Precision autophagy directed by receptor regulators – emerging examples within the TRIM family

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ABSTRACT
Selective autophagy entails cooperation between target recognition and assembly of the autophagic apparatus. Target recognition is conducted by receptors that often recognize tags, such as ubiquitin and galectins, although examples of selective autophagy independent of these tags are emerging. It is less known how receptors cooperate with the upstream autophagic regulators, beyond the well-characterized association of receptors with Atg8 or its homologs, such as LC3B (encoded by MAP1LC3B), on autophagic membranes. The molecular details of the emerging role in autophagy of the family of proteins called TRIMs shed light on the coordination between cargo recognition and the assembly and activation of the principal autophagy regulators. In their autophagy roles, TRIMs act both as receptors and as platforms (‘receptor regulators’) for the assembly of the core autophagy regulators, such as ULK1 and Beclin 1 in their activated state. As autophagic receptors, TRIMs can directly recognize endogenous or exogenous targets, obviating a need for intermediary autophagic tags, such as ubiquitin and galectins. The receptor and regulatory features embodied within the same entity allow TRIMs to govern cargo degradation in a highly exact process termed ‘precision autophagy’.

KEY WORDS: Receptor regulators, TRIMs, Autophagy

Introduction
Autophagy is a set of diverse processes, often classified as macro-autophagy, micro-autophagy and chaperone-mediated autophagy, which recognize and deliver endogenous cellular constituents or exogenous cargo to lysosomes for degradation (Mizushima et al., 2011). Autophagy can occur in bulk as a response to starvation, which recognize and deliver endogenous cellular constituents or exogenous cargo to lysosomes for degradation (Mizushima et al., 2011). The assembly of the core autophagy machinery is well documented in yeast with Atg8 and in mammals, the key autophagy factors (ATG) include ULK1 (one of four mammalian paralogs of Atg1) (Chan et al., 2007; Kundu and Thompson, 2008) and Beclin 1 (a paralog of yeast Atg6) (Liang et al., 1999). These principal autophagy regulators are controlled by upstream serine and threonine (Ser/Thr) protein kinases 5′-AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) (Egan et al., 2011; Kim et al., 2011, 2013; Russell et al., 2013), as well as E3 ligases and ubiquitylation (Nazio et al., 2013). Lipid kinases, most notably the class III phosphatidylinositol 3-kinase (PI3K) VPS34 (encoded by PIK3C3; which forms a complex with Beclin 1), co-activate autophagy by producing phosphatidylinositol-3-phosphate (PtdIns(3)P), a step that commits them to participating in autophagosome formation (Petiot et al., 2000); however, the roles of other mono-phosphoinositides such as phosphatidylinositol 5-phosphate have recently been suggested (Vicinanza et al., 2015). The protein kinases (ULK1), lipid kinases (Beclin1–VPS34) and the LC3-conjugation system are all physically connected in their role in controlling autophagy. First, PtdIns(3)P is recognized by WD repeat domain phosphoinositide-interacting protein 2 (WIPI2, the mammalian Atg18), which interacts with ATG16L1 and forms part of the LC3–PtdEtn conjugation system (Dooley et al., 2014). Second, ATG16L1 associates with FIP200 (also known as RB1CC1), a component of the ULK1 complex system (Fujita et al., 2013; Gammoh et al., 2013; Nishimura et al., 2013; Dooley et al., 2014). Autophagy is further coupled to the lysosomal systems. This occurs through the effects on autophagy of members of the key regulator of lysosomal biogenesis ‘microphthalmia/transcription factor E’ (MiT/TFE) family (including transcription factor EB; TFE) (Settembre et al., 2011; Perera et al., 2015) and through SNAREs (Itakura et al., 2012), which enable the maturation of autophagosomes into the autolysosome. Thus, all parts of the autophagy system are interconnected, thereby enabling spatial and temporal regulation of autophagy.

A morphologically emblematic event during autophagy is the formation in the cytoplasm of the membranous organelles termed autophagosomes; these are the executors of macro-autophagy (hereafter referred to as autophagy) (Mizushima et al., 2011). Autophagosomes are decorated in yeast with Atg8 and in mammals with LC3B [one of six mammalian (m)Atg8 paralogs – LC3A, LC3B and LC3C (encoded by MAP1LC3A, MAP1LC3B and MAP1LC3C, respectively) and GABARAP, GABARAPL1 and GABARAPL2 (Mizushima et al., 2011; Weidberg et al., 2011)]. mAtg8 proteins are conjugated at their C-terminus to a lipid, phosphatidylinositolamine (PtdEtn), which in turn mediates association with the autophagic membrane (Kabeya et al., 2000). Many other parts of the core autophagy machinery are well-conserved from yeast to humans (Mizushima et al., 2011). In mammals, the key autophagy factors (ATG) include ULK1 (one of four mammalian paralogs of Atg1) (Chan et al., 2007; Kundu and Thompson, 2008) and Beclin 1 (a paralog of yeast Atg6) (Li et al., 2013). These principal autophagy regulators are controlled by upstream serine and threonine (Ser/Thr) protein kinases 5′-AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) (Egan et al., 2011; Kim et al., 2011, 2013; Russell et al., 2013), as well as E3 ligases and ubiquitylation (Nazio et al., 2013). Lipid kinases, most notably the class III phosphatidylinositol 3-kinase (PI3K) VPS34 (encoded by PIK3C3; which forms a complex with Beclin 1), co-activate autophagy by producing phosphatidylinositol-3-phosphate [PtdIns(3)P], a step that commits them to participating in autophagosome formation (Petiot et al., 2000); however, the roles of other mono-phosphoinositides such as phosphatidylinositol 5-phosphate have recently been suggested (Vicinanza et al., 2015). The protein kinases (ULK1), lipid kinases (Beclin1–VPS34) and the LC3-conjugation system are all physically connected in their role in controlling autophagy. First, PtdIns(3)P is recognized by WD repeat domain phosphoinositide-interacting protein 2 (WIPI2, the mammalian Atg18), which interacts with ATG16L1 and forms part of the LC3–PtdEtn conjugation system (Dooley et al., 2014). Second, ATG16L1 associates with FIP200 (also known as RB1CC1), a component of the ULK1 complex system (Fujita et al., 2013; Gammoh et al., 2013; Nishimura et al., 2013; Dooley et al., 2014). Autophagy is further coupled to the lysosomal systems. This occurs through the effects on autophagy of members of the key regulator of lysosomal biogenesis ‘microphthalmia/transcription factor E’ (MiT/TFE) family (including transcription factor EB; TFE) (Settembre et al., 2011; Perera et al., 2015) and through SNAREs (Itakura et al., 2012), which enable the maturation of autophagosomes into the autolysosome. Thus, all parts of the autophagy system are interconnected, thereby enabling spatial and temporal regulation of autophagy.

The homing of the autophagy machinery to intended targets through receptors is an area of intense study (Birgisdottir et al., 2013; Rogov et al., 2014; Khaminets et al., 2015). Frequently,
Sequestosome-1-like receptors and cargo recognition mediated by tags

As noted above, the cargo entering the autophagosomes is often modified with tags, such as ubiquitin, phosphorylated ubiquitin and galectins (Koyano et al., 2014; Randow and Youle, 2014; Khaminets et al., 2015). These tags are then recognized by sequestosome-1-like receptors (SLRs) named so (Birgisdottir et al., 2009; Deschenes et al., 2013) after the founding member of this receptor family, sequestosome 1 (commonly known as p62) (Lamark et al., 2009). SLRs also include other receptors, such as neighbor of BRCA1 gene 1 (NBR1), Ca\(^{2+}\)-binding and coiled-coil (Lamark et al., 2009). SLRs also include other receptors, such as ubiquitin or galectins, while also binding mammalian (m)Atg8 proteins that connect them to autophagic membranes.

The TRIM protein family

TRIMs were first recognized as a family (Reymond et al., 2001) based on their common tri-partite domain organization, typically comprising an N-terminal RING domain, one or two B-box domains and a coiled-coil domain, although they also have additional features, including a variety of C-terminal domains, inclusive of SPRY domains (Fig. 2A,B; Table S1). TRIMs are conserved in metazoans, and the number of genes encoding them escalates in higher organisms (Sardielli et al., 2008; Boudinot et al., 2011); 82 TRIM genes (excluding the pseudogenes) have been identified in humans (Table S1).

TRIMs are involved in a variety of seemingly disparate cellular processes (Table S1); these include cell survival and death (Grignani et al., 1993), cell cycle and differentiation (Wang et al., 1998), metabolic states (Skurat et al., 2002), cell membrane repair (Cai et al., 2009), synaptic vesicle exocytosis (Li et al., 2001), senescence (Pearson et al., 2000), stem cell pluripotency (Sato et al., 2012) and erythrocyte differentiation (Blaybel et al., 2008; Barde et al., 2013), as well as the control of viral, bacterial and fungal infections (Nisole et al., 2005; Rakebrandt et al., 2014; Cao et al., 2015). These and additional roles are linked to a variety of health conditions. For instance, TRIMs have been implicated in autoimmune and inflammatory disorders (Jefferies et al., 2011; Kawai and Akira, 2011; Kimura et al., 2015) that are associated with genetic polymorphisms (French FMF Consortium, 1997; The International FMF Consortium Guido, 1997), as well as in insulin resistance (Karlberg et al., 2005; Song et al., 2013), urate metabolism (Köttgen et al., 2013), cancer (Hatakeyama, 2011), asthma (Shin et al., 2011; Collison et al., 2013), and neurodegenerative and neuromuscular diseases (Leonhardt et al., 1994; Khan et al., 2014). Among the best-studied roles for TRIMs is their role in cell-autonomous antiviral defense, a trend partially driven by intense research focusing on human immunodeficiency virus (HIV) (Stremlau et al., 2004; Nisole et al., 2005; Pertel et al., 2011; Versteeg et al., 2013).

