FEBS Letters xxx (2015) xxx–xxx

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Autophagy and proteins involved in vesicular trafficking

Celina Amaya [1], Claudio Marcelo Fader [1], María Isabel Colombo *

Laboratorio de Biología Celular y Molecular, Instituto de Histología y Embriología (IHEM)-CONICET, Facultad de Ciencias Médicas, Universidad Nacional de Cuyo, Casilla de Correo 56, Centro Universitario, Parque General San Martín, 5500 Mendoza, Argentina

ARTICLE INFO

Article history:
Received 14 August 2015
Revised 19 September 2015
Accepted 22 September 2015
Available online xxxx

Edited by Wilhelm Just

Keywords:
Autophagy
Rab GTPase
SNAP receptor
Autophagosome biogenesis
Autophagosome–lysosome fusion

ABSTRACT

Autophagy is an intracellular degradation system that, as a basic mechanism it delivers cytoplasmic components to the lysosomes in order to maintain adequate energy levels and cellular homeostasis. This complex cellular process is activated by low cellular nutrient levels and other stress situations such as low ATP levels, the accumulation of damaged proteins or organelles, or pathogen invasion. Autophagy as a multistep process involves vesicular transport events leading to tethering and fusion of autophagic vesicles with several intracellular compartments. This review summarizes our current understanding of the autophagic pathway with emphasis in the trafficking machinery (i.e. Rabs GTPases and SNAP receptors (SNAREs)) involved in specific steps of the pathway.

1. Introduction to autophagy

Three major types of autophagy have been described in mammalian cells so far: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). These autophagic processes differ not only in terms of mechanistic and morphological characteristics but also in the factors involved. Among these types, macroautophagy (hereafter autophagy) is the most comprehensively studied and best characterized process (for a review see [1]). This evolutionarily conserved "autodigestion program" has a critical role in the maintenance of the cellular metabolism according to the cellular nutritional status. Another critical role of autophagy is the removal of dysfunctional organelles in a fast and efficient way as well as to participate actively as a defense mechanism against invading pathogens [2–5] (see Fig. 1).

Upon autophagy induction, proteins and cytoplasmic components are trapped in double membrane structures known as autophagosomes which fuse with lysosomes to generate autolysosomes. The cargoes are subsequently broken down and the generated molecules (i.e. amino acids, nucleic acids, free fatty acids, cholesterol) are recycled back to the cytoplasm to be used by the cell in anabolic reactions.

The autophagosome biogenesis can be divided into three sequential steps: phagophore formation, elongation, and sealing of the isolation membrane to generate a double membrane compartment. The phagophore is believed to originate from specialized regions of the endoplasmic reticulum (i.e. endoplasmic reticulum exit sites, ERES, [6–8]); (for a recent review see [9]) as well as from endoplasmic reticulum–mitochondria contact sites [10]. Although the origin of the phagophore membrane is still a matter of debate, a bulk of evidence indicates that the growing phagophore takes up membrane inputs from more than one source. In fact, several membrane compartments including the endoplasmic reticulum (ER), mitochondria, the Golgi apparatus and the plasma membrane

Abbreviations: AMD, age-related macular degeneration of the eye; AMPK, AMP-activated protein kinase; ATG, autophagy-related protein; CMA, chaperone-mediated autophagy; COPII, coat protein complex II; DFCP1, double FYVE domain-containing protein 1; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERES, endoplasmic reticulum exit sites; FIP200, 200 kD focal adhesion kinase family-interacting protein; FYCO1, FYVE and coiled-coil domain-containing 1; GAP, GTPase activating protein; GAS, Group A *Streptococcus*; GcAVs, GAS-containing autophagosome-like vacuoles; GDP, guanosine diphosphate; GEF, guanosine nucleotide exchange factor; GTP, guanosine triphosphate; HCV, Hepatitis C virus; HD, Huntington disease; LC3, light chain 3; LRRK1, leucine-rich repeat kinase 1; mTOR, mechanistic target of rapamycin; MVB, multivesicular body; MW, molecular weight; NS4B, non-structural protein 4B; NSF, N-ethyl-maleimide-sensitive factor; PAS, phagophore assembly site; PE, phosphatidylethanolamine; PIK3C3, class III phosphatidylinositol 3 kinase; PKA, cAMP-dependent protein kinase; PtdIns3P, phosphatidylinositol 3-phosphate; RE, recycling endosome; SNAP, soluble N-ethyl-maleimide attachment proteins; SNARE, SNAP receptor; SQSTM1, sequestosome 1; STX, Syntaxin; TRAPP, transport protein particle; ULK1, unc-51 like autophagy activating kinase 1; VPS, vacuolar protein sorting; WIPI, WD-repeat-interacting phosphoinositide proteins.

* Corresponding author. Fax: +54 261 4494117.
E-mail address: mcolombo@fcm.uncu.edu.ar (M.I. Colombo).

[1] C. Amaya and C.M. Fader contributed equally to this review.

http://dx.doi.org/10.1016/j.febslet.2015.09.021
0014-5793/

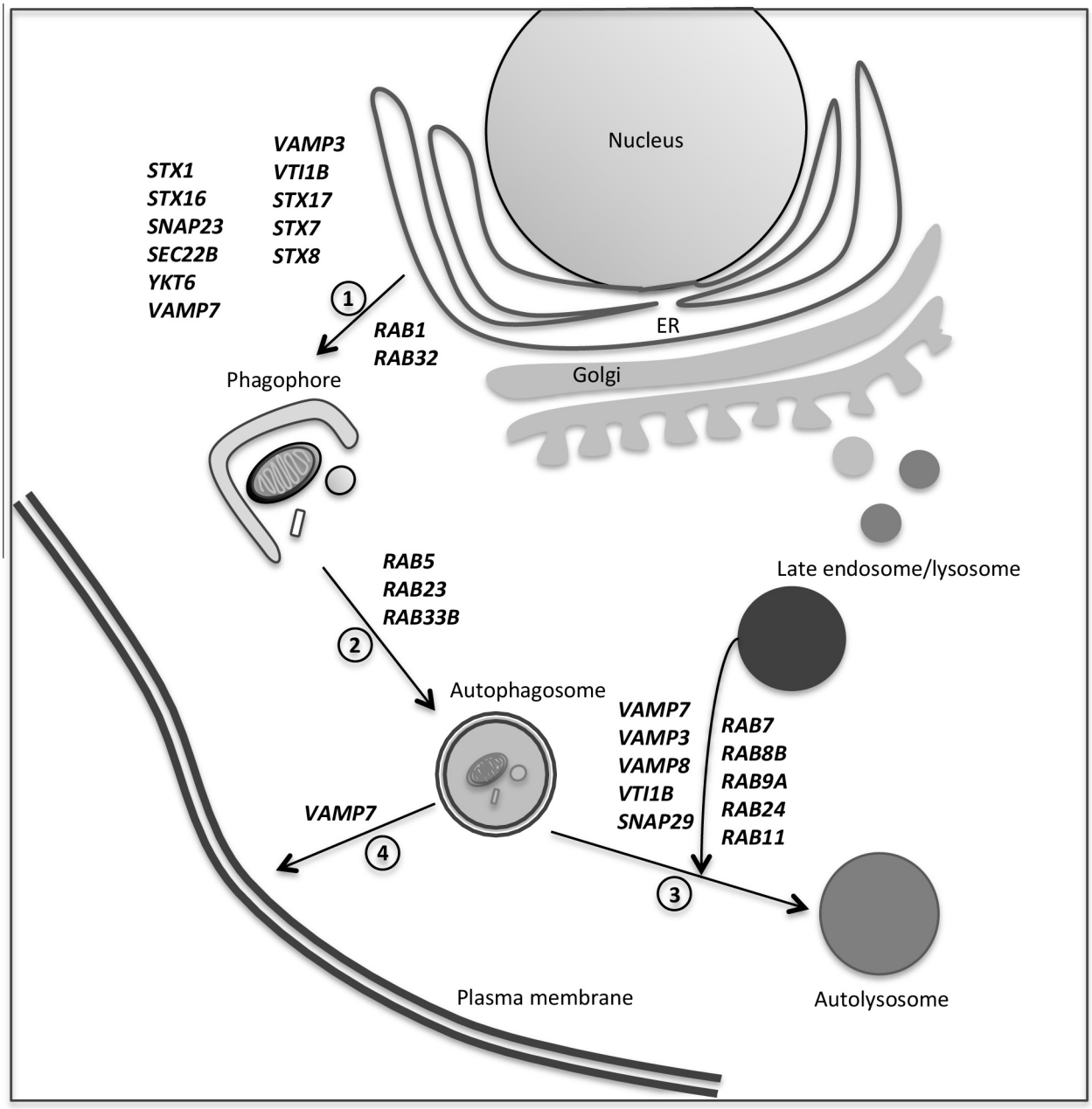

Fig. 1. Model: Regulation of autophagy by Rab GTPases and SNAREs. Participation of different proteins in the general autophagic process schematized in (1) phagophore formation from specialized regions of the endoplasmic reticulum; (2) phagophore elongation and sealing of the isolated membrane to generate a doublemembrane compartment called autophagosome; and (3) autophagosome maturation through interactions with late endosomes and lysosomes. (4) Autophagosomes may also fuse with the plasma membrane in order to release their content to the extracellular space.

seem to contribute to the formation of the phagosome (for a review see [11–14]). Subsequently, the newly formed autophagosome matures through interactions with late endosomes and lysosomes.

