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A ravenous defense: canonical and non-canonical autophagy in immunity

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While classically considered a survival mechanism employed during nutrient scarcity, the autophagy pathway operates in multiple scenarios wherein a return to homeostasis or degradative removal of an invader is required. Now recognized as a pathway with vast immunoregulatory power, autophagy can no longer serve as a 'one size fits all' term, as its machinery can be recruited to different pathogens, at different times, with different outcomes. Both canonical autophagy and the molecularly related, yet divergent pathways non-canonical autophagy are key players in proper host defense and allow us an opportunity to tailor infectious disease intervention and treatment to its specific pathway.

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Introduction

In 2016, Nobel Assembly at Karolinska Institutet awarded Yoshinori Ohsumi with the Nobel Prize in Medicine and Physiology for his groundbreaking work unraveling the molecular mechanisms that underlie the tightly regulated catabolic process of macroautophagy (herein referred to as autophagy). We now recognize that the reach of autophagy extends far beyond nutrient deprivation, into cellular quality control and host defense against internalized pathogens. While canonical autophagy likely evolved as a homeostatic response to cellular stress and/or nutrient deprivation, non-canonical autophagic functions are unified in the ancient theme of containment and suppression of inflammation. Similarly, efferocytosis, the immunotolerant clearance of dying host cells by tissue phagocytes, has recently been shown to rely upon recruitment of autophagy effectors to the phagosome through a non-canonical autophagic pathway called LC3-associated phagocytosis (LAP). Taken together, emerging evidence indicates that autophagy, through both canonical and non-canonical pathways, has diversified into a host defense mechanism, capable of confronting immunological and pathogenic stress and mediating immunological self-tolerance to both intracellular and extracellular threats.