TRIMs function as autophagic ‘receptor regulators’

A growing number of studies indicate that several TRIMs are linked to autophagy (Fig. 2C; Table S1) (Lipinski et al., 2010; Niida et al., 2010; Perera et al., 2011; McKnight et al., 2012; Barde et al., 2013; Pizon et al., 2013; Yang et al., 2013; Khan et al., 2014; Mandell et al., 2014; Choi et al., 2015; Kimura et al., 2015). TRIMs act as autophagy receptor regulators (meaning that they act as both receptors and platforms for assembly of autophagosome machinery) by two means. Firstly, TRIMs recognize their targets (Mandell et al., 2014; Kimura et al., 2015) by finding their cognate cargo (e.g. viral core, inflammasome components) through direct protein–protein binding without a need for ubiquitin or galectin intermediates (Figs 1 and 3A). Secondly, the same TRIMs that function as receptors then also act as platforms for the assembly of the core regulators of autophagy, such as ULK1, Beclin1, ATG16L1 (Mandell et al., 2014; Kimura et al., 2015) (Table S1). These two

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**Fig. 1. Precision autophagy.** (A) Precision autophagy is a receptor-regulator-based form of autophagy. A receptor-regulator protein (such as members of the TRIM family) has the ability to recognize targets directly, often without tags such as ubiquitin or galectins, and assembles regulators and effectors of autophagy to mediate precision (highly selective) autophagy. (B) Conventional selective autophagy is mediated by autophagic receptors that recognize targets through generic tags, such as ubiquitin or galectins, while also binding mammalian (m)Atg8 proteins that connect them to autophagic membranes. (C) Nonselective (bulk) autophagy sequesters mixtures of cytoplasmic components, including cytosol.

**Key**
- Target or cargo
- Ubiquitin or galectin tag
- Autophagic organelles
- Receptor
- Autophagy regulators
- LIR
- Receptor regulator
- mAtg8s


**COMMENTARY**
features distinguish TRIMs from SLRs (Table S2a) and from other unique receptors (Table S2b), and allow the execution of a highly selective form of autophagy, termed precision autophagy (Kimura et al., 2015).

**TRIMs as receptors**

TRIMs recognize both endogenous and exogenous cargo for autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific endogenous autophagy targets (Kimura et al., 2015). TRIM20 recognizes the inflammasome components pro-caspase 1, and NLR-family pyrin-domain-containing 1 and 3 proteins (NLRP1 and NLRP3), and presents them for autophagic degradation (Fig. 2C). TRIM21 targets the activated (dimerized) form of interferon NLRP3, and presents them for autophagic degradation (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C). For instance, TRIM20 (also known as MEFV) and TRIM21 have been shown to act as receptors for specific autophagy (Fig. 2C).

**TRIM receptors interact with mAtg8s**

A common feature of conventional receptors for selective autophagy (Birgisdottir et al., 2013; Randow and Youle, 2014; Rogov et al., 2014; Stolz et al., 2014), such as SLRs, is that they bind to mAtg8s (e.g. LC3B or LC3C), which links them to autophagosomal membranes. TRIM5, TRIM20 and TRIM21 (Mandell et al., 2014; Kimura et al., 2015) bind to mAtg8s (Fig. 2A). Other TRIMs interact with mAtg8s (Table S1) in vitro, as shown for TRIM16, TRIM17, TRIM22, TRIM49 and TRIM55 (Mandell et al., 2014). Colocalization between mAtg8s and the TRIMs listed above in the cytoplasm (Niida et al., 2010; Pizon et al., 2013; Mandell et al., 2014; Kimura et al., 2015), as well as with TRIM63 (Khan et al., 2014), corroborate the biochemical findings. Potential binding to mAtg8 has also been documented for TRIM19.
[also known as promyelocytic leukemia (PML) protein] and TRIM28 (Behrends et al., 2010; He et al., 2014). TRIM19 co-immunoprecipitates with LC3B and colocalizes with it in the nucleus (He et al., 2014); this is of interest given that LC3B shuttles between the nucleus and the cytosol upon deacetylation in association with autophagy activation (Huang et al., 2015) and plays a role in autophagic clearance of nuclear components (Dou et al., 2015).

The binding sites for mAtg8 (LIRs; Fig. 2A; Table S1) on several TRIMs have been mapped. TRIM5 has two LIRs, whereas TRIM20 has three LIRs (Mandell et al., 2014; Kimura et al., 2015). Only when all LIRs are mutated or deleted do TRIMs lose their ability to bind to mAtg8s (Mandell et al., 2014; Kimura et al., 2015). The TRIMs show a preference for GABARAPs and LC3A, and do not bind to LC3B when tested in vitro. Nevertheless, LC3B can be found in larger protein complexes with TRIMs when precipitated from cells (Pizon et al., 2013; He et al., 2014; Mandell et al., 2014). Thus, it is likely that LC3B forms larger complexes with TRIMs, possibly indirectly and in a manner that is mediated by an intermediary protein (e.g. p62, discussed below) or following putative post-translational modifications.

Some TRIMs bind to SLRs

Certain TRIMs have the ability to bind to SLRs, such as p62 (Fig. 3A); the known examples include TRIM5 (O’Connor et al., 2010), TRIM50 (Fusco et al., 2012), TRIM55 (Lange et al., 2005; Pizon et al., 2013; Mandell et al., 2014), TRIM13 (Tomar et al., 2012), TRIM17 and TRIM49 (Mandell et al., 2014), TRIM21 (Kimura et al., 2015), as well as TRIM65 (Blandin et al., 2013). Furthermore, p62 can colocalize with TRIM63 in the cytoplasm (Khan et al., 2014) and with TRIM19 in the nucleus within the nuclear PML bodies (Pankiv et al., 2010), although this might not be restricted to the nucleus because TRIM19 functions in the cytoplasm as well (Lin et al., 2004; Dutriex et al., 2015). The association with p62 might link TRIMs indirectly to LC3B (as discussed above); this is of significance for those TRIMs with no evidence of direct binding to LC3B. In contrast, TRIM16 and TRIM20 do not appear to associate with p62 (Mandell et al., 2014). Whether these TRIMs associate with other SLRs or do not interact with SLRs is unknown.

Similar to p62, some TRIMs can themselves be degraded by autophagy. For instance, TRIM50 (Fusco et al., 2012) and murine TRIM30, a homolog of human TRIM5, are degraded by autophagy (Choi et al., 2015). TRIM20, which mediates autophagic degradation of NLRP3, is degraded in autolysosomes but only in the presence of its target (Kimura et al., 2015).

TRIMs as autophagy regulators

TRIMs affect autophagy as a whole process (Lipinski et al., 2010; Perera et al., 2011; McKnight et al., 2012; Tomar et al., 2012; Barde et al., 2013; Pizon et al., 2013; Khan et al., 2014; Pineda et al., 2015) and interact with ATG factors (Behrends et al., 2010; Yang et al., 2013; Mandell et al., 2014; Kimura et al., 2015). Of the 82 human TRIMs, 49 TRIMs have an effect on autophagy (Table S1). The first screens of TRIMs (Mandell et al., 2014) assessed the role of the entire TRIM family on autophagy that had been induced by inhibition of mTOR, a classic way of activating autophagosome formation. Using this approach and pp242 as an mTOR inhibitor, 32 TRIMs were identified as regulating autophagy and TRIM5 was among those hits (Mandell et al., 2014). Another screen (Kimura et al., 2015) that aimed to identify TRIMs affecting immunologically induced autophagy utilized IFN-γ, which is known from earlier studies to induce autophagy but with incompletely understood molecular mechanisms. These studies have revealed that 24 TRIMs (including TRIM8, TRIM20 and TRIM21) are required for optimal induction of autophagy through IFN-γ (Kimura et al., 2015). Several genome-wide screens, albeit not aimed at studying TRIMs, indicate that a number of additional TRIMs (TRIM29, TRIM51 and TRIM69) modulate autophagy (Lipinski et al., 2010; McKnight et al., 2012). Furthermore, TRIM13, TRIM28, TRIM55, TRIM56 and TRIM63 have been reported in separate studies to affect autophagy (Tomar et al., 2012; Barde et al., 2013; Pizon et al., 2013; Yang et al., 2013; Khan et al., 2014; Kimura et al., 2015; Pineda et al., 2015).