2. Critical core machinery involved in autophagy

As a cellular degradation process, the autophagic pathway is delicately controlled, and numerous critical factors and regulatory kinases have been identified (for a review see [1,15]). A number of factors known as ATGs (for "autophagy-related proteins") are the main components involved in autophagy [16,17]. The large majority of these proteins are conserved from yeasts to humans with many yeast orthologs having been identified in mammalian cells.

One of the initial kinase complexes involved in autophagy is the ULK1 (UNC-51-like kinase complex 1) [18], which comprises ULK1, FIP200/RB1CC1 (the 200 kD focal adhesion kinase family-interacting protein), ATG13, and ATG101. The ULK1 kinase can be modulated by signals such as amino acid starvation via mTORC1 (mechanistic target of rapamycin complex 1), which senses amino acids availability and suppresses autophagy, or by glucose deprivation/ATP depletion via the AMP-activated protein kinase (AMPK). Low levels of ATP activate AMPK which, in turn, inhibits mTORC1 through phosphorylation and activation of the TSC1/2 complex and the GTPase Rheb [19], stimulating autophagy (for a more comprehensive analysis of these signalling pathways, please see [20–22]).

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

mTORC1 is an evolutionarily conserved serine–threonine kinase that functions as a central inhibitor of the autophagic pathway by suppressing the kinase activity of the ULK1 complex [21,23]. When mTOR is inhibited by starvation or by rapamycin treatment, ULK1 is activated and phosphorylates ATG13 and FIP200, allowing the subsequent recruitment of other critical complexes involved in autophagy (see below). Of note, the association of AMPK1 is prevented by this phosphorylation in ULK1, being this step an intersection between the glucose and amino acid signals that regulate autophagy [24–26].

A second critical complex that is recruited to the phagophore is the VPS34 (vacuolar protein sorting 34) lipid kinase complex (a class III phosphatidylinositol 3 kinase, PIK3C3) which also comprises Beclin1 (BECN1), VPS15 and ATG14 [27]. This complex generates PtdIns3P (phosphatidylinositol 3-phosphate) and this compound is subsequently bound by effectors like WIPI (WD-repeat-interacting phosphoinositide proteins) and DFCP1 (double FYVE domain-containing protein 1) that are necessary for the biogenesis of the autophagosome (reviewed in [28,29]) Subsequently, two ubiquitin-like conjugation systems participate in the process: the first one, leads to the generation of the ATG5–ATG12 conjugate that then, associates to ATG16L. This latter protein complex acts as an E3-like enzyme in the second conjugation system, which contributes to the binding of phosphatidylethanolamine (PE) to the ubiquitin-like Atg8/LC3 (microtubule-associated protein 1-light chain 3), ([30,31] and reviewed in [32]). These two complexes which are interrelated mediate membrane elongation and growth of the developing autophagosome [33].

Another important participant in phagophore expansion and autophagosome formation is ATG9A (a multi-spanning transmembrane protein), the only transmembrane protein among the ATG proteins. Upon autophagy induction, ATG9A may function as a membrane supplier via the formation of carriers from the trans-Golgi network to late endosomes, a process that is dependent on ULK1 and ATG13 [34], (reviewed in [35,36]).

In summary, the concerted action of the above mentioned ATGs and other interacting proteins that accomplish essential functions during autophagy allow the autophagosome generation and its subsequent fusion with compartments of the endocytic pathway, thus enabling the degradation and clearance of the trapped autophagic cargoes.

3. Rab GTPases: molecular components involved in tethering

Rab proteins are small GTPases that belong to the Ras-like GTPase superfamily and regulate the vesicle trafficking route. The intracellular vesicle transport involves a series of steps: (1) budding of a vesicle from the donor membrane, (2) targeting of the vesicle to the acceptor membrane, and (3) docking and fusion with the target membrane [37]. Rab proteins are mainly involved in the regulation of these steps.

All Rab GTPases have consensus amino acid sequences to bind GDP and GTP, being inactive when bound to GDP (cytoplasmic location) and active when bound to GTP (membrane location). Although these small GTPases possess some intrinsic activity to hydrolyze bound GTP to GDP [37] they require the activity of a GAP (GTPase activating protein) to perform their function. Rabs use this guanine nucleotide-dependent switch mechanism to regulate each of the four major steps in membrane traffic: vesicle budding, delivery, tethering, and fusion. These different processes are carried out by several effector molecules that bind to specific Rabs in their GTP-bound state [38]. Rab cascades seem to confer directionality to membrane traffic and couple each stage of transport with the next one along the pathway.

Rabs are also related to autophagy by regulating the transport and fusion of autophagosomes. However, it remains unclear how each Rab activation/inactivation cycle is finely regulated. Several Rabs have been shown to be involved in various stages of autophagy. There is evidence indicating that RAB1, RAB5, RAB7, RAB8A and B, RAB9A, RAB11, RAB23, RAB24, RAB25, RAB32, and RAB33B participate in certain steps of autophagosome development and maturation [39], but the specific function of some of them remains poorly characterized.

Herein, we highlight the recent research advances on autophagy regulation by Rab GTPases, emphasizing their roles in the regulation of autophagosome biogenesis and maturation.

4. Rabs involved in autophagosome biogenesis

4.1. RAB1

RAB1 is a small GTP-binding protein that specifically regulates the transport of newly synthesized proteins from the ER to the Golgi apparatus. RAB1 recruits p115, its effector, to the coat protein complex II (COPII) vesicles during budding from the ER, and then interacts with a set of COPII vesicle-associated SNAREs complex that promotes targeting to the Golgi apparatus [40].

Regarding its role in autophagy, several studies have shown that the isoform RAB1B is required for autophagosome biogenesis. In fact, in mammalian cells, studies conducted in our laboratory have demonstrated that the activity of RAB1B is required for autophagosome formation and that specific ER exit sites (i.e. ERES) have a critical role in the process. However, further transport from the *cis*/medial Golgi was not necessary as suggested by the lack of effect of Brefeldin A [7]. Subsequently, Graef et al. have analyzed the formation of autophagosomes in yeasts, showing that ERES are autophagic components that play a direct and essential role immediately downstream of the Atg1 kinase complex recruitment during the assembly of the autophagy machinery required for phagophore nucleation and expansion [8].

The role of RAB1 during autophagy was also demonstrated through the analysis of the transport protein particle (TRAPP), a guanine nucleotide-exchange factor (GEF) for RAB1 that exists in three complex forms. Whereas TRAPPI and TRAPPII tether coated vesicles through ER to Golgi and intra-Golgi traffic, respectively, TRAPPIII has been shown to be required for autophagy [41]. Moreover, in yeasts, the interaction of TRAPPIII with the RAB1 analogous Ypt1 being targeted at the phagophore assembly site (PAS) during autophagy was evaluated [42].

As mentioned above, autophagy also plays a key role during microorganisms invasion. One potential membrane source for antibacterial autophagy is the ER, and experiments with *Salmonella* suggest that this process occurs at specialized ER domains known as 'omegasomes' [43]. The association between ER-connected omegasome-like structures and autophagosomes was studied in detail in *Aspergillus nidulans*. In this model, it was demonstrated that autophagic structures are closely associated with similarly shaped structures formed by ER strands, and that the RAB1 analogous is required for autophagy localizing to expanding phagophores and autophagosomes. In agreement with our results in mammalian cells, *A. nidulans* autophagy does not require Golgi or post-Golgi traffic [44].

Interestingly, in a recent work, it was found that cytosolic *Salmonella* associated with autophagy components sequestosome 1 (SQSTM1) and LC3 replicates quickly, whereas the replication decreased when autophagy components and RAB1 were depleted, suggesting that autophagy facilitates *Salmonella* replication in the cytosol of HeLa cells [45].

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

4.2. RAB5

The small GTP-binding protein RAB5 is localized in early endosomes and on the cytoplasmic face of the plasma membrane. This Rab is involved in early endosome fusion [46] as a rate-limiting component of the machinery regulating membrane traffic in the early endocytic pathway [47]. The activity of RAB5 is important for processes such as the endocytosis of the low-density lipoprotein [48] and sorting of both the EGF receptor and the transferrin receptor through early endosomes [49].

The way RAB5 participates in autophagy regulated by growth factor availability has recently been determined. The p110β catalytic subunit of the class IA phosphatidylinositol 3 kinase acts as a molecular sensor for growth factor levels and induces autophagy by activating a RAB5-mediated signaling cascade. Dou et al. have shown that, upon growth factor limitation, p110β dissociates from the growth factor receptor complexes and interacts with RAB5. The p110β-RAB5 association maintains RAB5 in its GTP-bound state and enhances the RAB5-VPS34 interaction thus promoting autophagy [50].

Autophagy is also an important clearance route for several aggregate-prone protein illnesses including Huntington's disease (HD) where RAB5 has a role in this process, which is independent of its role on endocytosis. It has been shown that, in a fly/*Drosophila* model of HD as well as in mammalian cells, RAB5 acts at an early stage of autophagosome biogenesis in a macromolecular complex that contains BECN1 and VPS34 that regulate the ATG5–ATG12 conjugation [51].

It is also known that certain infectious processes are facilitated by autophagy. This is the case of Hepatitis C virus (HCV) that induces autophagy to accomplish replication. Su et al. have demonstrated that the HCV non-structural protein 4B (NS4B) induces autophagy independently of the mTOR pathway, and that RAB5 is crucial for the HCV-induced autophagosome formation [52].