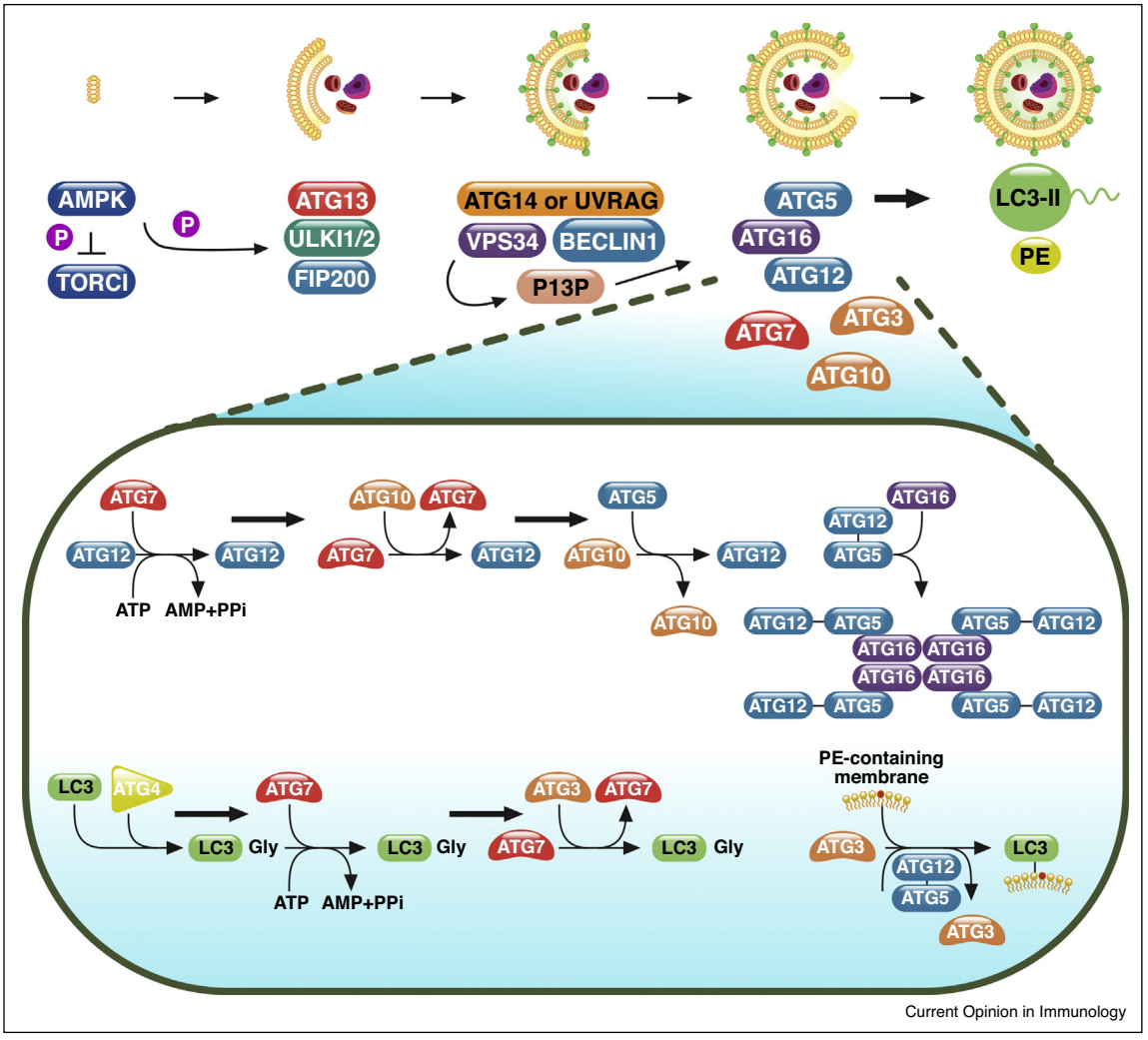
Canonical autophagy

Autophagy is the highly conserved process by which eukaryotic cells scavenge their own cytoplasmic contents through sequestration into a phagophore and subsequent fusion with a lysosome for degradation. This process of ' self-eating' is classically thought of as non-selective in response to nutrient deprivation and is largely orchestrated by the ATG family of proteins [1]. Upon starvation, autophagy progresses in six stages: inactivation of mTOR and pre-initiation complex formation, vesicle/phagophore nucleation, vesicle elongation, autophagosome formation, lysosome fusion, and component degradation [2] (Figure 1).

Extensive research has shown AMP-activated kinase (AMPK) to be the main energy sensing rheostat regulating the cells response to ATP/AMP imbalance [3]. When ATP levels decrease and AMP levels rise, AMPK becomes activated and inhibits mTOR complex 1 (mTORC1) activity [4], leading to nuclear localization of TFEB and Gln3, two autophagy-related transcription factors [5,6]. AMPK directly controls autophagy factors ULK1 (ATG1) and ATG13 through phosphorylation and sequestration [4]. Once free and active, ULK1 forms the autophagy pre-initiation complex with ATG13, FIP200, and ULK2 and phosphorylates ATG9 within nearby phospholipid membranes [7•].

The Beclin-1-binding partner, Ambra1, directly connects the activity of this preinitiation complex, considered the most upstream regulator of the autophagic process, to the Class III PI3K complex. Ambra1 binds the core components of the Class III PI3K complex, Beclin 1 and VPS34, at the cytoskeleton through an interaction with the dynein motor complex. Upon autophagy induction, ULK1 phosphorylates Ambra1, allowing it and its bound partners to re-localize to the ER and initiate vesicle nucleation. The activity and localization of the Ambra1 complex further support the role of the ER in autophagosome formation [8,9]. Interestingly, Ambra1 can act in an mTORC1-sensitive positive-feedback loop to promote

Figure 1



The molecular mechanisms of canonical autophagy. Normally held in check by mTOR, autophagy-inducing signals (such as nutrient deprivation) triggers the activation of AMPK, whose kinase activity simultaneously inhibits mTOR and activates the pre-initiation complex (ULK1/2, ATG13, FIP200). This complex then activates the Class III PI3K complex, composed of VPS34 and Beclin 1, along with either ATG14 or UVRAG. The Class III PI3K complex produces phosphatidylinositol 3-phosphate (PI3P), which acts as recruitment signal for the downstream ubiquitin-like conjugation systems, the ATG12-5 system and the LC3-PE system. The activity and coordination of these two systems facilitate the curvature and sealing of the autophagosome, as well as the lipidation and embedding of LC3-PE into the autophagosomal membrane.

K63-linked ubiquitination of ULK1 through recruitment of the E3-ubiquitin ligase TRAF6 [10].

In addition to Beclin 1 and VPS34, the Class III PI3K complex consists of ATG14 or UVRAG in a mutually exclusive manner [11]. VPS34, the class III PI3 kinase in the complex, generates PI3P (phosphatidylinositol 3-phosphate), which serves as a critical recruitment signal for the two downstream ubiquitin-like conjugation systems. These two systems, the ATG5-12 system and the LC3-PE system, are required for vesicle nucleation, elongation, and curvature of the forming autophagosomes [2]. E3-ligase complex ATG7 and ATG10 mediates the conjugation of ATG5 to ATG12 in association with ATG16L1 to form a multimeric complex. Subsequently, this ATG5/12/16L1 complex is critical for the generation of LC3-PE (or LC3-II), the lipidated form of LC3 (or LC3-I). Cytosolic LC3-I is cleaved by ATG4, and conjugated to phosphatidylethanolamine (PE) via the activity of ATG7 and ATG3 [12]. This lipidated LC3-PE bounds to the autophagosomal membrane and is required for subsequent fusion to lysosomes, wherein the autophagosomal contents are degraded and recycled [13,14••].

Traditionally, autophagy is considered a cell survival process; however, it is important to note that the