Two recent studies show that TRIMs directly assemble the cardinal autophagy regulators ULK1 and Beclin 1 into a protein complex that we have called the TRIMosome (Fig. 3B). Within a TRIMosome, individual TRIMs (e.g. TRIM5, TRIM6, TRIM17, TRIM20, TRIM21, TRIM22 and TRIM49) form protein complexes with both ULK1 and Beclin 1 (Mandell et al., 2014; Kimura et al., 2015). Induction of autophagy depends on a phosphorylation cascade that includes activation of ULK1 by AMPK-mediated phosphorylation at several sites, including Ser317 and Ser555 (Egan et al., 2011; Kim et al., 2011). TRIMosomes contain detectable amounts of AMPK (Kimura et al., 2015) and are enriched for the activated form of ULK1 – i.e. phosphorylated by AMPK at Ser317 and Ser555 (Egan et al., 2011; Kim et al., 2011). TRIMosomes contain detectable amounts of AMPK (Kimura et al., 2015) and are enriched for the activated form of ULK1 – i.e. phosphorylated by AMPK at Ser317 and Ser555 (Egan et al., 2011; Kim et al., 2011). Beclin 1 within the TRIMosome complexes is phosphorylated at Ser15 (Mandell et al., 2014), an indication of its activation by ULK1 (Russell et al., 2013), and at Ser91 and Ser94, indicative of activation by AMPK (Kim et al., 2013). These molecular events are reminiscent of the assembly of activated ULK1 and Beclin 1, which are anchored by immunity-related GTPase M (IRGM) (Chauhan et al., 2015), another type of platform for the assembly of autophagic machinery.

TRIM8, identified in a screen for IFN-γ-inducible autophagy regulators (Kimura et al., 2015), ubiquitylates and activates TGFβ-activated kinase 1 (TAK1; also known as NR2C2) (Li et al., 2011), which in turn activates AMPK (Xie et al., 2006), and so links to the...
key roles of AMPK described above. Several TRIMs (e.g. TRIM13 and TRIM5) show spatial juxtaposition to double FYVE-containing protein 1 (DFCP1) (Tomar et al., 2012; Mandell et al., 2014), a marker for the omegasome, which is believed to be the cradle for autophagosome formation from the endoplasmic reticulum (ER) (Axe et al., 2008). Other autophagy factors, FIP200 (an ULK1 interactor), VPS34, ATG14L and UVRAG (Beclin-1-interacting proteins), WIP12 [a PtdIns(3)P-binding protein interacting with ATG16L1], ATG16L1, ATG5 and ATG12 (an E3 ligase for mAtg8 lipidation), and activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1) have been detected in complexes with TRIMs (Behrends et al., 2010; Yang et al., 2013; Mandell et al., 2014; Kimura et al., 2015). TRIM5 activates this complex by promoting dissociation of the negative regulators Bcl-2 and TAB2 (Wei et al., 2008; Criollo et al., 2011; Takaesu et al., 2012) from Beclin 1 (Mandell et al., 2014); this is likely to occur in conjunction with the Beclin 1 phosphorylation events described above.

TRIM-dependent regulation can both acerate and decelerate autophagy. TRIM17, a negative regulator of pp242-induced autophagy, sequesters the autophagy machinery away from bulk autophagy (Mandell et al., 2014). Furthermore, even a specific TRIM protein might have positive and negative effects on autophagy, as in the case of TRIM28 (Barde et al., 2013; Yang et al., 2013; Mandell et al., 2014; Pineda et al., 2015). For its positive effect, TRIM28 activates VPS34 by modulating binding to Beclin 1 (Yang et al., 2013). For its negative effect, TRIM28, as an E3 ligase, has been reported to mediate proteasomal degradation of AMPK, potentially downregulating autophagy (Pineda et al., 2015). Splice variants of TRIM55 have different activities in the proteasome and autophagy systems during muscle cell differentiation (Pizon et al., 2013), increasing one or the other.

Precision autophagy

The definition of precision autophagy is based on the twofold principle that the same entity (e.g. a TRIM) recognizes directly its cognate autophagic cargo without a need for tags such as ubiquitin or galectins, and at the same time mediating the assembly of core ATG factors into autophagy-activating complexes (Kimura et al., 2015).

An important question arises as to whether the previously described conventional receptors could eventually fit into the broader definition of precision autophagy (Birgisdottir et al., 2013; Randow and Youle, 2014; Rogov et al., 2014; Stolz et al., 2014). These receptors, such as p62, associate with other factors, including autophagy-linked FYVE protein (ALFY; also known as WDFY3) (Clausen et al., 2010), which in turn binds to ATG5, ATG12 and ATG16L1 (Filimonenko et al., 2010). ULK1 and p62 colocalize on the ER in the early stages of autophagy initiation (Itakura and Mizushima, 2010), and p62 binds to ULK1 and ULK2 (Priggeon et al., 2003; Ro et al., 2014). NDP52 interacts with FIP200 (Wang et al., 2011), and recent studies with optineurin and NDP52 hint that these proteins affect the distribution of autophagy regulators such as ULK1, WIP11 and DFCP1 (Lazarou et al., 2015). These observations suggest that SLRs, either alone or in combination with other platforms, could act in precision autophagy akin to TRIMs, but more work is needed to establish such relationships. There are also other platform-forming complexes that, similar to TRIMs, assemble ATG factors, such as the exocyst complex (Bodemann et al., 2011) and IRGM (Chauhan et al., 2015); however, cargo receptors within such complexes have not been defined. Thus, a broader definition of precision autophagy might emerge that encompasses additional new or previously studied receptors and molecular assemblies.

Other autophagy receptors

Beyond the receptor classes of TRIMs (Table S1) and SLRs (Table S2a), unique autophagy receptors have also been described (Table S2b) that participate in specific forms of autophagy. Atg32 is a receptor for mitophagy in yeast (Kanki et al., 2009; Okamoto et al., 2009) and its equivalent, Bel2-L-13, has been identified in mammals (Murakawa et al., 2015). During reticulocyte development, Nix (also known as BNIPL) appears to be the receptor for mitophagy (Sandoval et al., 2008; Swartzen et al., 2009; Novak et al., 2010). FUNDC1 (Liu et al., 2012) and BNIP3 (Zhang et al., 2008; Zhu et al., 2013) contribute to mitophagy during hypoxia in mammals. Nevertheless, there is evidence that subsets of SLRs (Lazarou et al., 2015; Matsumoto et al., 2015) play a role in mammalian mitophagy in conjunction with the PINK1–Parkin–phosphorylated-ubiquitin system (Koyano et al., 2014; Lazarou et al., 2015), which is activated in response to mitochondrial damage. Of note, the mitochondria-specific phospholipid cardiolipin is directly recognized by LC3B (Chu et al., 2013), potentially short-circuiting or aiding receptor recognition. A further implication of lipid recognition in mitophagy comes from the contribution to this process of SMURF1 (Orvedahl et al., 2011) — a C2-domain-containing protein (indicative of a lipid recognition) — and IRGM, which binds to cardiolipin (Singh et al., 2010). How all of these receptors and factors connect with the upstream regulators of autophagy remains to be determined.

Other organelles are recognized by unique receptors in order to be targeted for autophagy. In yeast and Pichia, pexophagy occurs through the peroxisome-anchored receptors Atg30 and Atg36 (Faré et al., 2008; Motley et al., 2012); albeit pexophagy that is mediated by the SLR NBR1 has been described in mammalian cells (Deosaran et al., 2013). ER-phagy is facilitated by membrane-associated receptors, such as FAM134B in mammals (Khaminets et al., 2015) and its equivalent, Bcl2-L-13, has been identified in mammalian cells (Kanki et al., 2009; Okamoto et al., 2009). Other autophagy receptors

Role of TRIM-directed precision autophagy in disease

TRIMs have a role in infectious, autoimmune and neoplastic diseases (Ozato et al., 2008; Hatakeyama, 2011; Jefferies et al., 2011; Kawai and Akira, 2011). In the context of inflammatory etiology of disease, autophagy can suppress inflammasome output either indirectly (Saitoh et al., 2008; Schroder and Tschopp, 2010; Nakahira et al., 2011; Zhou et al., 2011), or directly through selective autophagy of assembled inflammasomes (Shi et al., 2012) or inflammasome components, such as that mediated by TRIM20 (Kimura et al., 2015). TRIM20, also known as PYRIN, is encoded through ubiquitin but through unique receptors. NCOA4 has a receptor role in autophagy of ferritin (Dowdle et al., 2014; Mancias et al., 2014); NCOA4 binds to mAtg8 proteins in a manner similar to that of TRIMs with the exception of LC3B and recruits the large 450-kDa ferritin complex to the autolysosome (Dowdle et al., 2014; Mancias et al., 2014), thereby contributing to iron homeostasis. STBD1, which binds to GABARAP and GABARAPL1, and glycogen synthase, which binds to Atg8 in Drosophila, could be receptors that recognise glycogen for autophagic degradation (Jiang et al., 2011; Zirin et al., 2013).

