



PERSPECTIVE

A guide to membrane atg8ylation and autophagy with reflections on immunity

Vojo Deretic^{1,2}  and Michael Lazarou^{3,4} 

The process of membrane atg8ylation, defined herein as the conjugation of the ATG8 family of ubiquitin-like proteins to membrane lipids, is beginning to be appreciated in its broader manifestations, mechanisms, and functions. Classically, membrane atg8ylation with LC3B, one of six mammalian ATG8 family proteins, has been viewed as the hallmark of canonical autophagy, entailing the formation of characteristic double membranes in the cytoplasm. However, ATG8s are now well described as being conjugated to single membranes and, most recently, proteins. Here we propose that the atg8ylation is coopted by multiple downstream processes, one of which is canonical autophagy. We elaborate on these biological outputs, which impact metabolism, quality control, and immunity, emphasizing the context of inflammation and immunological effects. In conclusion, we propose that atg8ylation is a modification akin to ubiquitylation, and that it is utilized by different systems participating in membrane stress responses and membrane remodeling activities encompassing autophagy and beyond.

Introduction

Canonical autophagy in mammalian cells is a multitasking process engaged in cytoplasmic quality control (Levine and Kroemer, 2019; Morishita and Mizushima, 2019), metabolism (Lahiri et al., 2019), and innate and adaptive immunity (Clarke and Simon, 2019; Deretic, 2021). The immune, metabolic, and quality control aspects of autophagy are intertwined in many of its physiological functions (Deretic and Kroemer, 2022). Autophagy is responsive to diverse inputs, and while the outputs may appear different, the molecular machineries involved are shared and redundantly utilized, creating sometimes unanticipated but biologically effectual overlaps. When autophagy fails, cellular, tissue, and organismal manifestations often present as dysregulated inflammation and other abnormalities. These contribute to a wide spectrum of diseases and pathological conditions reflected in animal models and human populations (Mizushima and Levine, 2020).

The term “autophagy” is often encountered in the literature as a conflation of diverse lysosomal degradative processes, including macroautophagy (herein “canonical autophagy”; Morishita and Mizushima, 2019), microautophagy (Schuck, 2020), chaperone-mediated autophagy (Bourdenx et al., 2021; Dong et al., 2021), and other systems such as formation of intraluminal vesicles and related processes in endosomes and lysosomes (Lee et al., 2020; Loi et al., 2019; Mejlvang et al., 2018). They all have a common purpose of importing substrates into membranous organelles where the

sequestered substrates are typically digested. This contributes to turnover of proteins, membranes, and whole organelles; destruction of microbes or their products; and generation of metabolic intermediates during starvation (Deretic and Kroemer, 2022; Gonzalez et al., 2020; Morishita and Mizushima, 2019). There are also non-degradative outcomes of autophagy, such as secretory autophagy (Ponpuak et al., 2015), which contributes to unconventional secretion of leaderless cytosolic proteins and excretion of bulkier material from the cytoplasm.

“Noncanonical autophagy” encompasses an assortment of autophagy-related processes akin to but different from canonical autophagy, in several cases, reflecting noncanonical activities of autophagy proteins that do not involve lysosomal degradation. These phenomena include LC3-associated phagocytosis (LAP; Sanjuan et al., 2007) and its variations (Galluzzi and Green, 2019; Ulferts et al., 2021) as well as a growing collection of diverse emerging manifestations (Goodwin et al., 2021; Guo et al., 2017a; Kumar et al., 2020; Lee et al., 2020; Leidal et al., 2020; Loi et al., 2019; Nakamura et al., 2020). A feature frequently shared by canonical and noncanonical autophagy is the engagement of mammalian ATG8 proteins (mATG8s). The mATG8 LC3B is traditionally used as an autophagy marker (Kabeya et al., 2000), although it cannot differentiate between canonical and non-canonical forms. Thus, it is necessary to reconsider what mATG8 lipidation and appearance of intracellular mATG8 puncta represent, and how we interpret them. A recent proposal is that the

¹Autophagy, Inflammation and Metabolism Center of Biochemical Research Excellence, University of New Mexico Health Sciences Center, Albuquerque, NM; ²Department of Molecular Genetics and Microbiology, University of New Mexico Health Sciences Center, Albuquerque, NM; ³Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia; ⁴Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Melbourne, Victoria, Australia.

Correspondence to Vojo Deretic: vderetic@salud.unm.edu; Michael Lazarou: michael.lazarou@monash.edu.

© 2022 Deretic and Lazarou. This article is available under a Creative Commons License (Attribution 4.0 International, as described at <https://creativecommons.org/licenses/by/4.0/>).

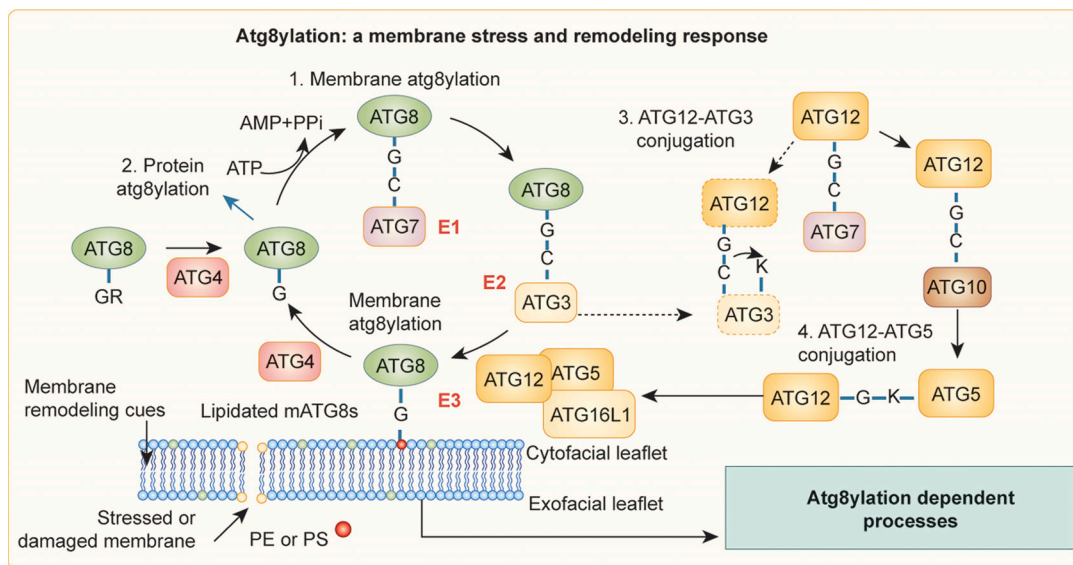


Figure 1. **Atg8ylation.** Membrane atg8ylation includes a ubiquitylation-like cycle of covalent modifications of membrane lipids (PE and PS) by ATG8 proteins. Note three conjugation processes (labeled 1–3): membrane Atg8ylation (driven by ATG16L1-centered E3 ligase), protein Atg8ylation, and ATG12-ATG3 conjugation as an atg8ylation-independent branch. Modified after Kumar et al. (2021b).

atg8ylation of membranes by mATG8s (Kumar et al., 2021b) represents a general membrane stress and remodeling response analogous to ubiquitylation of proteins. Under this concept, canonical autophagy (macroautophagy), LAP, and other non-canonical processes represent manifestations of the role of atg8ylation in membrane homeostasis (Kumar et al., 2021b). Here, we revisit the standard model of autophagy and related processes through the conceptual lens of atg8ylation as a general membrane stress and remodeling response (Fig. 1).

Atg8ylation as a membrane stress and remodeling response

There are six main mATG8s—LC3A, LC3B, LC3C, GABARAP, GABARAPL1, and GABARAPL2/GATE16 (He et al., 2003; Weidberg et al., 2010; Xin et al., 2001)—with LC3B being universally used as the principal autophagosomal membrane marker (Kabeya et al., 2000). Whereas mATG8s are found on autophagosomes (Mizushima, 2020), autophagosomes can form without mATG8s (Nguyen et al., 2016), and autophagosome generation is initiated before their membranes become decorated with mATG8s (Kumar et al., 2021a). Importantly, mATG8s including LC3B are found on a variety of membranes other than autophagosomes (Galluzzi and Green, 2019), where they participate in diverse biological and physiological processes. This includes LAP (Sanjuan et al., 2007), its variations (Galluzzi and Green, 2019), a cluster of other related phenomena involving phagosomes or stressed endosomes (Durgan et al., 2021; Fletcher et al., 2018; Florey et al., 2015b; Florey et al., 2011; Heckmann et al., 2019; Jacquin et al., 2017; Rai et al., 2019; Ulferts et al., 2021; Xu et al., 2019), and additional processes engaging a variety of endomembranes (Goodwin et al., 2021; Guo et al., 2017a; Kumar et al., 2020; Lee et al., 2020; Leidal et al., 2020; Loi et al., 2019; Nakamura et al., 2020). The growing diversity of phenomena involving mATG8 lipidation does not easily fit the current paradigm. In a recently proposed model (Kumar et al., 2021b),

membrane atg8ylation (Fig. 1, process 1) represents a generalized response to membrane stress or acts in membrane remodeling, analogous to the general role that ubiquitylation plays in tagging proteins (Hershko and Ciechanover, 1998; Mevissen and Komander, 2017). Ubiquitin and ATG8s are related in sequence and structure (Kumar et al., 2021b), and the lipidation of mATG8s, elaborated below, occurs on their C-terminal glycines, akin to the C-terminal glycine of ubiquitin (Mizushima, 2020). In addition, mATG8s can atg8ylate proteins (Fig. 1, process 2; Agrotis et al., 2019; Carosi et al., 2021; Nguyen et al., 2021). Like ubiquitylation, atg8ylation has a plethora of downstream effector outputs (Fig. 2), with autophagy being one of them. However, the full spectrum of membrane and protein atg8ylation targets, and their relatedness to membrane remodeling, is yet to be systematically explored outside of the autophagy paradigm.

Protein ubiquitylation tags them for extraction and degradation, whereas under unperturbed conditions, ubiquitylation modulates normal protein activity, localization, and interactions (Mevissen and Komander, 2017; Pohl and Dikic, 2019). Membrane atg8ylation is an analogous process acting on membranes. ATG8s are conjugated to specific membrane phospholipids, phosphatidylethanolamine (PE; Durgan et al., 2021; Ichimura et al., 2000; Lystad et al., 2019) or phosphatidylserine (PS; Durgan et al., 2021). Like ubiquitylation, atg8ylation depends on ATP and E1-like activating protein, ATG7 (Fig. 1). ATG7 is conjugated to the C-terminal glycine of Atg8s, exposed post-translationally through cleavage mediated by ATG4 family proteases. Atg8s are next transferred to E2-like protein ATG3, and finally to the lipids PE or PS on membranes guided by an E3-like complex ATG5-ATG12/ATG16L1 (Fig. 1; Mizushima, 2020; Mizushima et al., 2011). A “sidestep” conjugation between ATG12 and ATG3 can also occur (Fig. 1, process 3; Radoshevich et al., 2010) in addition to the canonical ATG5-ATG12 conjugation (Fig. 1, process 4). Thus far, the known functions of the

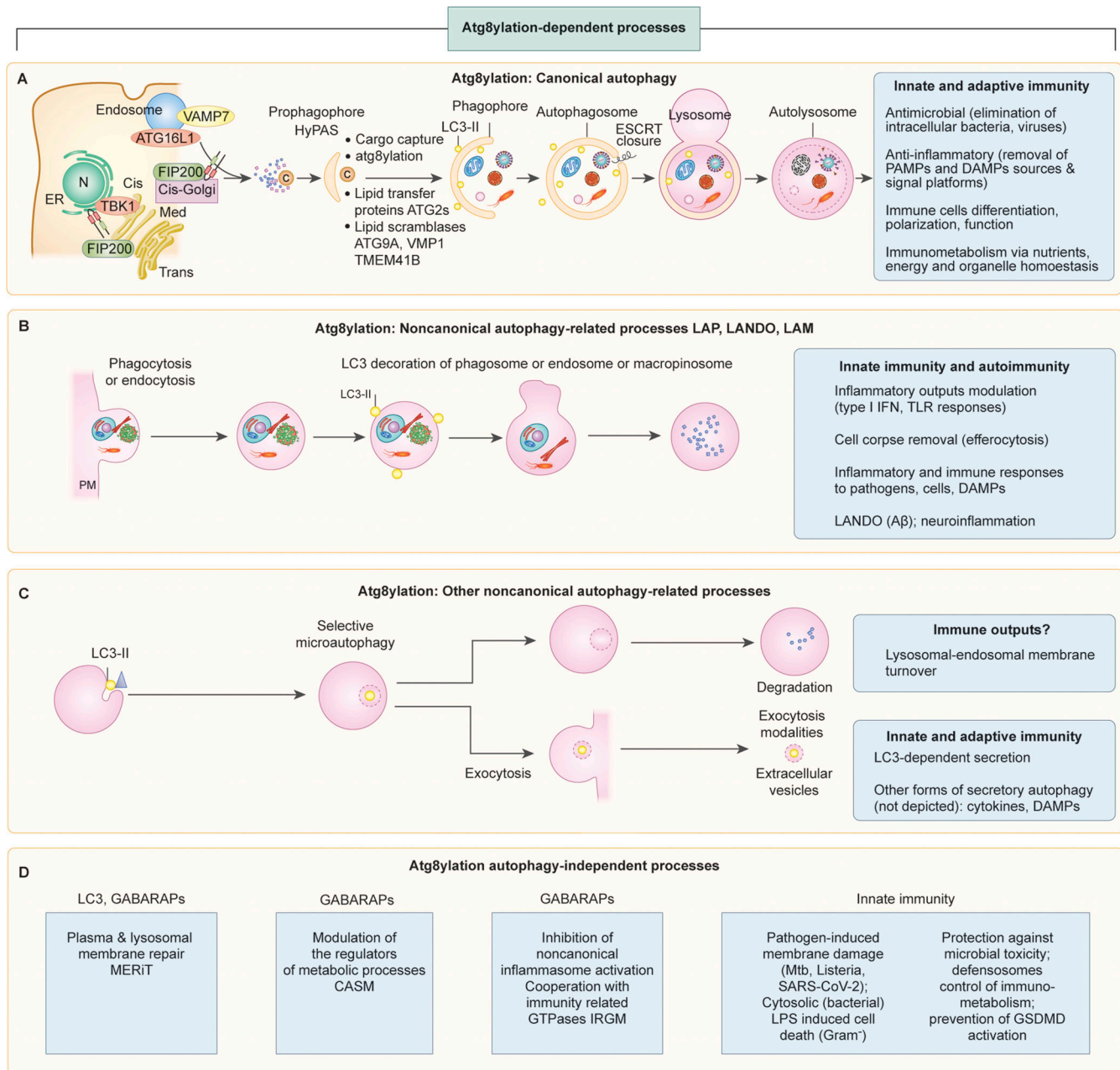


Figure 2. **Atg8ylation and its cell biological manifestations including canonical autophagy, noncanonical autophagy, and related nonautophagic processes.** (A) Canonical autophagy as a classic output of atg8ylation and the process of double-membrane autophagosome formation with atg8ylation-independent and atg8ylation-dependent stages. ATG8-negative prophagophore (HyPAS) is defined by fusion of FIP200⁺ early-secretory pathway/cis-Golgi-derived membrane with ATG16L1⁺ endosomal membranes. HyPAS converts to ATG8⁺ (usually referred as LC3⁺) phagophore, which sequesters the cargo and, upon ESCRT-catalyzed membrane closure, fuses with lysosomes leading to cargo degradation. (B and C) Noncanonical autophagy-related processes that do not involve formation of double-membrane autophagosomes and instead rely on atg8ylation of single-membrane organelles induced in response to membrane stress or other signals requiring membrane remodeling. (D) Processes utilizing atg8ylation that do not include canonical or noncanonical autophagy-related processes. Boxes indicate immunological processes associated with particular atg8ylation outputs. Details in the text.

noncanonical ATG12-ATG3 conjugation are endosomal positioning, exosome biogenesis, and viral budding (Murrow et al., 2015). The range of biological activities of either ATG12-ATG3 conjugation (Radoshevich et al., 2010) or protein atg8ylation (Agrotis et al., 2019; Carosi et al., 2021; Nguyen et al., 2021) are yet to be fully explored.

The known processes downstream of membrane atg8ylation (Fig. 2) are individually addressed in the next section. As listed in the Fig. 2 boxes, we herein often use immunity examples to illustrate the physiological impact of atg8ylation, which broadly affects diverse aspects of metabolism, quality control, and inflammation.

Autophagy and related processes as manifestations of atg8ylation

Canonical autophagy. The hallmark of canonical autophagy is the emergence of double-membrane autophagosomes in the cytoplasm (Morishita and Mizushima, 2019). Canonical autophagosomes (Morishita and Mizushima, 2019; Fig. 2 A) can capture diverse cytoplasmic cargoes that are recognized through a range of autophagy receptors (Lamark and Johansen, 2021). The autophagosomes are decorated by ATG8 family proteins, with LC3B being the most ubiquitously used marker of autophagy (Kabeya et al., 2000). Many mATG8-associated processes are termed using an LC3-based nomenclature; however, this does not exclude roles for other mATG8 family members including GABARAPs. Indeed, GABARAPs have been linked to atg8ylation-mediated activation of transcription factor EB (TFEB; Goodwin et al., 2021). We therefore note that, despite the LC3 nomenclature that is used in the field, and within this perspective, exploration into the role of each mATG8 family member is both warranted and necessary to gain a full understanding of atg8ylation-related processes. Given that studies do not always specify the LC3 subfamily member used, one may assume that it is typically LC3B. Therefore, when we refer to a study that reports a process as being decorated with or associated with LC3, be mindful that LC3B is the most likely member being discussed.

Canonical autophagy in mammals starts with the formation of a pro-phagophore via the fusion of FIP200-positive vesicles derived from the early secretory pathway (i.e., cis-Golgi) with ATG16L1-positive endosomal vesicles (Kumar et al., 2021a). The commitment to canonical autophagy is thus initiated through intermixing of two membrane sources contributed by the secretory and the endosomal pathways (Kumar et al., 2021a). Consequently, the pro-phagophore is referred to as a hybrid pre-autophagosomal structure (HyPAS). The HyPAS model (Fig. 2 A) of canonical autophagosome formation reconciles the two major schools of thought on the source of mammalian autophagic membranes, one being ER-centric (Axe et al., 2008; Hara et al., 2008; Hayashi-Nishino et al., 2009; Itakura and Mizushima, 2010; Itakura and Mizushima, 2011; Mizushima et al., 2011; Nishimura et al., 2017; Tooze and Yoshimori, 2010) and the other endosome-centric (Knævelsrud et al., 2013; Longatti et al., 2012; Moreau et al., 2011; Puri et al., 2013; Puri et al., 2018; Ravikumar et al., 2010; Soreng et al., 2018) and is consistent with additional studies including the reported role of the ER-Golgi intermediate compartment and coat protein II (COPII) vesicles (Ge et al., 2013; Ge et al., 2017; Ge et al., 2014). Additional contributors to autophagosomal membranes have also been reported (Hailey et al., 2010; Hamasaki et al., 2013; Nascimbeni et al., 2017; Nishida et al., 2009), which may participate at stages along the autophagosome formation pathway.

The HyPAS pro-phagophore is at first LC3B-negative (Kumar et al., 2021a), and it may be free of all mATG8s. While the latter notion remains to be established, it is consistent with the independence of the initial stages of autophagy from the atg8ylation system (Dalle Pezze et al., 2021; Itakura et al., 2012; Nguyen et al., 2016; Zachari et al., 2019). Atg8ylation is uncoupled from FIP200 and autophagosome formation, as observed early on with bacterial phagosomes (Kageyama et al.,

2011). The LC3-negative pro-phagophore can in principle make initial contacts with autophagic cargo receptors, since a significant number of these receptors directly bind to FIP200 to recruit initiation complexes (Ohnstad et al., 2020; Ravenhill et al., 2019; Smith et al., 2018; Turco et al., 2019; Vargas et al., 2019). These initial encounters between the cargo and the forming autophagosomes are subsequently augmented by atg8ylation and autophagy receptor-mATG8 interactions (Padman et al., 2019; Turco et al., 2019), which coincide with conversion of the pro-phagophore into an atg8ylated phagophore (Kumar et al., 2021a). The phagophore enlarges via a variety of mechanisms including direct delivery of phospholipids through lipid-transfer proteins such as ATG2 (Valverde et al., 2019) as well as lipid scramblases that relax lipid asymmetry between membrane leaflets to enable lipid flow into the growing phagophore (Maeda et al., 2020; Matoba et al., 2020). The enlarged phagophore enwrapping the cargo then closes with the help of the endosomal sorting complexes required for transport (ESCRT) machinery (Takahashi et al., 2018). Closed autophagosomes deliver the captured cargo to lysosomes for degradation via autophagosome-lysosome fusion (Zhao and Zhang, 2019).

Fig. 2 A also lists the principal immunological outputs of canonical autophagy. As recently reviewed (Deretic, 2021), this includes direct microbial elimination (xenophagy), anti-inflammatory action by removing pathogen- and damage-associated molecular patterns (PAMPs and DAMPs), and development and differentiation of immune cells as well as their polarization and function. There are unique connections with immunometabolism (Deretic, 2021) because of the tight integration of canonical autophagy with the nutrient and energy sensors mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), which together determine the “posture” of key immune cells, with their populations assuming either a robust inflammatory phenotype associated with proliferation or tissue repair characteristics associated with quiescence (O’Neill et al., 2016; Saravia et al., 2020).

Noncanonical autophagy-related processes

A number of noncanonical autophagy-related processes have been reported, and a diverse selection of newly described non-canonical trends involving mATG8s continue to emerge. The key feature of these phenomena is that they share certain but not all components with canonical autophagy and involve single instead of double membranes (Galluzzi and Green, 2019). The archetypal process in this category is LAP (Martinez et al., 2016; Sanjuan et al., 2007). Its close variations (LAP-related processes) on endosomal/phagosomal vesicles are LC3-associated endocytosis (LANDO; Heckmann et al., 2019) and LC3-associated micropinocytosis (LAM; Sonder et al., 2021; Fig. 2 B). They all exhibit the eponymous LC3 labeling but, unlike canonical autophagosomes, involve organelles with single delimiting membranes. We suggest that one may best grasp the relationship to canonical autophagy by viewing LAP and LAP-related processes as one half of the HyPAS pro-phagophore formation, engaging only the endosomal organelles where ATG16L1 E3 ligase resides but not the membranes coming from the early secretory pathway with FIP200 and its associated components. Consequently,

FIP200 is not needed for LAP-related processes, whereas it is critical for canonical autophagy.

LAP-related processes can be induced by various stressors and membrane-damaging agents, including pharmacological agents or microbial products perturbing phagosomes and endosomes (Durgan et al., 2021; Fletcher et al., 2018; Florey et al., 2015a; Florey et al., 2011; Jacquin et al., 2017; Ulferts et al., 2021; Xu et al., 2019). The immunological roles of LAP and LAP-related processes are listed in the box in Fig. 2 B. They include anti-inflammatory activity preventing autoimmunity and lupus (Martinez et al., 2016), antimicrobial action (Kageyama et al., 2011; Martinez et al., 2015), and orderly removal of dead or dying cells and cell fragments by efferocytosis, entosis, and phagocytosis (Boada-Romero et al., 2020; Florey et al., 2011; Kim et al., 2013; Martinez et al., 2011). The downregulation of stimulator of interferon genes (STING), normally transmitting signals of ectopic presence of viral or mitochondrial dsDNA in the cytosol, via a LAP-related process (Fischer et al., 2020), has the potential to directly limit type I IFN responses, but this remains to be established. LAP may favor immune tolerance in cancer micro-environments (Cunha et al., 2018), albeit it promotes Toll-like receptor (TLR) signaling through IRF7-stimulating type I IFN response (Henault et al., 2012). In the context of neuroinflammatory diseases, LANDO clears β -amyloid aggregates and suppresses microglia activation (Heckmann et al., 2019). Of note, not all endosomes and phagosomes undergo atg8ylation, which requires a specific stress or danger signal such as described above, as well as TLR signaling upon encounter of fungal, bacterial, and microbial products known as PAMPs (Delgado et al., 2008; Sanjuan et al., 2007).

A number of other processes unrelated to LAP are manifestations of membrane atg8ylation (Fig. 2, C and D). These diverse phenomena include selective microautophagy of mammalian lysosomal membranes in response to osmotic stress or glucose starvation (Lee et al., 2020), selective removal of excess ER during recovery from ER stress via piecemeal micro-ER-phagy (Loi et al., 2019), and unconventional secretion via extracellular vesicles and secretory autophagy. Atg8ylation participates in the formation of exosomes (Guo et al., 2017a) and secretion of specific cytosolic cargo by extracellular vesicles (Leidal et al., 2020). Among the reported innate immunity functions for exosomes impacted by atg8ylation is neutralization of bacterial toxins before they can attack the host cells (Keller et al., 2020).

