AUTOPHAGY
2023, VOL. 19, NO. 1, 44–53
https://doi.org/10.1080/15548627.2022.2070331

Taylor & Francis
Taylor & Francis Group

REVIEW

Multifaceted roles of TAX1BP1 in autophagy

Jesse White[a], Sujit Suklabaidya[a], Mai Tram Vo[b], Young Bong Choi[b], and Edward W. Harhaj[a]

[a]Department of Microbiology and Immunology, Penn State College School of Medicine, Hershey, Pennsylvania, USA; [b]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

ABSTRACT

TAX1BP1 is a selective macroautophagy/autophagy receptor that plays a central role in host defense to pathogens and in regulating the innate immune system. TAX1BP1 facilitates the xenophagic clearance of pathogenic bacteria such as *Salmonella typhimurium* and *Mycobacterium tuberculosis* and regulates TLR3 (toll-like receptor 3)-TLR4 and DDX58/RIG-I-like receptor (RLR) signaling by targeting TICAM1 and MAVS for autophagic degradation respectively. In addition to these canonical autophagy receptor functions, TAX1BP1 can also exert multiple accessory functions that influence the biogenesis and maturation of autophagosomes. In this review, we will discuss and integrate recent findings related to the autophagy function of TAX1BP1 and highlight outstanding questions regarding its functions in autophagy and regulation of innate immunity and host defense.

Abbreviations: ATG: autophagy related; CALCOCO: calcium binding and coiled-coil domain; CC: coiled-coil; CHUK/IKKα: conserved helix-loop-helix ubiquitous kinase; CLIR: noncanonical LC3-interacting region; GABARAP: gamma-aminobutyric acid receptor associated protein; HTLV-1: human T-lymphotropic virus 1; IFN: interferon; IL1B/IL1β: interleukin 1 beta; LIR: LC3-interacting region; LPS: lipopolysaccharide; MAP1LC3/LC3: microtubule-associated protein 1 light chain 3; MAPK/JNK: mitogen-activated protein kinase; mATG8: mammalian Atg8 homolog; MAVS: mitochondrial antiviral signaling protein; MEF: mouse embryonic fibroblast; MTB: *Mycobacterium tuberculosis*; MYD88: myeloid differentiation primary response gene 88; NBR1: NBR1, autophagy cargo receptor; NFKB/NF-κB: nuclear factor of kappa light polypeptide gene enhancer in B cells; OPTN: optineurin; Poly(I:C): polyinosinic:polycytidylic acid; PTM: post-translational modification; RB1CC1: RB1-inducible coiled-coil 1; RIPK: receptor (TNFRSF)-interacting serine-threonine kinase; RLR: DDX58/RIG-I-like receptor; RSV: respiratory syncytia virus; SKICH: SKIP carboxyl homology; SLR: SQSTM1 like receptor; SQSTM1: sequestosome 1; TAX1BP1: Tax1 (human T cell leukemia virus type I) binding protein 1; TBK1: TANK-binding kinase 1; TICAM1: toll-like receptor adaptor molecule 1; TLR: toll-like receptor; TNF: tumor necrosis factor; TNFAIP3: TNF alpha induced protein 3; TNFR: tumor necrosis factor receptor; TOM1: target of myb1 trafficking protein; TRAF: TNF receptor-associated factor; TRIM32: tripartite motif-containing 32; UBD: ubiquitin binding domain; ZF: zinc finger.

ARTICLE HISTORY
Received 29 November 2021
Revised 21 April 2022
Accepted 21 April 2022

KEYWORDS
Aggrephagy; autophagy; host defense; innate immune signaling; TAX1BP1; xenophagy

Introduction

TAX1BP1 (Tax1 (human T cell leukemia virus type I) binding protein 1) was first identified in a yeast two-hybrid screen as an interactant of the human T-lymphotropic virus 1 (HTLV-1) Tax oncoprotein [1]. Shortly thereafter, TAX1BP1 was also identified in independent yeast two-hybrid screens as a binding protein of the zinc finger protein TNFAIP3/A20 (TNF alpha induced protein 3) [2] and the E3 ubiquitin ligase TRAF6 (TNF receptor-associated factor 6) [3]. TAX1BP1 is expressed in all vertebrates and is evolutionarily conserved [4]. In humans, the *TAX1BP1* gene resides on chromosome 7 [5], and is expressed ubiquitously [6]. TAX1BP1 protein is expressed in all tissue types, with heightened expression in kidney and brain [7]. TAX1BP1 is organized into three macrodomains including an N-terminal SKIP carboxyl homology (SKICH) domain, a central oligomerization domain containing three coiled-coil (CC) regions, and a C-terminal ubiquitin binding domain (UBD) containing two zinc finger (ZF) domains (Figure 1) [6,8].

Historically, TAX1BP1 was first studied in the context of regulating cell death and inflammatory signaling pathways. Overexpression of TAX1BP1 inhibits TNF (tumor necrosis factor)-induced apoptosis and served as a substrate for CASP (caspase)-induced cleavage [2]. In addition to the regulation of cell death pathways, TAX1BP1 is also linked to NFKB/NF-κB (nuclear factor of kappa light polypeptide gene enhancer in B cells) signaling. IL1B/IL1β (interleukin 1 beta) stimulation promotes the interaction between TRAF6 and TAX1BP1. However, TAX1BP1 does not activate NFKB or MAPK/JNK (mitogen-activated protein kinase) pathways [3]. TAX1BP1-deficient mice were independently generated by our laboratory and another group with similar conclusions derived from functional studies with *tax1bp1* knockout fibroblasts [9,10]. TAX1BP1-deficient mouse embryonic fibroblasts (MEFs) exhibit enhanced and persistent NFkB signaling induced by TNF or IL1β stimulation. Notably, these effects were replicated *in vivo* since TAX1BP1-deficient mice were hypersensitive to inflammatory challenge by either TNF or IL1β [9]. Mechanistically, TAX1BP1 was found to function as an adaptor for TNFAIP3 to bind and inactivate its substrates RIPK1 (receptor (TNFRSF)-

CONTACT Edward W. Harhaj ewh110@psu.edu Department of Microbiology and Immunology, Penn State College of Medicine, Hershey, Pennsylvania, USA