Various proteinaceous targets and complexes are recognized not through ubiquitin but through unique receptors. NCOA4 has a receptor role in autophagy of ferritin (Dowdle et al., 2014; Mancias et al., 2014); NCOA4 binds to mAtg8 proteins in a manner similar to that of TRIMs with the exception of LC3B and recruits the large 450-kDa ferritin complex to the autolysosome (Dowdle et al., 2014; Mancias et al., 2014), thereby contributing to iron homeostasis. STBD1, which binds to GABARAP and GABARAPL1, and glycogen synthase, which binds to Atg8 in Drosophila, could be receptors that recognise glycogen for autophagic degradation (Jiang et al., 2011; Zirin et al., 2013).
polymorphisms commonly occur in its PRY/SPRY domain (Masters et al., 2009). TRIM20 variants with mutations in the PRY/SPRY domain show deficiency in the autophagic degradation of NLRP3 (Kimura et al., 2015). Additional FMF-associated polymorphisms fall within the TRIM20 LIR motifs (E403K in the first LIR motif, Y471X and E474K in the second LIR motif). Of note, TRIM20 expression is strongly induced by IFN-γ (Carthagena et al., 2009; Chae et al., 2011). Thus, TRIM expression is regulated, which in turn determines the outcome – i.e. the IFN-γ–TRIM–autophagy axis might suppress excessive inflammasome activation, in keeping with the notion that inflammasome activation can be inhibited by IFN-γ (Chae et al., 2011). This capacity could be compromised in FMF owing to TRIM20 polymorphisms, which reduces the autophagic degradation of inflammasome components.

One of the hallmarks of autoimmune diseases, such as systemic lupus erythematosus (SLE) and Sjögren syndrome, is the activation of type-1 IFN (Banchereau and Pascual, 2006). The autophagic receptor regulator TRIM21 directs precision autophagy of activated (dimerized) IRF-3, thereby reducing activation of type-I IFN (Kimura et al., 2015). This is also reflected in the related ability of TRIM21 to degrade inhibitor of NF-κB kinase (IKK), encoded by IKBKB through autophagy (Niida et al., 2010). TRIM21 also targets other factors that are responsible for type-I IFN activation, including IRF-5, IRF-7 and IRF-8, for degradation through proteasomal or, thus far, unknown mechanisms (Higgs et al., 2008, 2010; Espinosa et al., 2009; Yoshimi et al., 2009; Young et al., 2011; Lazzari et al., 2014). TRIMs are often described as autoantigens in autoimmune diseases and cancers, including TRIM21 and TRIM68 in SLE and Sjögren syndrome (Der et al., 1998; Billaut-Mulot et al., 2001), TRIM33 in dermatomyositis and the associated paraneoplastic phenomena (Targoff et al., 2006; Fujimoto et al., 2012), TRIM19 in primary biliary cirrhosis (Stinton et al., 2011), and TRIM28 in colon cancer (Kijanka et al., 2010; Hector et al., 2012) and dermatomyositis (Satoh et al., 2012). Furthermore, TRIMs as a protein family have been associated with the regulation of type-I IFN responses (Versteeg et al., 2013), in keeping with relationships described for TRIM21 above (Kimura et al., 2015).

TRIMs play a role in defense against viral pathogens (Nisole et al., 2005), which at least in the case of TRIM5 involves precision autophagy (Mandell et al., 2014). The Rhesus TRIM5 can execute precision autophagy of the HIV-1 capsid. In contrast, the weak affinity of human TRIM5 for the HIV-1 capsid precludes effective precision autophagy. As a consequence, Rhesus TRIM5, but not human TRIM5, contributes to defense against HIV-1 through precision autophagy. Antimicrobial roles of TRIMs that are mediated through autophagy might extend to a defense against other intracellular pathogens; this includes bacteria (Rakebrandt et al., 2014) and possibly fungi. For instance, the antifungal activity of TRIM62 that is conveyed by CARD9, a mediator of innate immunity signals, which although not yet formally linked to autophagy (Cao et al., 2015), is known to play a role in autophagy through the interactions it has with RUBICON (encoded by KIAA0226) (Yang et al., 2012).

A number of mutations and polymorphisms in TRIMs are known to be associated with cancer, neurodegeneration, neuro-muscular diseases, immune disease (e.g. FMF as described above), infections (as in the case of HIV-1 susceptibility), metabolic traits, neurodegeneration, psychiatric disorders, heart disease and aging processes (Table S1). Several TRIMs are also involved in oncogenesis (Table S1). A classic example of this is TRIM19, which is fused with retinoic acid receptor α (RARα) in acute PML disease (de Thé et al., 1991; Kakizuka et al., 1991). Furthermore, fusions between TRIM24 and B-Raf are found in liver cancer (Le Douarin et al., 1995), between TRIM27 and RET in papillary thyroid cancer (Hasegawa et al., 1996), and of TRIM4 with B-Raf in lung cancer (Zheng et al., 2014) or with MET in melanoma (Yeh et al., 2015). Among these, the TRIM19–RARα fusion protein is already known to be degraded by autophagy (Isakson et al., 2010; Wang et al., 2014), whereas clearance of TRIM19–RARα is a therapeutic target in acute PML disease (Nasr et al., 2008). Thus, precision autophagy of TRIM19–RARα and other oncogenic fusions could be beneficial in cancer treatment (Fig. 2C).

A recent sequencing of tumor tissues has revealed that TRIM23 is a previously unappreciated gene involved in cancer progression (Lawrence et al., 2014). TRIMs are also known to regulate tumor suppressor proteins such as p53 (encoded by TP53) (Hatakeyama, 2011). Indeed, TRIM24 (Alton et al., 2009), TRIM39 (Zhang et al., 2012a,b) and TRIM59 (Zhou et al., 2014) help to degrade p53. In addition, TRIM8, TRIM13, TRIM19, TRIM21 and TRIM25 also affect p53 stability (Bernardi et al., 2004; Joo et al., 2011; Caratozzolo et al., 2012; Reddy et al., 2014; Zhang et al., 2015). TRIM28, TRIM29 and TRIM32 antagonize p53 function (Wang et al., 2005; Yuan et al., 2010; Liu et al., 2014). In turn, TRIMs and p53 affect each other transcriptionally. TRIM3 increases the level of p53 (Cheung et al., 2010), and the expression of TRIM22 is increased by p53 (Obad et al., 2004), whereas that of TRIM9 is increased by mutated p53 (Okaichi et al., 2013). The relationship between TRIMs and p53 fit with the dual role of p53 in autophagy (Tasdemir et al., 2008; Tavernarakis et al., 2008).

A recent study has linked TRIM-directed autophagy with certain types of neurodegeneration (Khan et al., 2014). TRIM63 mediates autophagy to promote the turnover of nicotinic acetylcholine receptor in muscles to remodel neuromuscular junctions (Fig. 2C) (Kim et al., 2014). Thus, TRIMs and precision autophagy could play a wider role in neurodegenerative diseases.

**Conclusion and future perspectives**

The role of the TRIM proteins as autophagic receptors widens our understanding of the repertoire, versatility and capacity for selective autophagy in mammalian cells. In their role as assembly platforms, TRIMs provide a new paradigm for the organization, localization and homing of the autophagic apparatus in mammalian cells. The TRIM family has numerous members (82 members in humans), suggesting that they account for the regulation of a significant portion of selective autophagy. Moreover, the TRIM family has expanded over the course of evolution, suggesting that this family co-evolves with the expanding need for clearance of more complex or emerging targets. Given the breadth of the role of TRIMs in various diseases (Table S1), it will be important to explore precision autophagy – in addition to bulk autophagy – as a therapeutic target.

The integration of TRIMs with autophagy is multi-tiered. When TRIMs act as selective autophagy receptors, they also assemble the principal core autophagy regulators. This represents a key feature of precision autophagy. The physical ‘home’ or an embodiment of this dual role as both receptors and regulators is the TRIMosome (Fig. 3B), which furthermore might act as a mammalian equivalent of the phagophore-assembly site (PAS; also known as pre-autophagosomal structure) for precision autophagy. The TRIMosome proteinaceous organelle, or apparatus, initiates and executes autophagy in coordination with the recognition of its intended substrate.

The above concepts and relationships raise questions, such as how many TRIMs act as autophagic receptors and what are their specific targets? Do different TRIMs cooperate through their known
hetertrophic interactions in clearance of more complex (multivalent) targets? How is the autophagic role of TRIMs integrated with the other functions of TRIMs, including regulation of gene expression and pro-inflammatory signaling? What is the interplay between the E3 ligase activity of TRIMs and precision (or other forms of) to the initiation of the process? Can TRIMs also negatively regulate autophagy through competition or by direct inhibitory activities, and does this reflect the need for a homeostatic ‘off switch’ in order to limit autophagy after it has been initiated? Finally, are there receptors other than TRIMs that fit the concept of receptor regulators and precision autophagy? Answering these questions and gaining a further understanding of the TRIMs promises to enlighten us about the specifics of how autophagy is deployed in mammalian cells.

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Competing interests
The authors declare no competing or financial interests.

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Supplementary information
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References


TFI, a putative mediator of the ligand-dependent activation function (AF-2) of nuclear receptors, is fused to B-raf in the oncogenic protein T18. EMBO J. 14, 2020-2033.


The International FMP Consortium Guido (1997). Ancient missense mutations in a novel member of the Ro/56k family are likely to cause familial Mediterranean fever. Cell 90, 797-807.


**Summary**: Precision autophagy represents direct recognition of targets by receptors, such as TRIMs, that simultaneously organize core autophagy proteins, coupling recognition to autophagosome formation.
Table S1. TRIMs and autophagy.