Atg8ylation furthermore plays a role in a type of unconventional secretion of leaderless cytosolic proteins, or excretion/extrusion of cytoplasmic material, referred to as secretory autophagy (Gerstenmaier et al., 2015; Ponpuak et al., 2015). Secretory autophagy has been implicated in the export of a key proinflammatory cytokine, IL-1 β , and of the alarmin HMGB1 (Dupont et al., 2011; Karmakar et al., 2020; Kimura et al., 2017; Razani et al., 2012; Thorburn et al., 2009), albeit IL-1 β exit from cells uses multiple routes (Zhang et al., 2015; Zhang et al., 2020b), including prominently a passive release of IL-1 β from dying cells through gasdermin pores on the plasma membrane during pyroptosis (Broz et al., 2020; Evavold et al., 2018). Atg8ylation does not always protect the host: for example, it has been coopted by influenza A to promote its filamentous mode of budding from the plasma membrane (Beale et al., 2014).

In summary, atg8ylation participates in phenomena historically referred to as noncanonical autophagy but functionally representing a range of membrane stress responses and membrane remodeling processes. This diversity is mirrored by the equally diverse immunological and anti-inflammatory outputs of atg8ylation further discussed below. Despite atg8ylation being linked to noncanonical processes, how exactly mATG8s are functioning during many of these processes remains to be fully explored. It is likely that atg8ylation is involved in the formation/expansion of membrane vesicles, but mATG8s may also recruit factors through LC3 interaction region (LIR)/GABARAP interaction motif (GIM), thereby acting as scaffolds for protein complexes that play roles in signaling. In addition, atg8ylation may play an adaptor role to recruit factors within the lumen of vesicles. In the next section, we cover some of the recent advances in the signaling roles of membrane atg8ylation.

Atg8ylation and signaling

Membrane atg8ylation can affect multiple signaling systems and therefore functions beyond the proposed direct physical role in membrane remodeling during the formation of canonical autophagosomes (Maruyama et al., 2021) and noncanonical LAP-like structures (Galluzzi and Green, 2019). The atg8ylation that takes place during canonical autophagy is the most understood (Kabeya et al., 2000). During PINK1/Parkin mitophagy, atg8ylation can serve as an amplification signal by increasing the concentration of autophagy machineries on phagophores (Padman et al., 2019). Although PINK1/Parkin mitophagy is largely independent of mTOR and AMPK signaling (Vargas et al., 2019), most forms of canonical autophagy depend on these principal regulators of cellular metabolism (Deretic and Kroemer, 2022). Localized at least in part to lysosomes (Fig. 3), mTOR inhibits (whereas AMPK activates) protein complexes controlling autophagosome biogenesis. Lysosomes are also the site where these systems, along with phosphatases such as calcineurin, control TFEB, a key regulator of lysosomal biogenesis, with functional lysosomes being essential for the completion of canonical autophagy and other roles (Ballabio and Bonifacino, 2020).

A specific subset of mATG8s, GABARAPs, along with their atg8ylation onto membranes, help activate TFEB under different conditions (Goodwin et al., 2021; Kumar et al., 2020; Nakamura et al., 2020; Fig. 3) as follows. (1) GABARAPs bind to TFEB (Fig. 3, box 1), inhibit mTOR, and together with immunity-related GTPase M (IRGM), which stabilizes AMPK (Chauhan et al., 2015a), activate calcineurin phosphatase PPP3CB (Kumar et al., 2020). PPP3CB in turn dephosphorylates TFEB, resulting in its nuclear translocation and transcriptional activation of the lysosomal biogenesis program (Medina et al., 2015). (2) During lysosomal damage, atg8ylation stimulates the Ca²⁺ channel mucolipin/TRPML1 to activate TFEB via a phosphatase different from calcineurin (Nakamura et al., 2020; Fig. 3, box 2), possibly PP2A (Hasegawa et al., 2022). (3) Membrane atg8ylation at various locations in the cell indirectly affects the activation state of mTOR on the lysosome (Goodwin et al., 2021; Fig. 3, box 3). At the lysosome, mTOR is controlled by a set of Rag GTPases and folliculin (FLCN), which acts on RagC/D to maintain TFEB

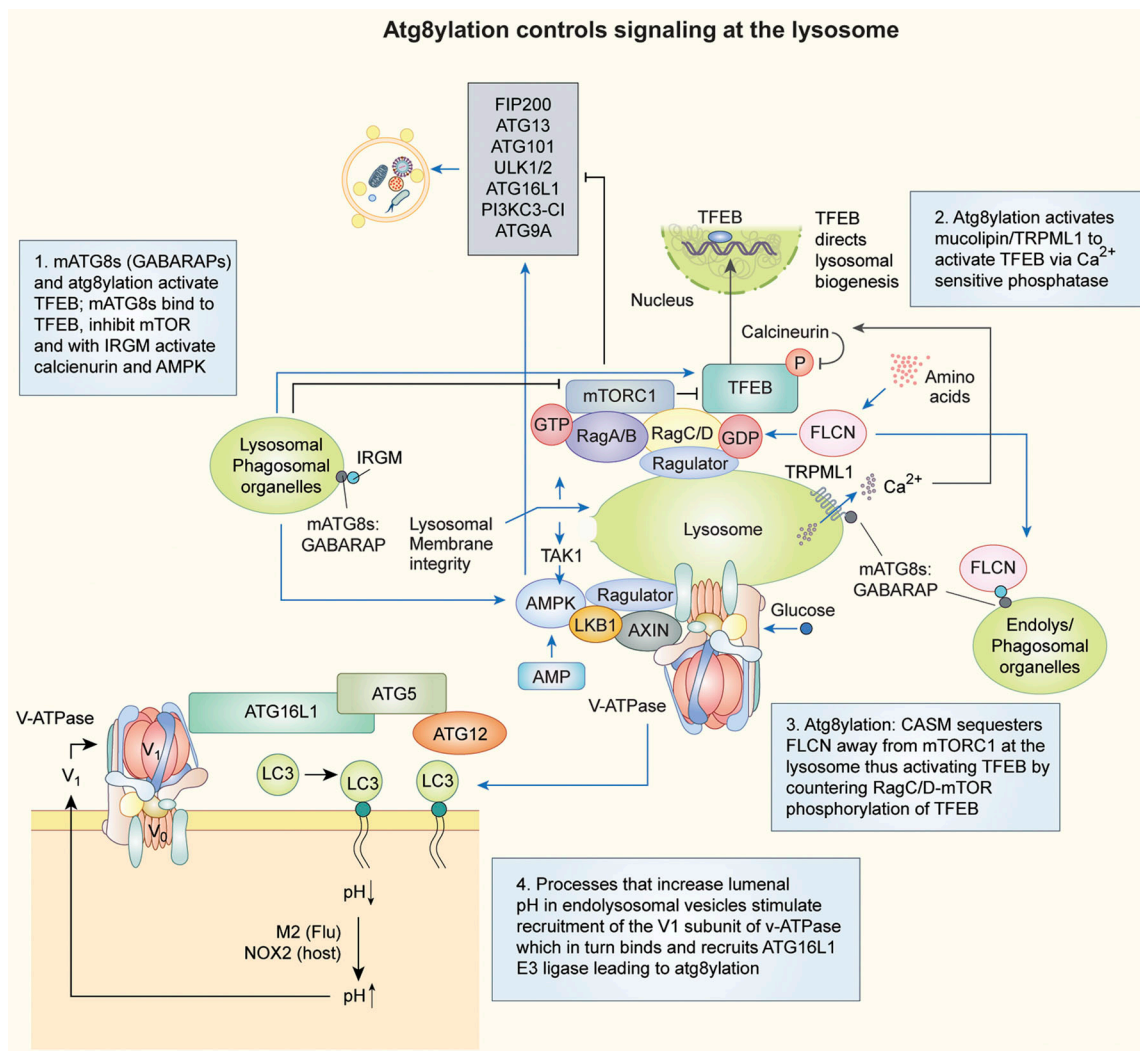


Figure 3. **Specific examples and circuitry of how atg8ylation controls different signaling and stress response processes at the lysosome.** Note that both mTOR and AMPK as well as their regulatory elements are localized at the lysosome. AMPK positively regulates canonical autophagy, whereas mTOR negatively regulates this atg8ylation-associated process. Boxes 1–4 describe four of the expanding list of autophagy-independent atg8ylation-dependent processes. This includes control of AMPK, mTOR, and TFEB by mATG8s and atg8ylation (Boxes 1–3). Box 4-associated schematic depicts how increase in luminal pH (phagosomes, organelles of the endolysosomal network) by the action of the influenza viroporin M2 that acts as an H⁺ channel or proton scavenging during superoxide production induce membrane atg8ylation (LC3 shown as an example of LAP and LAP-related processes). This occurs due to the increased recruitment of ATG16L1 via its direct binding to the V1 subunit of vacuolar H⁺-ATPase, upon elevated V₁V₀ assembly on membranes in response to neutralization of the luminal pH. Further details in the text.

phosphorylated by mTOR (Napolitano et al., 2020). Atg8ylation with GABARAPs elsewhere in the cell sequesters FLCN away from Rags-mTORC1 on the lysosome, resulting in TFEB activation. Such atg8ylation of membranes at remote sites includes canonical autophagy (e.g., mitophagy), phagocytosis of bacteria and associated LAP, and pharmacological stress (Goodwin et al., 2021).

How is membrane atg8ylation induced on endolysosomal and phagosomal vesicles? Agents that deacidify/increase luminal pH in endolysosomal vesicles (Ulferts et al., 2021) stimulate recruitment of the V₁ subunit of v-ATPase, which in turn recruits ATG16L1 E3 ligase (Xu et al., 2019; Fig. 3, box 4). This leads to direct membrane atg8ylation without formation of autophagosomes (Fischer et al., 2020; Hooper and Florey, 2021 Preprint;

Ulferts et al., 2021). Of relevance for the immunological subplot of this article, many of the known physiological examples of membrane atg8ylation involve interactions of host cells with microbes. This includes *Salmonella* (Xu et al., 2019) and viruses such as influenza (Ulferts et al., 2021), response to microbial or ectopic dsDNA in the cytosol (Fischer et al., 2020), and activation of NADPH oxidase (Hooper and Florey, 2021 Preprint) by phagocytic cells as they kill microbes (Nauseef, 2019).

In addition to lysosomal membrane atg8ylation, extensive physical damage of these membranes eventually elicits canonical autophagy to remove excessively damaged lysosomes by lysophagy. Damage of endolysosomal organelles occurs physiologically, e.g., during exposure to exogenous and endogenous agents including biologically active crystals of silica, monosodium urate,

and cholesterol (Maejima et al., 2013; Razani et al., 2012; Schroder and Tschoop, 2010), proteopathic fibrils or amyloid (Heneka et al., 2013; Masters et al., 2010; Papadopoulos et al., 2017; Parry et al., 2015), TRAIL-signaling induced lysosomal permeabilization (Werneburg et al., 2007), microbes including bacteria *Salmonella* and *Mycobacterium tuberculosis* (Chauhan et al., 2016; Fujita et al., 2013; Jia et al., 2018; Thurston et al., 2012; Watson et al., 2012), and coronaviruses including SARS-CoV-2 (Ghosh et al., 2020; Yue et al., 2018). A breach in lysosomal membrane integrity is subject to repair by ESCRTs (Jia et al., 2020b; Radulovic et al., 2018; Skowryra et al., 2018) or removal by canonical autophagy (Fujita et al., 2013; Jia et al., 2018; Jia et al., 2020b; Jia et al., 2020c; Maejima et al., 2013). Atg8ylation is a part of the canonical autophagy of excessively damaged lysosomes (lysophagy) set in motion by the inactivation of mTOR and the activation of AMPK (Fig. 3). The latter stages of lysophagy are aided by systems enabling selective autophagy of damaged lysosomes: the recognition of exposed luminal glycans by ubiquitin E3 ligases and protein ubiquitination (Yoshida et al., 2017), ubiquitin remodeling (Papadopoulos et al., 2017), atg8ylation of autophagosomal membrane (Maejima et al., 2013), and engagement of selective autophagy receptors possessing LIRs (Lamark and Johansen, 2021) and ubiquitin-binding or galectin-binding capabilities, including p62/SQSTM1 (Papadopoulos et al., 2017), TRIM16 (Chauhan et al., 2016), and TAX1BP1, along with its interactors TBK1 and FIP200 (Eapen et al., 2021).

In conclusion, membrane atg8ylation, whether occurring on a single membrane delimiting an organelle of the endocytic pathway or on the double membrane of the canonical autophagosome, plays a significant role in upstream signaling and downstream effector processes.

Atg8ylation and autophagy integrate innate immunity, metabolism, and quality control signals

The biological outputs of autophagy and its noncanonical forms fall into three categories: metabolic, quality control, and immune. These signals converge on the same key components in the context of membrane atg8ylation or canonical autophagy (Fig. 4). As discussed earlier, one may consider the canonical autophagy systems split into two halves coming together during the formation of autophagosomes (Axe et al., 2008; Fujita et al., 2013; Gammoh et al., 2013; Hara et al., 2008; Hayashi-Nishino et al., 2009; Itakura and Mizushima, 2010; Itakura and Mizushima, 2011; Kumar et al., 2021a; Mizushima et al., 2011; Nishimura et al., 2013; Nishimura et al., 2017; Tooze and Yoshimori, 2010): (1) the atg8ylation machinery centered on ATG16L1 as the key part of the atg8ylation E3 ligase (Fig. 4; component A); and (2) the FIP200 complex (Fig. 4; component B), whose participation distinguishes canonical autophagy from noncanonical autophagy-related processes. Three categories of signals converge on these components (Fig. 4): (a) inputs relayed by the immune and autoinflammatory signal transducing systems (Fig. 4, box 1); (b) inputs relayed by the nutrition-sensing signal transducing systems (Fig. 4, box 2); and (c) signals relayed from selective autophagy cargo receptors such as sequestosome 1/p62-like receptors (SLRs) and others (Fig. 4, box 3).

Pattern recognition receptors (PRRs). Among the innate immunity signals feeding into component A, centered on the atg8ylation E3 ligase ATG16L1 (Fig. 4), are microbial PAMPs or endogenous irritants and misplaced macromolecules referred to as DAMPs. The presence of PAMPs or DAMPs is recognized by innate immunity receptors collectively termed PRRs and relayed to the atg8ylation apparatus with or without canonical autophagy (Fig. 4). Nearly all classes of PRR act to stimulate atg8ylation. This includes TLRs (Delgado et al., 2008; Sanjuan et al., 2007) and NOD-like receptors (NLRs; Chauhan et al., 2015a; Cooney et al., 2010; Travassos et al., 2010), which recognize a wide variety of microbial products and induce atg8ylation. RIG-I-like receptors (RLRs) recognize short viral double-stranded RNA (dsRNA) and long dsRNA and detect absence of modifications in the 5' capped mRNA, whereas their adaptor mitochondrial antiviral signaling protein (MAVS) binds mATG8s and possibly participates in mitophagy (Sun et al., 2016). Of note, MAVS activates TBK1 (Liu et al., 2015), which in turn stimulates autophagy. Atg8ylation and its manifestations respond to cytosolic dsDNA recognized by the cGAS-STING system (Gui et al., 2019) and possibly to cytosolic dsRNA recognized by cGAS-like receptors, which also engage STING (Slavik et al., 2021). STING has been implicated in membrane atg8ylation (Fischer et al., 2020; Gui et al., 2019; Liu et al., 2019), canonical autophagy (Moretti et al., 2017; Rong et al., 2022; Zhang et al., 2020b), and noncanonical autophagy-related processes (Gui et al., 2019; Liu et al., 2019), many with innate immunity and other outputs (Gui et al., 2019; Moretti et al., 2017; Watson et al., 2015; Watson et al., 2012; Yamashiro et al., 2020) including neuroinflammation (Sliter et al., 2018). Several of these systems interact with ATG16L1, either directly (Cooney et al., 2010; Travassos et al., 2010) or with the help of an immunity-related small GTPase, IRGM (Chauhan et al., 2015a; Singh et al., 2006).

TBK1. TBK1 can regulate atg8ylation-associated activities and autophagy (Kumar et al., 2021a; Pilli et al., 2012; Thurston et al., 2009; Wild et al., 2011). It is a key innate immunity kinase (Fitzgerald et al., 2003) best known to immunologists for transducing PAMP and DAMP signals via cGAS-STING, TLR4-TRIF, and RIG-I-MAVS (Liu et al., 2015). As an example of integration of various signals, TBK1 is linked to metabolic signaling via AMPK (Zhao et al., 2018) and mTOR (Antonia et al., 2019; Zhu et al., 2019; Fig. 4). In the processes of atg8ylation and autophagy, TBK1 acts in a multitude of ways (Fig. 4). First, TBK1 phosphorylates STX17 at S202 (Kumar et al., 2019; Rong et al., 2022), which in turn affects FIP200 complexes and catalyzes the formation of the autophagic pro-phagophore HyPAS (Kumar et al., 2021a). Second, TBK1 activates the selective autophagy by directly phosphorylating SLRs: OPTN (Wild et al., 2011), p62/SQSTM1 (Pilli et al., 2012) and NDP52 and TAX1BP1 (Richter et al., 2016), in addition to forming physical complexes with NDP52 (Ravenhill et al., 2019; Thurston et al., 2009; Vargas et al., 2019). Third, and possibly critical for atg8ylation, TBK1 stabilizes lipidated LC3C and GABARAPL2 by phosphorylating them and protecting them from delipidation by ATG4 isoforms (Herhaus et al., 2020). In these functions, TBK1 is involved in antibacterial autophagy (Pilli et al., 2012; Thurston et al., 2009; Wild et al., 2011), antiviral autophagy (Sparrer et al., 2017; Yamashiro et al.,

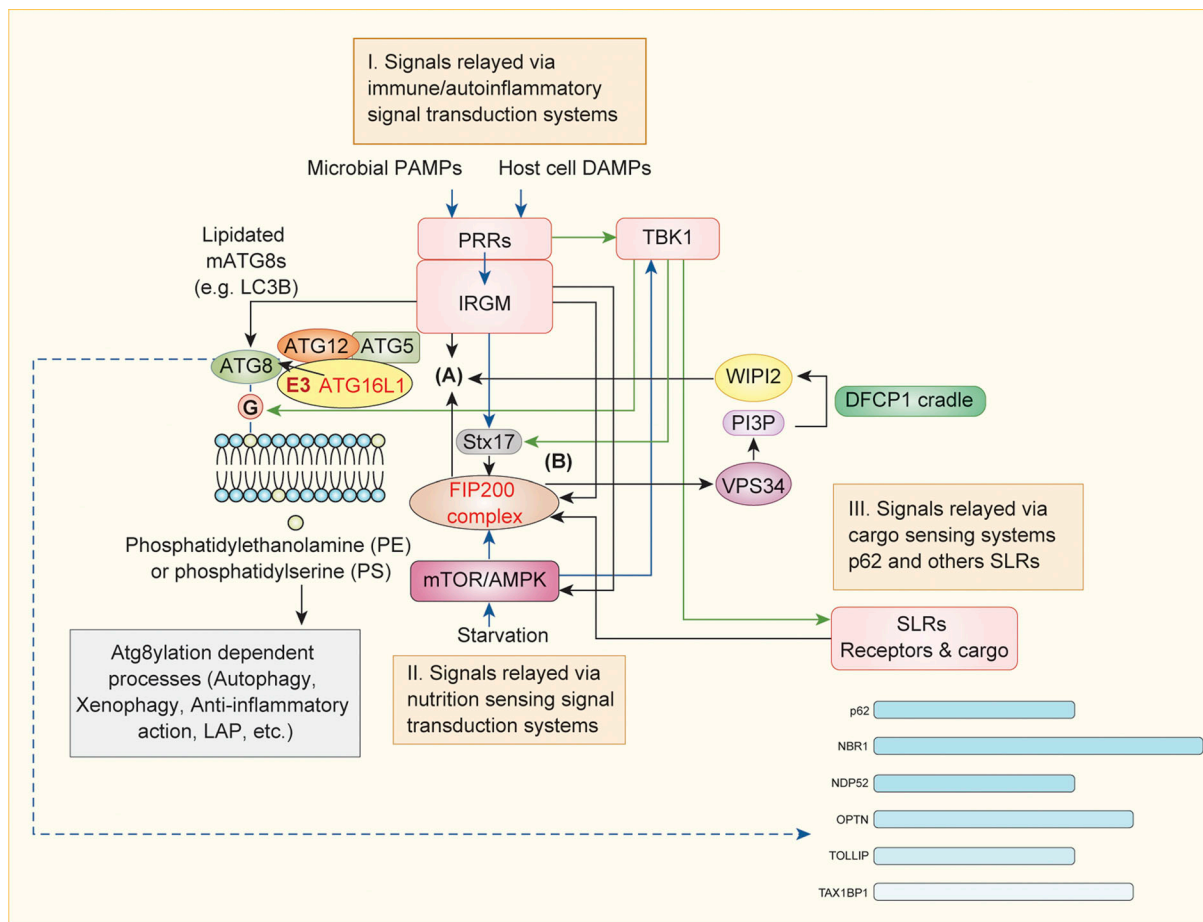


Figure 4. **Signaling inputs into the systems regulating atg8ylation and canonical autophagy.** To underscore that atg8ylation apparatus can act independently of canonical autophagy, the system is split into two parts (A and B). Atg8ylation E3 ligase centered upon ATG16L1 (A; see Fig. 1) and the FIP200 complex (B). For canonical autophagy, A and B come together (see Fig. 2). Three types of major inputs affecting components A or B or both are in peach-colored boxes (I–III) and fall in three categories: immune signals (I), signals coming from selective autophagy receptors (II), and metabolic signals (III). Immune signals are collected via PRRs assisted in many cases by immunity-related GTPases such as IRGM and often (but not exclusively) transduced via TBK1 to several components controlling atg8ylation and canonical autophagy apparatus. Cargo recognition by SLRs relays cargo capture, whereas SLRs can associate with FIP200 and in turn receive further signals from TBK1. Note that the ATG16L1 E3 ligase participates in FIP200 complex-independent standalone atg8ylation processes such as LAP and others (categorized in Fig. 1). Details in the text.

2020), mitophagy (Heo et al., 2015; Lazarou et al., 2015; Moore and Holzbaaur, 2016; Vargas et al., 2019), and even ER-phagy when it is provoked by bacterial PAMPs (Moretti et al., 2017).

IRGM. Human IRGM (Fig. 4) and its murine paralogs interact with mATG8s (Kumar et al., 2020), leading to multiple effector outputs. These include recruitment of STX17 (Kumar et al., 2018) as a component of the HyPAS fusion apparatus (Kumar et al., 2019) leading to the formation of autophagic pro-phagophores (Kumar et al., 2021a), as well as inhibition of mTOR (Kumar et al., 2020) and stabilization of AMPK (Chauhan et al., 2015a), which regulate the FIP200 complex en route to canonical autophagosomes (Kumar et al., 2021a). IRGM and its paralogs bind to both ATG16L1 and mATG8s and may present mATG8s to the ATG16L1 E3 ligase, leading to atg8ylation. Among the IRGM-dependent immunological effects is the protection of cells from excessive cGAS-STING and RIG-I-MAVS signaling (Jena et al., 2020), from excessive activation of the canonical (Mehto et al., 2019) and noncanonical inflammasomes, and from ensuing pyroptosis during bacterial invasion (Eren et al., 2020; Finethy et al., 2020).

Signals relayed via cargo sensing by selective autophagy receptors. Multiple SLRs (OPTN1, NDP52, SQSTM1, TAX1BP1, and NBR1) and other autophagy receptors recognize cargo and make initial contacts with ubiquitinated targets, followed by phagophore formation on the cargo surface (Lazarou et al., 2015; Ohnstad et al., 2020; Ravenhill et al., 2019; Smith et al., 2018; Turco et al., 2019; Vargas et al., 2019). These receptors transduce cargo recognition signals to the FIP200 half of the canonical autophagy apparatus (Fig. 4). These signals join those flowing from TBK1, an interactor and a modifier of SLRs in their antimicrobial roles (Pilli et al., 2012; Sparrer et al., 2017; Thurston et al., 2009; Wild et al., 2011) and in their role of removing mitochondria as sources of DAMPs (Heo et al., 2015; Lazarou et al., 2015; Sliter et al., 2018). In addition to SLRs, a whole group known as tripartite motif proteins (TRIMs) participate in autophagy (Kimura et al., 2016), in part by functioning as selective autophagy receptors (Mandell et al., 2014; Kimura et al., 2015; Jena et al., 2018; Di Rienzo et al., 2020; Saha et al., 2022), and as regulators of type I IFN responses (Versteeg et al., 2013).

