innate and adaptive immune responses, including neutrophil extracellular trap (NET) and inflammasome formation, type I interferon (IFN1) production, pathogen recognition, antigen processing and presentation, lymphocyte and monocyte development and function, and inflammatory regulation [3,4,5,6,7,8,9], thus playing an important part in keeping the balance of immune system. Perturbations in autophagy have been implicated in several autoimmune diseases, including multiple sclerosis, Crohn's disease, and rheumatoid arthritis [10,11].

As a systemic and complex chronic autoimmune disease with significant potential morbidity and mortality, SLE is characterized by abnormal activation of immune cells and production of autoantibodies against components generated from dying cells [12] that lead to immune complex deposition, complementary activation, and tissue injury in multiple organs [13]. It remains a big challenge to clinicians with its unclear etiology. Genetic and environmental factors are supposed to be involved in its diverse clinical manifestations. Nowadays, more and more lines of evidence from genetics, immunology, cell biology, and animal model studies elucidate the essential role of autophagy in the occurrence, development and severity of SLE [3]. In this review, we mainly focus on the relationship between autophagy and SLE.

1.1. Background of autophagy

Autophagy, a lysosome-mediated catabolic process, is responsible for degradation of numerous damaged cytoplasmic constituents [2]. It exists at a basal low level in normal conditions, but increases immediately in response to stress, such as nutrient and growth factor deprivation, endoplasmic reticulum (ER) stress, and pathogen infection [14], thus playing a pivotal role in maintaining nutrient recycling, intracellular homeostasis, and cell survival [15]. According to the ways it delivers cargos to the lysosomes, autophagy is divided into three major types: macroautophagy (hereafter referred to as autophagy), microautophagy, and chaperone-mediated autophagy, with macroautophagy being the most investigated and understood [16]. The overall degradative flux of autophagy may be divided into 5 steps (Fig. 1): autophagy initiation, phagophore elongation, phagophore closure, autophagosome fusion, and cargo degradation [17].

1.2. Autophagy initiation

Under stress, the uncoordinated 51 like autophagy activating kinase1 (ULK1) complex, formed by ULK1, FAK family-interacting protein of 200 kDa (FIP200), mATG13, and ATG101, is recruited onto a cup-shaped membrane assembly site termed phagophore [18], directing proteins and other membrane components, thus driving phagophore assembly and elongation [19]. In response to energy depletion, adenosine monophosphate kinase (AMPK) phosphorylates ULK1 at different sites, including Ser467, Ser555, Ser574, Ser637, Ser317, and Ser777, inducing autophagy[20]. However, mammalian target of rapamycin (mTOR), a major negative regulator of autophagy, prevents ULK1 activation by phosphorylating ULK1 at Ser 757, and disrupting the

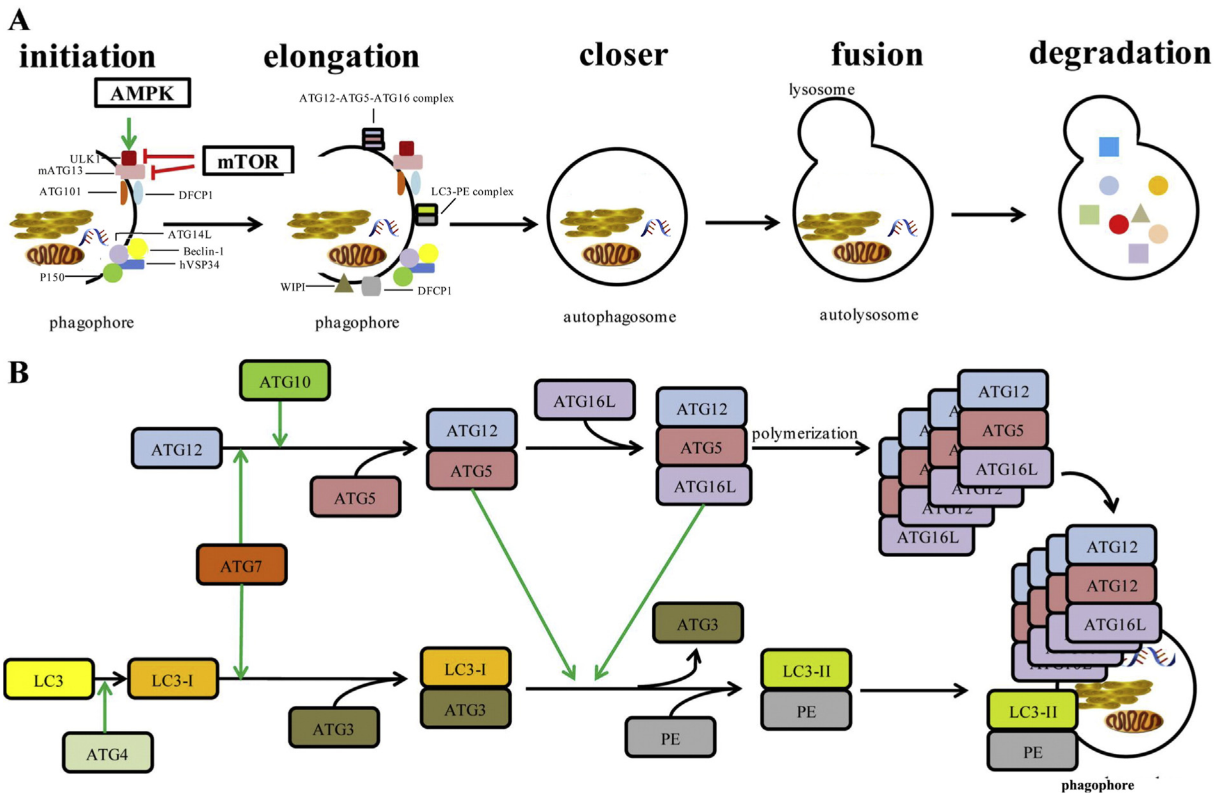

Fig. 1. (A). The ULK1 complex and PI3K complex are recruited to the newly formed phagophore at the early stage of autophagy initiation. Then, the initial phagophore elongates to engulf cargos and closes to form the autophagosome. Finally, the newly formed autophagosome fuses with the lysosome, forming the autolysosome whereby engulfed cargos are degraded. (B). The ATG12-ATG5 and LC3-PE pathways are involved in the elongation and closure stage of the phagophore. ATG12 is first activated by ATG7 and transferred to ATG10, and then ATG12 attaches to ATG5, forming the ATG12-ATG5 complex. Finally, ATG16L binds to the complex, forming the ATG12-ATG5-ATG16L complex which resides on the phagophore. LC3 is first processed by ATG4, forming LC3I, and then LC3I is activated and transferred to ATG3 by ATG7, forming the LC3I-ATG3 complex. Finally LC3I conjugates to PE, forming the LC3II-PE complex.