<table>
<thead>
<tr>
<th>Name</th>
<th>Gene ID</th>
<th>Alias</th>
<th>Domain organization</th>
<th>Autophagy</th>
<th>Disease / general physiology / mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIM1</td>
<td>11043</td>
<td>FXY2, RNF60, MRX101, MID2</td>
<td>R-B-B-CC-COS-FN3-SPRY</td>
<td>⌃ ⌅ ⌃</td>
<td>Opitz–Kaveggia syndrome (Jehee et al., 2005).</td>
</tr>
<tr>
<td>TRIM2</td>
<td>23321</td>
<td>CMT2R, RNF86</td>
<td>R-B-CC-FL-NHL</td>
<td>⌃</td>
<td>Charcot-Marie-Tooth disease (Ylikallio et al., 2013). Neurodegeneration in knockout mice (Balastik et al., 2008).</td>
</tr>
<tr>
<td>TRIM3</td>
<td>10612</td>
<td>BERP, HAC1, RNF22, RNF97</td>
<td>R-B-CC-FL-NHL</td>
<td>⌃ ⌅</td>
<td>Gene hypomethylated in obesity (Wang, X. et al., 2010). Glioblastoma (Chen et al., 2014). Liver cancer (Chao et al., 2014). Activated by p53 (Cheung et al., 2010). Resistance to seizure in knockout mice (Cheung et al., 2010). Regulates hippocampal plasticity and learning by suppressing synaptic γ-actin levels (Schreiber et al., 2015).</td>
</tr>
<tr>
<td>TRIM4</td>
<td>89122</td>
<td>RNF87</td>
<td>R-B-CC-PRY/SPRY</td>
<td>⌃ ⌅</td>
<td>Fused with BRAF in lung cancer (Zheng et al., 2014) and with MET in melanoma (Yeh et al., 2015). Affecting DHEAS levels in aging (Zhai et al., 2011). Huntington’s disease (Feyeux et al., 2012). Induces type I IFN response by ubiquitylating RIG-I (Yan et al., 2014).</td>
</tr>
<tr>
<td>TRIM5</td>
<td>85363</td>
<td>RNF88alpha, TRIM5α</td>
<td>R-B-CC-LIR-LIR-PR/Y/SPRY</td>
<td>⌃</td>
<td>Multiple sclerosis (Nexo et al., 2011). Restricts HIV-1 via TAK1 activation (Stremlau et al., 2004; Stremlau et al., 2006; Uchil et al., 2008; Pertel et al., 2011). Hepatitis B virus (Zhang, S. et al., 2013). TRIM5 and mouse Trim30 suppress NK-κB activation by targeting TAB2 and TAB3 (Shi et al., 2008; Tareen and Emerman, 2011). Trim30 suppresses NLRP3 inflammasome activation (Hu et al., 2010). Trim12c, another mouse homologue, induces</td>
</tr>
<tr>
<td><strong>TRIM6</strong></td>
<td>RNF89</td>
<td>R-B-CC-PRY/SPRY</td>
<td>+ (^i) N(^i), ii</td>
<td>ULK1, Beclin 1, R-B-CC-PRY/SPRY</td>
<td>Promotes IKKε-dependent type I IFN response (Rajsbaum et al., 2014). HIV-1 capsid binding (Yang et al., 2014). Hepatitis B virus (Zhang, S. et al., 2013). Stem cell pluripotency (Sato et al., 2012).</td>
</tr>
<tr>
<td><strong>TRIM7</strong></td>
<td>GNIP, RNF90</td>
<td>R-B-CC-PRY/SPRY</td>
<td>N(^i)</td>
<td></td>
<td>HIV-1 (Konig et al., 2008). Glycogen synthesis (Skurat et al., 2002).</td>
</tr>
<tr>
<td><strong>TRIM8</strong></td>
<td>GERP, RNF27</td>
<td>R-B-B-CC-X</td>
<td>+ (^i), iv</td>
<td></td>
<td>Induces NF-κB activation by TAK1 ubiquitination (Li et al., 2011). HIV-1 (Konig et al., 2008; Uchil et al., 2008). Regulates SOCS-1 (Toniato et al., 2002) and activates STAT3 by degrading PIAS3 (Okumura et al., 2010). Laryngeal cancer (Carinci et al., 2007), renal cell cancer (Caratozzolo et al., 2014) glioblastoma (Vincent et al., 2000; Micale et al., 2015). Stabilizes p53 (Caratozzolo et al., 2012).</td>
</tr>
<tr>
<td><strong>TRIM9</strong></td>
<td>SPRING, RNF91</td>
<td>R-B-B-CC-COS-FN3-SPRY</td>
<td>N(^i)</td>
<td></td>
<td>Synaptic vesicle exocytosis (Li et al., 2001). Axon branching promotion (Winkle et al., 2014). Parkinson's disease and dementia with Lewy body (Tanji et al., 2010). Atypical psychosis (Kanazawa et al., 2013). Suppresses NF-κB activation by stabilizing IκB (Shi et al., 2014). HIV-1 (Uchil et al., 2008). Increased expression by mutated p53 (Okaichi et al., 2013). Renal cell cancer (Lucas et al., 2005).</td>
</tr>
<tr>
<td><strong>TRIM10</strong></td>
<td>RNF9, HERF1, RFB30</td>
<td>R-B-CC-PRY/SPRY</td>
<td>+ (^i) + (^\text{iii})</td>
<td></td>
<td>Erythrocyte differentiation (Harada et al., 1999; Blaybel et al., 2008). Multiple autoimmune diseases (Sirotta et al., 2009). HIV-1 (Uchil et al., 2008).</td>
</tr>
<tr>
<td><strong>TRIM11</strong></td>
<td>BIA1, RNF92</td>
<td>R-B-CC-PRY/SPRY</td>
<td>N(^i), ii, iii</td>
<td></td>
<td>Alzheimer's disease-related neurotoxicity (Nikura et al., 2003). Limb-girdle muscular dystrophies (Aurino et al., 2008). Targets TBK1 and suppresses IFNβ (Lee et al., 2013). HIV-1 (Uchil et al., 2008; Raposo et al., 2013). Hepatitis B virus (Zhang, S. et al., 2013). Glioma (Di et al., 2013).</td>
</tr>
<tr>
<td>TRIM13</td>
<td>10206</td>
<td>CAR, LEU5, RFP2, DLEU5, RNF77</td>
<td>R-B-CC-(LIR)-TM</td>
<td>N, ii, +</td>
<td>p62 (Tomar et al., 2012).</td>
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<tr>
<td>TRIM15</td>
<td>89870</td>
<td>RNF93, ZNFB7, ZNF178</td>
<td>R-B-CC-PRY/SPRY</td>
<td>N, ii, iii</td>
<td></td>
</tr>
<tr>
<td>TRIM16</td>
<td>10626</td>
<td>EBBP</td>
<td>X-B-B-CC-(LIR)-PRY/SPRY</td>
<td>N, ii, iii</td>
<td>GABARAP (Mandell et al., 2014).</td>
</tr>
<tr>
<td>TRIM16L</td>
<td>147166</td>
<td>TRIM70</td>
<td>X-PRY/SPRY</td>
<td>N, ii, iii</td>
<td></td>
</tr>
<tr>
<td>TRIM17</td>
<td>51127</td>
<td>RBCC, terf, RNF16</td>
<td>R-B-CC-(LIR)-PRY/SPRY</td>
<td>. i, ii, +</td>
<td>ULK1, Beclin 1, p62, LC3A, GABARAP (Mandell et al., 2014).</td>
</tr>
<tr>
<td>TRIM18</td>
<td>4281</td>
<td>MID1, OS, FXY, OSX, OGS1, XPRF, BBBG1, XPRF,</td>
<td>R-B-B-CC-COS-FN3-PRY/SPRY</td>
<td>N, ii, iii</td>
<td></td>
</tr>
<tr>
<td><strong>TRIM19</strong> 5371</td>
<td>PML, MYL, PP8675, RNF71</td>
<td>R-B-B-CC-(LIR)-X</td>
<td>N. ii +i</td>
<td>LC3B (He et al., 2014). p62 (RARα-fusion protein) (Wang, Z. et al., 2014). Colocalizes with p62 (Pankiv et al., 2010). Degrades PML/RARA fusion oncoprotein (Isakson et al., 2010; Wang, Z. et al., 2014). Fused with RARα in acute promyelocytic leukemia (de The et al., 1991; Kakizuka et al., 1991). Suppresses NLRP3 and AIM2 inflammasome (Dowling et al., 2014) and NF-κB activation (Wu et al., 2003; Kuwayama et al., 2009). Activates STAT1 through phosphorylation (El Bougrini et al., 2011). Autoantibodies in primary biliary cirrhosis (Stinton et al., 2011). HIV-1, HCV, CMV, adenovirus, human foamy virus, vesicular stomatitis virus, influenza A, poliovirus, rabies, lymphocytic choriomeningitis virus, lassa virus, and Ebola virus (Nisole et al., 2005; Geoffroy and Chelbi-Alix, 2011; Kuroki et al., 2013). Liver (Xia et al., 2007; Chung and Tsai, 2009), gallbladder (Chang et al., 2007), breast (Plevova et al., 2007), gastric (Kim et al., 2011), and colon cancer (Satow et al., 2012). Glioblastoma (Kuwayama et al., 2009). Regulates p53 stability (Bernardi et al., 2004). Cell senescence (Pearson et al., 2000).</td>
<td></td>
</tr>
<tr>
<td><strong>TRIM20</strong> 4210</td>
<td>MEFV, FMF, Pyrin</td>
<td>PYRIN-B-CC-LIR-LI R-LIR-PRY/SPRY</td>
<td>N. ii +i</td>
<td>ULK1, Beclin 1, ATG16L1, LC3A, LC3C, GABARAP, GABARAPL1/2 (Mandell et al., 2014; Kimura et al., 2015). Degrades inflammasome component (NLRP3, NLRP1 and pro-caspase 1) and suppresses IL-1β activation. Degraded by autophagy (Kimura et al., 2015). Familial Mediterranean fever (FMF Consortium, 1997; The FMF Consortium 1997) and autoimmune diseases such as Henoch-Schönlein purpura (Gershoni-Baruch et al., 2003), rheumatic arthritis (Migita et al., 2008; Koca et al., 2010), Crohn’s disease (Fidder et al., 2005), ulcerative colitis (Giaglis et al., 2006), Behçet’s disease (Rabinovich et al., 2007), polyarteritis nodosa (Yalcinkaya et al., 2007), and ankylosing spondylitis (Akkoc et al., 2010; Cosan et al., 2010). Induces NF-κB activation or no effect (Yu et al., 2006; Chae et al., 2008). Multiple sclerosis (Shinar et al., 2003). Sweet’s syndrome (Jo et al., 2015). Myelodysplastic syndrome and acute myeloid</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>RNF94, STAF50, GPSTAF50</td>
<td>ULK1, Beclin 1, p62, LC3A, GABARAP (Mandell et al., 2014).</td>
<td>Overexpression suppresses TRIM17-dependent autophagy inhibition (Mandell et al., 2014).</td>
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</tr>
<tr>
<td>TRIM22 6737</td>
<td>R-B-(LIR)-PRY/SPRY</td>
<td>UCL1, Beclin 1, p62, LC3A, GABARAP, GABARAPL1/2, ATG2A/3/4B/4C/5/10/12/13/16L1/101, AMPK, FIP200, VPS34, UVRAG, and WIPI2 (Behrends et al., 2010; Kimura et al., 2015).</td>
<td>Degradates IKKβ and IRF3 to suppress type I IFN response (Wada et al., 2009; Niida et al., 2010; Kimura et al., 2015). May suppress antibody-coated Salmonella infection (Keeble et al., 2008; McEwan et al., 2013; Rakebrandt et al., 2014). Colocalizes with LC3B (Niida et al., 2010).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIM23 373</td>
<td>ARD1, ARFD1, RNF46</td>
<td>+1, -1, 1, II</td>
<td>TRL3- and RIG-I-mediated type I IFN response (Poole et al., 2009; Arimoto et al., 2010). Yellow Fever virus (Laurent-Rolle et al., 2014). Cytomegalovirus (Poole et al., 2009). Cancer gene mutated in tumors (Lawrence et al., 2014). Breast (Wang, Z. H. et al., 2011), colon (Liu, C. et al., 2012), and neck squamous cancer (Valach et al., 2012). Regulates adipocyte differentiation (Watanabe et al., 2015).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIM24</td>
<td>PTC6, TF1A, TIF1, RNF82, TIF1A, hTIF1, TIF1ALPHA</td>
<td>R-B-B-CC-PHD-BROMO</td>
<td>N, ii, iii</td>
<td>Fused with B-RAF in liver (Le Douarin et al., 1995) and lung cancer (Nakaoku et al., 2014), with FGFR1 in myeloproliferative syndrome (Belloni et al., 2005), and with RET in papillary thyroid carcinoma (Klugbauer and Rabes, 1999). Suppresses type I IFN response by suppressing STAT1 expression (Tisserand et al., 2011). Breast (Tsai et al., 2010; Chambon et al., 2011), non-small lung (Li et al., 2012), head and neck squamous (Cui et al., 2013), gastric (Miao et al., 2015), and liver cancer (Khetchoumian et al., 2007; Liu, X. et al., 2014). Glioma (Zhang, L. H. et al., 2015). Acute lymphoblastic (Silveira et al., 2013) and myeloid leukemia (Gandini et al., 2002). p53 degradation (Allton et al., 2009). Glucose (Pathiraja et al., 2015) and lipid metabolism (Jiang, S. et al., 2015).</td>
<td></td>
</tr>
<tr>
<td>TRIM25</td>
<td>EFP, Z147, RNF147, ZNF147</td>
<td>R-B-B-CC-PRY/SPRY</td>
<td>N, ii, iii</td>
<td>Promotes RIG-I/MAVS-mediated type I IFN response (Gack et al., 2007; Wang, P. et al., 2010; Inn et al., 2011; Liu, H. M. et al., 2012; Lee, N. R. et al., 2015). Targeted by Influenza A virus and dengue virus serotype 2 (Gack et al., 2009; Manokaran et al., 2015). HIV-1 (Uchil et al., 2008), feline leukemia virus replication (Koba et al., 2015) and Hepatitis B virus transcription (Zhang, S. et al., 2013). Measles vaccine immunity (Ovsyannikova et al., 2013). Breast (Ikeda et al., 2000; Urano et al., 2002), lung (Qin et al., 2012) and endometrial cancer (Nakayama et al., 2005; Dai et al., 2010). Regulates p53 (Zhang, P. et al., 2015).</td>
<td></td>
</tr>
<tr>
<td>TRIM26</td>
<td>AFP, RNF95, ZNF173</td>
<td>R-B-CC-PRY/SPRY</td>
<td>J, Ni, ii</td>
<td>Schizophrenia (de Jong et al., 2012; Ohi et al., 2013). Aspirin-related respiratory disease (Lee et al., 2012). Degrades IRF3 and suppresses type I IFN response (Wang, P. et al., 2015). HIV-1 (Uchil et al., 2008; Abdel-Mohsen et al., 2013; Raposo et al., 2013). Hepatitis B virus (Zhang, S. et al., 2013). Liver cancer (Wang, Y. et al., 2015b).</td>
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</table>
**TRIM27**