SLRs and TRIMs interact with components from both halves of the autophagic apparatus defined by FIP200 and ATG16L1 (Fig. 4, components A and B).

Metabolic signals. AMPK and mTOR are key activators of canonical autophagy at times of nutritional, energy, and growth factor limitations (Gonzalez et al., 2020; Morishita and Mizushima, 2019). Signals coming from macro- and micronutrients including intracellular levels of amino acids, glucose, acetyl coenzyme A (via acetylation and deacetylation of proteins), free fatty acids, etc., influence various components of the autophagy apparatus (Deretic and Kroemer, 2022). These inputs engage both halves of the canonical autophagy pathway: (a) the atg8ylation E3 ligase ATG16L1 half (Fig. 4, component A; Alsaadi et al., 2019) and (b) the FIP200 half (Fig. 4, component B; Egan et al., 2011; Ganley et al., 2009; Hosokawa et al., 2009; Jung et al., 2009; Kim et al., 2011). AMPK and mTOR are in turn affected by atg8ylation in a feedback loop (Goodwin et al., 2021; Kumar et al., 2020; Nakamura et al., 2020).

AMPK and mTOR functionally interact with the v-ATPase at the lysosome (Fig. 3; Eaton et al., 2021). This is important for components of the canonical autophagy pathway, and for atg8ylation processes in general via the ATG16L1 recruitment to and association with the V₁ subunit of the v-ATPase (Hooper and Florey, 2021 Preprint; Ulferts et al., 2021; Xu et al., 2019; Fig. 3, bottom left). The v-ATPase is a potent hub for integration of signals leading to canonical autophagy and other atg8ylation manifestations.

There is ample evidence for integration of metabolic and immune inputs in controlling atg8ylation and autophagic processes. AMPK, mTOR, and ULK1 are modulated by immune signal transducers IRGM (Chauhan et al., 2015a; Kumar et al., 2020), TBK1 (Antonia et al., 2019; Zhao et al., 2018; Zhu et al., 2019), and NOD2 and RIPK2 (Lupfer et al., 2013). This is also reflected in many overlaps of canonical and noncanonical autophagic processes (Deretic, 2021; Riffelmacher et al., 2018) with immunometabolism (Brady et al., 2018; O'Neill et al., 2016; Saravia et al., 2020).

Anti-inflammatory functions of atg8ylation and autophagy

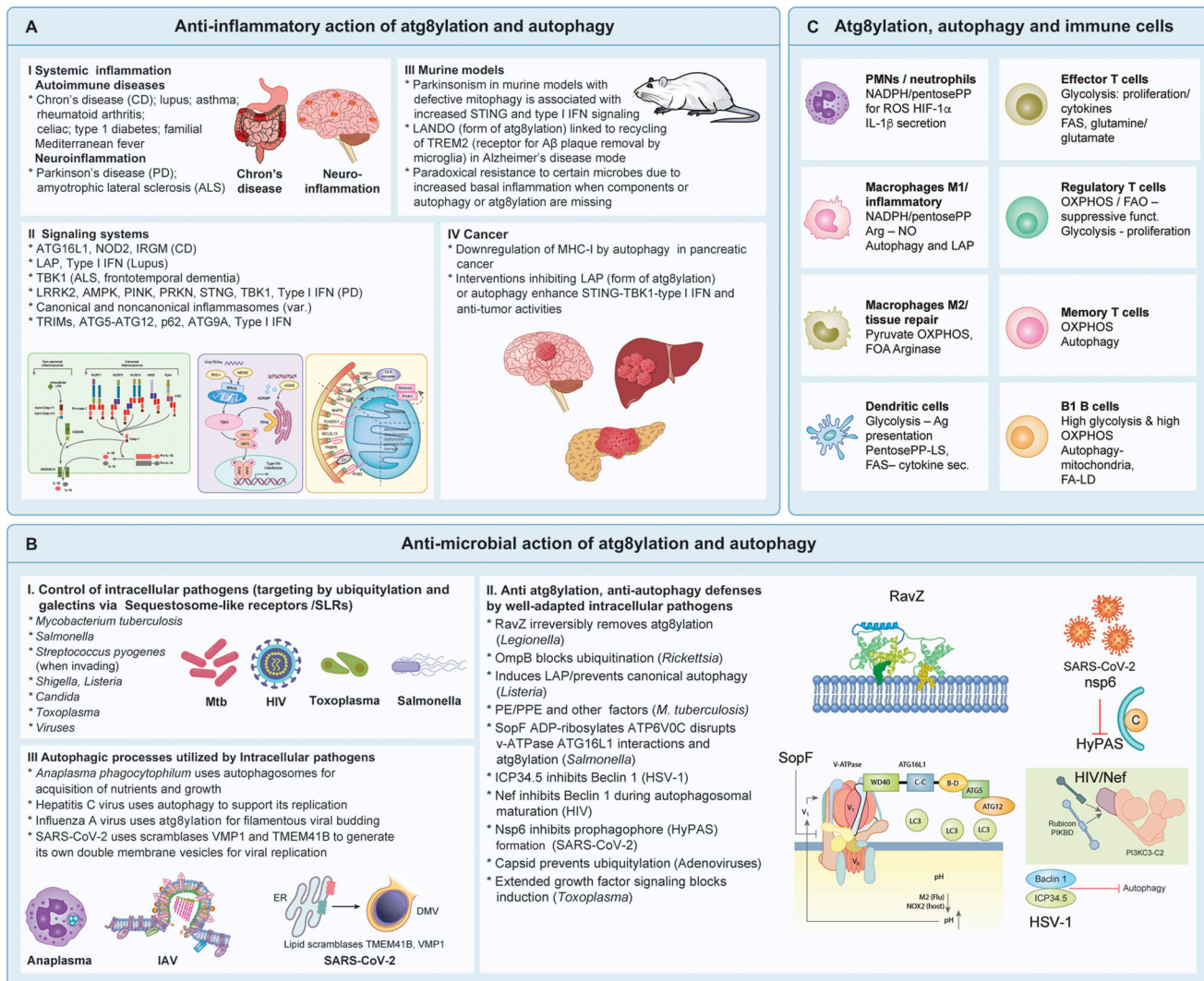
Deficiencies in canonical autophagy and noncanonical autophagy-related processes, along with the emerging concept of membrane atg8ylation, correlate with inflammatory or autoimmune disorders as detailed in recent reviews (Deretic, 2021; Galluzzi and Green, 2019; Youle, 2019). This includes (Fig. 5 A, box I) autoimmune diseases and conditions with systemic inflammation such as Crohn's disease (CD), lupus, asthma, rheumatoid arthritis, celiac disease, type 1 diabetes mellitus, and familial Mediterranean fever. These relationships extend to neurological disorders with inflammatory components, including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia. We refer the reader to a recent review for details (Deretic, 2021).

Some of the earliest genomewide association studies of any human disease (Consortium, 2007) revealed connections between polymorphisms in the genes encoding ATG16L1 and IRGM with the increased risk for CD. ATG16L1 and IRGM form a tripartite complex with NOD2 (Chauhan et al., 2015b), a familial CD

predisposition locus (Horowitz et al., 2021; Fig. 5 A, box II). This complex participates in anti-inflammatory processes via several mechanisms that involve canonical or noncanonical autophagy (Jena et al., 2018; Jena et al., 2020; Mehto et al., 2019; Singh et al., 2006), both of which are downstream outputs of atg8ylation.

Metabolic inputs and innate immunity systems may integrate with autophagic and other atg8ylation processes in the context of neurodegenerative diseases (Fig. 5 A, box II; Youle, 2019). TBK1 is a frequent site of mutations in ALS (Ahmad et al., 2016). TBK1 can be controlled by AMPK and ULK1, whereas TBK1 directly phosphorylates mTOR and activates both mTORC1 and mTORC2 in response to growth factors or PAMP-PRR signaling (Bodur et al., 2018; Tooley et al., 2021). LRRK2, a protein kinase affecting autophagy (Gomez-Suaga et al., 2012) and axonal transport of autophagosomes (Boecker et al., 2021), is commonly associated with familial PD as well as CD, leprosy, and certain cancers. LRRK2 positively regulates AMPK (Usmani et al., 2021). Metabolic changes have been observed in astrocytes derived from PD patients carrying a common LRRK2 mutation (Sonninen et al., 2020). It is worth noting that LRRK2 operates, among other compartments, within the endolysosomal system where various manifestations of atg8ylation take place. PD has been associated with inflammation, including elevated cytokines in both serum and cerebrospinal fluid (Dzambo et al., 2015). In mouse models, the regulators of mitophagy PINK1 and Parkin (Youle, 2019) have been difficult to connect with PD, likely owing to the stress-responsive nature of PINK1 and Parkin and the lack of stress exposure to lab mice. However, under conditions promoting mitochondrial stress and inflammation, manifestations of parkinsonism could be detected (Sliter et al., 2018), including during an extended aging period (Noda et al., 2020). The PD phenotype could be rescued by manipulating STING (I199N missense mutant allele of the murine Sting gene, *Tmem173*) in *Prkn*^{-/-} or *Pink1*^{-/-} mice (Sliter et al., 2018). These findings help connect the dots between failure in mitophagy (which includes atg8ylation), mitochondrial DNA release, cytosolic DNA sensing systems, and inflammation (Borsche et al., 2020; McArthur et al., 2018; Sliter et al., 2018; White et al., 2014). Although mitochondria are the major metabolic factories of the cell, here they are implicated as a source of DNA acting as a DAMP (Borsche et al., 2020), stimulating STING-TBK1 signaling to elicit a type I IFN response (Sliter et al., 2018).

Inflammasomes are cytosolic signaling complexes activated by PAMPs and DAMPs and can be canonical (Lamkanfi and Dixit, 2014) or noncanonical (Broz et al., 2020; Fig. 5 A, box II). They proteolytically activate IL-1 β and lead to its secretion along with other proinflammatory cytokines. A canonical inflammasome is centered on ASC (apoptosis-associated speck-like protein containing a CARD), pro-caspase 1, and microbial product sensors (Lamkanfi and Dixit, 2014), whereas non-canonical inflammasomes directly recognize cytosolic LPS and activate murine caspase-11 or human caspase-4 or -5, resulting in proteolytic processing of gasdermin D, causing pyroptosis (Broz et al., 2020). Autophagy or atg8ylation indirectly suppresses canonical inflammasome activation by reducing sources of DAMPs and reactive oxygen species (ROS; Nakahira et al., 2011; Sumpter et al., 2016; Zhou et al., 2011) or by



inflammation and related complications, LAP has roles in cancer progression. LAP regulates the production of anti-inflammatory cytokines in tumor-associated macrophages, which promotes immune tolerance in the cancer microenvironment by suppressing T lymphocytes (Cunha et al., 2018).

In summary, atg8ylation, in the context of autophagy or other autophagy-related and unrelated processes, is associated with nearly all key innate immunity systems and, with few exceptions, reduces inflammation. The systems and activities involved in anti-inflammatory activities of atg8ylation and canonical autophagy as one of its outputs engage both regulators of metabolism and key metabolic factories, i.e., mitochondria, with effects on immunometabolism that will be explored in the section on immune cells.

Antimicrobial functions of atg8ylation and autophagy

Xenophagy (Levine, 2005) is a term often encountered in describing autophagic elimination of intracellular microbes (Gomes and Dikic, 2014; Randow and Youle, 2014). Canonical autophagy or noncanonical atg8ylation processes can protect host cells against a variety of pathogens (Fig. 5 B, box I) including bacteria, viruses, and fungal pathogens. Mechanistic studies in vitro have established that selective autophagy receptors, in particular SLRs, recognize intracellular pathogens or vacuoles containing them when tagged by ubiquitin or galectins and execute their elimination by delivering the pathogens to degradative compartments (Gomes and Dikic, 2014; Randow and Youle, 2014). Some of the microbes studied in depth (Table S1) in this context are *Salmonella*, *Streptococcus*, and *Mycobacterium tuberculosis*. Additional notable examples of bacteria affected by autophagy or noncanonical atg8ylation processes include *Shigella flexneri* and *Listeria*. Besides bacteria, autophagy-related processes affect other microbes including viruses, fungal pathogens, and protozoa such as *Toxoplasma gondii* (Table S1).

The professional intracellular pathogens, such as intracellular bacteria (Engstrom et al., 2019; Laopanupong et al., 2021; Mitchell et al., 2018; Strong et al., 2020; Tan et al., 2018; Zhang et al., 2019b), viruses (Chang et al., 2019; Kumar et al., 2021a; Kyei et al., 2009; Orvedahl et al., 2007; Tiwari et al., 2020), and protozoa (Lopez Corcino et al., 2019), have evolved a multitude of ways to counter or disarm autophagy or components of atg8ylation (Xu et al., 2022; Xu et al., 2019; Fig. 5 B, box II). In extreme cases, highly adapted intracellular pathogens can use autophagy or factors contributing to atg8ylation and autophagy-related processes to support their own growth (Fig. 5 B, box III). This includes *Anaplasma phagocytophilum* (formerly known as *Ehrlichia*, from order Rickettsiales; Niu et al., 2012), hepatitis C virus (Lee and Ou, 2021; Twu et al., 2021), influenza A virus (Beale et al., 2014), and SARS-CoV-2 (Hoffmann et al., 2021; Schneider et al., 2021; Twu et al., 2021). Probably the most elegant examples of bacterial defenses come from studies of *Legionella pneumophila* and *Salmonella* (Fig. 5 B, box II). *L. pneumophila* encodes a factor, RavZ, that irreversibly counters atg8ylation by proteolytically removing mATG8s' C-terminal glycines, thus precluding lipidation (Choy et al., 2012). *Salmonella* SopF acts as an ADP-ribosylating enzyme modifying v-ATPase to block its recruitment of ATG16L1 and inhibit

atg8ylation (Xu et al., 2022; Xu et al., 2019). It is important to keep in mind that the majority of bacteria are not equipped to combat autophagy as one of the outputs of atg8ylation, and only a handful of highly adapted intracellular bacteria can persist in host cell's cytosol. Considering that mitochondria evolved from Rickettsia-like endosymbionts, this presents us with a clear example of a terminal bacterial-host adaptation in coevolution with autophagy (Deretic, 2010; Randow and Youle, 2014; Youle, 2019).

There is a relative dearth of studies of atg8ylation in animal models compared with the wealth of ex vivo studies using cellular models of microbial invasion. The available murine models suggest that xenophagy, even when it can be documented in vivo, is accompanied by an equal or more important action of canonical and noncanonical autophagy processes as atg8ylation outputs in protecting against excessive inflammation and tissue damage (Deretic, 2021; Deretic and Levine, 2018). A hyper-inflammatory state can be artificially generated in murine models when genes contributing to autophagy or atg8ylation are inactivated. This paradoxically presents itself as protective against infections in experimental situations (Fig. 5 A, box III). For example, inactivation of key atg8ylation genes and/or components of HyPAS in myeloid cells elevates respiratory tract inflammation and confers resistance to influenza in mice (Lu et al., 2016). Similar genetic maneuvers can be protective against murine herpesvirus reactivation (Park et al., 2016). Likewise, disrupting tissue macrophage quiescence by inactivating genes contributing to HyPAS but not atg8ylation, which normally maintains the anti-inflammatory state, confers resistance to *Listeria* in mice (Wang et al., 2020b). Autophagy or autophagy-related processes are important to prevent cytotoxicity upon stimulation with PAMPs (Levy et al., 2020) or IFN- γ (Orvedahl et al., 2019). Two conclusions can be drawn from these explorations: First, processes associated with autophagy-like phenomena and atg8ylation in principle play anti-inflammatory roles. Second, not all components of what has been classically considered canonical autophagy are needed.

Coronaviruses and SARS-CoV-2. The relationship between autophagy and coronaviruses has a relatively extensive history of studies preceding the emergence of SARS-CoV-2 and deserves special attention. Atg8ylation, autophagy, and coronaviruses intersect (Cottam et al., 2011; Cottam et al., 2014; Fung and Liu, 2019; Prentice et al., 2004; Reggiori et al., 2010). Depending on the viral species, autophagic processes have been reported to suppress coronaviruses (Guo et al., 2016; Ko et al., 2017), support their growth (Guo et al., 2017b; Prentice et al., 2004; Zhu et al., 2016), or have no effects (Schneider et al., 2012; Zhao et al., 2007). Both coronaviruses and canonical autophagy involve formation of intracellular double membranes. Coronaviruses remodel cellular membranes and generate protrusion-type viral-replication compartments (VRCs; Strating and van Kuppeveld, 2017), consisting of interconnected double membrane vesicles (DMVs), packets of merged DMVs, plus additional convoluted membranes, generating a compartment for active RNA synthesis complexes secluded away within DMVs (Snijder et al., 2020) to avoid recognition by cytoplasmic PRRs, thus minimizing antiviral type I IFN activation. Some aspects of

coronavirus VRCs include morphological features of autophagosomes (e.g., DMVs; [Snijder et al., 2006](#)) but are clearly distinct from canonical autophagosomes ([Reggiori et al., 2010](#)), although mATG8s (LC3) can be found in the vicinity ([Cottam et al., 2014](#); [Reggiori et al., 2010](#)). Unbiased global studies of host factors necessary for successful viral infection have all but ruled out the role of core ATG proteins while identifying a role for VMP1 and TMEM41B proteins ([Hoffmann et al., 2021](#); [Schneider et al., 2021](#)). The VMP1 and TMEM41B lipid scramblases ([Li et al., 2021](#)) play a general role in transfer of membrane lipids from the ER ([Ghanbarpour et al., 2021](#)) and may (independently of their role in autophagy) assist formation of SARS-CoV-2 DMVs ([Schneider et al., 2021](#)) harboring active RNA synthesis complexes ([Snijder et al., 2020](#); [Fig. 5 B](#), box III). Class III PI3-kinase is coactivated during DMV formation, and DFCP1 marks PI3P-positive domains involved in either autophagosome formation ([Axe et al., 2008](#)) or viral DMVs ([Twu et al., 2021](#)). It appears that coronavirus DMVs and canonical autophagosomes compete for membrane sources. In keeping with this, SARS-CoV-2 counteracts canonical autophagosome formation ([Kumar et al., 2021a](#); [Fig. 5 B](#), box II). SARS-CoV-2 nsp6 blocks autophagosomal pro-phagophore formation by interacting with nearly all components (SIGMAR1, VAMP7, E-SYT2, SERCA2, and TBK1) controlling HyPAS formation ([Kumar et al., 2021a](#)).

SARS-CoV-2 additionally interferes with other aspects of autophagosomal and lysosomal pathways. ORF3a affects autophagosome-lysosome fusion ([Hayn et al., 2021](#); [Miao et al., 2021](#)), whereas SARS-CoV-2 ORF7 interferes with autolysosomal acidification ([Hayn et al., 2021](#)). On the flip side, autophagy factors counter actions of SARS-CoV-2 proteins: ATG9A repairs plasma membrane damage induced by SARS-CoV-2 ORF3a ([Claude-Taupin et al., 2021](#)). Adding to these antagonistic relationships between the virus and the host, atg8ylation phenomena may play a role in countering COVID-19 pathogenesis. Cells release exosomes dubbed decoy exosomes or “defensosomes” ([Fig. 2 D](#)) that can soak up microbial toxins so that they do not attack cells ([Keller et al., 2020](#)). This happens in an ATG16L1-dependent fashion ([Keller et al., 2020](#)), and has been extended to the release of ACE2⁺ defensosomes that bind and block SARS-CoV-2 entry ([Ching et al., 2021 Preprint](#)). Presence of ACE2⁺ exosomes in bronchioalveolar lavages of critically ill COVID-19 patients was reported as being associated with reduced hospitalization times ([Ching et al., 2021 Preprint](#)). These findings suggest that atg8ylation and variants of secretory autophagy may contribute to antiviral defenses, albeit they can help viral egress in other cases, such as atg8ylation-dependent filamentous influenza A budding from the plasma membrane ([Beale et al., 2014](#)).

Immune cells, atg8ylation, and autophagy

The functions of ATG genes in immune cells have been extensively reviewed ([Clarke and Simon, 2019](#); [Deretic, 2021](#); [Deretic et al., 2013](#); [Macian, 2019](#); [Riffelmacher et al., 2018](#)). Since canonical autophagy (a classical downstream effector of atg8ylation) is a metabolic process, autophagy in immune cells manifests itself as an immunometabolic phenomenon ([O'Neill et al., 2016](#)), tracking with the known roles of mTOR and

AMPK ([Fig. 5 C](#)). This is reflected in the reported beneficial effects of metformin, a clinically used AMPK activator, which improves immune responses by enhancing survival of memory CD8⁺ T cells ([Bohme et al., 2020](#)) and moderates Th17 responses by CD⁺ T cells ([Bharath et al., 2020](#)) in infection, diabetes, and “inflammaging” contexts. Canonical autophagy is believed to support self-renewal and quiescence in immune stem cells, as well as cytoplasmic remodeling during immune cell differentiation ([Riffelmacher et al., 2018](#)). Atg8ylation components support neutrophils ([Riffelmacher et al., 2017](#)), B1a cells ([Clarke et al., 2018](#); [Miller et al., 2008](#)), invariant NKT cells ([Salio et al., 2014](#)) and NKT cells ([Zhu et al., 2018](#)). They are required for T cell survival and function ([Jia et al., 2011](#); [Li et al., 2006](#); [Pua et al., 2009](#)) and for preservation of effector and memory CD8⁺ T cells ([Puleston et al., 2014](#); [Xu et al., 2014](#)). Autophagy plays a role in the metabolism of CD8⁺ T cells, affecting their antitumor immunity ([DeVorkin et al., 2019](#)). These processes counter T cell anergy ([Mocholi et al., 2018](#)), whereas tissue-resident memory CD8⁺ cells and mucosa-associated invariant T cells display high autophagy levels ([Swadling et al., 2020](#)). Much of the role of atg8ylation in lymphocyte function is to enhance clearance of virus-infected and cancerous cells while minimizing excessive inflammation and tissue pathology.

The role of atg8ylation processes other than canonical autophagy in immune cells or in cells that are targets of cell-mediated immunity are only beginning to be investigated. This often includes modulation of cell surface receptors. Plasma membrane presence of the cystine transporter SLC7A11 is diminished in pancreatic ductal adenocarcinoma cells knocked down for ATG5 or ATG7 ([Mukhopadhyay et al., 2021](#)). A further example of receptor regulation ([Heckmann et al., 2019](#); [Ulland et al., 2017](#)) by atg8ylation processes and intersections between atg8ylation, autophagy, inflammation, and metabolism, is TREM2, a surface receptor required for microglial responses and a risk factor in sporadic Alzheimer’s disease ([Shi and Holtzman, 2018](#)). An atg8ylation process LANDO promotes recycling of the TREM2 which allows more efficient clearance of A β by the microglia and mitigates inflammatory microglial activation ([Heckmann et al., 2019](#); [Fig. 5 A](#), box III). However, TREM2 also plays a role in immunometabolism through control of mTOR and canonical autophagy and maintains microglial metabolic fitness, which fails in TREM2 hypomorphs and is correctable by cyclocreatine supplementation ([Ulland et al., 2017](#)). MHC-I downregulation contributes to pancreatic cancer being immunologically cold and recalcitrant to check point inhibitors immunotherapy ([Yamamoto et al., 2020](#); [Fig. 5 A](#), box IV). This downregulation depends on FIP200 and other components of the FIP200 complex, whereas Rubicon seems not to affect it ([Yamamoto et al., 2020](#)), thus ruling out LAP-like processes that depend on Rubicon ([Heckmann et al., 2019](#); [Martinez et al., 2015](#)). Until recently, it has been very difficult to envision how a single membrane endosome formed during MHC-I endocytosis might result in degradation by canonical autophagy. However, the latest findings ([Kumar et al., 2021a](#)) demonstrating that canonical autophagosomes are generated through fusion between endosomes and FIP200⁺ cis-Golgi membranes thus forming the HyPAS pro-phagophore can explain how endocytosed proteins/

receptors end up being degraded in canonical autolysosomes. Atg8ylation, in the form of LAP, by tumor-associated macrophages is immunosuppressive, as found in a murine model of melanoma where LAP reduces STING-mediated type I IFN response normally important to spur infiltrating antitumor T cells (Cunha et al., 2018). This aspect seems to be of general import, as enhanced STING-mediated type I IFN responses due to inhibition of atg8ylation or autophagy are beneficial in cancer or cancer treatment models (Poillet-Perez et al., 2020; Yamazaki et al., 2020; Fig. 5 A, box IV). Thus, various proteins at the surface of immune cells or of cells that are their targets are affected by atg8ylation systems with important immunological consequences.