4.3. RAB23

RAB23 is a GTPase related to the hedgehog signaling, a pathway responsible for the development of a wide array of vertebrate organs [53]. The localization of RAB23 has been analyzed by light and immunoelectron microscopy in a range of mammalian cell types and it has been found predominantly localized to the plasma membrane but also associated with intracellular vesicular structures co-localizing with RAB5 [54]. RAB23 is believed to regulate intracellular trafficking of one or more of hedgehog-signaling components during mouse development [55]. Besides, RAB23 has also been found in other systems performing different roles.

The function of RAB23 has also been studied in autophagic processes playing a role in bacterial infections. RAB23 is not localized to starvation-induced autophagosomes, but acts as an autophagy regulator during Group A *Streptococcus* (GAS) infection [56]. RAB23 is recruited to GAS-containing autophagosomes and it has been shown that knockdown of this protein impaired degradation of intracellular GAS, suggesting therefore, that RAB23 is required for GAS-containing autophagosome organization and clearance of this pathogen.

4.4. RAB32

RAB32 is a small GTPase that is known to be involved in the synchronization of mitochondrial fission in mammalian cells. Alto et al. have demonstrated that RAB32 interacts directly with the cAMP-dependent protein kinase (PKA), and regulates both the mitochondrial anchoring of PKA and dynamics [57]. Other studies carried out in melanocytes have identified a key role for RAB32 in the biogenesis of melanosomes and other lysosome-related organelles. Wasmeier et al. have observed that RAB32 localizes to perinuclear vesicles carrying the melanogenic proteins tyrosinase and tyrosinase-related protein 1. Their results were consistent with a role of RAB32 in the regulation of critical steps during the trafficking of molecules from the *trans*-Golgi network to melanosomes [58].

It has been shown that RAB32 is also required for the formation of autophagic vacuoles. In HeLa and COS cells, RAB32 is predominantly localized to the ER, and the overexpression of this protein leads to the formation of autophagic vesicles containing LC3, the ER-resident protein calnexin and the endosomal/lysosomal membrane protein LAMP2, even under optimum nutrient conditions [59]. Hirota et al. have demonstrated that RAB32 facilitates the formation of autophagosomes whose membranes were derived from the ER thus regulating the clearance of aggregated proteins by autophagy. Additionally, in *Drosophila*, RAB32 has been found to be related to lipid storage in the larval adipose tissue [60]. During this process, RAB32 affects the size of lipid droplets as well as lipid levels; however, further studies are necessary to elucidate the relationship between autophagy and lipid metabolism during development.

4.5. RAB33B

RAB33B is present in the *cis*-Golgi where it participates in Golgi-to-ER retrograde membrane trafficking [61]. Mutations in RAB33B have been investigated in the pathogenesis of the Dyggve–Melchior–Clausen's syndrome [62] and the Smith–McCort's dysplasia [63], thus establishing the important role of the retrograde Golgi traffic in both human syndromes.

It has been observed that RAB33 modulates autophagosome formation through the interaction with ATG16L, an essential factor in autophagosome membrane development [64]. However, subsequent studies have demonstrated that overexpression of OATL1 (a Rab-GAP for RAB33B) or RAB33B delays the maturation of autophagosomes, suggesting that OATL1 is recruited to autophagosomes to inactivate RAB33B and thus modulate the fusion between autophagosomes and lysosomes [65].

Apart from the findings indicating that the autophagy machinery is required for HCV replication [66], Blackham et al. have determined that replication and secretion of HCV is reduced upon downregulation of RAB33B, thus indicating that this Rab might be a pivotal factor in the virus replication cycle [67]. Nevertheless, whether RAB33B has a direct role in HCV-induced autophagy remains unclear.

5. Rabs required for autophagosome maturation

5.1. RAB7

RAB7 is a low MW GTPase that has been found mainly on late endosomes. By interacting with its partners (including upstream regulators and downstream effectors), RAB7 regulates mechanisms in endosomal sorting, biogenesis of lysosome and phagocytosis [68]. Particularly, RAB7 governs early-to-late endosomal maturation, microtubule minus-end as well as plus-end directed endosomal migration, and endosome–lysosome transport through different protein–protein interaction cascades [69,70].

Our studies were the first ones demonstrating the requirement for RAB7 in the autophagic pathway [71]. The role of RAB7 in autophagy (induced by amino acid starvation or rapamycin) was studied in CHO cells where the overexpression of RAB7 associated with autophagic vacuoles labeled with the autophagosome marker monodansylcadaverine was demonstrated. However, upon autophagy induction the RAB7T22N dominant negative mutant was

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

targeted to autophagic vacuoles, causing the accumulation of larger LC3-labeled autophagosomes and impaired autolysosome formation, indicating that a functional RAB7 is important for the normal progression of autophagy [71]. In a parallel study, it has been demonstrated by electron microscopy that the autophagosome marker LC3 co-localised with RAB7 and late endosomal/lysosomal markers. The experiments showed that RAB7 was not necessary for the initial maturation of autophagosomes, but it participated in the final maturation of late autophagic vacuoles. Moreover, recruitment of RAB7 to autophagic vacuoles was found to be retarded in cells deficient in the lysosomal membrane proteins LAMP1 and LAMP2, which accumulated in late autophagic vacuoles during starvation [72].

Tabata et al. provided interesting information about how the interaction of RAB7 with Rubicon (a RAB7 effector that controls endosome maturation [73]) regulates membrane traffic in mammal cells. They showed that Rubicon negatively regulates the endocytic pathway through their interactions with RAB7 [74]. Thus, the authors determined that the simultaneous interaction between Rubicon, the BECN1–VPS34 complex and RAB7, is an important step in the regulation of the endocytic pathway and autophagosome maturation.

It has been demonstrated that RAB7 directs the maturation of autophagosomes, by guiding the trafficking of cargos along microtubules to participate in the fusion step with lysosomes [70]. Pankiv et al. have studied the latter process and have identified an adaptor protein complex formed by LC3, RAB7 and the novel FYVE and coiled-coil domain-containing 1 protein (FYCO1) that promotes microtubule plus end-directed transport of autophagic vesicles [75].

The spatiotemporal regulation of RAB7 activity during autophagy has recently been studied by Toyofuku et al. These authors have shown that the leucine-rich repeat kinase 1 (LRRK1) regulates the autophagic flux by controlling RAB7 activity in autolysosome formation. Upon autophagy induction, LRRK1 was found to be recruited to lysosomes by VAMP7, where it was activated TBC1D2 (a RAB7 GAP), switching off the RAB7 signaling in order to promote the autophagic flux [76].

Unfortunately, autophagic vacuole maturation appears to be blocked in certain human disorders comprising neuronal ceroidlipofuscinosis and Danon's disease, suggesting that autophagy has important housekeeping or protective functions [77]. Many aggregation-based diseases, e.g. age-related macular degeneration of the eye (AMD) and Alzheimer's disease are due to a malfunctioning of the autophagic process where the regulation of RAB7 activity might be a therapeutic target.

5.2. RAB11

It is known that RAB11 is related to perinuclear recycling endosomes (RE) regulating the recycling of endocytosed proteins [78]. It has been observed that RAB11 depletion causes tubulation of RE, and gives rise to the accumulation of recycling carriers containing endocytosed transferrin and transferrin receptors beneath the plasma membrane. In addition, RAB11 is transported along microtubules to the cell periphery through association with recycling carriers, and it directly regulates vesicle exocytosis at the plasma membrane [79]. A particular exocytosis process regulated by RAB11 has been studied in detail in the K562 cell line. The experiments were aimed at analyzing the role of RAB11 in the regulation of transferrin receptor release via exosome secretion. In this work, it was found that the secretion of exosomes was inhibited in cells transfected with a dominant-negative mutant RAB11S25N, demonstrating that RAB11 modulates the exosome pathway [80].

Subsequently, the role of RAB11 in autophagy was also analyzed in K562 cells. We demonstrated that autophagy inducers such as starvation or rapamycin caused an enlargement of vacuoles decorated with RAB11 co-localizing with LC3. This convergence was abrogated by a RAB11 dominant negative mutant, indicating that a functional RAB11 is involved in the interaction between multivesicular bodies (MVBs) and the autophagic pathway [81]. More recently, Longatti et al. have proposed a model in which RAB11 is required for autophagosome formation by mediating vesicular transport from the RE to the expanding phagophore. They showed that under fed conditions, RAB11-positive REs have a role in recycling toward the plasma membrane, but, upon amino acid starvation, this Rab mediates vesicle formation from the RE directed to forming autophagosomes. This process is negatively regulated by TBC1D14, which functions as an effector for RAB11. TBC1D14 dissociates from RAB11-positive REs during starvation and accumulates in the Golgi complex. The overexpression of TBC1D14 causes tubulation of REs, accumulation of both the ULK1 complex and RAB11 in REs, and inhibition of vesicular transport from the RE [82].

Unlike the apparent role of RAB11 in autophagosome biogenesis, in *Drosophila melanogaster*, this protein seems to participate in autophagosome maturation. In this model, it was shown that, in response to autophagy induction, RAB11 translocates from REs to autophagosomes, interacting with the microtubule binding protein Hook, a negative regulator of endosome maturation. Hook anchors endosomes to microtubules, thus RAB11 would facilitate the fusion of endosomes and autophagosomes by removing Hook from mature late endosomes [83].

5.3. RAB8B

The Wnt/ß-catenin signaling plays an important role in embryonic development and adult tissue homeostasis. Experiments performed in *Xenopus laevis* and *Danio rerio*, have shown that RAB8B is an essential evolutionary conserved component of the Wnt/ß-catenin signaling pathway [84]. On the other hand, RAB8B seems to be involved in the regulated secretory pathway in AtT20 cells [85], and it is required for the apical transport and ciliogenesis in mice [86].