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>List of Proteins</th>
<th>Function</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFP, RNF76</td>
<td>R-B-CC-PRY/SPRY</td>
<td>Fused with RET in lymphoma (Takahashi et al., 1985) and papillary thyroid carcinoma (Hasegawa et al., 1996). Knockout mice susceptibility to streptozotocin-induced diabetes (Zaman et al., 2013). Binds and inhibits IKK-α, IKK-β, TBK1 and IKK-ε (Zha et al., 2006). Degrades NOD2 (Zurek et al., 2012). Targeted by HSV-1 (Conwell et al., 2015). HIV-1 (Uchil et al., 2008). Multiple cancer (Zoumpoulidou et al., 2012), including breast (Tezel et al., 2009), endometrial (Tsukamoto et al., 2009), ovarian (Horio et al., 2012), lung (Iwakoshi et al., 2012), and prostate cancer (Shaikhrahim et al., 2013). Acute lymphocytic leukemia (Urayama et al., 2013).</td>
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**TRIM28**

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<th>Function</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>KAP1, TF1B, RNF96, TIF1B, PPP1R157</td>
<td>R-B-B-CC-(LIR)-PHD-BROMO</td>
<td>Regulates microRNA to induce mitophagy for erythropoiesis (Barde et al., 2013). Induces autophagy in response to histone deacetylase inhibitor by promoting VPS34 to bind Beclin 1 (Yang et al., 2013). Suppresses autophagy by ubiquitination and degradation of AMPK and promotes tumor initiation (Pineda et al., 2015).</td>
<td>N, ii, iii</td>
</tr>
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</table>

