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Review

# Autophagy and Immune Senescence

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**With extension of the average lifespan, aging has become a heavy burden in society. Immune senescence is a key risk factor for many age-related diseases such as cancer and increased infections in the elderly, and hence has elicited much attention in recent years. As our body's guardian, the immune system maintains systemic health through removal of pathogens and damage. Autophagy is an important cellular 'clearance' process by which a cell internally delivers damaged organelles and macromolecules to lysosomes for degradation. Here, we discuss the most current knowledge of how impaired autophagy can lead to cellular and immune senescence. We also provide an overview, with examples, of the clinical potential of exploiting autophagy to delay immune senescence and/or rejuvenate immunity to treat various age-related diseases.**

## Trends

Autophagy is an important quality control mechanism to maintain cytoplasmic health and cellular homeostasis.

Autophagy is impaired during aging in various tissues across species including mammalian immune cells. With age, several key autophagy-regulating pathways shown to be important in rejuvenation or delayed aging are altered.

Autophagy-deficient immune cells show multiple aging phenotypes. Autophagy induction improves immune responses against microbial infections in the elderly.

Immune senescence is a risk factor for many late-onset diseases, such as cancer. Autophagy has emerged as a novel target for the prevention and/or treatment of some of these diseases.

## Autophagy: A Key Mechanism Controlling Immune Senescence

Autophagy is a highly conserved catabolic cellular process in which cells deliver their own components to lysosomes for degradation. There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy (hereafter referred to as autophagy) is so far the most thoroughly studied type and involves the formation of double-membrane autophagosomes that carry bulk cellular materials to lysosomes (Box 1). Through specific degradation of damaged organelles, protein aggregates, and intracellular pathogens, it has recently come to light that autophagy is a key quality control mechanism for cellular homeostasis, and with age is coupled to cellular senescence. Indeed, autophagy is impaired with age in different cell types, tissues, and organisms.

Immune senescence refers to a series of age-associated deteriorative changes in the development and function of the innate and adaptive immune systems. This causes inefficient control of infections and tissue damage. Impaired immune surveillance with age also increases the risk of tumorigenesis. Recent findings suggest that autophagy-deficient immune cells display features of premature aging, while aged macrophages and T cells have decreased autophagy [1,2]. Interestingly, treatments inducing autophagy are able to improve T cell and B cell responses against infections [1,3]. In this review we first discuss mechanisms of autophagy control of cellular senescence. Second, we examine the mechanisms of immune senescence with age, as well as the clinical potential of modulating autophagy to prevent or treat immune senescence-related diseases.

## Autophagy Controls Cellular Senescence

Impaired autophagy during aging has been reported in various mammalian tissues such as human brain [4] and murine T cells and macrophages [1,2]. Multiple autophagy signaling pathways and the lysosomal compartment are affected with age, and may together contribute

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## Box 1. The Process of Autophagy

(i) Upon autophagy induction, the activated ULK1 protein kinase complex forms proximally to the ER, mitochondria, or other membrane structures [107] (Figure I).

(ii) The class III PI3 K complex is recruited by the ULK1 complex, producing phosphatidylinositol 3-phosphate which drives the formation of the isolation membrane (autophagophore).

(iii) The autophagophore expands to engulf cytoplasmic materials including organelles and soluble components. This expansion requires two ubiquitin-like reactions, ATG12–ATG5–ATG16L and LC3–phosphatidylethanolamine (LC3-PE).

ATG12 is activated by ATG7 (E1-like) and then transferred to ATG5 by ATG10 (E2-like); ATG12–ATG5 forms a complex with ATG16L.

LC3 is activated by ATG7 (E1-like) and conjugated to PE by ATG3 (E2-like). Then ATG12–ATG5–ATG16L complex functions as an E3-like ligase to add the phosphatidylethanolamine tail for LC3 lipidation.

(iv) Finally, the elongated membrane closes to form mature autophagosomes, which fuse with lysosomes to begin degradation.

Starvation-induced bulk autophagy degradation is thought to be non-selective, whereas selective autophagy controls the quality of cytoplasmic constituents. The specific recognition of damaged organelles and protein aggregates is mediated by autophagy adaptors such as p62, NBR1, and NDP52. These adaptors recognize polyubiquitin chains on damaged proteins and organelles, and interact with autophagy proteins such as ULK1 [108] and LC3 to initiate autophagy and guide the engulfment process.