RAB8B has also a role in autophagy, contributing to the defense against intracellular pathogens. It has been demonstrated that RAB8B and its interacting partner TBK-1 contribute to autophagic elimination of *Mycobacterium tuberculosis* var. bovis BCG in macrophages. The study showed the co-localization of TBK-1 with RAB8B in autophagic organelles and suggested that TBK-1 would be necessary for autophagosome maturation and IL-1β-induced autophagic elimination of *M. tuberculosis* [87].

5.4. RAB24

RAB24 was originally found by Olkkonen et al. in the ER/*cis*-Golgi region and in late endosomal structures [88]. Subsequent studies have revealed that RAB24 possesses several unusual characteristics that distinguish it from other Rab proteins: (1) RAB24 exists predominantly in the GTP state when expressed in cultured cells; (2) post-translational geranylgeranylation of RAB24 is inefficient when compared to other Rabs; (3) most of the RAB24 in the cytoplasm is not associated with Rab GDP dissociation inhibitors. These findings suggest that RAB24 may function in vesicular transport through a mechanism that does not depend on GTP hydrolysis or GDP dissociation inhibitor-mediated recycling [89]. Additionally, RAB24 was tyrosine-phosphorylated when myc-RAB24 was overexpressed in cultured cells [90]. We have also analyzed the distribution of RAB24 throughout cell division, observing that RAB24 was located at the mitotic spindle in metaphase, at the midbody during telophase and in the furrow during cytokinesis.

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

Interestingly, we found that RAB24 directly interacts with microtubules and that an adequate level of RAB24 is necessary for normal cell division [91].

The participation of RAB24 in autophagy has been studied in our laboratory [92]. RAB24 showed a perinuclear reticular localization partially overlapping with ER markers, *cis*-Golgi, and the ER-Golgi intermediate compartment. When cells were starved to induce autophagy, the distribution of RAB24 localized to large dots, cup-shaped structures and ring-shaped vesicles. Some of these vesicles were labeled with monodansylcadaverine and co-localized with LC3, suggesting that RAB24 is involved in the autophagic pathway. The relationship between RAB24 with the autophagic pathway was also established in other studies. A partial co-localization of RAB24 and LC3 has been observed, together with an increase in RAB24 mRNA in nerve-injured hypoglossal motor neurons and in PC12 cells after treatment with a proteasome inhibitor. These data suggested that nerve injury promotes autophagy-like events where RAB24 may be involved [93]. In addition, in cultured rat cardiac myocytes subjected to glucose deprivation, polyubiquitinated proteins formed large perinuclear inclusions (aggresomes), which co-localized with γ-tubulin (a microtubule-organizing center marker) and Hsp70. Aggresomes also co-localized with LC3 and RAB24, which allowed concluding that glucose deprivation induces oxidative stress associated with aggresome formation and activation of autophagy in cultured cardiac myocytes [94].

RAB24 seems to be also involved in autophagic processes associated to bacterial infections. Experiments performed in CHO cells infected with *Coxiella burnetii*, the agent of Q fever in man, have shown that the bacterium multiplies in large, acidified, hydrolase-rich and fusogenic vacuoles with phagolysosomal-like characteristics. In this model, autophagy induced by amino acid deprivation increased the number of infected cells and the size of the vacuoles labeled with LC3 and RAB24 [95]. Interestingly, the overexpression of mutated forms of those proteins decreased the number and size of the vacuoles, suggesting that the transit along the autophagic pathway favors *Coxiella* infection by providing a niche that is propitious for bacterial survival and multiplication.

5.5. RAB25

The small GTPase RAB25, which is implicated in apical vesicle trafficking, has been linked to tumor aggressiveness and metastasis. It is overexpressed in approximately half of ovarian and breast cancers, and is associated with markedly decreased disease-free or survival in ovarian and breast cancers, respectively [96]. This Rab contributes to tumor progression by directing the localization of integrin-recycling vesicles and thereby enhancing the ability of tumor cells to invade the extracellular matrix [97]. In contrast, RAB25 has been identified as a tumor suppressor for colon cancer in humans due to its control on intestinal cell polarity [98].

A critical role for RAB25 in cellular energetics has recently been demonstrated. Cancer cells are metabolically stressed during tumor progression due to limited tumor vascularity and nutrients, growth factors and oxygen deficiency. It has been determined that RAB25, which is genomically amplified in multiple tumor lineages, is a key regulator of cellular bioenergetics and autophagy [99]. RAB25 increases cancer cell survival under nutrient stress via increased AKT activation and subsequent glucose uptake, glycogen storage and maintenance of cellular bioenergetics. Thus, RAB25 enlarges the glycogen stores providing an energy source and contributing to increase the tumor aggressiveness [100]. The function of RAB25 in autophagy has been studied in HEY and ES-2 human ovarian cancer cells, showing that autophagy was promoted by knockdown of RAB25 through stimulation of the ERK1/2 signaling pathway and increased BECN1 expression and conversion of LC3-I to LC3-II [101]. By showing that the knockdown of RAB25 promoted autophagy, inhibited cell proliferation and induced apoptosis, the authors revealed another tumorigenic role of RAB25 in ovarian cancer cells.

5.6. RAB9A

RAB9A and its effectors regulate transport of mannose 6-phosphate receptors from late endosomes to the *trans*-Golgi network. RAB9A and RAB32 act in adjacent pathways at the boundary between late endosomes and the biogenesis of lysosome-related organelles [102].

In connection with autophagy, RAB9A has been identified as an autophagy regulator during GAS infection. This Rab is recruited to GAS-containing autophagosome-like vacuoles (GcAVs) after autophagosomal maturation and its activity was required for GcAV enlargement and eventual lysosomal fusion [56]. Even though RAB9A is not localized to starvation-induced autophagosomes, this protein is necessary for autophagic degradation of intracellular GAS. Intriguingly, in neonatal rat ventricular cardiac myocytes, RAB9 has a role in non-canonical autophagy (i.e. BECN1 or VPS34-independent pathways). Raclopride, a dopamine receptor antagonist, significantly upregulated autophagy in cardiac myocytes via an mTOR independent pathway [103]. The siRNA-mediated knockdown of RAB9 resulted in decreased expression of autophagy markers in raclopride-treated cells, suggesting that the dopamine receptor plays a role in autophagy and that raclopride mediates a non-canonical autophagy pathway via RAB9 in cardiac myocytes.

The precise molecular mechanism of Rabs functions, its temporal ordering and spatial regulation during the autophagy pathway are not fully understood. The intensive study of autophagy has revealed many details about the role of RAB1, RAB5, RAB23, RAB32 and RAB33B in autophagosome formation, even in the infection progression of some virus and bacteria, and the pathogenesis of aggregate-prone protein illnesses as the HD. Subsequently, the autophagy progress has been greatly interpreted thank to the analysis of RAB7, RAB11, RAB8B, RAB24, RAB25 and RAB9 in the last steps of the autophagosome maturation process in appropriated models of Alzheimer's disease, *M. tuberculosis*, *Coxiella* and cancer. As several Rabs are involved in various diseases, the identification of Rabs effectors, regulators, and other associated proteins, as well as its molecular mechanisms may improve the development of more specific drugs and therapeutic approaches.

6. Molecular machinery involved in vesicle fusion: SNARES

As mentioned above, protein trafficking, in both the endocytic and secretory pathways, requires a sequence of events such as cargo selection and vesicle budding from the donor membrane, the translocation of this intermediary by transport along actin filaments or microtubules and the docking and fusion of vesicles with their proper target organelle [104]. The latter steps require the participation of a special group of proteins, including the GTPase Rabs described above and proteins known as soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptors (SNAREs). In yeast and mammalian cells, it has been found, that the SNARE superfamily comprises more than 60 members. In general, SNAREs are classified in two different groups: (I) v-SNARE (vesicular-associated membrane SNARE) which is localized in the donor membrane and (II) t-SNARE (target-associated membrane SNARE) which is localized in the acceptor membrane. Structurally, SNARE proteins are also classified as Q-SNAREs (in which a Gln/Q residue is the central amino acid of

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

the SNARE motif) or R-SNAREs (in which an Arg/R residue is the central amino acid). Q-SNAREs include t-SNARE proteins whereas R-SNAREs include v-SNAREs. Moreover, Q-SNAREs are subclassified into Qa-, Qb-, and Qc-SNAREs, depending on the amino acid sequence of the SNARE domain. In general, the SNARE fusion complex consists of four-helix bundles comprising three Q-SNAREs and one R-SNARE.

The main model proposed for cargo targeting to the proper compartment is focused in the role of the SNARE complex [105]. The current model, at least during neuronal exocytic events, claims that the pairing of Q-SNAREs (Syntaxin (STX) and SNAP-25) and R-SNARE (VAMP/synaptobrevin) between two opposing membranes contributes to the formation of a highly stable four-helix bundle [106]. Several biochemical, structural and genetic studies have shown that folding of this bundle would drive membranes to the fusion event [107]. Biophysical in vitro assays have shown that R- and Q-SNAREs provide the necessary energy for membrane fusion when the opposite membranes are separated by a distance inferior to 10 nm [108].

Initially, the SNARE proteins involved in the formation of the complex are localized in different membranes, acquiring a *trans*-configuration after membrane tethering. Afterward, all the SNARE proteins are localized to the same membrane where the complete SNARE complex temporally overlaps with membrane fusion, resulting in the formation of a *cis*-complex. Finally, the ternary *cis*-complex is disassembled by the chaperone ATPase NSF (N-ethyl-maleimide-sensitive factor) in conjunction with SNAPs (soluble N-ethyl-maleimide attachment proteins) [106,109].