Mitochondrial abundance and their functionality depend on atg8ylation through mitophagy, which is essential for proper function of immune cells, and therefore their participation in clearance of infection or cancer and tissue repair and homeostasis (Li et al., 2019; Nakahira et al., 2011; Sliter et al., 2018). Developmental mitophagy is immunologically important in nonimmune cells because retention of erythroid mitochondria can trigger autoimmune diseases such as lupus (Caielli et al., 2021). Given the evolutionary origins of mitochondria from cytosol invading bacteria, it is not surprising that mitochondria to this day serve as signaling platforms for activation of protective innate immunity in response to bacterial and viral PAMPs. Under pathological conditions, mitochondria themselves become sources of endogenous DAMPs (oxidized mtDNA, dsDNA, dsRNA, cardiolipin, ROS), which stimulate a variety of PRRs and contribute to degenerative and inflammatory states (Youle, 2019). Mitochondria are furthermore the principal contributors to immunometabolism (Mills et al., 2017). This is of particular significance in immune cells whereby switching between oxidative phosphorylation (OXPHOS) and glycolysis has to match or even determines activation levels of T cells, macrophages, dendritic cells (Mills et al., 2017), and as recently shown, neutrophils (Willson et al., 2022; Fig. 5 C). It is well known that glycolysis dominates in proinflammatory classically activated macrophages whereas OXPHOS predominates in alternatively activated macrophages involved in tissue repair (Mills et al., 2017). Even in neutrophils, where mitochondrial electron transport complexes are traditionally believed to have very limited expression, recent studies show that they nevertheless contribute to ROS formation and stabilization of HIF-1 α under hypoxic conditions in inflammatory sites (Willson et al., 2022), as during pulmonary complications in covid patients (Ackermann et al., 2021). Mitophagy has been shown to play an important role in immune cell metabolic switch from glycolysis to OXPHOS.

In conclusion, the common themes regarding the role of atg8ylation and autophagy as its thus far best studied output in immune cells include effects on immunometabolism, surface receptor expression, cytoplasmic immune signaling complexes, mitochondrial abundance, and quality control, all with consequences for proper function of immune cells and systems in various tissues and in diverse disease contexts.

Conclusions and outlook

The expanded concept of atg8ylation as a membrane stress response has many physiological effects based on quality control,

metabolism, and roles in immunity. Experimental analyses have revealed that many mammalian ATG genes, including mATG8s, function in processes other than canonical autophagy. The atg8ylation concept—a covalent modification of stressed or remodeling membranes—mirrors ubiquitin modification of proteins. The crossovers between ubiquitylation and atg8ylation exist, as evident from examples of the ubiquitylation of glycolipids such as bacterial LPS when eroding into the mammalian cell cytoplasm (Otten et al., 2021). Conversely, protein atg8ylation can occur (Agrotis et al., 2019; Nguyen et al., 2021).

Atg8ylation participates in an expanding list of processes and includes but is not limited to canonical and noncanonical autophagy as its manifestations. In this view, the noncanonical membrane modifications and remodeling processes such as LAP, LANDO, selective microautophagy, EV/exosome secretion, and secretory autophagy, are easier to systematically organize and understand. The concept of atg8ylation also offers a new perspective on drug development by differentiating atg8ylation from canonical autophagy as targets of interest in different diseases.

The immune functions of canonical and noncanonical autophagy, and the emerging concept of atg8ylation as a membrane stress response, have been summarized herein. They manifest themselves in interactions with microbial pathogens as well as in cancer and as containment of endogenous sources of inflammation. Classically, autophagy is based on digestion of self at times of starvation, organellar malfunction, or elimination of incoming microbes during infection. These functions are conflated in mitophagy, as a product of an evolutionary “truce” between the host and an endosymbiont of bacterial ancestry. Autophagy is likely tirelessly at work against microbial would-be invaders, and, as emphasized here, in protection against endogenous sources of inflammation. Harnessing the full potential of autophagy and atg8ylation in separate and more granular ways may help in protection against current and future pandemics, as well as in treatments of cancer, neurodegenerative, and other diseases.

Online supplemental material

Table S1 shows examples of intracellular microbes studied as targets for elimination by autophagy.

Acknowledgments

We thank Graham Timmins for comments on the manuscript.

V. Deretic was supported by National Institutes of Health grants R37AI042999 and R01AI11935 and National Institute of General Medical Sciences grant P20GM121176. M. Lazarou was supported by grants GNT1106471 and GNT1160315 from National Health and Medical Research Council, DP200100347 and future fellowship FT1601100063 from the Australian Research Council.

The authors declare no competing financial interests.

Submitted: 21 March 2022

Revised: 16 May 2022

Accepted: 26 May 2022

References

- Ackermann, M., H.J. Anders, R. Bilyy, G.L. Bowlin, C. Daniel, R. De Lorenzo, M. Egeblad, T. Henneke, A. Hidalgo, M. Hoffmann, et al. 2021. Patients with COVID-19: In the dark-NETs of neutrophils. *Cell Death Differ.* 28: 3125–3139. <https://doi.org/10.1038/s41418-021-00805-z>
- Agrotis, A., L. von Chamier, H. Oliver, K. Kiso, T. Singh, and R. Ketteler. 2019. Human ATG4 autophagy proteases counteract attachment of ubiquitin-like LC3/GABARAP proteins to other cellular proteins. *J. Biol. Chem.* 294: 12610–12621. <https://doi.org/10.1074/jbc.AC119.009977>
- Ahmad, L., S.Y. Zhang, J.L. Casanova, and V. Sancho-Shimizu. 2016. Human TBK1: A gatekeeper of neuroinflammation. *Trends Mol. Med.* 22:511–527. <https://doi.org/10.1016/j.molmed.2016.04.006>
- Alsaadi, R.M., T.T. Losier, W. Tian, A. Jackson, Z. Guo, D.C. Rubinsztein, and R.C. Russell. 2019. ULK1-mediated phosphorylation of ATG16L1 promotes xenophagy, but destabilizes the ATG16L1 Crohn's mutant. *EMBO Re.* 20:e46885. <https://doi.org/10.15252/embr.201846885>
- Andrade, R.M., M. Wessendarp, M.J. Gubbels, B. Striepen, and C.S. Subauste. 2006. CD40 induces macrophage anti-Toxoplasma gondii activity by triggering autophagy-dependent fusion of pathogen-containing vacuoles and lysosomes. *J. Clin. Investig.* 116:2366–2377. <https://doi.org/10.1172/JCI28796>
- Antonia, R.J., J. Castillo, L.E. Herring, D.S. Serafin, P. Liu, L.M. Graves, A.S. Baldwin, and R.S. Hagan. 2019. TBK1 limits mTORC1 by promoting phosphorylation of raptor Ser877. *Sci. Rep.* 9:13470. <https://doi.org/10.1038/s41598-019-49707-8>
- Axe, E.L., S.A. Walker, M. Manifava, P. Chandra, H.L. Roderick, A. Habermann, G. Griffiths, and N.T. Ktistakis. 2008. Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. *J. Cell Biol.* 182:685–701. <https://doi.org/10.1083/jcb.200803137>
- Ballabio, A., and J.S. Bonifacino. 2020. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat. Rev. Mol. Cell Biol.* 21:101–118. <https://doi.org/10.1038/s41580-019-0185-4>
- Beale, R., H. Wise, A. Stuart, B.J. Ravenhill, P. Digard, and F. Randow. 2014. A LC3-interacting motif in the influenza A virus M2 protein is required to subvert autophagy and maintain virion stability. *Cell Host Microbe.* 15: 239–247. <https://doi.org/10.1016/j.chom.2014.01.006>
- Bharath, L.P., M. Agrawal, G. McCambridge, D.A. Nicholas, H. Hasturk, J. Liu, K. Jiang, R. Liu, Z. Guo, J. Deeney, et al. 2020. Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. *Cell Metabol.* 32:44–55.e6. <https://doi.org/10.1016/j.cmet.2020.04.015>
- Bhushan, J., J.B. Radke, Y.C. Perng, M. McAllaster, D.J. Lenschow, H.W. Virgin, and L.D. Sibley. 2020. ISG15 connects autophagy and IFN-gamma-Dependent control of Toxoplasma gondii infection in human cells. *mBio.* 11:e00852-20. <https://doi.org/10.1128/mBio.00852-20>
- Birmingham, C.L., A.C. Smith, M.A. Bakowski, T. Yoshimori, and J.H. Brummell. 2006. Autophagy controls Salmonella infection in response to damage to the Salmonella-containing vacuole. *J. Biol. Chem.* 281: 11374–11383. <https://doi.org/10.1074/jbc.M509157200>
- Boada-Romero, E., J. Martinez, B.L. Heckmann, and D.R. Green. 2020. The clearance of dead cells by efferocytosis. *Nat. Rev. Mol. Cell Biol.* 21: 398–414. <https://doi.org/10.1038/s41580-020-0232-1>
- Bodur, C., D. Kazyken, K. Huang, B. Ekim Ustunel, K.A. Siroky, A.S. Tooley, I.E. Gonzalez, D.H. Foley, H.A. Acosta-Jaquez, T.M. Barnes, et al. 2018. The IKK-related kinase TBK1 activates mTORC1 directly in response to growth factors and innate immune agonists. *EMBO J.* 37:19–38. <https://doi.org/10.15252/embj.201696164>
- Boecker, C.A., J. Goldsmith, D. Dou, G.G. Cajka, and E.L.F. Holzbaur. 2021. Increased LRRK2 kinase activity alters neuronal autophagy by disrupting the axonal transport of autophagosomes. *Curr. Biol.* 31:2140–2154.e6. <https://doi.org/10.1016/j.cub.2021.02.061>
- Bohme, J., N. Martinez, S. Li, A. Lee, M. Marzuki, A.M. Tizazu, D. Ackart, J.H. Frenkel, A. Todd, E. Lachmandas, et al. 2020. Metformin enhances antimycobacterial responses by educating CD8+ T-cell immunometabolic circuits. *Nat. Commun.* 11:5225. <https://doi.org/10.1038/s41467-020-19095-z>
- Borsche, M., I.R. Konig, S. Delcambre, S. Petrucci, A. Balck, N. Bruggemann, A. Zimprich, K. Wasner, S.L. Pereira, M. Avenali, et al. 2020. Mitochondrial damage-associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism. *Brain.* 143:3041–3051. <https://doi.org/10.1093/brain/awaa246>
- Bourdenx, M., A. Martin-Segura, A. Scrivo, J.A. Rodriguez-Navarro, S. Kaushik, I. Tasset, A. Diaz, N.J. Storm, Q. Xin, Y.R. Juste, et al. 2021. Chaperone-mediated autophagy prevents collapse of the neuronal metastable proteome. *Cell.* 184:2696–2714.e25. <https://doi.org/10.1016/j.cell.2021.03.048>
- Brady, O.A., J.A. Martina, and R. Puertollano. 2018. Emerging roles for TFEF in the immune response and inflammation. *Autophagy.* 14:181–189. <https://doi.org/10.1080/15548627.2017.1313943>
- Broz, P., P. Pelegrin, and F. Shao. 2020. The gasdermins, a protein family executing cell death and inflammation. *Nat. Rev. Immunol.* 20:143–157. <https://doi.org/10.1038/s41577-019-0228-2>
- Bryk, R., S. Mundhra, X. Jiang, M. Wood, D. Pfau, E. Weber, S. Park, L. Zhang, C. Wilson, R. Van der Westhuyzen, et al. 2020. Potentiation of rifampin activity in a mouse model of tuberculosis by activation of host transcription factor EB. *PLoS Pathog.* 16:e1008567. <https://doi.org/10.1371/journal.ppat.1008567>
- Budzik, J.M., D.L. Swaney, D. Jimenez-Morales, J.R. Johnson, N.E. Garelis, T. Repasy, A.W. Roberts, L.M. Popov, T.J. Parry, D. Pratt, et al. 2020. Dynamic post-translational modification profiling of Mycobacterium tuberculosis-infected primary macrophages. *Elife.* 9:e51461. <https://doi.org/10.7554/eLife.51461>
- Burger, E., A. Araujo, A. Lopez-Yglesias, M.W. Rajala, L. Geng, B. Levine, L.V. Hooper, E. Burstein, and F. Yarovinsky. 2018. Loss of paneth cell autophagy causes acute susceptibility to Toxoplasma gondii-mediated inflammation. *Cell Host Microbe.* 23:177–190.e4. <https://doi.org/10.1016/j.chom.2018.01.001>
- Caielli, S., J. Cardenas, A.A. de Jesus, J. Baisch, L. Walters, J.P. Blanck, P. Balasubramanian, C. Stagnar, M. Ohouo, S. Hong, et al. 2021. Erythroid mitochondrial retention triggers myeloid-dependent type I interferon in human SLE. *Cell.* 184:4464–4479.e19. <https://doi.org/10.1016/j.cell.2021.07.021>
- Carosi, J.M., T.N. Nguyen, M. Lazarou, S. Kumar, and T.J. Sargeant. 2021. ATG8ylation of proteins: A way to cope with cell stress? *J. Cell Biol.* 220: e202108120. <https://doi.org/10.1083/jcb.202108120>
- Castillo, E.F., A. Dekonenko, J. Arko-Mensah, M.A. Mandell, N. Dupont, S. Jiang, M. Delgado-Vargas, G.S. Timmins, D. Bhattacharya, H. Yang, et al. 2012. Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation. *Proc. Natl. Acad. Sci. USA.* 109: E3168–E3176. <https://doi.org/10.1073/pnas.1210500109>
- Cemna, M., and J.H. Brummell. 2012. Interactions of pathogenic bacteria with autophagy systems. *Curr. Biol.* 22:R540–R545. <https://doi.org/10.1016/j.cub.2012.06.001>
- Chai, Q., X. Wang, L. Qiang, Y. Zhang, P. Ge, Z. Lu, Y. Zhong, B. Li, J. Wang, L. Zhang, et al. 2019. A Mycobacterium tuberculosis surface protein recruits ubiquitin to trigger host xenophagy. *Nat. Commun.* 10:1973. <https://doi.org/10.1038/s41467-019-09955-8>
- Chang, C., L.N. Young, K.L. Morris, S. von Bulow, J. Schoneberg, H. Yamamoto-Imoto, Y. Oe, K. Yamamoto, S. Nakamura, G. Stjepanovic, et al. 2019. Bidirectional control of autophagy by BECN1 BARA domain dynamics. *Mol. Cell.* 73:339–353.e6. <https://doi.org/10.1016/j.molcel.2018.10.035>
- Chauhan, S., S. Kumar, A. Jain, M. Ponpuak, M.H. Mudd, T. Kimura, S.W. Choi, R. Peters, M. Mandell, J.A. Bruun, et al. 2016. TRIMs and galectins globally cooperate and TRIM16 and galectin-3 Co-direct autophagy in endomembrane damage homeostasis. *Dev. Cell.* 39:13–27. <https://doi.org/10.1016/j.devcel.2016.08.003>
- Chauhan, S., M.A. Mandell, and V. Deretic. 2015a. IRGM governs the core autophagy machinery to conduct antimicrobial defense. *Mol. Cell.* 58: 507–521. <https://doi.org/10.1016/j.molcel.2015.03.020>
- Chauhan, S., M.A. Mandell, and V. Deretic. 2015b. Mechanism of action of the tuberculosis and Crohn disease risk factor IRGM in autophagy. *Autophagy.* 12:429–431. <https://doi.org/10.1080/15548627.2015.1084457>
- Chen, M., Q. Meng, Y. Qin, P. Liang, P. Tan, L. He, Y. Zhou, Y. Chen, J. Huang, R.F. Wang, and J. Cui. 2016. TRIM14 inhibits cGAS degradation mediated by selective autophagy receptor p62 to promote innate immune responses. *Mol. Cell.* 64:105–119. <https://doi.org/10.1016/j.molcel.2016.08.025>
- Ching, K.L., M. de Vries, J. Gago, K. Dancel-Manning, J. Sall, W.J. Rice, C. Barnett, F.X. Liang, L.E. Thorpe, B. Shopsin, et al. 2021. ACE2-containing defensosomes serve as decoys to inhibit SARS-CoV-2 infection. *bioRxiv.* (Preprint posted December 17, 2021). <https://doi.org/10.1101/2021.12.17.473223>
- Choy, A., J. Dancourt, B. Mugo, T.J. O'Connor, R.R. Isberg, T.J. Melia, and C.R. Roy. 2012. The Legionella effector RavZ inhibits host autophagy through irreversible Atg8 deconjugation. *Science.* 338:1072–1076. <https://doi.org/10.1126/science.1227026>
- Clarke, A.J., T. Riffelmacher, D. Braas, R.J. Cornell, and A.K. Simon. 2018. B1a B cells require autophagy for metabolic homeostasis and self-renewal. *J. Exp. Med.* 215:399–413. <https://doi.org/10.1084/jem.20170771>

- Clarke, A.J., and A.K. Simon. 2019. Autophagy in the renewal, differentiation and homeostasis of immune cells. *Nat. Rev. Immunol.* 19:170–183. <https://doi.org/10.1038/s41577-018-0095-2>
- Claude-Taupin, A., J. Jia, Z. Bhujabal, M. Garfa-Traore, S. Kumar, G.P.D. da Silva, R. Javed, Y. Gu, L. Allers, R. Peters, et al. 2021. ATG9A protects the plasma membrane from programmed and incidental permeabilization. *Nat. Cell Biol.* 23:846–858. <https://doi.org/10.1038/s41556-021-00706-w>
- Wellcome Trust Case Control Consortium. 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature.* 447:661–678. <https://doi.org/10.1038/nature05911>
- Cooney, R., J. Baker, O. Brain, B. Danis, T. Pichulik, P. Allan, D.J.P. Ferguson, B.J. Campbell, D. Jewell, and A. Simmons. 2010. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. *Nat. Med.* 16:90–97. <https://doi.org/10.1038/nm.2069>
- Cottam, E.M., H.J. Maier, M. Manifava, L.C. Vaux, P. Chandra-Schoenfelder, W. Gerner, P. Britton, N.T. Ktistakis, and T. Wileman. 2011. Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. *Autophagy.* 7:1335–1347. <https://doi.org/10.4161/auto.7.11.16642>
- Cottam, E.M., M.C. Whelband, and T. Wileman. 2014. Coronavirus NSP6 restricts autophagosome expansion. *Autophagy.* 10:1426–1441. <https://doi.org/10.4161/auto.29309>
- Cunha, L.D., M. Yang, R. Carter, C. Guy, L. Harris, J.C. Crawford, G. Quarato, E. Boada-Romero, H. Kalkavan, M.D.L. Johnson, et al. 2018. LC3-Associated phagocytosis in myeloid cells promotes tumor immune tolerance. *Cell.* 175:429–441.e16. <https://doi.org/10.1016/j.cell.2018.08.061>
- Dalle Pezze, P., E. Karanasiou, V. Kandia, M. Manifava, S.A. Walker, N. Gambardella Le Novere, and N.T. Ktistakis. 2021. ATG13 dynamics in nonselective autophagy and mitophagy: Insights from live imaging studies and mathematical modeling. *Autophagy.* 17:1131–1141. <https://doi.org/10.1080/15548627.2020.1749401>
- Delgado, M.A., R.A. Elmaoued, A.S. Davis, G. Kyei, and V. Deretic. 2008. Toll-like receptors control autophagy. *EMBO J.* 27:1110–1121. <https://doi.org/10.1038/emboj.2008.31>
- Deretic, V. 2010. Autophagy of intracellular microbes and mitochondria: Two sides of the same coin? *F1000 Biol. Rep.* 2:45. <https://doi.org/10.1038/B2-45>
- Deretic, V. 2021. Autophagy in inflammation, infection, and immunometabolism. *Immunity.* 54:437–453. <https://doi.org/10.1016/j.immuni.2021.01.018>
- Deretic, V., and G. Kroemer. 2022. Autophagy in metabolism and quality control: Opposing, complementary or interlinked functions. *Autophagy.* 18:283–292. <https://doi.org/10.1080/15548627.2021.1933742>
- Deretic, V., and B. Levine. 2018. Autophagy balances inflammation in innate immunity. *Autophagy.* 14:243–251. <https://doi.org/10.1080/15548627.2017.1402992>
- Deretic, V., T. Saitoh, and S. Akira. 2013. Autophagy in infection, inflammation and immunity. *Nat. Rev. Immunol.* 13:722–737. <https://doi.org/10.1038/nri3532>
- DeVorkin, L., N. Pavey, G. Carleton, A. Comber, C. Ho, J. Lim, E. McNamara, H. Huang, P. Kim, L.G. Zacharias, et al. 2019. Autophagy regulation of metabolism is required for CD8(+) T cell anti-tumor immunity. *Cell Rep.* 27:502–513.e5. <https://doi.org/10.1016/j.celrep.2019.03.037>
- Di Rienzo, M., A. Romagnoli, M. Antonioli, M. Piacentini, and G.M. Fimia. 2020. TRIM proteins in autophagy: Selective sensors in cell damage and innate immune responses. *Cell Death Differ.* 27:887–902. <https://doi.org/10.1038/s41418-020-0495-2>
- Dong, S., Q. Wang, Y.R. Kao, A. Diaz, I. Tasset, S. Kaushik, V. Thiruthuvanathan, A. Zintiridou, E. Nieves, M. Dzieciatkowska, et al. 2021. Chaperone-mediated autophagy sustains haematopoietic stem-cell function. *Nature.* 591:117–123. <https://doi.org/10.1038/s41586-020-03129-z>
- Dooley, H.C., M. Razi, H.E.J. Polson, S.E. Girardin, M.I. Wilson, and S.A. Tooze. 2014. WIPI2 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12-5-16L1. *Mol. Cell.* 55:238–252. <https://doi.org/10.1016/j.molcel.2014.05.021>
- Dupont, N., S. Jiang, M. Pilli, W. Ornatowski, D. Bhattacharya, and V. Deretic. 2011. Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1 β . *EMBO J.* 30:4701–4711. <https://doi.org/10.1038/emboj.2011.398>
- Durgan, J., A.H. Lystad, K. Sloan, S.R. Carlsson, M.I. Wilson, E. Marcassa, R. Ulferts, J. Webster, A.F. Lopez-Clavijo, M.J. Wakelam, et al. 2021. Non-canonical autophagy drives alternative ATG8 conjugation to phosphatidylserine. *Mol. Cell.* 81:2031–2040.e8. <https://doi.org/10.1016/j.molcel.2021.03.020>
- Dzambo, N., C.L. Geczy, and G.M. Halliday. 2015. Inflammation is genetically implicated in Parkinson's disease. *Neuroscience.* 302:89–102. <https://doi.org/10.1016/j.neuroscience.2014.10.028>
- Eapen, V.V., S. Swarup, M.J. Hoyer, J.A. Paulo, and J.W. Harper. 2021. Quantitative proteomics reveals the selectivity of ubiquitin-binding autophagy receptors in the turnover of damaged lysosomes by lysophagy. *Elife.* 10:e72328. <https://doi.org/10.7554/eLife.72328>
- Eaton, A.F., M. Merkulova, and D. Brown. 2021. The H(+)-ATPase (V-AT-Pase): From proton pump to signaling complex in health and disease. *Am. J. Physiol. Cell Physiol.* 320:C392–C414. <https://doi.org/10.1152/ajpcell.00442.2020>
- Egan, D.F., D.B. Shackelford, M.M. Mihaylova, S. Gelino, R.A. Kohnz, W. Mair, D.S. Vasquez, A. Joshi, D.M. Gwinn, R. Taylor, et al. 2011. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. *Science.* 331:456–461. <https://doi.org/10.1126/science.1196371>
- Engstrom, P., T.P. Burke, G. Mitchell, N. Ingabire, K.G. Mark, G. Golovkine, A.T. Iavarone, M. Rape, J.S. Cox, and M.D. Welch. 2019. Evasion of autophagy mediated by Rickettsia surface protein OspB is critical for virulence. *Nat. Microbiol.* 4:2538–2551. <https://doi.org/10.1038/s41564-019-0583-6>
- Eren, E., R. Planes, S. Bagayoko, P.J. Bordignon, K. Chaoui, A. Hessel, K. Santoni, M. Pinilla, B. Lagrange, O. Burlet-Schiltz, et al. 2020. Irgm2 and Gate-16 cooperatively dampen Gram-negative bacteria-induced caspase-11 response. *EMBO Rep.* 21:e50829. <https://doi.org/10.15252/embr.202050829>
- Evavold, C.L., J. Ruan, Y. Tan, S. Xia, H. Wu, and J.C. Kagan. 2018. The pore-forming protein gasdermin D regulates interleukin-1 secretion from living macrophages. *Immunity.* 48:35–44.e6. <https://doi.org/10.1016/j.immuni.2017.11.013>
- Finethy, R., J. Dockterman, M. Kutsch, N. Orench-Rivera, G.D. Wallace, A.S. Piro, S. Luoma, A.K. Haldar, S. Hwang, J. Martinez, et al. 2020. Dynamin-related Irgm proteins modulate LPS-induced caspase-11 activation and septic shock. *EMBO Rep.* 21:e50830. <https://doi.org/10.15252/embr.202050830>
- Fischer, T.D., C. Wang, B.S. Padman, M. Lazarou, and R.J. Youle. 2020. STING induces LC3B lipidation onto single-membrane vesicles via the V-ATPase and ATG16L1-WD40 domain. *J. Cell Biology.* 219:e202009128. <https://doi.org/10.1083/jcb.202009128>
- Fitzgerald, K.A., S.M. McWhirter, K.L. Faia, D.C. Rowe, E. Latz, D.T. Golenbock, A.J. Coyle, S.M. Liao, and T. Maniatis. 2003. IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat. Immunol.* 4:491–496. <https://doi.org/10.1038/ni921>
- Fletcher, K., R. Ulferts, T. Veith, N. Gammoh, J.M. Arasteh, U. Mayer, S.R. Carding, T. Wileman, R. Beale, and O. Florey. 2018. The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. *EMBO J.* 37:e97840. <https://doi.org/10.15252/embr.201797840>
- Florey, O., N. Gammoh, S.E. Kim, X. Jiang, and M. Overholtzer. 2015a. V-ATPase and osmotic imbalances activate endolysosomal LC3 lipidation. *Autophagy.* 11:88–99. <https://doi.org/10.4161/15548627.2014.984277>
- Florey, O., S.E. Kim, and M. Overholtzer. 2015b. Entosis: Cell-in-Cell formation that kills through entotic cell death. *Curr. Mol. Med.* 15:861–866. <https://doi.org/10.2174/1566524015666151026100042>
- Florey, O., S.E. Kim, C.P. Sandoval, C.M. Haynes, and M. Overholtzer. 2011. Autophagy machinery mediates macroendocytic processing and entotic cell death by targeting single membranes. *Nat. Cell Biol.* 13:1335–1343. <https://doi.org/10.1038/ncb2363>
- Franco, L.H., V.R. Nair, C.R. Scharn, R.J. Xavier, J.R. Torrealba, M.U. Shiloh, and B. Levine. 2017. The ubiquitin ligase Smurf1 functions in selective autophagy of *Mycobacterium tuberculosis* and anti-tuberculous host defense. *Cell Host Microbe.* 22:421–423. <https://doi.org/10.1016/j.chom.2017.08.005>
- Fujita, N., E. Morita, T. Itoh, A. Tanaka, M. Nakaoka, Y. Osada, T. Umemoto, T. Saitoh, H. Nakatogawa, S. Kobayashi, et al. 2013. Recruitment of the autophagic machinery to endosomes during infection is mediated by ubiquitin. *J. Cell Biol.* 203:115–128. <https://doi.org/10.1083/jcb.201304188>
- Fung, T.S., and D.X. Liu. 2019. Human coronavirus: Host-pathogen interaction. *Annu. Rev. Microbiol.* 73:529–557. <https://doi.org/10.1146/annurev-micro-020518-115759>
- Galluzzi, L., and D.R. Green. 2019. Autophagy-independent functions of the autophagy machinery. *Cell.* 177:1682–1699. <https://doi.org/10.1016/j.cell.2019.05.026>
- Gammoh, N., O. Florey, M. Overholtzer, and X. Jiang. 2013. Interaction between FIP200 and ATG16L1 distinguishes ULK1 complex-dependent and -independent autophagy. *Nat. Struct. Mol. Biol.* 20:144–149. <https://doi.org/10.1038/nsmb.2475>