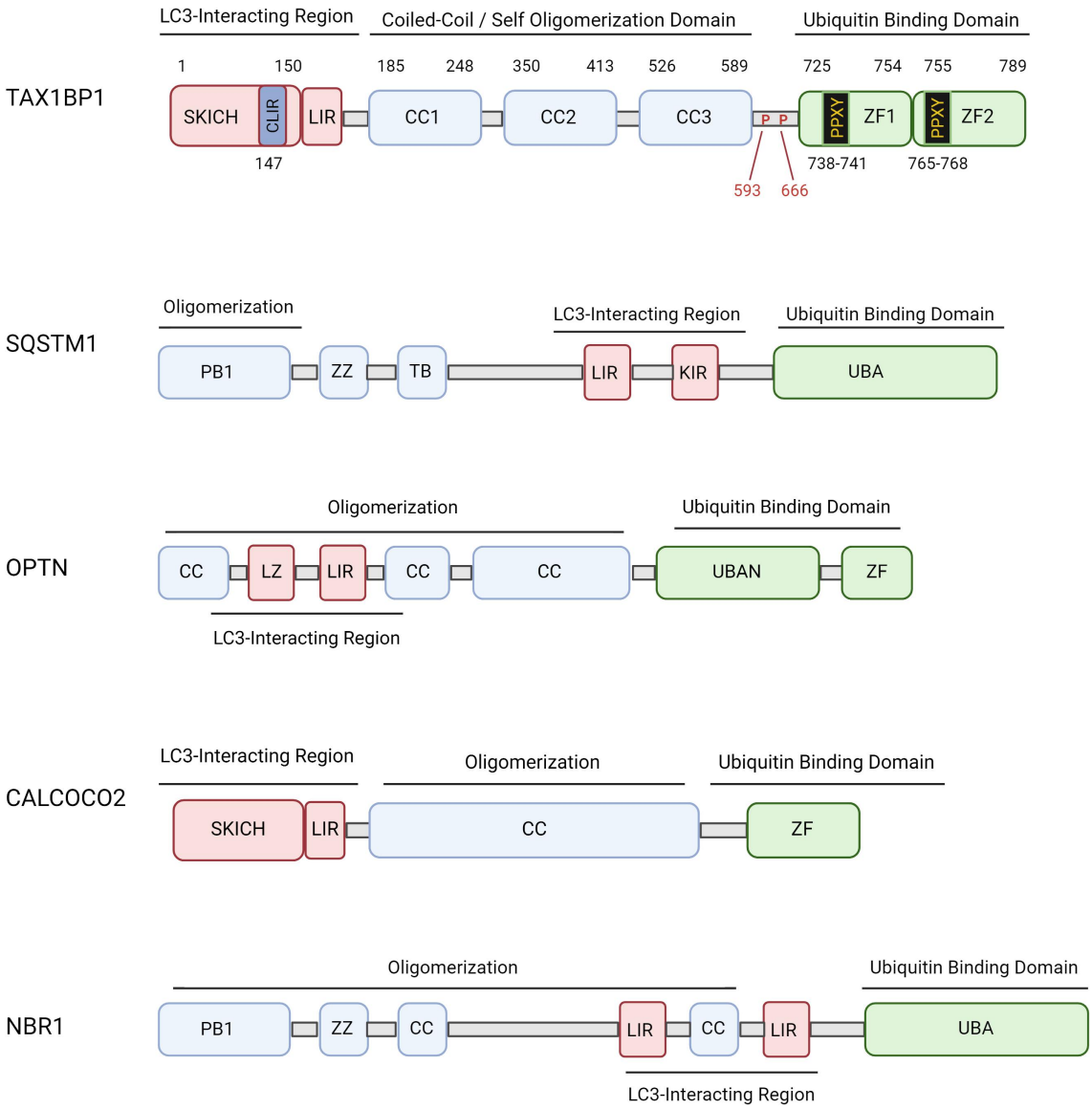

Figure 1. Domain structure of SLRs. TAX1BP1 contains a SKICH domain (containing the CLIR) and the LIR. The central region contains three coiled-coil domains which play a role in self oligomerization. Designated in red are phosphorylation sites critical for TAX1BP1 to suppress the activation of inflammatory signaling pathways [13].The C-terminal region contains two zinc finger domains of which ZF2 functions as a Ub binding domain. Each ZF domain contains a PPXY motif which are required for regulation of anti-inflammatory and anti-viral signaling [13,14]. In addition to TAX1BP1, the SLRs SQSTM1, OPTN, CALCOCO2 and NBR1 all share domains important for LC3 interaction, oligomerization and ubiquitin binding. Created with BioRender.

interacting serine-threonine kinase 1) and TRAF6 in TNFR and IL1 receptor pathways respectively [9,10]. Studies from our laboratory further identified the E3 ubiquitin ligases ITCH and RNF11 (ring finger protein 11) as TNFAIP3 and TAX1BP1 binding proteins that functioned as negative regulators of NFkB signaling [11–13]. We also found that TAX1BP1 interacts with TBK1 (TANK-binding kinase 1) and coordinates with TNFAIP3 to inhibit the DDX58/RIG-I-like receptor (RLR) pathway and virus-triggered type I interferon (IFN) expression [14]. TAX1BP1 also cooperated with ITCH to inhibit the RLR pathway by interacting with and promoting MAVS (mitochondrial antiviral signaling protein) degradation [15].

In 2012, TAX1BP1 was first implicated as an autophagy receptor with the identification of canonical and noncanonical LC3 (microtubule-associated protein 1 light chain 3)-interacting regions (LIRs) in the N-terminal region [16]. Since this discovery, the focus of the field has shifted toward investigating the function and regulation of TAX1BP1 in the context of autophagy. The goal of this review is to discuss and integrate recent findings on the functions of TAX1BP1 in autophagy and to identify outstanding questions regarding its autophagy functions and regulation of innate immunity and host defense.

Autophagy

Macroautophagy/autophagy is a highly conserved lysosomal degradation pathway utilized by cells to clear damaged or aggregated proteins and organelles. Autophagy occurs in a well-defined and highly regulated manner. First, a cup-shaped lipid bilayer (known as a phagophore) encloses around targeted

substrates. Three main groups of complexes, including the ULK1 (unc-51 like kinase 1) complex, the class 3 phosphatidylinositol 3-kinase (PtdIns3K) complex (and the Atg8-family protein lipidation machinery/complex, allow for efficient phagophore expansion and engulfment of substrates. The coordination of these complexes has been described elsewhere [17,18]. Following closure of the phagophore (now considered an "autophagosome") this lipid structure will either directly fuse with lysosomes to form "autolysosomes," or fuse with endosomes to form "amphisomes" as an intermediate fusion step. Ultimately, autophagosome substrates are cleared upon fusion with the lysosome [17–20].

In addition to general or nonselective autophagy, a bulk degradation system, that is activated by metabolic stresses, selective autophagy is mediated primarily by autophagy cargo receptors, including a family of proteins coined by Deretic and colleagues as SQSTM1 (sequestosome 1)-like receptors (SLRs), for the targeted degradation of specific substrates [21]. To this end, SLRs share three homologous features: an LIR(s), a self-oligomerization domain and a UBD (Figure 1). SLRs serve an adaptor-like role by tethering specific substrates to the phagophore. Typically, tethering occurs through an interaction between the UBD region on SLRs and polyubiquitin chains conjugated to substrates. Upon substrate binding, SLRs will merge with the developing phagophore through an interaction between the LIR on the SLRs and mammalian Atg8 homolog (mATG8) family member proteins lining the phagophore. Following substrate/SLR linkage to the phagophore, autophagy occurs as described above [22,23].

TAX1BP1 was first identified as an SLR by Newman *et al.* during their investigation of TBK1 addiction in KRAS-driven cancer cells [16]. Although it was established that KRAS-driven cancer cells required TBK1, constitutive autophagy, and NFKB activity for survival and proliferation [24,25], it was unknown how TBK1 regulated both autophagy and NFKB signaling downstream of KRAS. TBK1 had been previously implicated in NFKB signaling [26,27]. Furthermore, TBK1 had been shown to regulate autophagy during bacterial infection via the SLRs, such as CALCOCO2/NDP52 (calcium binding and coiled-coil domain 2) and OPTN (optineurin) [28,29]. Thus, the authors investigated the role of TBK1-mediated autophagy in the regulation of NFKB signaling. TAX1BP1 is a paralog of CALCOCO2 that could interact with TBK1 [14] and therefore was termed as CALCOCO3 and investigated as a potential autophagy receptor. TAX1BP1 was stabilized by chloroquine treatment, colocalized with LC3-positive vesicles, and interacted with several mATG8 family member proteins that coat nascent phagophores [16]. Along with these findings, the authors identified both canonical and noncanonical LIR (CLIR) motifs in TAX1BP1 [16]. This CLIR motif, defined by a leucine-valine-valine sequence, had previously been described to interact with the mATG8 family member LC3C to allow efficient engulfment of bacteria-containing phagosomes [30]. The authors found that alteration of either of these LIR regions impaired TAX1BP1 localization to the autophagosome [16]. Altogether, these findings established TAX1BP1 as a bona fide SLR thus paving the way for further investigation of its activity in autophagy.