The protein trafficking between eukaryotic organelles and intracellular compartments or the plasma membrane involves several R-SNAREs. To date, several isoforms of the VAMP family have been identified, consisting in VAMP1, 4 and 5 and the "brevin" subfamily such as VAMP2 (synaptobrevin), VAMP3 (cellubrevin) and VAMP8 (endobrevin). In addition, another set of R-SNAREs belonging to the "longin" subfamily such as VAMP7/TI-VAMP (tetanus toxin insensitive), SEC22, YKT6 and the yeast protein Nyv1 also participate in specific steps. These R-SNAREs are all characterized by an N-terminal extension termed "longin domain" [110,111]. Interestingly, each member has distinct or redundant functions and their expression levels differ among different species and tissues.

7. SNARES required in the initial steps of the pathway

For several years, it was assumed that SNAREs proteins did not have a role in the biogenesis and autophagosome maturation. Nevertheless, recent data have suggested that this protein family has an important participation in autophagosome formation as well as in autophagosome maturation, mediating autophagosome–endosome and autophagosome–lysosome fusion.

As mentioned above, autophagosomes are formed by the elongation and fusion of a flat membrane sac, called phagophore which engulfs cytoplasmic components in a double-membrane vacuole. It has been observed that several compartments appear to contribute molecules (proteins and lipids) to form the autophagosome, including the ER, Golgi apparatus, mitochondria and plasma membrane [11,112]. Several studies have been focused to analyze the molecular mechanisms that control this early stage of autophagy, being ATG proteins widely studied in this process, but it seems evident that the interaction with all these membranous compartments requires the participation of SNARE proteins.

Several yeast SNAREs, that are necessary for the endocytic and exocytic pathways, have been found to be implicated in autophagic events. Sec9p and Sso2p (SNAREs that are necessary for exocytosis) have an essential role in autophagosome biogenesis, regulating the formation of ATG9-positive structures [113]. It has also been demonstrated that Sec22p (that mediates fusion of ER-derived transport vesicles with an early Golgi compartment), Tlg2, and Ykt6p (other SNAREs involved in exocytosis) are implicated in autophagosome biogenesis, being Sso2p, Tlg2, Sec9p, Sec22p, and the Ykt6p complex, orthologous to the mammalian STX1, STX16, SNAP23, SEC22B, YKT6 [114]. Interestingly, these endocytic and exocytic SNAREs play an essential role in the reorganization of the ATG9 tubulovesicular clusters, which are required for autophagosome formation. These data suggest that autophagosome membrane expansion/closure seems to be a SNARE-dependent process.

Recent works carried out in mammalian cells have demonstrated that the interaction between VAMP7, VTI1B, STX7 and 8 regulate the homotypic fusion of pre-autophagosomal structures, favoring phagophore and autophagosome formation [114,115]. Moreover, we have also demonstrated that silencing of VAMP7 or overexpression of the N-terminal extension of VAMP7, which hampers SNARE pairing, causes a marked decrease in the total number of LC3-labeled structures and the LC3 II processing [116]. On the other hand, it has been shown that knocking down of the VAMP7 plasma membrane adaptor, Hrb, leads to the generation of the same phenotype as that caused by the silencing of VAMP7 [117], suggesting that autophagosome formation may originate at the plasma membrane. These data highlight the important role of VAMP7 and its partners in autophagosome formation. On the other hand, VAMP3 is a SNARE that has been attributed a role in constitutive exocytosis and vesicle recycling, contributing also to integrin recycling and cell attachment, spread and migration [118–122]. Recent studies conducted in Dr. Rubinsztein's laboratory have demonstrated that the maturation of ATG16L1-positive structures also requires the activity of VAMP3, which mediates the fusion with mATG9-positive vesicles. As a consequence, it has been observed that the depletion of VAMP3 impairs autophagosome formation [123]. Likewise, recent evidences have shown that STX17, an ER-resident SNARE protein, is able to bind ATG14 and retains it in the ER–mitochondria contact site. This result has shown that the ER–mitochondria contact site has an essential role in autophagosome biogenesis [10]. Interestingly, STX17 has also been identified as an autophagosomal SNARE required for fusion with the endosome/lysosome.

It is noteworthy that some SNAREs involved in autophagosome biogenesis are also able to mediate critical steps in autophagosome maturation (i.e. autophagosome–lysosome fusion).

8. SNARES involved in later stages of the autophagic pathway

Once the autophagosome is formed, several fusion steps are necessary to generate the autolysosome, a degradative organelle. These fusion events include the formation of the amphisome by fusion of the autophagosome with endocytic structures (i.e. early or late endosomes) and afterwards, the subsequent fusion with lysosomes. Alternatively, autophagosomes may fuse directly with lysosomes. Interestingly, we have demonstrated for the first time that the autophagosome-multivesicular bodies (late endosomes) fusion is regulated by VAMP3 in an erythroleukemia cell line [124], whereas VAMP7 (a SNARE that regulates exosome/lysosome and matrix metalloprotease secretion [81,125]) is involved in the fusion of autophagosomes or amphisomes with the lysosomes to generate an autolysosome [81]. Both VAMP8 and VTI1B are two R-SNAREs found in the endosomal system, particularly in late endosomes [126]. The important role of VAMP8 and VTI1B has also been observed in the xenophagic process, where both SNARE proteins are required for GAS-containing autophagosome-like vacuoles (xenophagosome)-lysosome fusion [127]. Furthermore, knockdown assays in HeLa cells have shown that the SNARE

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

proteins VTI1B and VAMP8 also mediate canonical fusion of autophagosomes with lysosomes [127].

Moreover, the SNARE protein STX17 has also been demonstrated to be involved in autophagosome–lysosome fusion, generating a SNARE complex with SNAP29 and VAMP8. Likewise, the depletion of STX17 causes accumulation of autophagosomes without any feature of degradation [128]. It is worth noting that the isolation membranes do not contain STX17, which is essential to autophagic degradation of the cytoplasm. It has been proposed that the late recruitment of STX17 to the autophagosome impairs premature fusion with the lysosome [128]. On the other hand, genetic studies in *Drosophila* have demonstrated that STX17 is recruited to the autophagosomal membrane and forms a complex with SNAP29 and VAMP7 during starvation-induced autophagy, favoring autophagosome–lysosome fusion [129]. It is interesting to note that VAMP8 is not present in flies, suggesting that STX17–SNAP29 complex binds different SNAREs depending of the spice. Whereas STX17–SNAP29 complex binds VAMP7 in mammalian cells, binds VAMP8 in yeasts [130]. A recent study has demonstrated that the fusogenic activity of this SNARE complex is spatially and temporally regulated by ATG14/Barkor/Atg14L. Moreover, it has been shown that ATG14 directly binds to the STX17–SNAP29 complex on the autophagosome surface. This complex, together VAMP8, promotes the autophagosome–lysosome fusion [131]. Another study, based on RNA-interference screening, has presented evidences that the STX5 SNARE is a positive modulator of autophagy since downregulation of this SNARE reduced the clearance of autophagy substrates. It is believed that STX5 regulates ER to Golgi transport allowing the maturation and transport of lysosomal proteases (i.e. cathepsins) [132].

A bulk of evidence has demonstrated that autophagy is not only a degradative process, but also it contributes to exocytosis events. We have demonstrated that VAMP7 is necessary to deliver autophagosomes/amphisomes to focal adhesions at the cell periphery upon autophagy induction by starvation. Interestingly, these VAMP7-labeled vesicles are loaded with ATP and the starvation stimulus caused the release of ATP to the extracellular space [116].

In *Drosophila,* it has been shown that the SNAP29 mutant favors the secretion of autophagosomes in the apical lumen thus increasing the amount of HOP-STAT92E (hopscotch signal transducer and activator of transcription protein at 92E) ligand and receptor at the plasma membrane [133]. These results are in line with several studies that have related autophagy to modulate the secretion of the contents of secretory granules or lysosomal structures in specialized cells or tissues [116,134–137].

To date, several works have demonstrated that the fusion of autophagic structures with the plasma membrane, such as lytic granules, melanosomes or lysosome-related organelles, is mediated by SNAREs. This phenomenon has also been demonstrated in patients that bear a mutated form of SNARE protein STX11 (familial haemophagocytic lymphohistiocytosis type 4), where cytotoxic T lymphocytes are not able to exert the degranulation process [138,139]. Likewise, two SNARE protein that regulate autophagosome–lysosome fusion (VAMP8 and VTI1B) have been found to have an important role in the exocytosis of lytic granules from cytotoxic T lymphocytes [139]. In general, these results clearly demonstrate that autophagy participates in both degradative and secretory pathways, contributing to the maintenance of the cellular homeostasis.

9. Concluding remarks

As indicated above, several membrane sources, including mitochondria, the ER, the Golgi apparatus, and the plasma membrane are believed to contribute to autophagosome biogenesis. It is likely that this contribution involves the delivery, tethering and fusion of vesicles with the forming phagophore. However, to date, in spite of some controversial results, very little is known about the participation of specific Rab GTPases or SNAREs in the initial steps of phagophore formation and how these proteins regulate homotypic and heterotypic fusion of autophagosome precursor vesicles. Future studies will unravel the interplay between components of the autophagy machinery and specific constituents of the vesicular transport and tethering/fusion machinery (as suggested by the results obtained by Graef et al. [8]) not only at the level of autophagosome biogenesis but also in other steps of the pathway.