- Ganley, I.G., D.H. Lam, J. Wang, X. Ding, S. Chen, and X. Jiang. 2009. ULK1-ATG13-FIP200 complex mediates mTOR signaling and is essential for autophagy. *J. Biol. Chem.* 284:12297–12305. <https://doi.org/10.1074/jbc.M900573200>
- Ge, L., D. Melville, M. Zhang, and R. Schekman. 2013. The ER-Golgi intermediate compartment is a key membrane source for the LC3 lipidation step of autophagosome biogenesis. *Elife*. 2:e00947. <https://doi.org/10.7554/eLife.00947>
- Ge, L., M. Zhang, S.J. Kenny, D. Liu, M. Maeda, K. Saito, A. Mathur, K. Xu, and R. Schekman. 2017. Remodeling of ER-exit sites initiates a membrane supply pathway for autophagosome biogenesis. *EMBO Rep.* 18:1586–1603. <https://doi.org/10.15252/embr.201744559>
- Ge, L., M. Zhang, and R. Schekman. 2014. Phosphatidylinositol 3-kinase and COPII generate LC3 lipidation vesicles from the ER-Golgi intermediate compartment. *Elife*. 3:e04135. <https://doi.org/10.7554/eLife.04135>
- Gerstenmaier, L., R. Pilla, L. Herrmann, H. Herrmann, M. Prado, G.J. Villafano, M. Kolonko, R. Reimer, T. Soldati, J.S. King, and M. Hagedorn. 2015. The autophagic machinery ensures nonlytic transmission of mycobacteria. *Proc. Natl. Acad. Sci. USA.* 112:E687–E692. <https://doi.org/10.1073/pnas.1423318112>
- Ghanbarpour, A., D.P. Valverde, T.J. Melia, and K.M. Reinisch. 2021. A model for a partnership of lipid transfer proteins and scramblases in membrane expansion and organelle biogenesis. *Proc. Natl. Acad. Sci. USA.* 118:e2101562118. <https://doi.org/10.1073/pnas.2101562118>
- Ghosh, S., T.A. Dellibovi-Ragheb, A. Kerviel, E. Pak, Q. Qiu, M. Fisher, P.M. Takvorian, C. Bleck, V.W. Hsu, A.R. Fehr, et al. 2020. β -Coronaviruses use lysosomes for egress instead of the biosynthetic secretory pathway. *Cell*. 183:1520–1535.e14. <https://doi.org/10.1016/j.cell.2020.10.039>
- Giraud-Gatineau, A., J.M. Coya, A. Maure, A. Biton, M. Thomson, E.M. Bernard, J. Marrec, M.G. Gutierrez, G. Larrouy-Maumus, R. Brosch, et al. 2020. The antibiotic bedaquiline activates host macrophage innate immune resistance to bacterial infection. *Elife*. 9:e55692. <https://doi.org/10.7554/eLife.55692>
- Gluschko, A., M. Herb, K. Wiegmann, O. Krut, W.F. Neiss, O. Utermohlen, M. Kronke, and M. Schramm. 2018. The β 2 integrin Mac-1 induces protective LC3-associated phagocytosis of *Listeria* monocytes. *Cell Host Microbe*. 23:324–337.e5. <https://doi.org/10.1016/j.chom.2018.01.018>
- Gomes, L.C., and I. Dikic. 2014. Autophagy in antimicrobial immunity. *Mol. Cell*. 54:224–233. <https://doi.org/10.1016/j.molcel.2014.03.009>
- Gomez-Suaga, P., B. Luzon-Toro, D. Churamani, L. Zhang, D. Bloor-Young, S. Patel, P.G. Woodman, G.C. Churchill, and S. Hilfiker. 2012. Leucine-rich repeat kinase 2 regulates autophagy through a calcium-dependent pathway involving NAADP. *Hum. Mol. Genet.* 21:511–525. <https://doi.org/10.1093/hmg/ddr481>
- Gonzalez, A., M.N. Hall, S.C. Lin, and D.G. Hardie. 2020. AMPK and TOR: The Yin and Yang of cellular nutrient sensing and growth control. *Cell Metabol.* 31:472–492. <https://doi.org/10.1016/j.cmet.2020.01.015>
- Goodwin, J.M., W.G. Walkup 4th, K. Hooper, T. Li, C. Kishi-Itakura, A. Ng, T. Lehmborg, A. Jha, S. Komminen, K. Fletcher, et al. 2021. GABARAP sequesters the FLCN-FNIP tumor suppressor complex to couple autophagy with lysosomal biogenesis. *Sci. Adv.* 7:eabj2485. <https://doi.org/10.1126/sciadv.abj2485>
- Gui, X., H. Yang, T. Li, X. Tan, P. Shi, M. Li, F. Du, and Z.J. Chen. 2019. Autophagy induction via STING trafficking is a primordial function of the cGAS pathway. *Nature*. 567:262–266. <https://doi.org/10.1038/s41586-019-1006-9>
- Guo, H., M. Chitiprolu, L. Roncevic, C. Javalet, F.J. Hemming, M.T. Trung, L. Meng, E. Latreille, C. Tanese de Souza, D. McCulloch, et al. 2017a. Atg5 disassociates the VIVO-ATPase to promote exosome production and tumor metastasis independent of canonical macroautophagy. *Dev. Cell*. 43:716–730.e7. <https://doi.org/10.1016/j.devcel.2017.11.018>
- Guo, L., H. Yu, W. Gu, X. Luo, R. Li, J. Zhang, Y. Xu, L. Yang, N. Shen, L. Feng, and Y. Wang. 2016. Autophagy negatively regulates transmissible gastroenteritis virus replication. *Sci. Rep.* 6:23864. <https://doi.org/10.1038/srep23864>
- Guo, X., M. Zhang, X. Zhang, X. Tan, H. Guo, W. Zeng, G. Yan, A.M. Memon, Z. Li, Y. Zhu, et al. 2017b. Porcine epidemic diarrhea virus induces autophagy to benefit its replication. *Viruses*. 9:E53. <https://doi.org/10.3390/v9030053>
- Gutierrez, M.G., S.S. Master, S.B. Singh, G.A. Taylor, M.I. Colombo, and V. Deretic. 2004. Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages. *Cell*. 119:753–766. <https://doi.org/10.1016/j.cell.2004.11.038>
- Hailey, D.W., A.S. Rambold, P. Satpute-Krishnan, K. Mitra, R. Sougrat, P.K. Kim, and J. Lippincott-Schwartz. 2010. Mitochondria supply membranes for autophagosome biogenesis during starvation. *Cell*. 141:656–667. <https://doi.org/10.1016/j.cell.2010.04.009>
- Hamasaki, M., N. Furuta, A. Matsuda, A. Nezu, A. Yamamoto, N. Fujita, H. Oomori, T. Noda, T. Haraguchi, Y. Hiraoka, et al. 2013. Autophagosomes form at ER-mitochondria contact sites. *Nature*. 495:389–393. <https://doi.org/10.1038/nature11910>
- Hara, T., A. Takamura, C. Kishi, S.I. Iemura, T. Natsume, J.L. Guan, and N. Mizushima. 2008. FIP200, a ULK-interacting protein, is required for autophagosome formation in mammalian cells. *J. Cell Biol.* 181:497–510. <https://doi.org/10.1083/jcb.200712064>
- Hasegawa, J., E. Tokuda, Y. Yao, T. Sasaki, K. Inoki, and L.S. Weisman. 2022. PP2A-dependent TFEB activation is blocked by PIKfyve-induced mTORC1 activity. *Mol. Biol. Cell*. 33:ar26. <https://doi.org/10.1091/mbc.E21-06-0309>
- Hayashi-Nishino, M., N. Fujita, T. Noda, A. Yamaguchi, T. Yoshimori, and A. Yamamoto. 2009. A subdomain of the endoplasmic reticulum forms a cradle for autophagosome formation. *Nat. Cell Biol.* 11:1433–1437. <https://doi.org/10.1038/ncb1991>
- Hayn, M., M. Hirschenberger, L. Koepke, R. Nchioua, J.H. Straub, S. Klute, V. Hunszinger, F. Zech, C. Prelli Bozzo, W. Aftab, et al. 2021. Systematic functional analysis of SARS-CoV-2 proteins uncovers viral innate immune antagonists and remaining vulnerabilities. *Cell Rep.* 35:109126. <https://doi.org/10.1016/j.celrep.2021.109126>
- He, H., Y. Dang, F. Dai, Z. Guo, J. Wu, X. She, Y. Pei, Y. Chen, W. Ling, C. Wu, et al. 2003. Post-translational modifications of three members of the human MAP1LC3 family and detection of a novel type of modification for MAP1LC3B. *J. Biol. Chem.* 278:29278–29287. <https://doi.org/10.1074/jbc.M303800200>
- Heckmann, B.L., B.J.W. Teubner, B. Tummers, E. Boada-Romero, L. Harris, M. Yang, C.S. Guy, S.S. Zakharenko, and D.R. Green. 2019. LC3-Associated endocytosis facilitates beta-amyloid clearance and mitigates neurodegeneration in murine Alzheimer's disease. *Cell*. 178:536–551.e14. <https://doi.org/10.1016/j.cell.2019.05.056>
- Henault, J., J. Martinez, J.M. Riggs, J. Tian, P. Mehta, L. Clarke, M. Sasaki, E. Latz, M.M. Brinkmann, A. Iwasaki, et al. 2012. Noncanonical autophagy is required for type I interferon secretion in response to DNA-immune complexes. *Immunity*. 37:986–997. <https://doi.org/10.1016/j.immuni.2012.09.014>
- Heneka, M.T., M.P. Kummer, A. Stutz, A. Delekate, S. Schwartz, A. Vieira-Saenger, A. Griep, D. Axt, A. Remus, T.C. Tzeng, et al. 2013. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*. 493:674–678. <https://doi.org/10.1038/nature11729>
- Heo, J.M., A. Ordureau, J.A. Paulo, J. Rinehart, and J.W. Harper. 2015. The PINK1-PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. *Mol. Cell*. 60:7–20. <https://doi.org/10.1016/j.molcel.2015.08.016>
- Herhaus, L., R.M. Bhaskara, A.H. Lystad, U. Gestal-Mato, A. Covarrubias-Pinto, F. Bonn, A. Simonsen, G. Hummer, and I. Dikic. 2020. TBK1-mediated phosphorylation of LC3C and GABARAP-L2 controls autophagosome shedding by ATG4 protease. *EMBO Rep.* 21:e48317. <https://doi.org/10.15252/embr.201948317>
- Hershko, A., and A. Ciechanover. 1998. The ubiquitin system. *Annu. Rev. Biochem.* 67:425–479. <https://doi.org/10.1146/annurev.biochem.67.1.425>
- Hoffmann, H.H., W.M. Schneider, K. Rozen-Gagnon, L.A. Miles, F. Schuster, B. Razoosky, E. Jacobson, X. Wu, S. Yi, C.M. Rudin, et al. 2021. TMEM41B is a pan-flavivirus host factor. *Cell*. 184:133–148.e20. <https://doi.org/10.1016/j.cell.2020.12.005>
- Hooper, K., and O. Florey. 2021. V-ATPase is a universal regulator of LC3 associated phagocytosis and non-canonical autophagy. *bioRxiv*. (Preprint posted May 20, 2021).
- Horowitz, J.E., N. Warner, J. Staples, E. Crowley, N. Gosalia, R. Murchie, C. Van Hout, K. Fiedler, G. Welch, A.K. King, et al. 2021. Mutation spectrum of NOD2 reveals recessive inheritance as a main driver of early onset Crohn's disease. *Sci. Rep.* 11:5595. <https://doi.org/10.1038/s41598-021-84938-8>
- Hosokawa, N., T. Hara, T. Kaizuka, C. Kishi, A. Takamura, Y. Miura, S.I. Iemura, T. Natsume, K. Takehana, N. Yamada, et al. 2009. Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. *Mol. Biol. Cell*. 20:1981–1991. <https://doi.org/10.1091/mbc.e08-12-1248>
- Ichimura, Y., T. Kirisako, T. Takao, Y. Satomi, Y. Shimonishi, N. Ishihara, N. Mizushima, I. Tanida, E. Kominami, M. Ohsumi, et al. 2000. A ubiquitin-like system mediates protein lipidation. *Nature*. 408:488–492. <https://doi.org/10.1038/35044114>
- Inomata, M., S. Xu, P. Chandra, S.N. Meydani, G. Takemura, J.A. Philips, and J.M. Leong. 2020. Macrophage LC3-associated phagocytosis is an

- immune defense against *Streptococcus pneumoniae* that diminishes with host aging. *Proc. Natl. Acad. Sci. USA*. 117:33561–33569. <https://doi.org/10.1073/pnas.2015368117>
- Intemann, C.D., T. Thye, S. Niemann, E.N.L. Browne, M. Amanua Chinbuah, A. Enimil, J. Gyapong, I. Osei, E. Owusu-Dabo, S. Helm, et al. 2009. Autophagy gene variant IRGM -261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.* 5:e1000577. <https://doi.org/10.1371/journal.ppat.1000577>
- Itakura, E., C. Kishi-Itakura, I. Koyama-Honda, and N. Mizushima. 2012. Structures containing Atg9A and the ULK1 complex independently target depolarized mitochondria at initial stages of Parkin-mediated mitophagy. *J. Cell Sci.* 125:1488–1499. <https://doi.org/10.1242/jcs.094110>
- Itakura, E., and N. Mizushima. 2010. Characterization of autophagosome formation site by a hierarchical analysis of mammalian Atg proteins. *Autophagy*. 6:764–776. <https://doi.org/10.4161/auto.6.6.12709>
- Itakura, E., and N. Mizushima. 2011. p62 Targeting to the autophagosome formation site requires self-oligomerization but not LC3 binding. *J. Cell Biol.* 192:17–27. <https://doi.org/10.1083/jcb.201009067>
- Jacquin, E., S. Leclerc-Mercier, C. Judon, E. Blanchard, S. Fraitag, and O. Florey. 2017. Pharmacological modulators of autophagy activate a parallel noncanonical pathway driving unconventional LC3 lipidation. *Autophagy*. 13:854–867. <https://doi.org/10.1080/15548627.2017.1287653>
- Jena, K.K., S.P. Kolapalli, S. Mehto, P. Nath, B. Das, P.K. Sahoo, A. Ahad, G.H. Syed, S.K. Raghav, S. Senapati, et al. 2018. TRIM16 controls assembly and degradation of protein aggregates by modulating the p62-NRF2 axis and autophagy. *EMBO J.* 37:e98358. <https://doi.org/10.15252/embj.201798358>
- Jena, K.K., S. Mehto, P. Nath, N.R. Chauhan, R. Sahu, K. Dhar, S.K. Das, S.P. Kolapalli, K.C. Murmu, A. Jain, et al. 2020. Autoimmunity gene IRGM suppresses cGAS-STING and RIG-I-MAVS signaling to control interferon response. *EMBO Rep.* 21:e50051. <https://doi.org/10.15252/embr.202050051>
- Jia, J., Y.P. Abudu, A. Claude-Taupin, Y. Gu, S. Kumar, S.W. Choi, R. Peters, M.H. Mudd, L. Allers, M. Salemi, et al. 2018. Galectins control mTOR in response to endomembrane damage. *Mol. Cell.* 70:120–135.e8. <https://doi.org/10.1016/j.molcel.2018.03.009>
- Jia, J., B. Bissa, L. Brecht, L. Allers, S.W. Choi, Y. Gu, M. Zbinden, M.R. Burge, G. Timmins, K. Hallows, et al. 2020a. AMPK, a regulator of metabolism and autophagy, is activated by lysosomal damage via a novel galectin-directed ubiquitin signal transduction system. *Mol. Cell.* 77:951–969.e9. <https://doi.org/10.1016/j.molcel.2019.12.028>
- Jia, J., A. Claude-Taupin, Y. Gu, S.W. Choi, R. Peters, B. Bissa, M.H. Mudd, L. Allers, S. Pallikkuth, K.A. Lidke, et al. 2020b. Galectin-3 coordinates a cellular system for lysosomal repair and removal. *Dev. Cell.* 52:69–87.e8. <https://doi.org/10.1016/j.devcel.2019.10.025>
- Jia, J., A. Claude-Taupin, Y. Gu, S.W. Choi, R. Peters, B. Bissa, M.H. Mudd, L. Allers, S. Pallikkuth, K.A. Lidke, et al. 2020c. MERIT, a cellular system coordinating lysosomal repair, removal and replacement. *Autophagy*. 16:1539–1541. <https://doi.org/10.1080/15548627.2020.1779451>
- Jia, K., C. Thomas, M. Akbar, Q. Sun, B. Adams-Huet, C. Gilpin, and B. Levine. 2009. Autophagy genes protect against *Salmonella typhimurium* infection and mediate insulin signaling-regulated pathogen resistance. *Proc. Natl. Acad. Sci. USA*. 106:14564–14569. <https://doi.org/10.1073/pnas.0813319106>
- Jia, W., H.H. Pua, Q.J. Li, and Y.W. He. 2011. Autophagy regulates endoplasmic reticulum homeostasis and calcium mobilization in T lymphocytes. *J. Immunol.* 186:1564–1574. <https://doi.org/10.4049/jimmunol.1001822>
- Jounai, N., F. Takeshita, K. Kobiyama, A. Sawano, A. Miyawaki, K.Q. Xin, K.J. Ishii, T. Kawai, S. Akira, K. Suzuki, and K. Okuda. 2007. The Atg5 Atg12 conjugate associates with innate antiviral immune responses. *Proc. Natl. Acad. Sci. USA*. 104:14050–14055. <https://doi.org/10.1073/pnas.0704014104>
- Jung, C.H., C.B. Jun, S.H. Ro, Y.M. Kim, N.M. Otto, J. Cao, M. Kundu, and D.H. Kim. 2009. ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. *Mol. Biol. Cell.* 20:1992–2003. <https://doi.org/10.1091/mbc.e08-12-1249>
- Kabeya, Y., N. Mizushima, T. Ueno, A. Yamamoto, T. Kirisako, T. Noda, E. Kominami, Y. Ohsumi, and T. Yoshimori. 2000. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosomal membranes after processing. *EMBO J.* 19:5720–5728. <https://doi.org/10.1093/emboj/19.21.5720>
- Kageyama, S., H. Omori, T. Saitoh, T. Sone, J.L. Guan, S. Akira, F. Imamoto, T. Noda, and T. Yoshimori. 2011. The LC3 recruitment mechanism is separate from Atg9L1-dependent membrane formation in the autophagic response against *Salmonella*. *Mol. Biol. Cell.* 22:2290–2300. <https://doi.org/10.1091/mbc.E10-11-0893>
- Kanayama, M., and M.L. Shinohara. 2016. Roles of autophagy and autophagy-related proteins in antifungal immunity. *Front. Immunol.* 7:47. <https://doi.org/10.3389/fimmu.2016.00047>
- Karmakar, M., M. Minns, E.N. Greenberg, J. Diaz-Aponte, K. Pestonjamas, J.L. Johnson, J.K. Rathkey, D.W. Abbott, K. Wang, F. Shao, et al. 2020. N-GSDMD trafficking to neutrophil organelles facilitates IL-1 β release independently of plasma membrane pores and pyroptosis. *Nat. Commun.* 11:2212. <https://doi.org/10.1038/s41467-020-16043-9>
- Keller, M.D., K.L. Ching, F.X. Liang, A. Dhabaria, K. Tam, B.M. Ueberheide, D. Unutmaz, V.J. Torres, and K. Cadwell. 2020. Decoy exosomes provide protection against bacterial toxins. *Nature*. 579:260–264. <https://doi.org/10.1038/s41586-020-2066-6>
- Kim, J., M. Kundu, B. Viollet, and K.L. Guan. 2011. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* 13:132–141. <https://doi.org/10.1038/ncb2152>
- Kim, J.Y., H. Zhao, J. Martinez, T.A. Doggett, A.V. Kolesnikov, P.H. Tang, Z. Ablonczy, C.C. Chan, Z. Zhou, D.R. Green, and T.A. Ferguson. 2013. Noncanonical autophagy promotes the visual cycle. *Cell*. 154:365–376. <https://doi.org/10.1016/j.cell.2013.06.012>
- Kimmey, J.M., J.P. Huynh, L.A. Weiss, S. Park, A. Kambal, J. Debnath, H.W. Virgin, and C.L. Stallings. 2015. Unique role for ATG5 in neutrophil-mediated immunopathology during *M. tuberculosis* infection. *Nature*. 528:565–569. <https://doi.org/10.1038/nature16451>
- Kimura, T., A. Jain, S.W. Choi, M.A. Mandell, K. Schroder, T. Johansen, and V. Deretic. 2015. TRIM-mediated precision autophagy targets cytoplasmic regulators of innate immunity. *J. Cell Biol.* 210:973–989. <https://doi.org/10.1083/jcb.201503023>
- Kimura, T., J. Jia, S. Kumar, S.W. Choi, Y. Gu, M. Mudd, N. Dupont, S. Jiang, R. Peters, F. Farzam, et al. 2017. Dedicated SNAREs and specialized TRIM cargo receptors mediate secretory autophagy. *EMBO J.* 36:42–60. <https://doi.org/10.15252/embj.201695081>
- Kimura, T., M. Mandell, and V. Deretic. 2016. Precision autophagy directed by receptor regulators—emerging examples within the TRIM family. *J. Cell Sci.* 129:881–891. <https://doi.org/10.1242/jcs.163758>
- Knaevelsrud, H., K. Soreng, C. Raiborg, K. Haberg, F. Rasmussen, A. Brech, K. Liestol, T.E. Rusten, H. Stenmark, T.P. Neufeld, et al. 2013. Membrane remodeling by the PX-BAR protein SNX18 promotes autophagosome formation. *J. Cell Biol.* 202:331–349. <https://doi.org/10.1083/jcb.201205129>
- Ko, S., M.J. Gu, C.G. Kim, Y.C. Kye, Y. Lim, J.E. Lee, B.C. Park, H. Chu, S.H. Han, and C.H. Yun. 2017. Rapamycin-induced autophagy restricts porcine epidemic diarrhea virus infectivity in porcine intestinal epithelial cells. *Antivir. Res.* 146:86–95. <https://doi.org/10.1016/j.antiviral.2017.08.010>
- Kumar, S., Y. Gu, Y.P. Abudu, J.A. Bruun, A. Jain, F. Farzam, M. Mudd, J.H. Anonsen, T.E. Rusten, G. Kasof, et al. 2019. Phosphorylation of Syntaxin 17 by TBK1 controls autophagy initiation. *Dev. Cell.* 49:130–144.e6. <https://doi.org/10.1016/j.devcel.2019.01.027>
- Kumar, S., A. Jain, S.W. Choi, G.P.D. da Silva, L. Allers, M.H. Mudd, R.S. Peters, J.H. Anonsen, T.E. Rusten, M. Lazarou, and V. Deretic. 2020. Mammalian Atg8 proteins and the autophagy factor IRGM control mTOR and TFEB at a regulatory node critical for responses to pathogens. *Nat. Cell Biol.* 22:973–985. <https://doi.org/10.1038/s41556-020-0549-1>
- Kumar, S., A. Jain, F. Farzam, J. Jia, Y. Gu, S.W. Choi, M.H. Mudd, A. Claude-Taupin, M.J. Wester, K.A. Lidke, et al. 2018. Mechanism of Stx17 recruitment to autophagosomes via IRGM and mammalian Atg8 proteins. *J. Cell Biol.* 217:997–1013. <https://doi.org/10.1083/jcb.201708039>
- Kumar, S., R. Javed, M. Mudd, S. Pallikkuth, K.A. Lidke, A. Jain, K. Tangavelou, S.R. Gudmundsson, C. Ye, T.E. Rusten, et al. 2021a. Mammalian hybrid pre-autophagosomal structure HyPAS generates autophagosomes. *Cell*. 184:5950–5969.e22. <https://doi.org/10.1016/j.cell.2021.10.017>
- Kumar, S., J. Jia, and V. Deretic. 2021b. Atg8ylation as a general membrane stress and remodeling response. *Cell Stress*. 5:128–142. <https://doi.org/10.15698/cst2021.09.255>
- Kyei, G.B., C. Dinkins, A.S. Davis, E. Roberts, S.B. Singh, C. Dong, L. Wu, E. Kominami, T. Ueno, A. Yamamoto, et al. 2009. Autophagy pathway intersects with HIV-1 biosynthesis and regulates viral yields in macrophages. *J. Cell Biol.* 186:255–268. <https://doi.org/10.1083/jcb.200903070>
- Lahiri, V., W.D. Hawkins, and D.J. Klionsky. 2019. Watch what you (self-) Eat: Autophagic mechanisms that modulate metabolism. *Cell Metabol.* 29:803–826. <https://doi.org/10.1016/j.cmet.2019.03.003>