**TRIM29**

<table>
<thead>
<tr>
<th>Gene(s)</th>
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<th>Function</th>
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</tr>
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<tbody>
<tr>
<td>ATDC</td>
<td>X-B-B-CC-X</td>
<td>Ataxia-telangiectasia group D (Leonhardt et al., 1994). Activates NF-κB (Tang et al., 2013). HIV-1 (Konig et al., 2008). Lung (Hawthorn et al., 2006;</td>
<td>N, ii, iii</td>
</tr>
<tr>
<td>TRIM31</td>
<td>RNF, HCG1, HCGI, C6orf13</td>
<td>R-B-CC-X</td>
<td>+(^i)</td>
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</table>
|--------|-------------------------|-----------------|--------|--
<p>|        |                         |                 |        |Intelligence in attention deficit/hyperactivity disorder (ADHD) (Rizzi et al., 2011). HIV-1 (Uchil et al., 2008). Hepatitis B virus (Zhang, S. et al., 2013). Gastric (Sugiura, 2011) and non-small cell lung cancer (Li, H. et al., 2014a).|
| TRIM32 | HT2A, BBS11, TATIP, LGMD2H | R-B-CC-NHL | Ni, ii | iii |
|        |                         |                 |        |Limb-girdle muscular dystrophy, including type 2H (Frosk et al., 2002; Saccone et al., 2008; Blandin et al., 2013). Bardet-Biedl syndrome type 11 (Chiang et al., 2006). Alzheimer's disease (Yokota et al., 2006). Amyotrophic lateral sclerosis muscles (Bernardini et al., 2013). ADHD (Lionel et al., 2011; Lionel et al., 2014). Pluripotency (Bahnassawy et al., 2015). Degrades PIASy and activates NF-κB (Albor et al., 2006). Activates STING and mediates type I IFN (Zhang, J. et al., 2012). HIV-1 (Uchil et al., 2008; Abdel-Mohsen et al., 2013). Head and neck cancer (Horn et al., 2004; Kano et al., 2008). Antagonize p53 by degradation (Liu, J. et al., 2014).|
| TRIM33 | ECTO, PTC7, RFG7, TF1G, TIF1G, TIFGAMMA, TIF1GAMMA | R-B-CC-PHD-BROMO | Ji | Ni, ii |
|        |                         |                 |        |Autoantibodies in dermatomyositis (Targoff et al., 2006; Fujimoto et al., 2012). Autism (Xia et al., 2014). Mediates RNA-induced NLRP3 inflammasome activation (Weng et al., 2014). Targeted by adenovirus (Forrester et al., 2012). Wilms' tumor (Natrajan et al., 2007). Cystic pancreas tumor (Vincent et al., 2009), colon (Jain et al., 2011), head and|</p>
<table>
<thead>
<tr>
<th>TRIM</th>
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<th>Symbol</th>
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<td>TRIM34</td>
<td>53840</td>
<td>IFP1, RNF21</td>
<td>R-B-CC-SPRY</td>
<td>+i, ii</td>
</tr>
<tr>
<td>TRIM35</td>
<td>23087</td>
<td>HLS5, MAIR</td>
<td>R-B-CC-PRY/SPRY</td>
<td>Nii, iii</td>
</tr>
<tr>
<td>TRIM36</td>
<td>55521</td>
<td>RNF98, HAPRIN, RBCC728</td>
<td>R-B-B-CC-COS-FN3-SPRY</td>
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<tr>
<td>TRIM37</td>
<td>4591</td>
<td>MUL, POB1, TEF3</td>
<td>R-B-CC-MATH</td>
<td>Nii, iii</td>
</tr>
<tr>
<td>TRIM38</td>
<td>10475</td>
<td>RNF15, RORET</td>
<td>R-B-CC-PRY/SPRY</td>
<td>+i, ii</td>
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<tr>
<td>TRIM39</td>
<td>56658</td>
<td>TFP, RNF23, TRIM39B</td>
<td>R-B-CC-PRY/SPRY</td>
<td>Nii, iii</td>
</tr>
</tbody>
</table>

- Neck squamous (Li, H. et al., 2014b), and liver cancer (Herquel et al., 2011; Ding et al., 2014). Chronic myelomonocytic leukemia (Aucagne et al., 2011).
- HIV-1 binding (Yang et al., 2014). Metabolic traits in mice (Orozco et al., 2009).
- Targets IRF7 and suppresses type I IFN response (Wang, Y. et al., 2015a).
- Prostate cancer (Fujimura et al., 2014), ovarian endometriosis (Ren et al., 2014).
<table>
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<tr>
<th>Gene</th>
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<tr>
<td>TRIM40</td>
<td>RNF35</td>
<td>SLE (Barcellos et al., 2009), multiple autoimmune disease (Siroti et al., 2009). Suppresses NF-κB activation by neddylation of IKKγ (Noguchi et al., 2011). Gastrointestinal cancer (Noguchi et al., 2011).</td>
</tr>
<tr>
<td></td>
<td>R-B-CC-X</td>
<td></td>
</tr>
<tr>
<td>TRIM41</td>
<td>RINCK</td>
<td>Hepatitis B virus (Zhang, S. et al., 2013). Colon cancer (Zhang, P. et al., 2012).</td>
</tr>
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<td></td>
<td>R-B-CC-PRY/SPRY</td>
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<tr>
<td>TRIM42</td>
<td>R-B-CC-COS-FN3</td>
<td>intellectural disability (Kashevarova et al., 2014). Aniridia (Zhang, X. et al., 2015). Activates NF-κB (Luo et al., 2015). HIV-1 (Konig et al., 2008). Head and neck squamous (Jarvinen et al., 2008), esophageal (Peters et al., 2010), and gastric cancer (Kashimoto et al., 2012; Ong et al., 2013).</td>
</tr>
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<td></td>
<td>R-B-CC-SPRY</td>
<td></td>
</tr>
<tr>
<td>TRIM43</td>
<td>MC7, DIPB,</td>
<td>Serum urate concentration (Kottgen et al., 2013). Chimeric mRNA fused with MUC1 and KRTCAP2 in ovarian cancer (Kannan et al., 2015).</td>
</tr>
<tr>
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<tr>
<td>TRIM44</td>
<td>X-B-CC-X</td>
<td>White matter lesions of the brain (Fornage et al., 2011; Lopez et al., 2015).</td>
</tr>
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<td>X-B-CC-PX</td>
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<td>TRIM45</td>
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<td>Suppresses NF-κB activity (Shibata et al., 2012).</td>
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<td>TRIM46</td>
<td>GENEY,</td>
<td>Serum urate concentration (Kottgen et al., 2013). Chimeric mRNA fused with MUC1 and KRTCAP2 in ovarian cancer (Kannan et al., 2015).</td>
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<td>TRIM49</td>
<td>RNF18, RNF49A,</td>
<td>ULK1, Beclin 1, p62, LC3A, and GABARAP (Mandell et al., 2014).</td>
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<tr>
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<td>TRIM50</td>
<td>R-B-CC-PRY/SPRY</td>
<td>Degraded by autophagy (Fusco et al., 2012).</td>
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<td>MURF,</td>
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<td>TRIM60</td>
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</table>

Protein aggregate myopathy (Olive et al., 2015).
Early phase of heart muscle differentiation (Lange et al., 2005; Perera et al., 2011; Pizon et al., 2013).
Activates STING and TBK1, and induces type I IFN response (Tsuchida et al., 2010). HIV-1 (Konig et al., 2008; Uchil et al., 2008). Pestivirus (Wang, J. et al., 2011a). Yellow fever virus, dengue virus serotype 2, and human coronavirus virus (Liu, B. et al., 2014).
<p>| TRIM61 391712 | R-B-CC-PRY/SPRY | + i | N i, ii | iPS cells from Leber congenital amaurosis (Lustremant et al., 2013). |
| TRIM62 55223 | DEAR1 | R-B-CC-PRY/SPRY | N i, ii, iii | Skeletal muscle atrophy (Schmidt et al., 2014). Regulates CARD9-mediated anti-fungal immunity (Cao et al., 2015). Breast (Lott et al., 2009) and lung cancer (Quintas-Cardama et al., 2014). Acute myeloid leukemia (Quintas-Cardama et al., 2015). |
| TRIM63 84676 | IRF, SMRZ, MURF1, MURF2, RNF28 | R-B-CC-(LIR)-COS | N i, ii, iii | Turnover of nicotinoic acetylcholine receptors and colocalizes with p62 and LC3A (Khan et al., 2014). Muscular dystrophy (Bodine et al., 2001; Blandin et al., 2013). Protein aggregate myopathy (Olive et al., 2015). |
| TRIM64 120146 | TRIM64A | R-B-CC-SPRY | N i, ii, iii | |
| TRIM65 201292 | 4732463G12R | R-B-CC-SPRY | i, ii, iii | White matter lesions of brain (Fornage et al., 2011; Lopez et al., 2015). A repressor of microRNA activity (Li, S. et al., 2014). |
| TRIM66 9866 | TIF1D; C11orf29; TIF1DELT A | B-B-CC-PHD-BROMO | N i, ii, iii | Osteosarcoma (Chen, Y. et al., 2015). HIV-1 (Konig et al., 2008). |
| TRIM67 440730 | TNL | R-B-B-CC-COS-FN3-SPRY | N i, ii, iii | |
| TRIM69 140691 | Trif, HSD34, RNF36, HSD-34 | R-B-PRY/SPRY | iv | |</p>
<table>
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<th>Description</th>
<th>Function</th>
<th>Notes</th>
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<td>N ii, iii</td>
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<td>TRIM72</td>
<td>MG53</td>
<td>R-B-CC-PRY/SPRY</td>
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<td>TRIM50B</td>
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<td>TRIM74</td>
<td>TRIM50C</td>
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<td>+ i, N i, ii</td>
</tr>
<tr>
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<td>TRIM75P</td>
<td>R-B-CC-PRY/SPRY</td>
<td>N ii, + ii</td>
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<tr>
<td>TRIM76</td>
<td>CMYA5, SPRYD2, C5orf10</td>
<td>X-B-CC-FN-PRY-SPRY</td>
<td>J i, N i, ii</td>
</tr>
</tbody>
</table>

a, Gene names are hyper-linked to NCBI.
b, R, RING finger; B, B-box; CC, Coiled-coil domain; FN3, fibronectin type III repeat; PRY, PRY domain; SPRY domain; NHL, NHL repeats; FL, Filamin type immunoglobulin; MATH, meprin and tumor-necrosis factor receptor-associated factor (TRAF) homology domain; PHD, plant homeodomain; BROMO, BROMO domain; ARF, ADP ribosylation factor-like domain; PYRIN, pyrin domain; COS, C-terminal subgroup one signature domain; LIR, LC3-interacting region; (LIR), presence of a LIR detected by biochemical means but precise mapping of the LIR sequences not yet completed; X, no known domain detected.
c, Results from five independent autophagy screens.
d, +, absence/knockdown reduces autophagy; -, absence/knockdown increases autophagy; N, no change.
e, (i) pp242-induced autophagy in mRFP-GFP-LC3B expressing HeLa cells (Mandell et al., 2014); (ii) IFN-γ-induced autophagy in THP-1 cells (Kimura et al., 2015); (iii) basal autophagy in mRFP-GFP-LC3B expressing HeLa cells (Mandell et al., 2014) (iv) basal autophagy in GFP-LC3
expressing H4 cells (human neuroglioma cell lines) (Lipinski et al., 2010); (v) starvation-induced autophagy in GFP-LC3-HEK cells (McKnight et al., 2012).