References

[1] Boya, P., Reggiori, F. and Codogno, P. (2013) Emerging regulation and functions of autophagy. Nat. Cell Biol. 15 (7), 713–720.
[2] Mizushima, N., Levine, B., Cuervo, A.M. and Klionsky, D.J. (2008) Autophagy fights disease through cellular self-digestion. Nature 451 (7182), 1069–1075.
[3] Eskelinen, E.-L. and Saftig, P. (2009) Autophagy: a lysosomal degradation pathway with a central role in health and disease. Biochim. Biophys. Acta 1793 (4), 664–673.
[4] Knecht, E., Aguado, C., Cárcel, J., Esteban, I., Esteve, J.M., Ghislat, G., Moruno, J. F., Vidal, J.M. and Sáez, R. (2009) Intracellular protein degradation in mammalian cells: recent developments. Cell. Mol. Life Sci. 66 (15), 2427–2443.
[5] Gomes, L.C. and Dikic, I. (2014) Autophagy in antimicrobial immunity. Mol. Cell 54 (2), 224–233 (Cell Press).
[6] Axe, E.L., Walker, S.A., Manifava, M., Chandra, P., Roderick, H.L., Habermann, A., Griffiths, G. and Ktistakis, N.T. (2008) Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. J. Cell Biol. 182 (4), 685–701.
[7] Zoppino, F.C.M., Militello, R.D., Slavin, I., Álvarez, C. and Colombo, M.I. (2010) Autophagosome formation depends on the small GTPase rab1 and functional ER exit sites. Traffic 11 (9), 1246–1261.
[8] Graef, M., Friedman, J.R., Graham, C., Babu, M. and Nunnari, J. (2013) ER exit sites are physical and functional core autophagosome biogenesis components. Mol. Biol. Cell 24 (18), 2918–2931.
[9] Sanchez-Wandelmer, J., Ktistakis, N.T. and Reggiori, F. (2015) ERES: sites for autophagosome biogenesis and maturation? J. Cell Sci. 128 (2), 185–192.
[10] Hamasaki, M., Shibutani, S.T. and Yoshimori, T. (2013) Up-to-date membrane biogenesis in the autophagosome formation. Curr. Opin. Cell Biol. 25 (4), 455–460.
[11] Militello, R.D. and Colombo, M.I. (2011) A membrane is born: origin of the autophagosomal compartment. Curr. Mol. Med. 11 (3), 197–203.
[12] Weidberg, H., Shpilka, T., Shvets, E., Abada, A., Shimron, F. and Elazar, Z. (2011) LC3 and GATE-16 N termini mediate membrane fusion processes required for autophagosome biogenesis. Dev. Cell 20 (4), 444–454.
[13] Shibutani, S.T. and Yoshimori, T. (2014) A current perspective of autophagosome biogenesis. Cell Res. 24 (1), 58–68.
[14] Müller, A.J. and Proikas-Cezanne, T. (2015) Function of human WIPI proteins in autophagosomal rejuvenation of endomembranes? FEBS Lett. 589 (14), 1546–1551.
[15] Kraft, C. and Martens, S. (2012) Mechanisms and regulation of autophagosome formation. Curr. Opin. Cell Biol. 24 (4), 496–501.
[16] Xie, Z. and Klionsky, D.J. (2007) Autophagosome formation: core machinery and adaptations. Nat. Cell Biol. 9 (10), 1102–1109.
[17] Mizushima, N. and Komatsu, M. (2011) Autophagy: renovation of cells and tissues. Cell 147 (4), 728–741.
[18] Noda, N.N. and Fujioka, Y. (2015) Atg1 family kinases in autophagy initiation. Cell. Mol. Life Sci. 72 (16), 3083–3096.
[19] Inoki, K., Li, Y., Xu, T. and Guan, K.-L. (2003) Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes Dev. 17 (15), 1829–1834.
[20] Fader, C.M., Aguilera, M.O. and Colombo, M.I. (2014) Autophagy response: manipulating the mTOR-controlled machinery by amino acids and pathogens. Amino Acids.
[21] Russell, R.C., Yuan, H.-X. and Guan, K.-L. (2014) Autophagy regulation by nutrient signaling. Cell Res. 24 (1), 42–57.
[22] Jung, C.H., Ro, S.H., Cao, J., Otto, N.M. and Kim Do-Hyung, D.H. (2010) MTOR regulation of autophagy. FEBS Lett. 584 (7), 1287–1295.
[23] Hosokawa, N., Hara, T., Kaizuka, T., Kishi, C., Takamura, A., Miura, Y., Iemura, S.-I., Natsume, T., Takehana, K., Yamada, N., Guan, J.-L., Oshiro, N. and Mizushima, N. (2009) Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Mol. Biol. Cell 20 (7), 1981–1991.
[24] Ganley, I.G., Lam, D.H., Wang, J., Ding, X., Chen, S. and Jiang, X. (2009) ULK1. ATG13.FIP200 complex mediates mTOR signaling and is essential for autophagy. J. Biol. Chem. 284 (18), 12297–12305.