- Lamark, T., and T. Johansen. 2021. Mechanisms of selective autophagy. *Annu. Rev. Cell Dev. Biol.* 37:143–169. <https://doi.org/10.1146/annurev-cellbio-120219-035530>
- Lamkanfi, M., and V.M. Dixit. 2014. Mechanisms and functions of inflammasomes. *Cell.* 157:1013–1022. <https://doi.org/10.1016/j.cell.2014.04.007>
- Laopanupong, T., P. Prombutara, P. Kanjanasirirat, S. Benjaskulluecha, A. Boonmee, T. Palaga, S. Meresse, J. Paha, T.A.P. Siregar, T. Khumpanied, et al. 2021. Lysosome repositioning as an autophagy escape mechanism by *Mycobacterium tuberculosis* Beijing strain. *Sci. Rep.* 11:4342. <https://doi.org/10.1038/s41598-021-83835-4>
- Lazarou, M., D.A. Sliter, L.A. Kane, S.A. Sarraf, C. Wang, J.L. Burman, D.P. Sideris, A.I. Fogel, and R.J. Youle. 2015. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature.* 524:309–314. <https://doi.org/10.1038/nature14893>
- Lee, C., L. Lamech, E. Johns, and M. Overholtzer. 2020. Selective lysosome membrane turnover is induced by nutrient starvation. *Dev. Cell.* 55: 289–297.e4. <https://doi.org/10.1016/j.devcel.2020.08.008>
- Lee, J., and J.H.J. Ou. 2022. Hepatitis C virus and intracellular antiviral response. *Curr. Opin. Virol.* 52:244–249. <https://doi.org/10.1016/j.coviro.2021.12.010>
- Leidal, A.M., H.H. Huang, T. Marsh, T. Solvik, D. Zhang, J. Ye, F. Kai, J. Goldsmith, J.Y. Liu, Y.H. Huang, et al. 2020. The LC3-conjugation machinery specifies the loading of RNA-binding proteins into extracellular vesicles. *Nat. Cell Biol.* 22:187–199. <https://doi.org/10.1038/s41556-019-0450-y>
- Levine, B. 2005. Eating oneself and uninvited guests; autophagy-related pathways in cellular defense. *Cell.* 120:159–162. <https://doi.org/10.1016/j.cell.2005.01.005>
- Levine, B., and G. Kroemer. 2019. Biological functions of autophagy genes: A disease perspective. *Cell.* 176:11–42. <https://doi.org/10.1016/j.cell.2018.09.048>
- Levy, A., A. Stedman, E. Deutsch, F. Donnadieu, H.W. Virgin, P.J. Sansonetti, and G. Nigro. 2020. Innate immune receptor NOD2 mediates LGR5(+) intestinal stem cell protection against ROS cytotoxicity via mitophagy stimulation. *Proc. Natl. Acad. Sci. USA.* 117:1994–2003. <https://doi.org/10.1073/pnas.1902788117>
- Li, C., E. Capan, Y. Zhao, J. Zhao, D. Stolz, S.C. Watkins, S. Jin, and B. Lu. 2006. Autophagy is induced in CD4+ T cells and important for the growth factor-withdrawal cell death. *J. Immunol.* 177:5163–5168. <https://doi.org/10.4049/jimmunol.177.8.5163>
- Li, W., Y. Li, S. Siraj, H. Jin, Y. Fan, X. Yang, X. Huang, X. Wang, J. Wang, L. Liu, et al. 2019. FUN14 domain-containing 1-mediated mitophagy suppresses Hepatocarcinogenesis by inhibition of inflammasome activation in mice. *Hepatology.* 69:604–621. <https://doi.org/10.1002/hep.30191>
- Li, Y.E., Y. Wang, X. Du, T. Zhang, H.Y. Mak, S.E. Hancock, H. McEwen, E. Pandzic, R.M. Whan, Y.C. Aw, et al. 2021. TMEM41B and VMP1 are scramblases and regulate the distribution of cholesterol and phosphatidylserine. *J. Cell Biol.* 220:e202103105. <https://doi.org/10.1083/jcb.202103105>
- Liang, X.H., L.K. Kleeman, H.H. Jiang, G. Gordon, J.E. Goldman, G. Berry, B. Herman, and B. Levine. 1998. Protection against fatal Sindbis virus encephalitis by beclin, a novel Bcl-2-interacting protein. *J. Virol.* 72: 8586–8596. <https://doi.org/10.1128/JVI.72.11.8586-8596.1998>
- Ligeon, L.A., M. Pena-Francesch, L.D. Vanoaica, N.G. Nunez, D. Talwar, T.P. Dick, and C. Munz. 2021. Oxidation inhibits autophagy protein deconjugation from phagosomes to sustain MHC class II restricted antigen presentation. *Nat. Commun.* 12:1508. <https://doi.org/10.1038/s41467-021-21829-6>
- Lin, C.Y., T. Nozawa, A. Minowa-Nozawa, H. Toh, M. Hikichi, J. Iibushi, and I. Nakagawa. 2020. Autophagy receptor tollip facilitates bacterial autophagy by recruiting galectin-7 in response to group A Streptococcus infection. *Front. Cell. Infect. Microbiol.* 10:583137. <https://doi.org/10.3389/fcimb.2020.583137>
- Liu, D., H. Wu, C. Wang, Y. Li, H. Tian, S. Siraj, S.A. Sehgal, X. Wang, J. Wang, Y. Shang, et al. 2019. STING directly activates autophagy to tune the innate immune response. *Cell Death Differ.* 26:1735–1749. <https://doi.org/10.1038/s41418-018-0251-z>
- Liu, S., X. Cai, J. Wu, Q. Cong, X. Chen, T. Li, F. Du, J. Ren, Y.T. Wu, N.V. Grishin, and Z.J. Chen. 2015. Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation. *Science.* 347:aaa2630. <https://doi.org/10.1126/science.aaa2630>
- Liu, S., B.W.Y. Mok, S. Deng, H. Liu, P. Wang, W. Song, P. Chen, X. Huang, M. Zheng, S.Y. Lau, et al. 2021. Mammalian cells use the autophagy process to restrict avian influenza virus replication. *Cell Rep.* 35:109213. <https://doi.org/10.1016/j.celrep.2021.109213>
- Liu, T., Q. Tang, K. Liu, W. Xie, X. Liu, H. Wang, R.F. Wang, and J. Cui. 2016. TRIM11 suppresses AIM2 inflammasome by degrading AIM2 via p62-dependent selective autophagy. *Cell Rep.* 16:1988–2002. <https://doi.org/10.1016/j.celrep.2016.07.019>
- Loi, M., A. Raimondi, D. Morone, and M. Molinari. 2019. ESCRT-III-driven piecemeal micro-ER-phagy remodels the ER during recovery from ER stress. *Nat. Commun.* 10:5058. <https://doi.org/10.1038/s41467-019-12991-z>
- Longatti, A., C.A. Lamb, M. Razi, S. Yoshimura, F.A. Barr, and S.A. Tooze. 2012. TBC1D14 regulates autophagosome formation via Rab11- and ULK1-positive recycling endosomes. *J. Cell Biol.* 197:659–675. <https://doi.org/10.1083/jcb.201111079>
- Lopez Corcino, Y., S. Gonzalez Ferrer, L.E. Mantilla, S. Trikeriotis, J.S. Yu, S. Kim, S. Hansen, J.A.C. Portillo, and C.S. Subauste. 2019. Toxoplasma gondii induces prolonged host epidermal growth factor receptor signaling to prevent parasite elimination by autophagy: Perspectives for in vivo control of the parasite. *Cell Microbiol.* 21:e13084. <https://doi.org/10.1111/cmi.13084>
- Lu, Q., C.C. Yokoyama, J.W. Williams, M.T. Baldrige, X. Jin, B. DesRochers, T. Bricker, C.B. Wilen, J. Bagaitkar, E. Loginicheva, et al. 2016. Homeostatic control of innate lung inflammation by vici syndrome gene Epg5 and additional autophagy genes promotes influenza pathogenesis. *Cell Host Microbe.* 19:102–113. <https://doi.org/10.1016/j.chom.2015.12.011>
- Lupfer, C., P.G. Thomas, P.K. Anand, P. Vogel, S. Milasta, J. Martinez, G. Huang, M. Green, M. Kundu, H. Chi, et al. 2013. Receptor interacting protein kinase 2-mediated mitophagy regulates inflammasome activation during virus infection. *Nat. Immunol.* 14:480–488. <https://doi.org/10.1038/ni.2563>
- Lystad, A.H., S.R. Carlsson, L.R. de la Ballina, K.J. Kauffman, S. Nag, T. Yoshimori, T.J. Melia, and A. Simonsen. 2019. Distinct functions of ATG16L1 isoforms in membrane binding and LC3B lipidation in autophagy-related processes. *Nat. Cell Biol.* 21:372–383. <https://doi.org/10.1038/s41556-019-0274-9>
- Macian, F. 2019. Autophagy in T Cell function and aging. *Front. Cell Dev. Biol.* 7:213. <https://doi.org/10.3389/fcell.2019.00213>
- Maculins, T., E. Verschuere, T. Hinkle, M. Choi, P. Chang, C. Chalouni, S. Rao, Y. Kwon, J. Lim, A.K. Katakam, et al. 2021. Multiplexed proteomics of autophagy-deficient murine macrophages reveals enhanced antimicrobial immunity via the oxidative stress response. *Elife.* 10:e62320. <https://doi.org/10.7554/eLife.62320>
- Maeda, S., H. Yamamoto, L.N. Kinch, C.M. Garza, S. Takahashi, C. Otomo, N.V. Grishin, S. Forli, N. Mizushima, and T. Otomo. 2020. Structure, lipid scrambling activity and role in autophagosome formation of ATG9A. *Nat. Struct. Mol. Biol.* 27:1194–1201. <https://doi.org/10.1038/s41594-020-00520-2>
- Maejima, I., A. Takahashi, H. Omori, T. Kimura, Y. Takabatake, T. Saitoh, A. Yamamoto, M. Hamasaki, T. Noda, Y. Isaka, and T. Yoshimori. 2013. Autophagy sequesters damaged lysosomes to control lysosomal biogenesis and kidney injury. *EMBO J.* 32:2336–2347. <https://doi.org/10.1038/emboj.2013.171>
- Mandell, M.A., A. Jain, J. Arko-Mensah, S. Chauhan, T. Kimura, C. Dinkins, G. Silvestri, J. Munch, F. Kirchoff, A. Simonsen, et al. 2014. TRIM proteins regulate autophagy and can target autophagic substrates by direct recognition. *Dev. Cell.* 30:394–409. <https://doi.org/10.1016/j.devcel.2014.06.013>
- Manzanillo, P.S., J.S. Ayres, R.O. Watson, A.C. Collins, G. Souza, C.S. Rae, D.S. Schneider, K. Nakamura, M.U. Shiloh, and J.S. Cox. 2013. The ubiquitin ligase parkin mediates resistance to intracellular pathogens. *Nature.* 501:512–516. <https://doi.org/10.1038/nature12566>
- Martinez, J., J. Almdendinger, A. Oberst, R. Ness, C.P. Dillon, P. Fitzgerald, M.O. Hengartner, and D.R. Green. 2011. Microtubule-associated protein 1 light chain 3 α (LC3)-associated phagocytosis is required for the efficient clearance of dead cells. *Proc. Natl. Acad. Sci. USA.* 108:17396–17401. <https://doi.org/10.1073/pnas.1113421108>
- Martinez, J., L.D. Cunha, S. Park, M. Yang, Q. Lu, R. Orchard, Q.Z. Li, M. Yan, L. Janke, C. Guy, et al. 2016. Noncanonical autophagy inhibits the auto-inflammatory, lupus-like response to dying cells. *Nature.* 533:115–119. <https://doi.org/10.1038/nature17950>
- Martinez, J., R.K.S. Malireddi, Q. Lu, L.D. Cunha, S. Pelletier, S. Gingras, R. Orchard, J.L. Guan, H. Tan, J. Peng, et al. 2015. Molecular characterization of LC3-associated phagocytosis reveals distinct roles for Rubicon, NOX2 and autophagy proteins. *Nat. Cell Biol.* 17:893–906. <https://doi.org/10.1038/ncb3192>
- Maruyama, T., J.M. Alam, T. Fukuda, S. Kageyama, H. Kirisako, Y. Ishii, I. Shimada, Y. Ohsumi, M. Komatsu, T. Kanki, et al. 2021. Membrane

- perturbation by lipidated Atg8 underlies autophagosome biogenesis. *Nat. Struct. Mol. Biol.* 28:583–593. <https://doi.org/10.1038/s41594-021-00614-5>
- Masters, S.L., A. Dunne, S.L. Subramanian, R.L. Hull, G.M. Tannahill, F.A. Sharp, C. Becker, L. Franchi, E. Yoshihara, Z. Chen, et al. 2010. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1 β in type 2 diabetes. *Nat. Immunol.* 11:897–904. <https://doi.org/10.1038/ni.1935>
- Matoba, K., T. Kotani, A. Tsutsumi, T. Tsuji, T. Mori, D. Noshiro, Y. Sugita, N. Nomura, S. Iwata, Y. Ohsumi, et al. 2020. Atg9 is a lipid scramblase that mediates autophagosomal membrane expansion. *Nat. Struct. Mol. Biol.* 27:1185–1193. <https://doi.org/10.1038/s41594-020-00518-w>
- McArthur, K., L.W. Whitehead, J.M. Heddleston, L. Li, B.S. Padman, V. Oorschot, N.D. Geoghegan, S. Chappaz, S. Davidson, H. San Chin, et al. 2018. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. *Science*. 359:eaao6047. <https://doi.org/10.1126/science.aao6047>
- Medina, D.L., S. Di Paola, I. Peluso, A. Armani, D. De Stefani, R. Venditti, S. Montefusco, A. Scotto-Rosato, C. Prezioso, A. Forrester, et al. 2015. Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. *Nat. Cell Biol.* 17:288–299. <https://doi.org/10.1038/ncb3114>
- Mehto, S., K.K. Jena, P. Nath, S. Chauhan, S.P. Kolapalli, S.K. Das, P.K. Sahoo, A. Jain, G.A. Taylor, and S. Chauhan. 2019. The Crohn's disease risk factor IRGM limits NLRP3 inflammasome activation by impeding its assembly and by mediating its selective autophagy. *Mol. Cell*. 73:429–445.e7. <https://doi.org/10.1016/j.molcel.2018.11.018>
- Mejlvang, J., H. Olsvik, S. Svenning, J.A. Bruun, Y.P. Abudu, K.B. Larsen, A. Brech, T.E. Hansen, H. Brenne, T. Hansen, et al. 2018. Starvation induces rapid degradation of selective autophagy receptors by endosomal microautophagy. *J. Cell Biol.* 217:3640–3655. <https://doi.org/10.1083/jcb.201711002>
- Mevisen, T.E.T., and D. Komander. 2017. Mechanisms of deubiquitinase specificity and regulation. *Annu. Rev. Biochem.* 86:159–192. <https://doi.org/10.1146/annurev-biochem-061516-044916>
- Miao, G., H. Zhao, Y. Li, M. Ji, Y. Chen, Y. Shi, Y. Bi, P. Wang, and H. Zhang. 2021. ORF3a of the COVID-19 virus SARS-CoV-2 blocks HOPS complex-mediated assembly of the SNARE complex required for autolysosome formation. *Dev. Cell*. 56:427–442.e5. <https://doi.org/10.1016/j.devcel.2020.12.010>
- Millarte, V., S. Schlienger, S. Kalin, and M. Spiess. 2022. Rabaptin5 targets autophagy to damaged endosomes and *Salmonella* vacuoles via FIP200 and ATG16L1. *EMBO Rep.* 23:e53429. <https://doi.org/10.15252/embr.202153429>
- Miller, B.C., Z. Zhao, L.M. Stephenson, K. Cadwell, H.H. Pua, H.K. Lee, N.N. Mizushima, A. Iwasaki, Y.W. He, W. Swat, and H.W. Virgin 4th. 2008. The autophagy gene ATG5 plays an essential role in B lymphocyte development. *Autophagy*. 4:309–314. <https://doi.org/10.4161/auto.5474>
- Mills, E.L., B. Kelly, and L.A.J. O'Neill. 2017. Mitochondria are the powerhouses of immunity. *Nat. Immunol.* 18:488–498. <https://doi.org/10.1038/ni.3704>
- Minowa-Nozawa, A., T. Nozawa, K. Okamoto-Furuta, H. Kohda, and I. Nakagawa. 2017. Rab35 GTPase recruits NDP52 to autophagy targets. *EMBO J.* 36:2790–2807. <https://doi.org/10.15252/emboj.201796463>
- Mitchell, G., M.I. Cheng, C. Chen, B.N. Nguyen, A.T. Whiteley, S. Kianian, J.S. Cox, D.R. Green, K.L. McDonald, and D.A. Portnoy. 2018. *Listeria* monocytogenes triggers noncanonical autophagy upon phagocytosis, but avoids subsequent growth-restricting xenophagy. *Proc. Natl. Acad. Sci. USA*. 115:E210–E217. <https://doi.org/10.1073/pnas.1716055115>
- Miyakawa, K., M. Nishi, M. Ogawa, S. Matsunaga, M. Sugiyama, H. Nishitsuji, H. Kimura, M. Ohnishi, K. Watashi, K. Shimotohno, et al. 2022. Galectin-9 restricts hepatitis B virus replication via p62/SQSTM1-mediated selective autophagy of viral core proteins. *Nat. Commun.* 13:531. <https://doi.org/10.1038/s41467-022-28171-5>
- Mizushima, N. 2020. The ATG conjugation systems in autophagy. *Curr. Opin. Cell Biol.* 63:1–10. <https://doi.org/10.1016/j.celb.2019.12.001>
- Mizushima, N., and B. Levine. 2020. Autophagy in human diseases. *N. Engl. J. Med.* 383:1564–1576. <https://doi.org/10.1056/NEJMra2022774>
- Mizushima, N., T. Yoshimori, and Y. Ohsumi. 2011. The role of Atg proteins in autophagosome formation. *Annu. Rev. Cell Dev. Biol.* 27:107–132. <https://doi.org/10.1146/annurev-cellbio-092910-154005>
- Mocholi, E., S.D. Dowling, Y. Botbol, R.C. Gruber, A.K. Ray, S. Vastert, B. Shafiq-Zagardo, P.J. Coffey, and F. Macian. 2018. Autophagy is a tolerance-avoidance mechanism that modulates TCR-mediated signaling and cell metabolism to prevent induction of T cell anergy. *Cell Rep.* 24:1136–1150. <https://doi.org/10.1016/j.celrep.2018.06.065>
- Montespan, C., S.A. Marvin, S. Austin, A.M. Burrage, B. Roger, F. Rayne, M. Faure, E.M. Campell, C. Schneider, R. Reimer, et al. 2017. Multi-layered control of Galectin-8 mediated autophagy during adenovirus cell entry through a conserved PPxY motif in the viral capsid. *PLoS Pathog.* 13:e1006217. <https://doi.org/10.1371/journal.ppat.1006217>
- Moore, A.S., and E.L.F. Holzbaur. 2016. Dynamic recruitment and activation of ALS-associated TBK1 with its target optineurin are required for efficient mitophagy. *Proc. Natl. Acad. Sci. USA*. 113:E3349–E3358. <https://doi.org/10.1073/pnas.1523810113>
- Moreau, K., B. Ravikumar, M. Renna, C. Puri, and D.C. Rubinsztein. 2011. Autophagosome precursor maturation requires homotypic fusion. *Cell*. 146:303–317. <https://doi.org/10.1016/j.cell.2011.06.023>
- Moretti, J., S. Roy, D. Bozec, J. Martinez, J.R. Chapman, B. Ueberheide, D.W. Lamming, Z.J. Chen, T. Horng, G. Yeretsian, et al. 2017. STING senses microbial viability to orchestrate stress-mediated autophagy of the endoplasmic reticulum. *Cell*. 171:809–823.e13. <https://doi.org/10.1016/j.cell.2017.09.034>
- Morishita, H., and N. Mizushima. 2019. Diverse cellular roles of autophagy. *Annu. Rev. Cell Dev. Biol.* 35:453–475. <https://doi.org/10.1146/annurev-cellbio-100818-125300>
- Mostowy, S., V. Sancho-Shimizu, M.A. Hamon, R. Simeone, R. Brosch, T. Johansen, and P. Cossart. 2011. p62 and NDP52 proteins target intracytosolic *Shigella* and *Listeria* to different autophagy pathways. *J. Biol. Chem.* 286:26987–26995. <https://doi.org/10.1074/jbc.M111.223610>
- Mukhopadhyay, S., D.E. Biancur, S.J. Parker, K. Yamamoto, R.S. Banh, J.A. Paulo, J.D. Mancias, and A.C. Kimmelman. 2021. Autophagy is required for proper cysteine homeostasis in pancreatic cancer through regulation of SLC7A11. *Proc. Natl. Acad. Sci. USA*. 118:e2021475118. <https://doi.org/10.1073/pnas.2021475118>
- Murrow, L., R. Malhotra, and J. Debnath. 2015. ATG12-ATG3 interacts with Alix to promote basal autophagic flux and late endosome function. *Nat. Cell Biol.* 17:300–310. <https://doi.org/10.1038/ncb3112>
- Nakagawa, I., A. Amano, N. Mizushima, A. Yamamoto, H. Yamaguchi, T. Kamimoto, A. Nara, J. Funao, M. Nakata, K. Tsuda, et al. 2004. Autophagy defends cells against invading group A *Streptococcus*. *Science*. 306:1037–1040. <https://doi.org/10.1126/science.1103966>
- Nakahira, K., J.A. Haspel, V.A.K. Rathinam, S.J. Lee, T. Dolinay, H.C. Lam, J.A. Englert, M. Rabinovitch, M. Cernadas, H.P. Kim, et al. 2011. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat. Immunol.* 12:222–230. <https://doi.org/10.1038/ni.1980>
- Nakamura, S., S. Shigeyama, S. Minami, T. Shima, S. Akayama, T. Matsuda, A. Esposito, G. Napolitano, A. Kuma, T. Namba-Hamano, et al. 2020. LC3 lipidation is essential for TFEB activation during the lysosomal damage response to kidney injury. *Nat. Cell Biol.* 22:1252–1263. <https://doi.org/10.1038/s41556-020-00583-9>
- Napolitano, G., C. Di Malta, A. Esposito, M.E.G. de Araujo, S. Pece, G. Bertalot, M. Matarese, V. Benedetti, A. Zampelli, T. Stasyk, et al. 2020. A substrate-specific mTORC1 pathway underlies Birt-Hogg-Dube syndrome. *Nature*. 585:597–602. <https://doi.org/10.1038/s41586-020-2444-0>
- Nascimbeni, A.C., F. Giordano, N. Dupont, D. Grasso, M.I. Vaccaro, P. Codogno, and E. Morel. 2017. ER-plasma membrane contact sites contribute to autophagosome biogenesis by regulation of local PI3P synthesis. *EMBO J.* 36:2018–2033. <https://doi.org/10.15252/emboj.201797006>
- Nauseef, W.M. 2019. The phagocyte NOX2 NADPH oxidase in microbial killing and cell signaling. *Curr. Opin. Immunol.* 60:130–140. <https://doi.org/10.1016/j.coi.2019.05.006>
- Nguyen, T.N., B.S. Padman, J. Usher, V. Oorschot, G. Ramm, and M. Lazarou. 2016. Atg8 family LC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation. *J. Cell Biol.* 215:857–874. <https://doi.org/10.1083/jcb.201607039>
- Nguyen, T.N., B.S. Padman, S. Zellner, G. Khuu, L. Uoselis, W.K. Lam, M. Skulsupaisarn, R.S.J. Lindblom, E.M. Watts, C. Behrends, and M. Lazarou. 2021. ATG4 family proteins drive phagophore growth independently of the LC3/GABARAP lipidation system. *Mol. Cell*. 81:2013–2030.e9:2013. <https://doi.org/10.1016/j.molcel.2021.03.001>
- Nicola, A.M., P. Albuquerque, L.R. Martinez, R.A. Dal-Rosso, C. Saylor, M. De Jesus, J.D. Nosanchuk, and A. Casadevall. 2012. Macrophage autophagy in immunity to *Cryptococcus neoformans* and *Candida albicans*. *Infect. Immun.* 80:3065–3076. <https://doi.org/10.1128/IAI.00358-12>
- Niida, M., M. Tanaka, and T. Kamitani. 2010. Downregulation of active IKK beta by Ro52-mediated autophagy. *Mol. Immunol.* 47:2378–2387. <https://doi.org/10.1016/j.molimm.2010.05.004>