Xenophagy

A key innate host defense function of SLRs is xenophagy, whereby these receptors facilitate the direct clearance of intracellular pathogens through autophagy. SLRs including OPTN, CALCOCO2 and SQSTM1/p62 were first described as critical mediators of xenophagy of pathogenic bacteria [28,29,31,32]. TAX1BP1 was subsequently identified as an SLR that was required for xenophagic clearance of cytosolic *Salmonella typhimurium* [4]. TAX1BP1 was recruited to *Salmonella* during infection and siRNA-mediated knockdown of TAX1BP1, CALCOCO2 and OPTN led to an accumulation of ubiquitylated *Salmonella* in the cytosol. The ZF2 domain of TAX1BP1, which mediates an interaction with polyubiquitin chains [9], was found to interact with K63-linked polyubiquitin chains coated on *Salmonella* and thus promote the autophagic clearance of the bacteria [4]. This group also found that TAX1BP1 was capable of binding both K48-linked and linearized tetraubiquitin polyubiquitin chains, as well as a wide array of mATG8 family member proteins including LC3B, LC3C, GABARAPL1 (gamma-aminobutyric acid (GABA) type A receptor-associated protein-like 1) and GABARAPL2 (Figure 2a, Table 1) [4]. It is worth noting that although TAX1BP1 could bind to both LC3B and LC3C, CALCOCO2 and OPTN were limited to strictly LC3C binding [4]. This observed versatility in ubiquitin and mATG8 family member binding suggest there may be prominent, nonredundant functions for TAX1BP1 in xenophagy.

The xenophagy function of TAX1BP1 has also been extended to the autophagic clearance of *Mycobacterium tuberculosis* (MTB) [33,34]. This function was first uncovered through a screen of host proteins that underwent post-translational modifications (PTMs) during MTB infection of macrophages, and TAX1BP1 was identified as an MTB-inducible phosphoprotein [34]. The authors investigated the SLR function of TAX1BP1 during MTB infection and demonstrated that loss of TAX1BP1 in macrophages led to an accumulation of ubiquitin-positive MTB, as well as a decrease in LC3-positive MTB, suggesting that TAX1BP1 recruits MTB to the phagophore [34]. Shortly thereafter, LGALS8/galectin 8 (lectin, galactose binding, soluble 8) was identified as a cofactor of TAX1BP1 in the xenophagy of MTB [33]. Specifically, following loss of phagosome integrity, LGALS8 links MTB to TAX1BP1 allowing for its autophagic clearance. Interestingly, TAX1BP1 was found to interact with LGALS8 in a ubiquitin-independent manner. This interaction occurred between the CC3 and UBD domains (LGALS8-binding domain) in TAX1BP1 and the carbohydrate recognition domain 2 in LGALS8 (Figure 2a, Table 1). Upon disruption of this interaction, a decrease in TAX1BP1- and LC3-positive MTB was observed [33]. Together, these studies strongly implicate TAX1BP1 as an SLR targeting MTB for xenophagy during infection.

Although the xenophagy function of TAX1BP1 in the clearance of pathogenic bacteria has been well established, its function in response to viral infections is less clear. It is noteworthy that TAX1BP1 was first identified as a binding protein of the HTLV-1 Tax protein [1], and has since been found to interact with several other viral proteins including

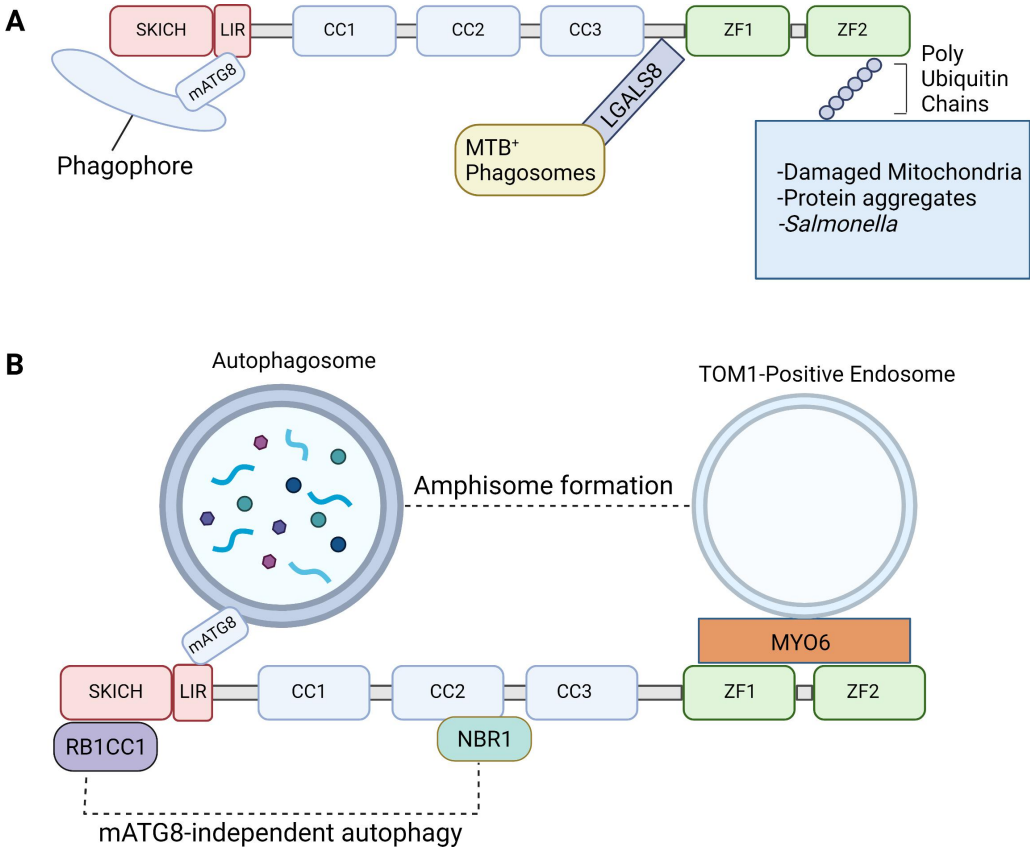

Figure 2. TAX1BP1 adaptor functions in mATG8-dependent and mATG8-independent autophagy. (A) TAX1BP1 binds to substrates with its ZF domains and tethers these substrates to the phagophore with its LIR domain. LGALS8 positive phagosomes are sequestered in a similar manner; however, TAX1BP1 binds LGALS8 via its LGALS8-binding domain, residing between the CC3 and UBD [33]. (B) TAX1BP1 has two well documented accessory functions. It promotes mATG8-independent autophagy by binding NBR1 with the C-terminal half of its CC2 domain (termed the "N-Domain") and simultaneuously recruits RB1CC1 through its SKICH domain [73]. TAX1BP1 also aids in amphisome formation by binding extra-phagosomal LC3 with its LIR domain and the MYO6 tail with its UBD [4,74,85]. Created with BioRender.

the N-protein of measles virus [35]; the RSV-N protein of respiratory syncytia virus [36]; the M [37], NSP6 [38], NSP9 and ORF3A proteins of severe acute respiratory syndrome coronavirus 2 [39]; the E2 protein of papilloma virus [40]; and the human papillomavirus 16 E6 protein [41]. Autophagy plays a dynamic role in response to viral infections [42]. However, the role of TAX1BP1 interaction with these viral proteins remains poorly understood. TAX1BP1 appears to promote viral replication of both measles virus and respiratory syncytia virus. The underlying mechanisms behind these proviral effects has yet to be elucidated [35,36]. It is possible that TAX1BP1 also plays a critical role in xenophagy and the autophagic regulation of specific viruses. Although TAX1BP1 may generally restrict viral replication, it is possible that certain viruses may have co-opted TAX1BP1 autophagy function for the benefit of the virus. Additional studies are needed to determine the role of TAX1BP1 and other SLRs in viral replication.

Aggrephagy and innate immunity

A recent study by Youle and colleagues has identified TAX1BP1 as an aggrephagy receptor that clears cytotoxic protein aggregates, particularly in the brain [7]. The authors identified an essential role for TAX1BP1 and its ZF2 domain in protein aggregate clearance (Figure 2a, Table 1) [7]. Specifically, TAX1BP1 was shown to limit aggregate formation and promote cell viability upon overexpression of cytotoxic proteins such as polyQ-HTT (associated with Huntington disease) and TARDBP/TDP-43 (associated with amyotrophic lateral sclerosis) [43–46]. The importance of TAX1BP1 in aggrephagy *in vivo* was demonstrated using a mouse strain developed by Iha et al. in which the ZF2 domain of TAX1BP1 was ablated (ΔZF) [7,9]. Aged ΔZF mice accumulated increased amounts of lipofuscin – a hallmark of the age-related faltering of proteostasis [47] – compared to their wild-type counterparts. This discovery of TAX1BP1 as an aggrephagy receptor aligns with other findings related to its function in regulating innate immune signaling pathways.