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

[25] Hosokawa, N., Hara, T., Kaizuka, T., Kishi, C., Takamura, A., Miura, Y., Iemura, S., Natsume, T., Takehana, K., Yamada, N., Guan, J.-L., Oshiro, N. and Mizushima, N. (2009) Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Mol. Biol. Cell 20 (7), 1981–1991.
[26] Jung, C.H., Jun, C.B., Ro, S.-H., Kim, Y.-M., Otto, N.M., Cao, J., Kundu, M. and Kim, D.-H. (2009) ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol. Biol. Cell 20 (7), 1992–2003.
[27] Itakura, E. and Mizushima, N. (2010) Characterization of autophagosome formation site by a hierarchical analysis of mammalian Atg proteins. Autophagy 6 (6), 764–776.
[28] Martens, S. and Bachmair, A. (2015) How cells coordinate waste removal through their major proteolytic pathways. Nat. Cell Biol. 17 (7), 841–842.
[29] Proikas-Cezanne, T., Takacs, Z., Dönnes, P. and Kohlbacher, O. (2015) WIPI proteins: essential PtdIns3P effectors at the nascent autophagosome. J. Cell Sci. 128 (2), 207–217.
[30] Kirisako, T. (1999) Formation process of autophagosome is traced with Apg8/Aut7p in yeast. J. Cell Biol. 147 (2), 435–446.
[31] Kabeya, Y., Mizushima, N., Ueno, T., Yamamoto, A., Kirisako, T., Noda, T., Kominami, E., Ohsumi, Y. and Yoshimori, T. (2000) LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. EMBO J. 19 (21), 5720–5728.
[32] Geng, J. and Klionsky, D.J. (2008) The Atg8 and Atg12 ubiquitin-like conjugation systems in macroautophagy. 'Protein modifications: beyond the usual suspects' review series. EMBO Rep. 9 (9), 859–864.
[33] Xie, Z., Nair, U. and Klionsky, D.J. (2008) Atg8 controls phagophore expansion during autophagosome formation. Mol. Biol. Cell 19 (8), 3290–3298.
[34] Young, A.R.J., Chan, E.Y.W., Hu, X.W., Köchl, R., Crawshaw, S.G., High, S., Hailey, D.W., Lippincott-Schwartz, J. and Tooze, S.A. (2006) Starvation and ULK1-dependent cycling of mammalian Atg9 between the TGN and endosomes. J. Cell Sci. 119 (Pt 18), 3888–3900.
[35] Webber, J.L., Young, A.R.J. and Tooze, S.A. (2007) Atg9 trafficking in Mammalian cells. Autophagy 3 (1), 54–56.
[36] Zavodszky, E., Vicinanza, M. and Rubinsztein, D.C. (2013) Biology and trafficking of ATG9 and ATG16L1, two proteins that regulate autophagosome formation. FEBS Lett. 587 (13), 1988–1996.
[37] Bento, C.F., Puri, C., Moreau, K. and Rubinsztein, D.C. (2013) The role of membrane-trafficking small GTPases in the regulation of autophagy. J. Cell Sci. 126 (Pt 5), 1059–1069.
[38] Grosshans, B.L., Ortiz, D. and Novick, P. (2006) Rabs and their effectors: achieving specificity in membrane traffic. Proc. Natl. Acad. Sci. U.S.A. 103 (32), 11821–11827.
[39] Ao, X., Zou, L. and Wu, Y. (2014) Regulation of autophagy by the Rab GTPase network. Cell Death Differ. 21 (3), 348–358.
[40] Allan, B.B., Moyer, B.D. and Balch, W.E. (2000) Rab1 recruitment of p115 into a cis-SNARE complex: programming budding COPII vesicles for fusion. Science 289 (5478), 444–448.
[41] Barrowman, J., Bhandari, D., Reinisch, K. and Ferro-Novick, S. (2010) TRAPP complexes in membrane traffic: convergence through a common Rab. Nat. Rev. Mol. Cell Biol. 11 (11), 759–763.
[42] Lynch-Day, M.A., Bhandari, D., Menon, S., Huang, J., Cai, H., Bartholomew, C.R., Brumell, J.H., Ferro-Novick, S. and Klionsky, D.J. (2010) Trs85 directs a Ypt1 GEF, TRAPPIII, to the phagophore to promote autophagy. Proc. Natl. Acad. Sci. U.S.A. 107 (17), 7811–7816.
[43] Huang, J., Birmingham, C.L., Shahnazari, S., Shiu, J., Zheng, Y.T., Smith, A.C., Campellone, K.G., DoHeo, W., Gruenheid, S., Meyer, T., Welch, M.D., Ktistakis, N.T., Kim, P.K., Klionsky, D.J. and Brumell, J.H. (2011) Antibacterial autophagy occurs at PtdIns(3)P-enriched domains of the endoplasmic reticulum and requires Rab1 GTPase. Autophagy 7 (1), 17–26.
[44] Pinar, M., Pantazopoulou, A. and Peñalva, M.A. (2013) Live-cell imaging of *Aspergillus nidulans* autophagy: RAB1 dependence, Golgi independence and ER involvement. Autophagy 9 (7), 1024–1043.
[45] Yu, H.B., Croxen, M.A., Marchiando, A.M., Ferreira, R.B.R., Cadwell, K., Foster, L. J. and Brett Finlay, B. (2014) Autophagy facilitates Salmonella replication in HeLa cells. mBio 5 (2).
[46] Gorvel, J.P., Chavrier, P., Zerial, M. and Gruenberg, J. (1991) Rab5 controls early endosome fusion in vitro. Cell 64 (5), 915–925.
[47] Bucci, C., Parton, R.G., Mather, I.H., Stunnenberg, H., Simons, K., Hoflack, B. and Zerial, M. (1992) The small GTPase rab5 functions as a regulatory factor in the early endocytic pathway. Cell 70 (5), 715–728.
[48] Zeigerer, A., Gilleron, J., Bogorad, R.L., Marsico, G., Nonaka, H., Seifert, S., Epstein-Barash, H., Kuchimanchi, S., Peng, C.G., Ruda, V.M., Del Conte-Zerial, P., Hengstler, J.G., Kalaidzidis, Y., Koteliansky, V. and Zerial, M. (2012) Rab5 is necessary for the biogenesis of the endolysosomal system in vivo. Nature 485 (7399), 465–470.
[49] Wegener, C.S., Malerød, L., Pedersen, N.M., Prodiga, C., Bakke, O., Stenmark, H. and Brech, A. (2010) Ultrastructural characterization of giant endosomes induced by GTPase-deficient Rab5. Histochem. Cell Biol. 133 (1), 41–55.
[50] Dou, Z., Pan, J.A., Dbouk, H.A., Ballou, L.M., DeLeon, J.L., Fan, Y., Chen, J.S., Liang, Z., Li, G., Backer, J.M., Lin, R.Z. and Zong, W.X. (2013) Class IA PI3K p110β subunit promotes autophagy through Rab5 small GTPase in response to growth factor limitation. Mol. Cell 50 (1), 29–42.
[51] Ravikumar, B., Imarisio, S., Sarkar, S., O'Kane, C.J. and Rubinsztein, D.C. (2008) Rab5 modulates aggregation and toxicity of mutant huntingtin through macroautophagy in cell and fly models of Huntington disease. J. Cell Sci. 121 (Pt 10), 1649–1660.
[52] Su, W.-C., Chao, T.-C., Huang, Y.-L., Weng, S.-C., Jeng, K.-S. and Lai, M.M.C. (2011) Rab5 and class III phosphoinositide 3-kinase Vps34 are involved in hepatitis C virus NS4B-induced autophagy. J. Virol. 85 (20), 10561–10571.
[53] Evans, T.M., Ferguson, C., Wainwright, B.J., Parton, R.G. and Wicking, C. (2003) Rab23, a negative regulator of hedgehog signaling, localizes to the plasma membrane and the endocytic pathway. Traffic 4 (12), 869–884.
[54] Evans, T.M., Simpson, F., Parton, R.G. and Wicking, C. (2005) Characterization of Rab23, a negative regulator of sonic hedgehog signaling. Methods Enzymol. 403, 759–777.
[55] Wang, Y., Ng, E.L. and Tang, B.L. (2006) Rab23: What exactly does it traffic? Traffic 7 (6), 746–750.
[56] Nozawa, T., Aikawa, C., Goda, A., Maruyama, F., Hamada, S. and Nakagawa, I. (2012) The small GTPases Rab9A and Rab23 function at distinct steps in autophagy during Group A Streptococcus infection. Cell. Microbiol. 14 (8), 1149–1165.
[57] Alto, N.M., Soderling, J. and Scott, J.D. (2002) Rab32 is an A-kinase anchoring protein and participates in mitochondrial dynamics. J. Cell Biol. 158 (4), 659–668.
[58] Wasmeier, C., Romao, M., Plowright, L., Bennett, D.C., Raposo, G. and Seabra, M.C. (2006) Rab38 and Rab32 control post-Golgi trafficking of melanogenic enzymes. J. Cell Biol. 175 (2), 271–281.
[59] Hirota, Y. and Tanaka, Y. (2009) A small GTPase, human Rab32, is required for the formation of autophagic vacuoles under basal conditions. Cell. Mol. Life Sci. 66 (17), 2913–2932.
[60] Wang, C., Liu, Z. and Huang, X. (2012) Rab32 is important for autophagy and lipid storage in drosophila. PLoS One 7 (2).
[61] Starr, T., Sun, Y., Wilkins, N. and Storrie, B. (2010) Rab33b and Rab6 are functionally overlapping regulators of Golgi homeostasis and trafficking. Traffic 11 (5), 626–636.
[62] Alshammari, M.J., Al-Otaibi, L. and Alkuraya, F.S. (2012) Mutation in RAB33B, which encodes a regulator of retrograde Golgi transport, defines a second Dyggve–Melchior–Clausen locus. J. Med. Genet. 49 (7), 455–461.
[63] Dupuis, N., Lebon, S., Kumar, M., Drunat, S., Graul-Neumann, L.M., Gressens, P. and El Ghouzzi, V. (2013) A novel RAB33B mutation in Smith–McCort dysplasia. Hum. Mutat. 34 (2), 283–286.
[64] Fukuda, M. and Itoh, T. (2008) Direct link between Atg protein and small GTPase Rab: Atg16L functions as a potential Rab33 effector in mammals. Autophagy 4 (6), 824–826.
[65] Itoh, T., Kanno, E., Uemura, T., Waguri, S. and Fukuda, M. (2011) OATL1, a novel autophagosome-resident Rab33B-GAP, regulates autophagosomal maturation. J. Cell Biol. 192 (5), 838–853.
[66] Dreux, M., Gastaminza, P., Wieland, S.F. and Chisari, F.V. (2009) The autophagy machinery is required to initiate hepatitis C virus replication. Proc. Natl. Acad. Sci. U.S.A. 106 (33), 14046–14051.
[67] Blackham, S., Baillie, A., Al-Hababi, F., Remlinger, K., You, S., Hamatake, R. and McGarvey, M.J. (2010) Gene expression profiling indicates the roles of host oxidative stress, apoptosis, lipid metabolism, and intracellular transport genes in the replication of hepatitis C virus. J. Virol. 84 (10), 5404–5414.
[68] Zhang, M., Chen, L., Wang, S. and Wang, T. (2009) Rab7: roles in membrane trafficking and disease. Biosci. Rep. 29 (3), 193–209.
[69] Wang, T., Ming, Z., Xiaochun, W. and Hong, W. (2011) Rab7: role of its protein interaction cascades in endo-lysosomal traffic. Cell. Signal. 23, 516–521.
[70] Hyttinen, J.M.T., Niittykoski, M., Salminen, A. and Kaarniranta, K. (2013) Maturation of autophagosomes and endosomes: a key role for Rab7. Biochim. Biophys. Acta – Mol. Cell Res. 1833 (3), 503–510.
[71] Gutierrez, M.G., Master, S.S., Singh, S.B., Taylor, G.A., Colombo, M.I. and Deretic, V. (2004) Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages. Cell 119 (6), 753–766.
[72] Jäger, S., Bucci, C., Tanida, I., Ueno, T., Kominami, E., Saftig, P. and Eskelinen, E.-L. (2004) Role for Rab7 in maturation of late autophagic vacuoles. J. Cell Sci. 117 (Pt 20), 4837–4848.
[73] Sun, Q., Westphal, W., Wong, K.N., Tan, I. and Zhong, Q. (2010) Rubicon controls endosome maturation as a Rab7 effector. Proc. Natl. Acad. Sci. U.S.A. 107 (45), 19338–19343.
[74] Tabata, K., Matsunaga, K., Sakane, A., Sasaki, T., Noda, T. and Yoshimori, T. (2010) Rubicon and PLEKHM1 negatively regulate the endocytic/autophagic pathway via a novel Rab7-binding domain. Mol. Biol. Cell 21 (23), 4162–4172.
[75] Pankiv, S., Alemu, E.A., Brech, A., Bruun, J.A., Lamark, T., Øvervatn, A., Bjørkøy, G. and Johansen, T. (2010) FYCO1 is a Rab7 effector that binds to LC3 and PI3P to mediate microtubule plus end – directed vesicle transport. J. Cell Biol. 188 (2), 253–269.
[76] Toyofuku, T., Morimoto, K., Sasawatari, S. and Kumanogoh, A. (2015) LRRK1 regulates autophagy through turning on the TBC1D2-dependent Rab7 inactivation. Mol. Cell. Biol. 35 (17), 3044–3058.
[77] Eskelinen, E.L. (2005) Maturation of autophagic vacuoles in Mammalian cells. Autophagy 1 (1), 1–10.
[78] Lock, J.G. and Stow, J.L. (2005) Rab11 in recycling endosomes regulates the sorting and basolateral transport of E-cadherin. Mol. Biol. Cell 16 (4), 1744–1755.
[79] Takahashi, S., Kubo, K., Waguri, S., Yabashi, A., Shin, H.-W., Katoh, Y. and Nakayama, K. (2012) Rab11 regulates exocytosis of recycling vesicles at the plasma membrane. J. Cell Sci. 125 (17), 4049–4057.
[80] Savina, A., Vidal, M. and Colombo, M.I. (2002) The exosome pathway in K562 cells is regulated by Rab11. J. Cell Sci. 115 (Pt 12), 2505–2515.