\(^{f}\) Autophagy-related binding proteins (experimental evidence).

\(^{g}\) Additional details include autophagy-related cell biological and physiological observations.

\(^{h}\) General information on known medical, genetic, and biological significance.

Note, TRIM43B, TRIM49B, TRIM49C, TRIM49D1, TRIM49D2, TRIM52, TRIM64, TRIM64B, TRIM64C, and TRIM77 had no information associated with autophagy and disease, and are omitted from the table.
### Table S2. Other autophagic receptors

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<th>Class / Name</th>
<th>Gene ID</th>
<th>Alias</th>
<th>LIR or AIM</th>
<th>Ubiquitin-binding domain; modifications</th>
<th>Receptor property</th>
<th>Autophagic function</th>
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</thead>
<tbody>
<tr>
<td>Sequestosome 1</td>
<td>8878</td>
<td>p62, A170, FTDALS3, OSIL, PDB3, ZIP3, p60, p62B</td>
<td>LIR, phosphorylated by TBK1</td>
<td>UBA, Ser-403 human (Ser-405 mouse) phosphorylated by TBK1 (Pili et al., 2012), casein kinase 2 (Matsumoto et al., 2011), and ULK1 (Ro et al., 2014; Lim et al., 2015); Ser-409 (mouse) by Ulk1 (Lim et al., 2015)</td>
<td>LC3B (Bjorkoy et al., 2005), LC3A/C, GABARAPs (Pankiv et al., 2007), ULK1 (Ro et al., 2014), ULK2 (Pridgeon et al., 2003), NBR1 (Lamark et al., 2003), NDP52 (Cemma et al., 2011), Optineurin (Wild et al., 2011), SMURF1 (Matsumoto et al., 2015), TOLLIP (Lu, K. et al., 2014). TRIMs: TRIM5 (O'Connor et al., 2010), TRIM50 (Fusco et al., 2012), TRIM55 (Lange et al., 2005; Pizon et al., 2013), TRIM13 (Tomar et al., 2012), TRIM17, TRIM49, and TRIM55 (Mandell et al., 2014), TRIM21 (Kimura et al., 2015).</td>
<td>The first identified autophagic receptor (Bjorkoy et al., 2005). Multiple roles in selective autophagy, including autophagy of protein aggregates (Bjorkoy et al., 2005), mitochondria (Matsumoto et al., 2015), peroxisomes (Deosaran et al., 2013), mid body rings (Isakson et al., 2013), zymogen granules (Grasso et al., 2011), xenophagy (Thurston et al., 2009; Wild et al., 2011).</td>
</tr>
<tr>
<td>NBR1</td>
<td>4077</td>
<td>1A1-3B, IA13B, M17S2, MIG19</td>
<td>LIR</td>
<td>UBA</td>
<td>Binds LC3A/B/C, GABARAPs (Kirkin et al., 2009) and p62 (Lamark et al., 2003).</td>
<td>Effects degradation of aggregated proteins (Kirkin et al., 2009), peroxisomes (Deosaran et al., 2013), mid body rings (Isakson et al., 2013).</td>
</tr>
<tr>
<td>NDP52</td>
<td>10241</td>
<td>CALCOCO2</td>
<td>LIR</td>
<td>UBZ</td>
<td>Preferential LC3C binding (Thurston et al., 2009; von Muhlinen et al., 2012). Binds GABARAPL1/2 (Rual et al., 2005), p62 (Cemma et al., 2011), Tax1bp1 (Morriswood et al., 2007), FIP200 (Wang, J. et al., 2011b). Absent in the mouse.</td>
<td>Effects degradation of poly-ubiquitylated cargo (Thurston et al., 2009; Thurston et al., 2012; von Muhlinen et al., 2012). Implicated in PINK1- mediated mitophagy (Lazarou et al., 2015).</td>
</tr>
<tr>
<td>TAX1BP1</td>
<td>8887</td>
<td>CALCOCO3, T6BP</td>
<td>LIR</td>
<td>2 UBZs</td>
<td>Binds LC3B/C and GABARAP (Newman et al., 2012), NDP52 (Morriswood et al., 2007), Optineurin (Journo</td>
<td>Implicated in PINK1-mediated mitophagy (Lazarou et al., 2015).</td>
</tr>
</tbody>
</table>

References (Reference list accompanying the Table is in the Supplementary Information)
Optineurin 
10133
ALS12, FIP2, GLC1E, HIP7, HYPL, NRP, TFIIIA-INTP
LIR, phosphorylated by TBK1
UBAN and ZnF
Binds LC3A/B, GABARAPs, p62 (Wild et al., 2011), Tax1bp1 (Journo et al., 2009), and TRIM76 (Blandin et al., 2013). Phosphorylation enhances ubiquitin and mAtg8s binding (Wild et al., 2011).
Effects degradation of poly-ubityllylated cargo (Wild et al., 2011). Implicated in PINK1- mediated mitophagy (Lazarou et al., 2015).

**TOLLIP**
54472
IL-1RAcPIP 2 LIRs
CUE
Effects degradation of polyQ protein aggregates (Lu, K. et al., 2014).

### b. Other unique receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>LIR</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Nix</strong> 665</td>
<td>BNIP3L, BNIP3a</td>
<td>Mitochondrial integral protein. Binds LC3A/B, GABARAP, GABARAPL1/2 (Schwarten et al., 2009; Novak et al., 2010) BNIP3 (Rual et al., 2005). Mitophagy (Sandoval et al., 2008; Novak et al., 2010).</td>
</tr>
<tr>
<td><strong>BNIP3</strong> 664</td>
<td>NIP3</td>
<td>Mitochondrial integral protein. Binds LC3B (Hanna et al., 2012; Zhu et al., 2013) and Nix (Rual et al., 2005). Mitophagy (Zhang et al., 2008).</td>
</tr>
<tr>
<td><strong>SMURF1</strong> 57154</td>
<td></td>
<td>Binds p62 (Barrios-Rodiles et al., 2005). Mitophagy and xenophagy (Sindbis and herpes simplex viruses) (Orvedahl et al., 2011).</td>
</tr>
<tr>
<td><strong>Bcl2-L-13</strong> 23786</td>
<td>BCL-RAMB O, Bcl2-L-13, MIL1</td>
<td>A homologue of yeast Atg32 (Murakawa et al., 2015). Binds LC3B Atg32 (Murakawa et al., 2015) and GABARAPL2 (Rual et al., 2005). Mitophagy (Murakawa et al., 2015).</td>
</tr>
<tr>
<td><strong>Fam134B</strong> 54463</td>
<td>JK1; JK-1</td>
<td>ER resident protein binding LC3A/C, GABARAPL1/2. Homologous to yeast Atg40 (Khaminets et al., 2015). ER-phagy (Khaminets et al., 2015).</td>
</tr>
<tr>
<td>LIR (identified in AP2A1)</td>
<td>bind LC3B (Tian et al., 2013).</td>
<td>Receptors for aggregation-prone proteins (amyloid precursor protein) in Alzheimer’s disease (Tian et al., 2013).</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>LIR</td>
<td>bind LC3B (Sandilands et al., 2012).</td>
<td>A proto-oncogene product and a receptor for active Src in cancer cells (Sandilands et al., 2012).</td>
</tr>
<tr>
<td>LIR</td>
<td>Binds GABARAPs (Behrends et al., 2010; Jiang et al., 2010).</td>
<td>Implied in autophagic degradation of glycogen (Jiang et al., 2011).</td>
</tr>
<tr>
<td>LIR</td>
<td>A mitochondrial-specific phospholipid. Binds LC3B (Chu et al., 2013). Binds IRGM (Singh et al 2010)</td>
<td>Mediates mitophagy (Chu et al., 2013) and affects mitochondrial functionality (Singh et al, 2010).</td>
</tr>
<tr>
<td>c. Receptors in yeast, Picha, and Drosophila</td>
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<tr>
<td>Atg19</td>
<td>YOL082W, CVT19</td>
<td>Binds Atg8 (Kim et al., 2002) and aminopeptidase I and α-mannosidase (Baxter et al., 2005).</td>
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<td>Atg40</td>
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<td>Glycogen synthase (Drosophila)</td>
<td>Dmel_CG6904, CG6904, CG6940, GS</td>
<td>LIR</td>
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</tbody>
</table>
Gene names are hyper-linked to NCBI.

LIR, LC3-interacting motif; AIM, Atg8-interacting motif (in yeast and other species).

UBA, a three-helix bundle UBD that has affinity for monoubiquitin and K63 ubiquitin linkages. UBAN, a parallel coiled-coiled dimer UBD that has specificity for linear ubiquitin chains; UBZ, a zinc finger ββα-fold UBD that binds to monoubiquitin and polyubiquitin.
Supplementary References for the tables


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