One of the hallmarks of innate immune signal transduction pathways is the aggregation of adaptor and/or effector proteins during the process of their activation. Most innate immune signaling networks rely upon the formation of these aggregated proteins to transmit downstream signals. Two pertinent examples of these aggregated innate immune signaling proteins are MAVS and TICAM1/TRIF (toll like receptor adaptor molecule 1). MAVS is a mitochondrial anchored protein that directs the innate immune response to RNA virus infection following activation by RLRs, ultimately triggering type I IFN induction through IRF3 (interferon regulatory factor 3) and cytokine production through NFKB [15,48,49] (Figure 3a). MAVS also

Table 1. TAX1BP1-interacting proteins and functions in autophagy.

Protein	TAX1BP1 domain interaction	Function	Source
Canonical SLR Function			
Atg8-family proteins	LIR	TAX1BP1 interacts with mATG8 family member proteins to anchor its substrates to the phagophore.	[4,16,31]
LC3C	CLIR	TAX1BP1 interacts with the mATG8 family member LC3C to entrap ubiquitinated *Salmonella* within the autophagosome.	[4,16,31]
LGALS8/galectin 8	LGALS8 Binding Domain / CC3-UBD	TAX1BP1 interacts with LGALS8 to anchor MTB-positive phagosomes to the phagophore.	[33]
TRIM32	Unknown	TAX1BP1 interacts with TRIM32 to degrade TICAM1 following TLR3/TLR4 stimulation.	[51]
Ubiquitinated protein aggregates	ZF2	TAX1BP1 interacts with and clears ubiquitinated protein aggregates through autophagy.	[7]
Polyubiquitinated Mitochondria	ZF2*	TAX1BP1 facilitates PRKN-mediated mitophagy through an interaction with polyubiquitin chains on the outer membrane of damaged mitochondria.	[69]
Accessory Function			
NBR1	CC2/ "N-Domain"	TAX1BP1 interacts with NBR1 in mATG8-independent autophagy.	[73]
RB1CC1	SKICH	TAX1BP1 interacts with RB1CC1 in mATG8-independent autophagy. It is thought that this interaction promotes phagophore engulfment in the absence of mATG8 family members.	[73]
MYO6 (myosin VI)	ZF2	TAX1BP1 interacts with MYO6 to influence amphisome formation by bridging autophagosomes to TOM1-positive endosomes.	[74,75]
*Presumed interaction domain			

induces apoptosis through the MAP2K7 (mitogen-activated protein kinase kinase 7)-MAPK9/JNK2 pathway [50] (Figure 3a). During RLR signaling, MAVS forms prion-like aggregates to activate and propagate downstream signaling and type I IFN induction [48]. These aggregates are very large, resistant to detergent and are potent activators of IFN regulatory factor 3. TICAM1 functions as an essential adaptor protein for TLR3 (toll-like receptor 3)-TLR4 signaling [51–54], and also as a member of the necrosome during necroptosis [55–59] (Figure 3b). TICAM1 also forms oligomeric complexes/aggregates that induce inflammatory signaling and are cleared by autophagy [60]. Interestingly, TAX1BP1 has been implicated in the autophagic degradation of both MAVS and TICAM1 [15,51,55,60].

We have found that TAX1BP1 regulates MAVS and downstream cell death during RNA virus infection. Transfection of the double stranded RNA mimetic polyinosinic:polycytidylic acid (poly[I:C]) or RNA virus infection triggered the degradation of TAX1BP1 which was blocked by the autophagy inhibitor, 3-methyladenine [15]. TAX1BP1 was found to localize to mitochondria and interact with MAVS during RNA virus infection. Basal levels of MAVS were stabilized in TAX1BP1-deficient cells; furthermore, TAX1BP1 promoted a virus-induced interaction between MAVS and the E3 ubiquitin ligase ITCH, resulting in MAVS K48-linked polyubiquitination and degradation [15]. Our unpublished preliminary data indicate that MAVS aggregates are increased in uninfected and virus-infected TAX1BP1 knockout cells, suggesting that TAX1BP1 clears MAVS aggregates that form spontaneously and in response to RNA virus infection.

TICAM1 functions as an adaptor molecule downstream of TLR3 and TLR4 to induce the production of type I IFN and proinflammatory cytokines in response to dsRNA and lipopolysaccharide (LPS) respectively [52,53] (Figure 3b). TAX1BP1 was first shown to target TICAM1 for autophagy-mediated degradation to regulate TLR3 and TLR4 signaling in a TRIM32 (tripartite motif-containing 32)-dependent manner. TICAM1 is degraded via autophagy/lysosomes following TLR stimulation with either poly(I:C) or LPS, and this degradation was found to require TRIM32, TAX1BP1, and canonical autophagy machinery. TRIM32 may function as an adaptor for TICAM1 degradation by bridging TAX1BP1 to TICAM1 [51].

A related study based on a multiplex proteomics screen also linked TAX1BP1 to TICAM1 degradation [60]. Both TICAM1 and MYD88 (myeloid differentiation primary response gene 88) form large oligomers/aggregates during TLR4 signaling [54]. In bone marrow-derived macrophages lacking ATG16L1 (involved in LC3 lipidation [61]), TICAM1 oligomers, but not MYD88 oligomers, were resistant to degradation, suggesting that TICAM1 is degraded through selective autophagy. Furthermore, TAX1BP1 (along with SQSTM1 and CALCOCO1) was stabilized by loss of ATG16L1 during LPS stimulation indicating that it undergoes autophagic degradation during LPS stimulation. TICAM1 and TAX1BP1 interacted in response to LPS stimulation, and this interaction was stabilized by the loss of ATG16L1. TAX1BP1 targeting of TICAM1 was critical for the inhibition of TLR4 signaling in macrophages [60]. It is likely that the aggrephagy function of TAX1BP1 is important for TICAM1 degradation following TLR4 stimulation.

Outside of canonical TLR4 signaling, TICAM1, along with other RIP homotypic interacting motif domain-containing proteins (RIPK1, RIPK3, ZBP1 [Z-DNA binding protein 1]), assemble together to form aggregated structures termed necrosomes during the induction of necroptosis [56–59]. TAX1BP1 was identified as a central regulator of necroptosis signaling via TLR3 and TLR4 [55]. Necroptosis induction led to the accumulation of detergent-insoluble necrosome proteins that was enhanced in bone marrow-derived macrophages lacking ATG16L1. TAX1BP1, SQSTM1, and CALCOCO1 also accumulated in detergent-insoluble fractions following the induction of necroptosis, which was further enhanced by the loss of ATG16L1. Loss of TAX1BP1, but not SQSTM1 or CALCOCO1, sensitized cells to necroptosis, indicating that TAX1BP1 is a key regulator of TLR3- and TLR4-induced necroptosis [55]. The precise target(s) of TAX1BP1 in these pathways remains unknown.