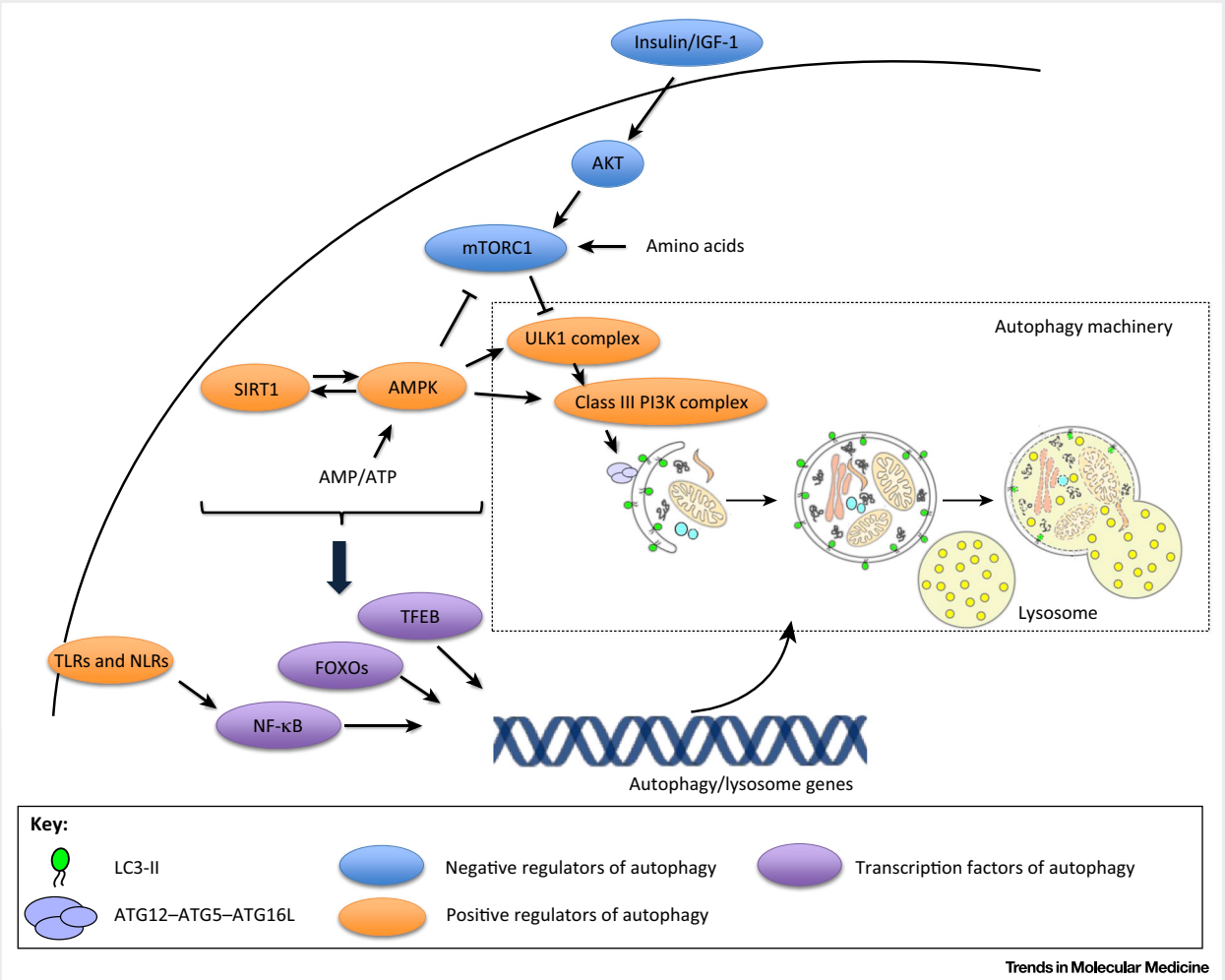


Figure I. Autophagy-Controlling Pathways. As a stress response, autophagy is regulated by multiple signals including growth factors, nutrients, energy supply, cytokines, and infections. Particular transcription factors also integrate stress signals to control autophagy. Autophagy has different functions according to its cargo, including quality control (e.g., mitophagy), intracellular pathogen removal (xenophagy), and energy supply/metabolism control (lipophagy).