- Nishida, Y., S. Arakawa, K. Fujitani, H. Yamaguchi, T. Mizuta, T. Kanaseki, M. Komatsu, K. Otsu, Y. Tsujimoto, and S. Shimizu. 2009. Discovery of Atg5/Atg7-independent alternative macroautophagy. *Nature*. 461:654–658. <https://doi.org/10.1038/nature08455>
- Nishimura, T., T. Kaizuka, K. Cadwell, M.H. Sahani, T. Saitoh, S. Akira, H.W. Virgin, and N. Mizushima. 2013. FIP200 regulates targeting of Atg16L1 to the isolation membrane. *EMBO Rep.* 14:284–291. <https://doi.org/10.1038/embor.2013.6>
- Nishimura, T., N. Tamura, N. Kono, Y. Shimanaka, H. Arai, H. Yamamoto, and N. Mizushima. 2017. Autophagosome formation is initiated at phosphatidylinositol synthase-enriched ER subdomains. *EMBO J.* 36: 1719–1735. <https://doi.org/10.15252/embj.201695189>
- Niu, H., Q. Xiong, A. Yamamoto, M. Hayashi-Nishino, and Y. Rikihisa. 2012. Autophagosomes induced by a bacterial Beclin 1 binding protein facilitate obligatory intracellular infection. *Proc. Natl. Acad. Sci. USA*. 109: 20800–20807. <https://doi.org/10.1073/pnas.1218674109>
- Noad, J., A. von der Malsburg, C. Pathe, M.A. Michel, D. Komander, and F. Randow. 2017. LUBAC-synthesized linear ubiquitin chains restrict cytosol-invading bacteria by activating autophagy and NF- κ B. *Nat. Microbiol.* 2:17063. <https://doi.org/10.1038/nmicrobiol.2017.63>
- Noda, S., S. Sato, T. Fukuda, N. Tada, Y. Uchiyama, K. Tanaka, and N. Hattori. 2020. Loss of Parkin contributes to mitochondrial turnover and dopaminergic neuronal loss in aged mice. *Neurobiol. Dis.* 136:104717. <https://doi.org/10.1016/j.nbd.2019.104717>
- Nozawa, T., S. Sano, A. Minowa-Nozawa, H. Toh, S. Nakajima, K. Murase, C. Aikawa, and I. Nakagawa. 2020. TBC1D9 regulates TBK1 activation through Ca²⁺ signaling in selective autophagy. *Nat. Commun.* 11:770. <https://doi.org/10.1038/s41467-020-14533-4>
- O'Neill, L.A.J., R.J. Kishton, and J. Rathmell. 2016. A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* 16:553–565. <https://doi.org/10.1038/nri.2016.70>
- Ogawa, M., T. Yoshimori, T. Suzuki, H. Sagara, N. Mizushima, and C. Sasaki. 2005. Escape of intracellular Shigella from autophagy. *Science*. 307:727–731. <https://doi.org/10.1126/science.1106036>
- Ohman, T., L. Teirila, A.M. Laheesmaa-Korpinen, W. Cypryk, V. Veckman, S. Saijo, H. Wolff, S. Hautaniemi, T.A. Nyman, and S. Matikainen. 2014. Dectin-1 pathway activates robust autophagy-dependent unconventional protein secretion in human macrophages. *J. Immunol.* 192: 5952–5962. <https://doi.org/10.4049/jimmunol.1303213>
- Ohnstad, A.E., J.M. Delgado, B.J. North, I. Nasa, A.N. Kettenbach, S.W. Schultz, and C.J. Shoemaker. 2020. Receptor-mediated clustering of FIP200 bypasses the role of LC3 lipidation in autophagy. *EMBO J.* 39: e104948. <https://doi.org/10.15252/embj.2020104948>
- Orvedahl, A., D. Alexander, Z. Tallozy, Q. Sun, Y. Wei, W. Zhang, D. Burns, D.A. Leib, and B. Levine. 2007. HSV-1 ICP34.5 confers neurovirulence by targeting the Beclin 1 autophagy protein. *Cell Host Microbe*. 1:23–35. <https://doi.org/10.1016/j.chom.2006.12.001>
- Orvedahl, A., S. Macpherson, R. Sumpter Jr., Z. Tallozy, Z. Zou, and B. Levine. 2010. Autophagy protects against sindbis virus infection of the central nervous system. *Cell Host Microbe*. 7:115–127. <https://doi.org/10.1016/j.chom.2010.01.007>
- Orvedahl, A., M.R. McAllister, A. Sansone, B.F. Dunlap, C. Desai, Y.T. Wang, D.R. Balce, C.J. Luke, S. Lee, R.C. Orchard, et al. 2019. Autophagy genes in myeloid cells counteract IFN γ -induced TNF-mediated cell death and fatal TNF-induced shock. *Proc. Natl. Acad. Sci. USA*. 116:16497–16506. <https://doi.org/10.1073/pnas.1822157116>
- Otten, E.G., E. Werner, A. Crespillo-Casado, K.B. Boyle, V. Dharamdasani, C. Pathe, B. Santhanam, and F. Randow. 2021. Ubiquitylation of lipopolysaccharide by RNF213 during bacterial infection. *Nature*. 594:111–116. <https://doi.org/10.1038/s41586-021-03566-4>
- Padman, B.S., T.N. Nguyen, L. Uoselis, M. Skulsupaisarn, L.K. Nguyen, and M. Lazarou. 2019. LC3/GABARAPs drive ubiquitin-independent recruitment of Optineurin and NDP52 to amplify mitophagy. *Nat. Commun.* 10:408. <https://doi.org/10.1038/s41467-019-08335-6>
- Pahari, S., S. Negi, M. Aqdas, E. Arnett, L.S. Schlesinger, and J.N. Agrewala. 2020. Induction of autophagy through CLEC4E in combination with TLR4: An innovative strategy to restrict the survival of *Mycobacterium tuberculosis*. *Autophagy*. 16:1021–1043. <https://doi.org/10.1080/15548627.2019.1658436>
- Paik, S., J.K. Kim, C. Chung, and E.K. Jo. 2019. Autophagy: A new strategy for host-directed therapy of tuberculosis. *Virulence*. 10:448–459. <https://doi.org/10.1080/21505594.2018.1536598>
- Palma, C., C. La Rocca, V. Gigantino, G. Aquino, G. Piccaro, D. Di Silvestre, F. Prambilla, R. Rossi, F. Bonacina, M.T. Lepore, et al. 2021. Caloric restriction promotes immunometabolic reprogramming leading to protection from tuberculosis. *Cell Metabol.* 33:300–318.e12. <https://doi.org/10.1016/j.cmet.2020.12.016>
- Papadopoulos, C., P. Kirchner, M. Bug, D. Grum, L. Koerver, N. Schulze, R. Poehler, A. Dressler, S. Fengler, K. Arhzaouy, et al. 2017. VCP/p97 cooperates with YOD1, UBXD1 and PLAA to drive clearance of ruptured lysosomes by autophagy. *EMBO J.* 36:135–150. <https://doi.org/10.15252/embj.201695148>
- Park, S., M.D. Buck, C. Desai, X. Zhang, E. Loginicheva, J. Martinez, M.L. Freeman, T. Saitoh, S. Akira, J.L. Guan, et al. 2016. Autophagy genes enhance murine gammaherpesvirus 68 reactivation from latency by preventing virus-induced systemic inflammation. *Cell Host Microbe*. 19: 91–101. <https://doi.org/10.1016/j.chom.2015.12.010>
- Parry, T.L., J.H. Melehan, M.J. Ranek, and M.S. Willis. 2015. Functional amyloid signaling via the inflammasome, necrosome, and signalosome: New therapeutic targets in heart failure. *Front. Cardiovasc. Med.* 2:25. <https://doi.org/10.3389/fcvm.2015.00025>
- Pilli, M., J. Arko-Mensah, M. Ponpuak, E. Roberts, S. Master, M.A. Mandell, N. Dupont, W. Ornatowski, S. Jiang, S.B. Bradfute, et al. 2012. TBK-1 promotes autophagy-mediated antimicrobial defense by controlling autophagosome maturation. *Immunity*. 37:223–234. <https://doi.org/10.1016/j.immuni.2012.04.015>
- Pohl, C., and I. Dikic. 2019. Cellular quality control by the ubiquitin-proteasome system and autophagy. *Science*. 366:818–822. <https://doi.org/10.1126/science.aax3769>
- Poillet-Perez, L., D.W. Sharp, Y. Yang, S.V. Laddha, M. Ibrahim, P.K. Bommareddy, Z.S. Hu, J. Vieth, M. Haas, M.W. Bosenberg, et al. 2020. Autophagy promotes growth of tumors with high mutational burden by inhibiting a T-cell immune response. *Nat. Cancer*. 1:923–934. <https://doi.org/10.1038/s43018-020-00110-7>
- Ponpuak, M., A.S. Davis, E.A. Roberts, M.A. Delgado, C. Dinkins, Z. Zhao, H.W. Virgin 4th, G.B. Kyei, T. Johansen, I. Vergne, and V. Deretic. 2010. Delivery of cytosolic components by autophagic adaptor protein p62 endows autophagosomes with unique antimicrobial properties. *Immunity*. 32:329–341. <https://doi.org/10.1016/j.immuni.2010.02.009>
- Ponpuak, M., M.A. Mandell, T. Kimura, S. Chauhan, C. Cleyrat, and V. Deretic. 2015. Secretory autophagy. *Curr. Opin. Cell Biol.* 35:106–116. <https://doi.org/10.1016/j.cob.2015.04.016>
- Prabakaran, T., C. Bodda, C. Krapp, B.C. Zhang, M.H. Christensen, C. Sun, L. Reinert, Y. Cai, S.B. Jensen, M.K. Skouboe, et al. 2018. Attenuation of cGAS-STING signaling is mediated by a p62/SQSTM1-dependent autophagy pathway activated by TBK1. *EMBO J.* 37:e97858. <https://doi.org/10.15252/embj.201797858>
- Prentice, E., W.G. Jerome, T. Yoshimori, N. Mizushima, and M.R. Denison. 2004. Coronavirus replication complex formation utilizes components of cellular autophagy. *J. Biol. Chem.* 279:10136–10141. <https://doi.org/10.1074/jbc.M306124200>
- Pua, H.H., J. Guo, M. Komatsu, and Y.W. He. 2009. Autophagy is essential for mitochondrial clearance in mature T lymphocytes. *J. Immunol.* 182: 4046–4055. <https://doi.org/10.4049/jimmunol.0801143>
- Puleston, D.J., H. Zhang, T.J. Powell, E. Lipina, S. Sims, I. Panse, A.S. Watson, V. Cerundolo, A.R. Townsend, P. Klenerman, and A.K. Simon. 2014. Autophagy is a critical regulator of memory CD8(+) T cell formation. *Elife*. 3. <https://doi.org/10.7554/eLife.03706>
- Puri, C., M. Renna, C.F. Bento, K. Moreau, and D.C. Rubinsztein. 2013. Diverse autophagosome membrane sources coalesce in recycling endosomes. *Cell*. 154:1285–1299. <https://doi.org/10.1016/j.cell.2013.08.044>
- Puri, C., M. Vicinanza, A. Ashkenazi, M.J. Gratian, Q. Zhang, C.F. Bento, M. Renna, F.M. Menzies, and D.C. Rubinsztein. 2018. The RAB1A-positive compartment is a primary platform for autophagosome assembly mediated by WIPI2 recognition of PI3P-RAB11A. *Dev. Cell*. 45:114–131.e8. <https://doi.org/10.1016/j.devcel.2018.03.008>
- Radoshevich, L., L. Murrell, N. Chen, E. Fernandez, S. Roy, C. Fung, and J. Debnath. 2010. ATG12 conjugation to ATG3 regulates mitochondrial homeostasis and cell death. *Cell*. 142:590–600. <https://doi.org/10.1016/j.cell.2010.07.018>
- Radulovic, M., K.O. Schink, E.M. Wenzel, V. Nahse, A. Bongiovanni, F. Lafont, and H. Stenmark. 2018. ESCRT-mediated lysosome repair precedes lysophagy and promotes cell survival. *EMBO J.* 37:e99753. <https://doi.org/10.15252/embj.201899753>
- Rai, S., M. Arasteh, M. Jefferson, T. Pearson, Y. Wang, W. Zhang, B. Bicsak, D. Divekar, P.P. Powell, R. Naumann, et al. 2019. The ATG5-binding and coiled coil domains of ATG16L1 maintain autophagy and tissue homeostasis in mice independently of the WD domain required for LC3-associated phagocytosis. *Autophagy*. 15:599–612. <https://doi.org/10.1080/15548627.2018.1534507>

- Randow, F., and R.J. Youle. 2014. Self and nonself: How autophagy targets mitochondria and bacteria. *Cell Host Microbe*. 15:403–411. <https://doi.org/10.1016/j.chom.2014.03.012>
- Ravenhill, B.J., K.B. Boyle, N. von Muhlinen, C.J. Ellison, G.R. Masson, E.G. Otten, A. Foeglein, R. Williams, and F. Randow. 2019. The cargo receptor NDP52 initiates selective autophagy by recruiting the ULK complex to cytosol-invading bacteria. *Mol. Cell*. 74:320–329.e6. <https://doi.org/10.1016/j.molcel.2019.01.041>
- Ravikumar, B., K. Moreau, L. Jahreiss, C. Puri, and D.C. Rubinsztein. 2010. Plasma membrane contributes to the formation of pre-autophagosomal structures. *Nat. Cell Biol.* 12:747–757. <https://doi.org/10.1038/ncb2078>
- Razani, B., C. Feng, T. Coleman, R. Emanuel, H. Wen, S. Hwang, J.P. Ting, H.W. Virgin, M.B. Kastan, and C.F. Semenkovich. 2012. Autophagy links inflammasomes to atherosclerotic progression. *Cell Metabol.* 15:534–544. <https://doi.org/10.1016/j.cmet.2012.02.011>
- Reggiori, F., I. Monastyrska, M.H. Verheije, T. Cali, M. Ulasli, S. Bianchi, R. Bernasconi, C.A.M. de Haan, and M. Molinari. 2010. Coronaviruses Hijack the LC3-I-positive EDEMosomes, ER-derived vesicles exporting short-lived ERAD regulators, for replication. *Cell Host Microbe*. 7: 500–508. <https://doi.org/10.1016/j.chom.2010.05.013>
- Richter, B., D.A. Sliter, L. Herhaus, A. Stolz, C. Wang, P. Beli, G. Zaffagnini, P. Wild, S. Martens, S.A. Wagner, et al. 2016. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. *Proc. Natl. Acad. Sci. USA*. 113: 4039–4044. <https://doi.org/10.1073/pnas.1523926113>
- Riffelmacher, T., A. Clarke, F.C. Richter, A. Stranks, S. Pandey, S. Danielli, P. Hublitz, Z. Yu, E. Johnson, T. Schwerd, et al. 2017. Autophagy-dependent generation of free fatty acids is critical for normal neutrophil differentiation. *Immunity*. 47:466–480.e5. <https://doi.org/10.1016/j.immuni.2017.08.005>
- Riffelmacher, T., F.C. Richter, and A.K. Simon. 2018. Autophagy dictates metabolism and differentiation of inflammatory immune cells. *Autophagy*. 14:199–206. <https://doi.org/10.1080/15548627.2017.1362525>
- Rong, Y., S. Zhang, N. Nandi, Z. Wu, L. Li, Y. Liu, Y. Wei, Y. Zhao, W. Yuan, C. Zhou, et al. 2022. STING controls energy stress-induced autophagy and energy metabolism via STX17. *J. Cell Biol.* 221:e202202060. <https://doi.org/10.1083/jcb.202202060>
- Saha, B., M. Salemi, G.L. Williams, S. Oh, M.L. Paffett, B. Phinney, and M.A. Mandell. 2022. Interactomic analysis reveals a homeostatic role for the HIV restriction factor TRIM5 α in mitophagy. *Cell Rep.* 39:110797. <https://doi.org/10.1016/j.celrep.2022.110797>
- Saitoh, T., N. Fujita, T. Hayashi, K. Takahara, T. Satoh, H. Lee, K. Matsunaga, S. Kageyama, H. Omori, T. Noda, et al. 2009. Atg9a controls dsDNA-driven dynamic translocation of STING and the innate immune response. *Proc. Natl. Acad. Sci. USA*. 106:20842–20846. <https://doi.org/10.1073/pnas.0911267106>
- Salio, M., D.J. Puleston, T.S.M. Mathan, D. Shepherd, A.J. Stranks, E. Adamopoulou, N. Veerapen, G.S. Besra, G.A. Hollander, A.K. Simon, and V. Cerundolo. 2014. Essential role for autophagy during invariant NKT cell development. *Proc. Natl. Acad. Sci. USA*. 111:E5678–E5687. <https://doi.org/10.1073/pnas.1413935112>
- Sanjuan, M.A., C.P. Dillon, S.W.G. Tait, S. Moshiah, F. Dorsey, S. Connell, M. Komatsu, K. Tanaka, J.L. Cleveland, S. Withoff, and D.R. Green. 2007. Toll-like receptor signalling in macrophages links the autophagy pathway to phagocytosis. *Nature*. 450:1253–1257. <https://doi.org/10.1038/nature06421>
- Saravia, J., J.L. Raynor, N.M. Chapman, S.A. Lim, and H. Chi. 2020. Signaling networks in immunometabolism. *Cell Res.* 30:328–342. <https://doi.org/10.1038/s41422-020-0301-1>
- Sasai, M., N. Sakaguchi, J.S. Ma, S. Nakamura, T. Kawabata, H. Bando, Y. Lee, T. Saitoh, S. Akira, A. Iwasaki, et al. 2017. Essential role for GABARAP autophagy proteins in interferon-inducible GTPase-mediated host defense. *Nat. Immunol.* 18:899–910. <https://doi.org/10.1038/ni.3767>
- Schneider, M., K. Ackermann, M. Stuart, C. Wex, U. Protzer, H.M. Schatzl, and S. Gilch. 2012. Severe acute respiratory syndrome coronavirus replication is severely impaired by MG132 due to proteasome-independent inhibition of M-calpain. *J. Virol.* 86:10112–10122. <https://doi.org/10.1128/JVI.01001-12>
- Schneider, W.M., J.M. Luna, H.H. Hoffmann, F.J. Sanchez-Rivera, A.A. Leal, A.W. Ashbrook, J. Le Pen, I. Ricardo-Lax, E. Michailidis, A. Peace, et al. 2021. Genome-scale identification of SARS-CoV-2 and pan-coronavirus host factor networks. *Cell*. 184:120–132.e14. <https://doi.org/10.1016/j.cell.2020.12.006>
- Schroder, K., and J. Tschoopp. 2010. The inflammasomes. *Cell*. 140:821–832. <https://doi.org/10.1016/j.cell.2010.01.040>
- Schuck, S. 2020. Microautophagy—distinct molecular mechanisms handle cargoes of many sizes. *J. Cell Sci.* 133:jcs246322. <https://doi.org/10.1242/jcs.246322>
- Selleck, E.M., R.C. Orchard, K.G. Lassen, W.L. Beatty, R.J. Xavier, B. Levine, H.W. Virgin, and L.D. Sibley. 2015. A noncanonical autophagy pathway restricts *Toxoplasma gondii* growth in a strain-specific manner in IFN- γ -Activated human cells. *mBio*. 6:e01157-15. <https://doi.org/10.1128/mBio.01157-15>
- Shi, C.S., K. Shenderov, N.N. Huang, J. Kabat, M. Abu-Asab, K.A. Fitzgerald, A. Sher, and J.H. Kehrl. 2012. Activation of autophagy by inflammatory signals limits IL-1 β production by targeting ubiquitinated inflammasomes for destruction. *Nat. Immunol.* 13:255–263. <https://doi.org/10.1038/ni.2215>
- Shi, Y., and D.M. Holtzman. 2018. Interplay between innate immunity and alzheimer disease: APOE and TREM2 in the spotlight. *Nat. Rev. Immunol.* 18:759–772. <https://doi.org/10.1038/s41577-018-0051-1>
- Singh, S.B., A.S. Davis, G.A. Taylor, and V. Deretic. 2006. Human IRGM induces autophagy to eliminate intracellular mycobacteria. *Science*. 313: 1438–1441. <https://doi.org/10.1126/science.1129577>
- Skowrya, M.L., P.H. Schlesinger, T.V. Naismith, and P.I. Hanson. 2018. Triggered recruitment of ESCRT machinery promotes endolysosomal repair. *Science*. 360:eaar5078. <https://doi.org/10.1126/science.aar5078>
- Slavik, K.M., B.R. Morehouse, A.E. Ragucci, W. Zhou, X. Ai, Y. Chen, L. Li, Z. Wei, H. Bahre, M. Konig, et al. 2021. cGAS-like receptors sense RNA and control 3'2'-cGAMP signalling in *Drosophila*. *Nature*. 597:109–113. <https://doi.org/10.1038/s41586-021-03743-5>
- Sliter, D.A., J. Martinez, L. Hao, X. Chen, N. Sun, T.D. Fischer, J.L. Burman, Y. Li, Z. Zhang, D.P. Narendra, et al. 2018. Parkin and PINK1 mitigate STING-induced inflammation. *Nature*. 561:258–262. <https://doi.org/10.1038/s41586-018-0448-9>
- Smith, M.D., M.E. Harley, A.J. Kemp, J. Wills, M. Lee, M. Arends, A. von Kriegsheim, C. Behrends, and S. Wilkinson. 2018. CCPG1 is a non-canonical autophagy cargo receptor essential for ER-phagy and pancreatic ER proteostasis. *Dev. Cell*. 44:217–232.e11. <https://doi.org/10.1016/j.devcel.2017.11.024>
- Snijder, E.J., R.W.A.L. Limpens, A.H. de Wilde, A.W.M. de Jong, J.C. Zevenhoven-Dobbe, H.J. Maier, F.F.G.A. Faas, A.J. Koster, and M. Barcana. 2020. A unifying structural and functional model of the coronavirus replication organelle: Tracking down RNA synthesis. *PLoS Biol.* 18: e3000715. <https://doi.org/10.1371/journal.pbio.3000715>
- Snijder, E.J., Y. van der Meer, J. Zevenhoven-Dobbe, J.J.M. Onderwater, J. van der Meulen, H.K. Koerten, and A.M. Mommaas. 2006. Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. *J. Virol.* 80: 5927–5940. <https://doi.org/10.1128/JVI.02501-05>
- Sonder, S.L., S.C. Hager, A.S.B. Heitmann, L.B. Frankel, C. Dias, A.C. Simonsen, and J. Nylandsted. 2021. Restructuring of the plasma membrane upon damage by LC3-associated macropinocytosis. *Sci. Adv.* 7: eabg1969. <https://doi.org/10.1126/sciadv.abg1969>
- Sonninen, T.M., R.H. Hamalainen, M. Koskivi, M. Oksanen, A. Shakirzyanova, S. Wojciechowski, K. Puttonen, N. Naumenko, G. Goldsteins, N. Laham-Karam, et al. 2020. Metabolic alterations in Parkinson's disease astrocytes. *Sci. Rep.* 10:14474. <https://doi.org/10.1038/s41598-020-71329-8>
- Soreng, K., M.J. Munson, C.A. Lamb, G.T. Bjorndal, S. Pankiv, S.R. Carlsson, S.A. Tooze, and A. Simonsen. 2018. SNX18 regulates ATG9A trafficking from recycling endosomes by recruiting Dynamins-2. *EMBO Rep.* 19: e44837. <https://doi.org/10.15252/embr.201744837>
- Sparrer, K.M.J., S. Gableske, M.A. Zurenski, Z.M. Parker, F. Full, G.J. Baumgart, J. Kato, G. Pacheco-Rodriguez, C. Liang, O. Pornillos, et al. 2017. TRIM23 mediates virus-induced autophagy via activation of TBK1. *Nat. Microbiol.* 2:1543–1557. <https://doi.org/10.1038/s41564-017-0017-2>
- Strating, J.R., and F.J. van Kuppeveld. 2017. Viral rewiring of cellular lipid metabolism to create membranous replication compartments. *Curr. Opin. Cell Biol.* 47:24–33. <https://doi.org/10.1016/j.cob.2017.02.005>
- Strong, E.J., K.L. Jurcik Smith, N.K. Saini, T.W. Ng, S.A. Porcelli, and S. Lee. 2020. Identification of autophagy-inhibiting factors of *Mycobacterium tuberculosis* by high-throughput loss-of-function screening. *Infect. Immun.* 88:e00269-20. <https://doi.org/10.1128/IAI.00269-20>
- Sumptner, R., Jr., S. Sirasanagandla, A.F. Fernandez, Y. Wei, X. Dong, L. Franco, Z. Zou, C. Marchal, M.Y. Lee, D.W. Clapp, et al. 2016. Fanconi anemia proteins function in mitophagy and immunity. *Cell*. 165: 867–881. <https://doi.org/10.1016/j.cell.2016.04.006>
- Sun, X., L. Sun, Y. Zhao, Y. Li, W. Lin, D. Chen, and Q. Sun. 2016. MAVS maintains mitochondrial homeostasis via autophagy. *Cell Dis.* 2:16024. <https://doi.org/10.1038/celldisc.2016.24>