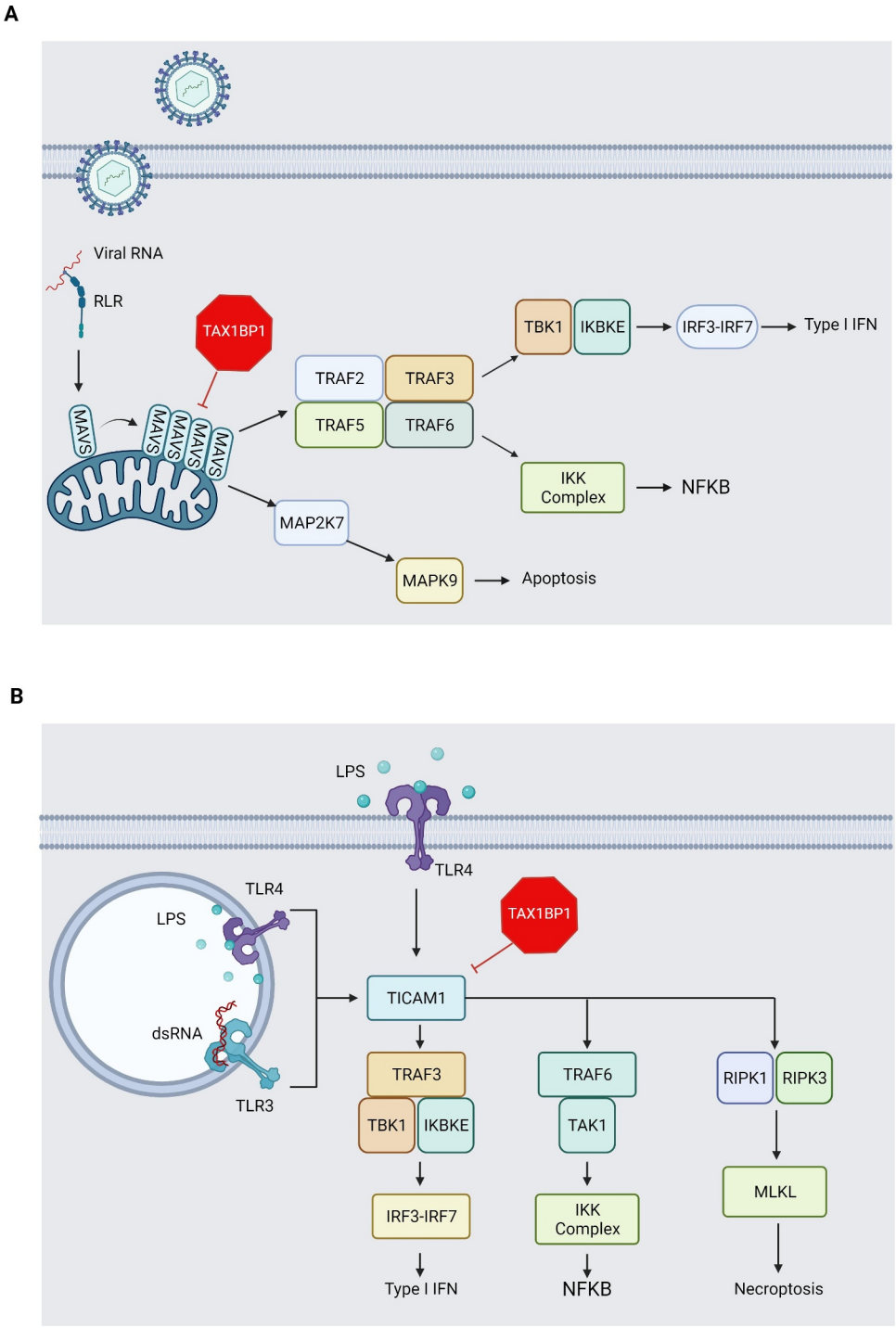

Figure 3. TAX1BP1 inhibits RLR and TLR3-TLR4 signaling pathways. (A) During RNA virus infection, cytosolic RLRs activate MAVS which then forms functional aggregates. MAVS aggregate formation triggers the induction of type I IFN, proinflammatory cytokines, and apoptosis [15,48–50]. TAX1BP1 targets MAVS for degradation to inhibit RLR signaling. (B) TLR3 and TLR4 serve as innate immune receptors for dsRNA and LPS respectively, which then recruit the adaptor protein, TICAM1. TICAM1 subsequently induces type I IFN and proinflammatory cytokines, or recruits other RHIM-domain containing proteins (RIPK1, RIPK3) to initiate cell death by necroptosis [51–59]. TAX1BP1 targets TICAM1 for degradation to inhibit TLR3-TLR4 signaling. Created with BioRender.

Mitophagy and lysophagy

Mitochondria play critical roles in metabolism and also regulate inflammation and cell death, including MAVS signaling [62,63] and mitochondrial outer membrane permeabilization (MOMP)-induced apoptosis [15,64,65]. Damaged mitochondria can elicit pathogenic inflammation due to the leakage of mitochondrial DNA and activation of the cGAS-STING pathway [66]. The maintenance and clearance of damaged mitochondria through autophagy (termed mitophagy) represents a key mechanism of restraining innate immunity and inflammation. This process is initiated through activity of the kinase PINK1 (PTEN induced putative kinase 1) and the E3 ligase PRKN/parkin [67]. Mitochondrial dysfunction triggers PINK1 to phosphorylate ubiquitin on the outer mitochondrial membrane which then

activates PRKN-induced polyubiquitination. Polyubiquitin chains catalyzed by PRKN recruit SLRs for the clearance of damaged mitochondria [68,69].

The precise roles of SLRs in PRKN-dependent mitophagy (hereafter referred to as mitophagy) have been dissected by the Youle group whereby mitophagy efficiency was measured by cytochrome C oxidase II turnover following the induction of mitochondrial damage with combined treatment of antimycin A and oligomycin. The model system used for these experiments included both single KO-HeLa cells – where each of SQSTM1, CALCOCO2, OPTN, NBR1 (NBR1 autophagy cargo receptor), and TAX1BP1 were individually ablated – as well as single-SLR expressing HeLa cells where each of the aforementioned SLRs were individually reintroduced into a penta-KO background [69]. Using this system the authors concluded that CALCOCO2 and OPTN are the dominant SLRs facilitating mitophagy, whereas TAX1BP1 plays a more minor role (Figure 2a, Table 1) [69]. It remains to be determined if the ascribed roles for SLRs in mitophagy are global, or if SLR-mitophagy activity varies by tissue type or stimulus.

Lysophagy refers to the autophagic clearance of damaged lysosomes. A recent quantitative proteomics screen revealed the recruitment of multiple ubiquitin binding autophagy receptors (TAX1BP1, OPTN, CALCOCO2) to damaged lysosomes [70]. TAX1BP1 and TBK1 were further identified as critical factors for lysophagic flux and lysophagy in both HeLa cells and induced neurons. TAX1BP1-mediated lysophagy required its SKICH domain which is important for interactions with TBK1 and RB1CC1/FIP200 (RB1-inducible coiled-coil 1), a member of the ULK1 autophagy initiating complex [70].

Accessory roles of TAX1BP1 in canonical and noncanonical autophagy

In addition to its role as a cargo adaptor, multiple accessory functions of TAX1BP1 in canonical and noncanonical autophagy have recently emerged. TAX1BP1 has been found to exert multiple roles in autophagy including polyubiquitin-dependent stimulation of LC3 lipidation [71], the initiation of autophagy through an interaction with RB1CC1 [72,73] and amphisome formation dependent on an interaction with the actin motor protein MYO6 (myosin VI) [4,74,75].

The mATG8 family members serve foundational roles in canonical autophagy – most prominently in cargo binding [73,76–79]. Interestingly, multiple groups have reported the persistence of autophagy in the absence of the mATG8-phagophore conjugation machinery ("mATG8-independent autophagy") [80–82]. TAX1BP1 has been shown to play a major role in this mATG8-independent autophagy. Its involvement in this pathway was first observed in the clearance of the ferritin regulator, nuclear receptor coactivator 4. TAX1BP1 mediated nuclear receptor coactivator 4 clearance in a RB1CC1- or TBK1-dependent manner in the absence of ATG7 – a critical factor in mATG8 lipidation [72]. Similar findings were observed for the clearance of NBR1, an SLR. In this context TAX1BP1 rescued NBR1 flux in a RB1CC1-dependent manner [73]. The same study identified a novel NBR1-binding domain ("N-Domain") in the second half of TAX1BP1's CC2 domain (Figure 2b, Table 1). This binding allows TAX1BP1 to promote RB1CC1 clustering around NBR1 by serving as an adaptor where it restricts NBR1 with its N-Domain and recruits RB1CC1 to its SKICH domain (Figure 2b, Table 1) [73]. The TAX1BP1 recruitment of RB1CC1 was shown to mediate autophagic degradation of ubiquitin condensates formed by SQSTM1 and NBR1 [83]. Based on these studies it appears that TAX1BP1 is a critical player in mATG8-independent autophagy by initiating phagophore biogenesis around substrates through recruitment and clustering of RB1CC1 [73].

In addition to its role in autophagosome biogenesis, TAX1BP1 can also influence the maturation of the autophagosome in certain contexts. The final step in autophagosome maturation consists of fusion with the lysosome. Preceding this terminal fusion event, autophagosomes may undergo an intermediary fusion event with endosomes or multivesicular bodies to become amphisomes [4,75,84]. Although the contextual requirement of amphisome formation is not well defined, TAX1BP1 promotes amphisome formation in response to *Salmonella* infection through an interaction with MYO6, which appears to be required for the clearance of *Salmonella* through autophagy [4,75]. MYO6 bridges endosomes and autophagosomes through interactions with TOM1 (target of myb1 trafficking protein) and TAX1BP1 (or CALCOCO2, OPTN), respectively [4,85]. Specifically, SLRs bind extra-phagosomal LC3 via their LIR domains and the MYO6 tail region through UBDs (Figure 2b, Table 1) [74,75]. There is likely redundancy among SLRs in this process; however, TAX1BP1 was shown to be essential for the autophagic clearance of *Salmonella typhimurium* [4].

Open questions and future directions

Prominent roles have been identified for TAX1BP1 in xenophagy, aggrephagy, lysophagy and mATG8-independent autophagy; however, many questions remain regarding its functions and regulation in these pathways. Although TAX1BP1 has been found to be important for the clearance of *Salmonella typhimurium* [4] and MTB [33], its function has not yet been explored in the context of other intracellular bacteria or viruses, although it can interact with multiple viral proteins [1,35–41]. TAX1BP1 likely plays a dynamic role during viral infections in a virus-specific manner, and may perhaps be co-opted by certain viruses to benefit the viral life cycle. TAX1BP1 functions as an important aggrephagy receptor in the brain [7], and its aggrephagy function extends to the regulation of innate immune signaling pathways. TAX1BP1 targets TICAM1 aggregates in TLR4 signaling [51,60] and also MAVS aggregates in the RLR pathway based upon our unpublished observations. It is plausible that TAX1BP1 could negatively regulate other innate immune signaling pathways that rely on activation-dependent formation of signaling aggregates/oligomers [54,86–88]. It is also unknown if TAX1BP1 is important for autophagic clearance of certain damaged organelles such as the endoplasmic reticulum (reticulophagy), peroxisomes (pexophagy) or the nucleus (nucleophagy).

Beyond its function in targeting cargo to autophagosomes, much remains unknown with regard to the regulation of TAX1BP1. Key areas of exploration include the regulation of TAX1BP1 function by PTMs, and the coordination of TAX1BP1 with other SLRs. TAX1BP1 is known to be phosphorylated in multiple contexts [13,34], and interacts with various E3 ligases and deubiquitinating enzymes [10,11,15,89,90]. Phosphorylation of other SLRs has been shown to drive various aspects of their function [91–94] – it is likely that TAX1BP1 function is also regulated through PTMs. In this regard, we have demonstrated that CHUK/IKKα phosphorylates TAX1BP1 on multiple serine residues to inhibit NFKB signaling pathways [13]; however, whether this extends to its autophagy function in other pathways remains an open question. In addition to PTMs, little is known about how TAX1BP1 cooperates with other SLRs for the clearance of various cargos. Dichotomous roles have been described for SLRs in the clearance of aggregrates, and it remains unclear how these receptors coordinate to facilitate autophagic clearance. Hetero-SLR complexes have been documented in certain contexts including a TAX1BP1-NBR1 interaction in mATG8-independent autophagy [73], and an interaction between TAX1BP1, SQSTM1, and CALCOCO2 during protein aggregate clearance [7]. Despite these interesting observations, it is still not fully understood how, why, or in what other settings these hetero-SLR complexes may occur.

New discoveries on TAX1BP1 in the realm of autophagy have been occurring at a rapid pace. Novel functions ascribed to TAX1BP1 suggest that it may serve as a promising target in diseases associated with neurodegeneration, infectious diseases and chronic inflammation. Further expanding the knowledge of how TAX1BP1 regulates autophagy may lead to the development of novel therapeutics for these diseases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Institutes of Health [R01AI162815]; National Institutes of Health [R01CA214131].

References

[1] Gachon F, Peleraux A, Thebault S, et al. CREB-2, a cellular CRE-dependent transcription repressor, functions in association with Tax as an activator of the human T-cell leukemia virus type 1 promoter. J Virol. 1998 Oct;72(10):8332–8337.
[2] De Valck D, Jin DY, Heyninck K, et al. The zinc finger protein A20 interacts with a novel anti-apoptotic protein which is cleaved by specific caspases. Oncogene. [1999 Jul 22];18(29):4182–4190.
[3] Ling L, Goeddel DV. T6BP, a TRAF6-interacting protein involved in IL-1 signaling. Proc Natl Acad Sci U S A. [2000 Aug 15];97 (17):9567–9572.
[4] DA T, PT M, Allen M, et al. The autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy. PLoS Pathog. 2015 [2015 October 9];11(10):e1005174.
[5] Nagaraja GM, Kandpal RP. Chromosome 13q12 encoded Rho GTPase activating protein suppresses growth of breast carcinoma cells, and yeast two-hybrid screen shows its interaction with several proteins. Biochem Biophys Res Commun. [2004 Jan 16];313(3):654–665.
[6] Verstrepen L, Verhelst K, Carpentier I, et al. TAX1BP1, a ubiquitin-binding adaptor protein in innate immunity and beyond. Trends Biochem Sci. 2011 Jul;36(7):347–354.
[7] Sarraf SA, Shah HV, Kanfer G, et al. Loss of TAX1BP1-directed autophagy results in protein aggregate accumulation in the brain. Mol Cell. [2020 Dec 3];80(5):779–795 e10.
[8] MA C, Spínola AM, Buts L, et al. The structure of TAX1BP1 UBZ1+2 provides insight into target specificity and adaptability. J Mol Biol. 2014 [2014 February 1];426(3):674–690.
[9] Iha H, Peloponese JM, Verstrepen L, et al. Inflammatory cardiac valvulitis in TAX1BP1-deficient mice through selective NF-kappaB activation. EMBO J. [2008 Feb 20];27(4):629–641.
[10] Shembade N, Harhaj NS, Liebl DJ, et al. Essential role for TAX1BP1 in the termination of TNF-alpha-, IL-1- and LPS-mediated NF-kappaB and JNK signaling. EMBO J. [2007 Sep 5];26(17):3910–3922.
[11] Shembade N, NS H, Parvatiyar K, et al. The E3 ligase Itch negatively regulates inflammatory signaling pathways by controlling the function of the ubiquitin-editing enzyme A20. Nat Immunol. 2008 [2008 March 1];9(3):254–262.
[12] Shembade N, Parvatiyar K, Harhaj NS, et al. The ubiquitin-editing enzyme A20 requires RNF11 to downregulate NF-kappaB signalling. EMBO J. [2009 Mar 4];28(5):513–522.
[13] Shembade N, Pujari R, Harhaj NS, et al. The kinase IKKalpha inhibits activation of the transcription factor NF-kappaB by phosphorylating the regulatory molecule TAX1BP1. Nat Immunol. [2011 Jul 17];12(9):834–843.
[14] Parvatiyar K, Barber GN, Harhaj EW. TAX1BP1 and A20 inhibit antiviral signaling by targeting TBK1-IKKi kinases. J Biol Chem. [2010 May 14];285(20):14999–15009.
[15] Choi YB, Shembade N, Parvatiyar K, et al. TAX1BP1 restrains virus-induced apoptosis by facilitating itch-mediated degradation of the mitochondrial adaptor MAVS. Mol Cell Biol. [2017 Jan 1];37(1). 10.1128/MCB.00422-16.
[16] Newman AC, Scholefield CL, Kemp AJ, et al. TBK1 kinase addiction in lung cancer cells is mediated via autophagy of Tax1bp1/Ndp52 and non-canonical NF-kappaB signalling. PLoS One. 2012;7(11):e50672.
[17] Tj M, AH L, Simonsen A. Autophagosome biogenesis: from membrane growth to closure. J Cell Biol. 2020 [2020 June 1];219(6): e202002085.
[18] YG Z, Zhang H. Autophagosome maturation: an epic journey from the ER to lysosomes. J Cell Biol. 2019 [2019 March 4];218(3):757–770.
[19] TE R, Vaccari T, Lindmo K, et al. ESCRTs and Fab1 regulate distinct steps of autophagy. Curr Biol. 2007 [2007 October 1];17 (20):1817–1825.
[20] Filimonenko M, Stuffers S, Raiborg C, et al. Functional multivesicular bodies are required for autophagic clearance of protein aggregates associated with neurodegenerative disease. J Cell Biol. 2007 [2007 November 5];179(3):485–500.
[21] Deretic V. Autophagy in immunity and cell-autonomous defense against intracellular microbes. Immunol Rev. 2011 [2011 March 1];240(1):92–104.
[22] Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. Nat Rev Immunol. 2013 [2013 October 1];13 (10):722–737.
[23] Birgisdottir AB, Lamark T, Johansen T. The LIR motif - crucial for selective autophagy. J Cell Sci. [2013 Aug 1];126(Pt 15):3237–3247.
[24] Chien Y, Kim S, Bumeister R, et al. RalB GTPase-mediated activation of the IκB family kinase TBK1 couples innate immune signaling to tumor cell survival. Cell. 2006 [2006 October 1];127 (1):157–170.
[25] DA B, Tamayo P, JS B, et al. Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. Nature. 2009 [2009 November 1];462(7269):108–112.
[26] T-L C, Gioia R, J-s G, et al. Are the IKKs and IKK-related kinases TBK1 and IKK-ε similarly activated? Trends Biochem Sci. 2008 [2008 April 1];33(4):171–180.