- Swadling, L., L.J. Pallett, M.O. Diniz, J.M. Baker, O.E. Amin, K.A. Stegmann, A.R. Burton, N.M. Schmidt, A. Jeffery-Smith, N. Zakeri, et al. 2020. Human liver memory CD8(+) T cells use autophagy for tissue residence. *Cell Rep.* 30:687–698.e6. <https://doi.org/10.1016/j.celrep.2019.12.050>
- Takahashi, Y., H. He, Z. Tang, T. Hattori, Y. Liu, M.M. Young, J.M. Serfass, L. Chen, M. Gebru, C. Chen, et al. 2018. An autophagy assay reveals the ESCRT-III component CHMP2A as a regulator of phagophore closure. *Nat. Commun.* 9:2855. <https://doi.org/10.1038/s41467-018-05254-w>
- Tal, M.C., M. Sasai, H.K. Lee, B. Yordy, G.S. Shadel, and A. Iwasaki. 2009. Absence of autophagy results in reactive oxygen species-dependent amplification of RLR signaling. *Proc. Natl. Acad. Sci. USA.* 106:2770–2775. <https://doi.org/10.1073/pnas.0807694106>
- Tan, J.M.J., N. Mellouk, S.E. Osborne, D.A. Ammendolia, D.N. Dyer, R. Li, D. Brunen, J.M. van Rijn, J. Huang, M.A. Czuczman, et al. 2018. An ATG16L1-dependent pathway promotes plasma membrane repair and limits *Listeria* monocytogenes cell-to-cell spread. *Nat. Microbiol.* 3:1472–1485. <https://doi.org/10.1038/s41564-018-0293-5>
- Thorburn, J., H. Horita, J. Redzic, K. Hansen, A.E. Frankel, and A. Thorburn. 2009. Autophagy regulates selective HMGB1 release in tumor cells that are destined to die. *Cell Death Differ.* 16:175–183. <https://doi.org/10.1038/cdd.2008.143>
- Thurston, T.L.M., G. Ryzhakov, S. Bloor, N. von Muhlinen, and F. Randow. 2009. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nat. Immunol.* 10:1215–1221. <https://doi.org/10.1038/ni.1800>
- Thurston, T.L., M.P. Wandel, N. von Muhlinen, A. Foeglein, and F. Randow. 2012. Galectin 8 targets damaged vesicles for autophagy to defend cells against bacterial invasion. *Nature.* 482:414–418. <https://doi.org/10.1038/nature10744>
- Tiwari, S.K., J.W. Dang, N. Lin, Y. Qin, S. Wang, and T.M. Rana. 2020. Zika virus depletes neural stem cells and evades selective autophagy by suppressing the Fanconi anemia protein FANCC. *EMBO Rep.* 21:e49183. <https://doi.org/10.15252/embr.201949183>
- Tooley, A.S., D. Kazyken, C. Bodur, I.E. Gonzalez, and D.C. Fingar. 2021. The innate immune kinase TBK1 directly increases mTORC2 activity and downstream signaling to Akt. *J. Biol. Chem.* 297:100942. <https://doi.org/10.1016/j.jbc.2021.100942>
- Tooze, S.A., and T. Yoshimori. 2010. The origin of the autophagosomal membrane. *Nat. Cell Biol.* 12:831–835. <https://doi.org/10.1038/ncb0910-831>
- Travassos, L.H., L.A.M. Carneiro, M. Ramjeet, S. Hussey, Y.G. Kim, J.G. Magalhaes, L. Yuan, F. Soares, E. Chea, L. Le Bourhis, et al. 2010. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. *Nat. Immunol.* 11:55–62. <https://doi.org/10.1038/ni.1823>
- Tsapras, P., S. Petridi, S. Chan, M. Geborys, A.C. Jacomin, A.P. Sagona, P. Meier, and I.P. Nezis. 2022. Selective autophagy controls innate immune response through a TAK1/TAB2/SH3PX1 axis. *Cell Rep.* 38:110286. <https://doi.org/10.1016/j.celrep.2021.110286>
- Tumbarello, D.A., P.T. Manna, M. Allen, M. Bycroft, S.D. Arden, J. Kendrick-Jones, and F. Buss. 2015. The autophagy receptor TAX1BP1 and the molecular motor Myosin VI are required for clearance of *Salmonella typhimurium* by autophagy. *PLoS Pathog.* 11:e1005174. <https://doi.org/10.1371/journal.ppat.1005174>
- Tur, J., S. Pereira-Lopes, T. Vico, E.A. Marin, J.P. Munoz, M. Hernandez-Alvarez, P.J. Cardona, A. Zorzano, J. Lloberas, and A. Celada. 2020. Mitofusin 2 in macrophages links mitochondrial ROS production, cytokine release, phagocytosis, autophagy, and bactericidal activity. *Cell Rep.* 32:108079. <https://doi.org/10.1016/j.celrep.2020.108079>
- Turco, E., M. Witt, C. Abert, T. Bock-Bierbaum, M.Y. Su, R. Trapannone, M. Sztacho, A. Danieli, X. Shi, G. Zaffagnini, et al. 2019. FIP200 claw domain binding to p62 promotes autophagosome formation at ubiquitin condensates. *Mol. Cell.* 74:330–346.e11. <https://doi.org/10.1016/j.molcel.2019.01.035>
- Twu, W.I., J.Y. Lee, H. Kim, V. Prasad, B. Cerikan, U. Haselmann, K. Tabata, and R. Bartenschlager. 2021. Contribution of autophagy machinery factors to HCV and SARS-CoV-2 replication organelle formation. *Cell Rep.* 37:110049. <https://doi.org/10.1016/j.celrep.2021.110049>
- Ulferts, R., E. Marcassa, L. Timimi, L.C. Lee, A. Daley, B. Montaner, S.D. Turner, O. Florey, J.K. Baillie, and R. Beale. 2021. Subtractive CRISPR screen identifies the ATG16L1/vacuolar ATPase axis as required for non-canonical LC3 lipidation. *Cell Rep.* 37:109899. <https://doi.org/10.1016/j.celrep.2021.109899>
- Ulland, T.K., W.M. Song, S.C.C. Huang, J.D. Ulrich, A. Sergushichev, W.L. Beatty, A.A. Loboda, Y. Zhou, N.J. Cairns, A. Kambal, et al. 2017. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell.* 170:649–663.e13. <https://doi.org/10.1016/j.cell.2017.07.023>
- Usmani, A., F. Shavarebi, and A. Hiniker. 2021. The cell biology of LRRK2 in Parkinson's disease. *Mol. Cell. Biol.* 41:e00660-20. <https://doi.org/10.1128/MCB.00660-20>
- Valverde, D.P., S. Yu, V. Boggavarapu, N. Kumar, J.A. Lees, T. Walz, K.M. Reinisch, and T.J. Melia. 2019. ATG2 transports lipids to promote autophagosome biogenesis. *J. Cell Biol.* 218:1787–1798. <https://doi.org/10.1083/jcb.201811139>
- Vargas, J.N.S., C. Wang, E. Bunker, L. Hao, D. Maric, G. Schiavo, F. Randow, and R.J. Youle. 2019. Spatiotemporal control of ULK1 activation by NDP52 and TBK1 during selective autophagy. *Mol. Cell.* 74:347–362.e6. <https://doi.org/10.1016/j.molcel.2019.02.010>
- Versteeg, Gijs A., R. Rajsbaum, M.T. Sánchez-Aparicio, Ana M. Maestre, J. Valdiviezo, M. Shi, K.-S. Inn, A. Fernandez-Sesma, J. Jung, and A. García-Sastre. 2013. The E3-ligase TRIM family of proteins regulates signaling pathways triggered by innate immune pattern-recognition receptors. *Immunity.* 38:384–398. <https://doi.org/10.1016/j.immuni.2012.11.013>
- von Muhlinen, N., M. Akutsu, B.J. Ravenhill, A. Foeglein, S. Bloor, T.J. Rutherford, S.M.V. Freund, D. Komander, and F. Randow. 2012. LC3C, bound selectively by a noncanonical LIR motif in NDP52, is required for antibacterial autophagy. *Mol. Cell.* 48:329–342. <https://doi.org/10.1016/j.molcel.2012.08.024>
- Wan, J., E. Weiss, S. Ben Mkaddem, M. Mabire, P.M. Choinier, O. Picq, T. Thibault-Sogorb, P. Hegde, D. Pishvaie, M. Bens, et al. 2020. LC3-associated phagocytosis protects against inflammation and liver fibrosis via immunoreceptor inhibitory signaling. *Sci. Translat. Med.* 12:eaaw8523. <https://doi.org/10.1126/scitranslmed.aaw8523>
- Wang, J., M. Meng, M. Li, X. Guan, J. Liu, X. Gao, Q. Sun, J. Li, C. Ma, and L. Wei. 2020a. Integrin $\alpha 5 \beta 1$, as a receptor of fibronectin, binds the FbaA protein of group A *Streptococcus* to initiate autophagy during infection. *mBio.* 11:e01729-20. <https://doi.org/10.1128/mBio.01729-20>
- Wang, Y., P. Sharma, M. Jefferson, W. Zhang, B. Bone, A. Kipar, D. Bitto, J.L. Coombes, T. Pearson, A. Man, et al. 2021. Non-canonical autophagy functions of ATG16L1 in epithelial cells limit lethal infection by influenza A virus. *EMBO J.* 40:e105543. <https://doi.org/10.15252/embj.2020105543>
- Wang, Y.T., K. Zaitsev, Q. Lu, S. Li, W.T. Schaiff, K.W. Kim, L. Droit, C.B. Wilen, C. Desai, D.R. Balce, et al. 2020b. Select autophagy genes maintain quiescence of tissue-resident macrophages and increase susceptibility to *Listeria* monocytogenes. *Nat. Microbiol.* 5:272–281. <https://doi.org/10.1038/s41564-019-0633-0>
- Watson, R.O., S.L. Bell, D.A. MacDuff, J.M. Kimmey, E.J. Diner, J. Olivas, R.E. Vance, C.L. Stallings, H.W. Virgin, and J.S. Cox. 2015. The cytosolic sensor cGAS detects *Mycobacterium tuberculosis* DNA to induce type I interferons and activate autophagy. *Cell Host Microbe.* 17:811–819. <https://doi.org/10.1016/j.chom.2015.05.004>
- Watson, R.O., P.S. Manzanillo, and J.S. Cox. 2012. Extracellular *M. tuberculosis* DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. *Cell.* 150:803–815. <https://doi.org/10.1016/j.cell.2012.06.040>
- Weidberg, H., E. Shvets, T. Shpilka, F. Shimron, V. Shinder, and Z. Elazar. 2010. LC3 and GATE-16/GABARAP subfamilies are both essential yet act differently in autophagosome biogenesis. *EMBO J.* 29:1792–1802. <https://doi.org/10.1038/emboj.2010.74>
- Werneburg, N.W., M.E. Guicciardi, S.F. Bronk, S.H. Kaufmann, and G.J. Gores. 2007. Tumor necrosis factor-related apoptosis-inducing ligand activates a lysosomal pathway of apoptosis that is regulated by Bcl-2 proteins. *J. Biol. Chem.* 282:28960–28970. <https://doi.org/10.1074/jbc.M705671200>
- White, M.J., K. McArthur, D. Metcalf, R.M. Lane, J.C. Cambier, M.J. Herold, M.F. van Delft, S. Bedoui, G. Lessene, M.E. Ritchie, et al. 2014. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. *Cell.* 159:1549–1562. <https://doi.org/10.1016/j.cell.2014.11.036>
- Wild, P., H. Farhan, D.G. McEwan, S. Wagner, V.V. Rogov, N.R. Brady, B. Richter, J. Korac, O. Waidmann, C. Choudhary, et al. 2011. Phosphorylation of the autophagy receptor optineurin restricts *Salmonella* growth. *Science.* 333:228–233. <https://doi.org/10.1126/science.1205405>
- Willson, J.A., S. Arienti, P. Sadiku, L. Reyes, P. Coelho, T. Morrison, G. Rinaldi, D.H. Dockrell, M.K.B. Whyte, and S.R. Walmsley. 2022. Neutrophil HIF-1 α stabilization is augmented by mitochondrial ROS produced via the glycerol 3-phosphate shuttle. *Blood.* 139:281–286. <https://doi.org/10.1182/blood.2021011010>
- Xie, H., C. Li, M. Zhang, N. Zhong, and L. Chen. 2017. Association between IRGM polymorphisms and tuberculosis risk: A meta-analysis. *Med.* 96:e8189. <https://doi.org/10.1097/MD.0000000000008189>

- Xin, Y., L. Yu, Z. Chen, L. Zheng, Q. Fu, J. Jiang, P. Zhang, R. Gong, and S. Zhao. 2001. Cloning, expression patterns, and chromosome localization of three human and two mouse homologues of GABA(A) receptor-associated protein. *Genomics*. 74:408–413. <https://doi.org/10.1006/geno.2001.6555>
- Xu, X., K. Araki, S. Li, J.H. Han, L. Ye, W.G. Tan, B.T. Konieczny, M.W. Bruinsma, J. Martinez, E.L. Pearce, et al. 2014. Autophagy is essential for effector CD8(+) T cell survival and memory formation. *Nat. Immunol.* 15:1152–1161. <https://doi.org/10.1038/ni.3025>
- Xu, Y., S. Cheng, H. Zeng, P. Zhou, Y. Ma, L. Li, X. Liu, F. Shao, and J. Ding. 2022. ARF GTPases activate *Salmonella* effector SopF to ADP-ribosylate host V-ATPase and inhibit endomembrane damage-induced autophagy. *Nat. Struct. Mol. Biol.* 29:67–77. <https://doi.org/10.1038/s41594-021-00710-6>
- Xu, Y., P. Zhou, S. Cheng, Q. Lu, K. Nowak, A.K. Hopp, L. Li, X. Shi, Z. Zhou, W. Gao, et al. 2019. A bacterial effector reveals the V-ATPase-ATG16L1 Axis that initiates xenophagy. *Cell*. 178:552–566 e520. <https://doi.org/10.1016/j.cell.2019.06.007>
- Yamamoto, K., A. Venida, J. Yano, D.E. Biancur, M. Kakiuchi, S. Gupta, A.S.W. Sohn, S. Mukhopadhyay, E.Y. Lin, S.J. Parker, et al. 2020. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. *Nature*. 581:100–105. <https://doi.org/10.1038/s41586-020-2229-5>
- Yamashiro, L.H., S.C. Wilson, H.M. Morrison, V. Karalis, J.Y.J. Chung, K.J. Chen, H.S. Bateup, M.L. Szpara, A.Y. Lee, J.S. Cox, and R.E. Vance. 2020. Interferon-independent STING signaling promotes resistance to HSV-1 in vivo. *Nat. Commun.* 11:3382. <https://doi.org/10.1038/s41467-020-17156-x>
- Yamazaki, T., A. Kirchmair, A. Sato, A. Buque, M. Rybstein, G. Petroni, N. Bloy, F. Finotello, L. Stafford, E. Navarro Manzano, et al. 2020. Mitochondrial DNA drives abscondal responses to radiation that are inhibited by autophagy. *Nat. Immunol.* 21:1160–1171. <https://doi.org/10.1038/s41590-020-0751-0>
- Yano, T., S. Mita, H. Ohmori, Y. Oshima, Y. Fujimoto, R. Ueda, H. Takada, W.E. Goldman, K. Fukase, N. Silverman, et al. 2008. Autophagic control of *Listeria* through intracellular innate immune recognition in *Drosophila*. *Nat. Immunol.* 9:908–916. <https://doi.org/10.1038/ni.1634>
- Yoshida, Y., S. Yasuda, T. Fujita, M. Hamasaki, A. Murakami, J. Kawawaki, K. Iwai, Y. Saeki, T. Yoshimori, N. Matsuda, and K. Tanaka. 2017. Ubiquitination of exposed glycoproteins by SCF(FBXO27) directs damaged lysosomes for autophagy. *Proc. Natl. Acad. Sci. USA*. 114:8574–8579. <https://doi.org/10.1073/pnas.1702615114>
- Youle, R.J. 2019. Mitochondria-Striking a balance between host and endosymbiont. *Science*. 365:eaaw9855. <https://doi.org/10.1126/science.aaw9855>
- Yue, Y., N.R. Nabar, C.S. Shi, O. Kamenyeva, X. Xiao, I.Y. Hwang, M. Wang, and J.H. Kehrl. 2018. SARS-coronavirus open reading frame-3a drives multimodal necrotic cell death. *Cell Death Dis.* 9:904. <https://doi.org/10.1038/s41419-018-0917-y>
- Zachari, M., S.R. Gudmundsson, Z. Li, F.M. Cugliandolo, M. Manifava, R. Shah, M. Smith, J. Stronge, E. Karanasios, C. Piunti, C. Kishi-Itakura, et al. 2020. Selective autophagy of mitochondria on a ubiquitin-endoplasmic-reticulum platform. *Dev. Cell*. 55:251. <https://doi.org/10.1016/j.devcel.2020.10.002>
- Zhang, B.C., R. Nandakumar, L.S. Reinert, J. Huang, A. Laustsen, Z.L. Gao, C.L. Sun, S.B. Jensen, A. Trolldborg, S. Assil, et al. 2020a. STEEP mediates STING ER exit and activation of signaling. *Nat. Immunol.* 21:868–879. <https://doi.org/10.1038/s41590-020-0730-5>
- Zhang, M., S.J. Kenny, L. Ge, K. Xu, and R. Schekman. 2015. Translocation of interleukin-1 β into a vesicle intermediate in autophagy-mediated secretion. *Elife*. 4:e11205. <https://doi.org/10.7554/eLife.11205>
- Zhang, M., L. Liu, X. Lin, Y. Wang, Y. Li, Q. Guo, S. Li, Y. Sun, X. Tao, D. Zhang, et al. 2020b. A translocation pathway for vesicle-mediated unconventional protein secretion. *Cell*. 181:637–652.e15. <https://doi.org/10.1016/j.cell.2020.03.031>
- Zhang, R., M. Varela, W. Vallentgoed, G. Forn-Cuni, M. van der Vaart, and A.H. Meijer. 2019a. The selective autophagy receptors Optineurin and p62 are both required for zebrafish host resistance to mycobacterial infection. *PLoS Pathog.* 15:e1007329. <https://doi.org/10.1371/journal.ppat.1007329>
- Zhang, Y., Y. Yao, X. Qiu, G. Wang, Z. Hu, S. Chen, Z. Wu, N. Yuan, H. Gao, J. Wang, et al. 2019b. *Listeria* hijacks host mitophagy through a novel mitophagy receptor to evade killing. *Nat. Immunol.* 20:433–446. <https://doi.org/10.1038/s41590-019-0324-2>
- Zhao, P., K.I. Wong, X. Sun, S.M. Reilly, M. Uhm, Z. Liao, Y. Skorobogatko, and A.R. Saltiel. 2018. TBK1 at the crossroads of inflammation and energy homeostasis in adipose tissue. *Cell*. 172:731–743.e12. <https://doi.org/10.1016/j.cell.2018.01.007>
- Zhao, Y.G., and H. Zhang. 2019. Autophagosome maturation: An epic journey from the ER to lysosomes. *J. Cell Biol.* 218:757–770. <https://doi.org/10.1083/jcb.201810099>
- Zhao, Z., L.B. Thackray, B.C. Miller, T.M. Lynn, M.M. Becker, E. Ward, N.N. Mizushima, M.R. Denison, and H.W. Virgin 4th. 2007. Coronavirus replication does not require the autophagy gene ATG5. *Autophagy*. 3: 581–585. <https://doi.org/10.4161/auto.4782>
- Zhou, R., A.S. Yazdi, P. Menu, and J. Tschopp. 2011. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 469:221–225. <https://doi.org/10.1038/nature09663>
- Zhu, L., Y. Li, X. Xie, X. Zhou, M. Gu, Z. Jie, C.J. Ko, T. Gao, B.E. Hernandez, X. Cheng, and S.C. Sun. 2019. TBKBP1 and TBK1 form a growth factor signalling axis mediating immunosuppression and tumorigenesis. *Nat. Cell Biol.* 21:1604–1614. <https://doi.org/10.1038/s41556-019-0429-8>
- Zhu, L., C. Mou, X. Yang, J. Lin, and Q. Yang. 2016. Mitophagy in TGEV infection counteracts oxidative stress and apoptosis. *Oncotarget*. 7: 27122–27141. <https://doi.org/10.18632/oncotarget.8345>
- Zhu, L., X. Xie, L. Zhang, H. Wang, Z. Jie, X. Zhou, J. Shi, S. Zhao, B. Zhang, X. Cheng, and S.C. Sun. 2018. TBK-binding protein 1 regulates IL-15-induced autophagy and NKT cell survival. *Nat. Commun.* 9:2812. <https://doi.org/10.1038/s41467-018-05097-5>

Supplemental material

Provided online is Table S1. Table S1 shows examples of intracellular microbes studied as targets for elimination by autophagy.