[27] Jl P. NF-kappa B activation by a signaling complex containing TRAF2, TANK and TBK1, a novel IKK-related kinase. EMBO J. 1999 [1999 December 1];18(23):6694–6704.
[28] Thurston TLM, Ryzhakov G, Bloor S, et al. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. Nat Immunol. 2009 [2009 November 1];10(11):1215–1221.
[29] Wild P, Farhan H, Mcewan DG, et al. Phosphorylation of the autophagy receptor optineurin restricts salmonella growth. Science. 2011 [2011 July 8];333(6039):228–233.
[30] Muhlinen VN, Akutsu M, Ravenhill JB, et al. LC3C, bound selectively by a noncanonical LIR motif in NDP52, is required for antibacterial autophagy. Mol Cell. 2012 [2012 November 1];48 (3):329–342.
[31] Birmingham CL, Brumell JH. Autophagy recognizes intracellular *Salmonella enterica* serovar typhimurium in damaged vacuoles. Autophagy. 2006 [2006 July 22];2(3):156–158.
[32] Zheng YT, Shahnazari S, Brech A, et al. The adaptor protein p62/SQSTM1 targets invading bacteria to the autophagy pathway. J Immunol. 2009 [2009 November 1];183(9):5909–5916.
[33] Bell SL, Lopez KL, Cox JS, et al. Galectin-8 senses phagosomal damage and recruits selective autophagy adapter TAX1BP1 to control mycobacterium tuberculosis infection in macrophages. mBio. [2021 Aug 31];12(4):e0187120.
[34] Budzik JM, Swaney DL, Jimenez-Morales D, et al. Dynamic post-translational modification profiling of Mycobacterium tuberculosis-infected primary macrophages. eLife. 2020 [2020 January 17];9. 10.7554/eLife.51461.
[35] Petkova D, Verlhac P, Rozières A, et al. Distinct contributions of autophagy receptors in measles virus replication. Viruses. 2017 [2017 May 22];9(5):123.
[36] Descamps D, Peres de Oliveira A, Gonnin L, et al. Depletion of TAX1BP1 amplifies innate immune responses during respiratory syncytial virus infection. J Virol. [2021 Aug 25];95(22). JVI0091221. 10.1128/JVI.00912-21.
[37] Chen Z, Wang C, Feng X, et al. Comprehensive analysis of the host-virus interactome of SARS-CoV-2. BioRxiv; 2021.
[38] Laurent EMN, Sofianatos Y, Komarova A, et al. Global BioID-based SARS-CoV-2 proteins proximal interactome unveils novel ties between viral polypeptides and host factors involved in multiple COVID19-associated mechanisms. BioRxiv; 2020.
[39] Stukalov A, Girault V, Grass V, et al. Multilevel proteomics reveals host perturbations by SARS-CoV-2 and SARS-CoV. Nature. 2021 [2021 June 10];594(7862):246–252.
[40] Wang X, Naidu SR, Sverdrup F, et al. Tax1BP1 interacts with papillomavirus E2 and regulates E2-Dependent transcription and stability. J Virol. 2009 [2009 March 1];83(5):2274–2284.
[41] Poirson J, Biquand E, Straub M-L, et al. Mapping the interactome of HPV E6 and E7 oncoproteins with the ubiquitin-proteasome system. FEBS J. 2017 [2017 October 1];284(19):3171–3201.
[42] Ahmad L, Mostowy S, Sancho-Shimizu V. Autophagy-virus interplay: from cell biology to human disease. Front Cell Dev Biol. 2018;6:155.
[43] Barmada SJ, Skibinski G, Korb E, et al. Cytoplasmic mislocalization of TDP-43 is toxic to neurons and enhanced by a mutation associated with familial amyotrophic lateral sclerosis. J Neurosci. 2010 [2010 January 13];30(2):639–649.
[44] Barmada SJ, Serio A, Arjun A, et al. Autophagy induction enhances TDP43 turnover and survival in neuronal ALS models. Nat Chem Biol. 2014 [2014 August 1];10(8):677–685.
[45] Iwata A, Christianson JC, Bucci M, et al. Increased susceptibility of cytoplasmic over nuclear polyglutamine aggregates to autophagic degradation. Proc Nat Acad Sci. 2005 [2005 October 13];102 (37):13135–13140.
[46] Ravikumar B. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy.Hum Mol Genet. 2002 [2002 May 1];11(9):1107–1117.
[47] Moreno-Garcia A, Kun A, Calero O, et al. An overview of the role of lipofuscin in age-related neurodegeneration. Front Neurosci. 2018;12:464.
[48] Hou F, Sun L, Zheng H, et al. MAVS forms functional prion-like aggregates to activate and propagate antiviral innate immune response. Cell. 2011 [2011 August 1];146(3):448–461.
[49] Liu B, Gao C. Regulation of MAVS activation through post-translational modifications. Curr Opin Immunol. 2018 [2018 February 1];50:75–81.
[50] Huang Y, Liu H, Li S, et al. MAVS-MKK7-JNK2 defines a novel apoptotic signaling pathway during viral infection. PLoS Pathog. 2014 Mar;10(3):e1004020.
[51] Yang Q, Liu -T-T, Lin H, et al. TRIM32-TAX1BP1-dependent selective autophagic degradation of TRIF negatively regulates TLR3/4-mediated innate immune responses. PLoS Pathog. 2017 [2017 September 12];13(9):e1006600.
[52] Vogel SN. TLRs: differential adapter utilization by toll-like receptors mediates TLR-specific patterns of gene expression.Mol interv. 2003 [2003 December 1];3(8):466–477.
[53] Visintin A, Latz E, Monks BG, et al. Lysines 128 and 132 enable lipopolysaccharide binding to MD-2, leading to toll-like receptor-4 aggregation and signal transduction. J Biol Chem. 2003 [2003 November 1];278(48):48313–48320.
[54] Gay NJ, Symmons MF, Gangloff M, et al. Assembly and localization of Toll-like receptor signalling complexes. Nat Rev Immunol. 2014 [2014 August 1];14(8):546–558.
[55] Lim J, Park H, Heisler J, et al. Autophagy regulates inflammatory programmed cell death via turnover of RHIM-domain proteins. eLife. 2019 [2019 July 9];8. 10.7554/eLife.44452
[56] Vanden Berghe T, Hassannia B, Vandenabeele P. An outline of necrosome triggers.Cell Mol Life Sci. 2016 [2016 June 1];73(11–12):2137–2152.
[57] Orozco S, Yatim N, Werner MR, et al. RIPK1 both positively and negatively regulates RIPK3 oligomerization and necroptosis. Cell Death Differ. 2014 [2014 October 1];21(10):1511–1521.
[58] Cho Y, Challa S, Moquin D, et al. Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. Cell. 2009 [2009 June 1];137 (6):1112–1123.
[59] Li J, Mcquade T, Siemer B, et al. The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. Cell. 2012 [2012 July 1];150(2):339–350.
[60] Samie M, Lim J, Verschueren E, et al. Selective autophagy of the adaptor TRIF regulates innate inflammatory signaling. Nat Immunol. 2018 Mar;19(3):246–254.
[61] Nishimura T, Tooze SA. Emerging roles of ATG proteins and membrane lipids in autophagosome formation. Cell Discov. 2020 [2020 December 1];6(1). 10.1038/s41421-020-0161-3.
[62] Ablasser A, Hur S. Regulation of cGAS- and RLR-mediated immunity to nucleic acids.Nat Immunol. 2020 [2020 January 1];21(1):17–29.
[63] Onomoto K, Onoguchi K, Yoneyama M. Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. Cell Mol Immunol. 2021 [2021 March 1];18(3):539–555.
[64] Guan K, Zheng Z, Song T, et al. MAVS regulates apoptotic cell death by decreasing K48-linked ubiquitination of voltage-dependent anion channel 1. Mol Cell Biol. 2013 Aug;33 (16):3137–3149.
[65] Lei Y, Moore CB, Liesman RM, et al. MAVS-mediated apoptosis and its inhibition by viral proteins. PLoS ONE. 2009 [2009 March 7];4(5):e5466.
[66] Weinberg ES, Sena AL, Navdeep CS. Mitochondria in the regulation of innate and adaptive immunity.Immunity. 2015 [2015 March 1];42(3):406–417.
[67] Sliter DA, Martinez J, Hao L, et al. Parkin and PINK1 mitigate STING-induced inflammation. Nature. 2018 Sep;561 (7722):258–262.
[68] Baumann K. Autophagy: mitophagy receptors unravelled. Nat Rev Mol Cell Biol. 2015 Oct;16(10):580.
[69] Lazarou M, Sliter DA, Kane LA, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature. [2015 Aug 20];524(7565):309–314.

[70] Eapen VV, Swarup S, Hoyer MJ, et al. Quantitative proteomics reveals the selectivity of ubiquitin-binding autophagy receptors in the turnover of damaged lysosomes by lysophagy. eLife. 2021 [2021 September 29];10. 10.7554/eLife.72328.
[71] Chang C, Shi X, Jensen LE, et al. Reconstitution ofcargo-induced LC3 lipidation inmammalian selective autophagy. Sci Adv. 2021 [Apr 23];7(17). 10.1126/sciadv.abg4922.
[72] Goodwin JM, Dowdle WE, Dejesus R, et al. Autophagy-independent lysosomal targeting regulated by ULK1/2-FIP200 and ATG9. Cell Rep. 2017 [2017 September 1];20(10):2341–2356.
[73] Ohnstad AE, Delgado JM, North BJ, et al. Receptor-mediated clustering of FIP200 bypasses the role of LC3 lipidation in autophagy. EMBO J. 2020 [2020 December 15];39(24). 10.15252/embj.2020104948.
[74] Tumbarello DA, Kendrick-Jones J, Buss F. Myosin VI and its cargo adaptors - linking endocytosis and autophagy.J Cell Sci. 2013 [2013 June 15];126(12):2561–2570.
[75] Tumbarello DA, Waxse BJ, Arden SD, et al. Autophagy receptors link myosin VI to autophagosomes to mediate Tom1-dependent autophagosome maturation and fusion with the lysosome. Nat Cell Biol. 2012 [2012 October 1];14(10):1024–1035.
[76] Nakatogawa H, Ichimura Y, Ohsumi Y. Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion.Cell. 2007 [2007 July 1];130(1):165–178.
[77] Fujita N, Hayashi-Nishino M, Fukumoto H, et al. An Atg4B mutant hampers the lipidation of LC3 paralogues and causes defects in autophagosome closure. Mol Biol Cell. 2008 [2008 November 1];19(11):4651–4659.
[78] Manil-Segalen M, Lefebvre C, Jenzer C, et al. The C. elegans LC3 acts downstream of GABARAP to degrade autophagosomes by interacting with the HOPS subunit VPS39. Dev Cell. [2014 Jan 13];28(1):43–55.
[79] Sou Y-S, Waguri S, Iwata J-I, et al. The Atg8 conjugation system is indispensable for proper development of autophagic isolation membranes in mice. Mol Biol Cell. 2008 [2008 November 1];19(11):4762–4775.
[80] Nishida Y, Arakawa S, Fujitani K, et al. Discovery of Atg5/Atg7-independent alternative macroautophagy. Nature. 2009 [2009 October 1];461(7264):654–658.
[81] Honda S, Arakawa S, Nishida Y, et al. Ulk1-mediated Atg5-independent macroautophagy mediates elimination of mitochondria from embryonic reticulocytes. Nat Commun. 2014 [2014 September 1];5(1). 10.1038/ncomms5004.
[82] Nguyen TN, Padman BS, Usher J, et al. Atg8 family LC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation. J Cell Biol. [2016 Dec 19];215(6):857–874.
[83] Turco E, Savova A, Gere F, et al. Reconstitution defines the roles of p62, NBR1 and TAX1BP1 in ubiquitin condensate formation and autophagy initiation. Nat Commun. 2021 [2021 December 1];12(1). 10.1038/s41467-021-25572-w.
[84] Fader CM, Colombo MI. Autophagy and multivesicular bodies: two closely related partners.Cell Death Differ. 2009 [2009 January 1];16(1):70–78.
[85] Hu S, Wang Y, Gong Y, et al. Mechanistic insights into recognitions of ubiquitin and myosin VI by autophagy receptor TAX1BP1. J Mol Biol. 2018 [2018 September 1];430(18):3283–3296.
[86] Zhang C, Shang G, Gui X, et al. Structural basis of STING binding with and phosphorylation by TBK1. Nature. 2019 [2019 March 1];567(7748):394–398.
[87] Newton K, Dixit VM. Signaling in innate immunity and inflammation.Cold Spring Harb Perspect Biol. 2012 [2012 March 1];4(3):a006049–a006049.
[88] Zhang X, Bai X-C, Chen ZJ. Structures and mechanisms in the cGAS-STING innate immunity pathway.Immunity. 2020 [2020 July 1];53(1):43–53.
[89] Shembade N, Harhaj E. A20 inhibition of NFkappaB and inflammation: targeting E2:E3 ubiquitin enzyme complexes. Cell Cycle. [2010 Jul 1];9(13):2481–2482.
[90] Shembade N, Ma A, Harhaj EW. Inhibition of NF-kappaB signaling by A20 through disruption of ubiquitin enzyme complexes. Science. [2010 Feb 26];327(5969):1135–1139.
[91] Ravenhill BJ, Boyle KB, Von Muhlinen N, et al. The cargo receptor NDP52 initiates selective autophagy by recruiting the ULK complex to cytosol-invading bacteria. Mol Cell. 2019 [2019 April 1];74(2):320–329.e6.
[92] Zhou Z, Liu J, Fu T, et al. Phosphorylation regulates the binding of autophagy receptors to FIP200 Claw domain for selective autophagy initiation. Nat Commun. 2021 [2021 December 1];12(1):1570.
[93] Shi X, Chang C, Yokom AL, et al. The autophagy adaptor NDP52 and the FIP200 coiled-coil allosterically activate ULK1 complex membrane recruitment. eLife. 2020 [2020 August 10];9. 10.7554/eLife.59099.
[94] Bansal M, Moharir SC, Sailasree SP, et al. Optineurin promotes autophagosome formation by recruiting the autophagy-related Atg12-5-16L1 complex to phagophores containing the Wipi2 protein. J Biol Chem. 2018 [2018 January 1];293(1):132–147.