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

[81] Fader, C.M., Sánchez, D., Furlán, M. and Colombo, M.I. (2008) Induction of autophagy promotes fusion of multivesicular bodies with autophagic vacuoles in K562 cells. Traffic 9 (2), 230–250.
[82] Longatti, A., Lamb, C.A., Razi, M., Yoshimura, S.I., Barr, F.A. and Tooze, S.A. (2012) TBC1D14 regulates autophagosome formation via Rab11- and ULK1-positive recycling endosomes. J. Cell Biol. 197 (5), 659–675.
[83] Szatmári, Z., Kis, V., Lippai, M., Hegedus, K., Faragó, T., Lorincz, P., Tanaka, T., Juhász, G. and Sass, M. (2014) Rab11 facilitates cross-talk between autophagy and endosomal pathway through regulation of Hook localization. Mol. Biol. Cell 25 (4), 522–531.
[84] Demir, K., Kirsch, N., Beretta, C.A., Erdmann, G., Ingelfinger, D., Moro, E., Argenton, F., Carl, M., Niehrs, C. and Boutros, M. (2013) RAB8B is required for activity and caveolar endocytosis of LRP6. Cell Rep. 4 (6), 1224–1234.
[85] Chen, S., Liang, M.C., Chia, J.N., Ngsee, J.K. and Ting, A.E. (2001) Rab8b and its interacting partner TRIP8b are involved in regulated secretion in AtT20 cells. J. Biol. Chem. 276 (16), 13209–13216.
[86] Sato, T., Iwano, T., Kunii, M., Matsuda, S., Mizuguchi, R., Jung, Y., Hagiwara, H., Yoshihara, Y., Yuzaki, M., Harada, R. and Harada, A. (2014) Rab8a and Rab8b are essential for several apical transport pathways but insufficient for ciliogenesis. J. Cell Sci. 127 (Pt 2), 422–431.
[87] Pilli, M., Arko-Mensah, J., Ponpuak, M., Roberts, E., Master, S., Mandell, M.A., Dupont, N., Ornatowski, W., Jiang, S., Bradfute, S.B., Bruun, J.A., Hansen, T.E., Johansen, T. and Deretic, V. (2012) TBK-1 promotes autophagy-mediated antimicrobial defense by controlling autophagosome maturation. Immunity 37 (2), 223–234.
[88] Olkkonen, V.M., Dupree, P., Killisch, I., Lütcke, A., Zerial, M. and Simons, K. (1993) Molecular cloning and subcellular localization of three GTP-binding proteins of the rab subfamily. J. Cell Sci. 106 (Pt 4), 1249–1261.
[89] Erdman, R.A., Shellenberger, K.E., Overmeyer, J.H. and Maltese, W.A. (2000) Rab24 is an atypical member of the Rab GTPase family. Deficient GTPase activity, GDP dissociation inhibitor interaction, and prenylation of Rab24 expressed in cultured cells. J. Biol. Chem. 275 (6), 3848–3856.
[90] Ding, J., Soule, G., Overmeyer, J.H. and Maltese, W.A. (2003) Tyrosine phosphorylation of the Rab24 GTPase in cultured mammalian cells. Biochem. Biophys. Res. Commun. 312 (3), 670–675.
[91] Militello, R.D., Munafó, D.B., Berón, W., López, L.A., Monier, S., Goud, B. and Colombo, M.I. (2013) Rab24 is required for normal cell division. Traffic 14 (5), 502–518.
[92] Munafó, D.B. and Colombo, M.I. (2002) Induction of autophagy causes dramatic changes in the subcellular distribution of GFP-Rab24. Traffic 3 (7), 472–482.
[93] Egami, Y., Kiryu-Seo, S., Yoshimori, T. and Kiyama, H. (2005) Induced expressions of Rab24 GTPase and LC3 in nerve-injured motor neurons. Biochem. Biophys. Res. Commun. 337 (4), 1206–1213.
[94] Marambio, P., Toro, B., Sanhueza, C., Troncoso, R., Parra, V., Verdejo, H., García, L., Quiroga, C., Munafo, D., Díaz-Elizondo, J., Bravo, R., González, M.J., Diaz-Araya, G., Pedrozo, Z., Chiong, M., Colombo, M.I. and Lavandero, S. (2010) Glucose deprivation causes oxidative stress and stimulates aggresome formation and autophagy in cultured cardiac myocytes. Biochim. Biophys. Acta – Mol. Basis Dis. 1802 (6), 509–518.
[95] Gutierrez, M.G., Vázquez, C.L., Munafó, D.B., Zoppino, F.C.M., Berón, W., Rabinovitch, M. and Colombo, M.I. (2005) Autophagy induction favours the generation and maturation of the Coxiella-replicative vacuoles. Cell. Microbiol. 7 (7), 981–993.
[96] Cheng, K.W., Lahad, J.P., Kuo, W.-L., Lapuk, A., Yamada, K., Auersperg, N., Liu, J., Smith-McCune, K., Lu, K.H., Fishman, D., Gray, J.W. and Mills, G.B. (2004) The RAB25 small GTPase determines aggressiveness of ovarian and breast cancers. Nat. Med. 10 (11), 1251–1256.
[97] Caswell, P.T., Spence, H.J., Parsons, M., White, D.P., Clark, K., Cheng, K.W., Mills, G.B., Humphries, M.J., Messent, A.J., Anderson, K.I., McCaffrey, M.W., Ozanne, B.W. and Norman, J.C. (2007) Rab25 associates with α5β1 integrin to promote invasive migration in 3D microenvironments. Dev. Cell 13 (4), 496–510.
[98] Krishnan, M., Lapierre, L.A., Knowles, B.C. and Goldenring, J.R. (2013) Rab25 regulates integrin expression in polarized colonic epithelial cells. Mol. Biol. Cell 24 (6), 818–831.
[99] Mitra, S., Cheng, K.W. and Mills, G.B. (2012) Rab25 in cancer: a brief update. Biochem. Soc. Trans. 40 (6), 1404–1408.
[100] Cheng, K.W., Agarwal, R., Mitra, S., Lee, J.S., Carey, M., Gray, J.W. and Mills, G. B. (2012) Rab25 increases cellular ATP and glycogen stores protecting cancer cells from bioenergetic stress. EMBO Mol. Med. 4 (2), 125–141.
[101] Liu, Y., Tao, X., Jia, L., Cheng, K.W., Lu, Y., Yu, Y. and Feng, Y. (2012) Knockdown of RAB25 promotes autophagy and inhibits cell growth in ovarian cancer cells. Mol. Med. Rep. 6 (5), 1006–1012.
[102] Nottingham, R.M., Ganley, I.G., Barr, F.A., Lambright, D.G. and Pfeffer, S.R. (2011) RUTBC1 protein, a Rab9A effector that activates GTP hydrolysis by Rab32 and Rab33B proteins. J. Biol. Chem. 286 (38), 33213–33222.
[103] Yan, H., Li, W.L., Xu, J.J., Zhu, S.Q., Long, X. and Che, J.P. (2013) D2 dopamine receptor antagonist raclopride induces non-canonical autophagy in cardiac myocytes. J. Cell. Biochem. 114 (1), 103–110.
[104] Zylbersztejn, K. and Galli, T. (2011) Vesicular traffic in cell navigation. FEBS J. 278 (23), 4497–4505.
[105] Chaineau, M., Danglot, L. and Galli, T. (2009) Multiple roles of the vesicular-SNARE TI-VAMP in post-Golgi and endosomal trafficking. FEBS Lett. 583, 3817–3826.
[106] Martens, S. and McMahon, H.T. (2008) Mechanisms of membrane fusion: disparate players and common principles. Nat. Rev. Mol. Cell Biol. 9 (7), 543–556.
[107] Brunger, A.T., Weninger, K., Bowen, M. and Chu, S. (2009) Single-molecule studies of the neuronal SNARE fusion machinery. Annu. Rev. Biochem. 78, 903–928.
[108] Li, F., Pincet, F., Perez, E., Eng, W.S., Melia, T.J., Rothman, J.E. and Tareste, D. (2007) Energetics and dynamics of SNAREpin folding across lipid bilayers. Nat. Struct. Mol. Biol. 14 (10), 890–896.
[109] Jahn, R. and Südhof, T.C. (1999) Membrane fusion and exocytosis. Annu. Rev. Biochem. 68, 863–911.
[110] Rossi, V., Banfield, D.K., Vacca, M., Dietrich, L.E.P., Ungermann, C., D'Esposito, M., Galli, T. and Filippini, F. (2004) Longins and their longin domains: regulated SNAREs and multifunctional SNARE regulators. Trends Biochem. Sci. 29 (12), 682–688.
[111] Wen, W., Chen, L., Wu, H., Sun, X., Zhang, M. and Banfield, D.K. (2006) Identification of the yeast R-SNARE Nyv1p as a novel longin domain-containing protein. Mol. Biol. Cell 17 (10), 4282–4299.
[112] Tooze, S.A. (2013) Current views on the source of the autophagosome membrane. Essays Biochem. 55, 29–38.
[113] Nair, U., Jotwani, A., Geng, J., Gammoh, N., Richerson, D., Yen, W.-L., Griffith, J., Nag, S., Wang, K., Moss, T., Baba, M., McNew, J.A., Jiang, X., Reggiori, F., Melia, T.J. and Klionsky, D.J. (2011) SNARE proteins are required for macroautophagy. Cell 146 (2), 290–302.
[114] Moreau, K., Ravikumar, B., Puri, C. and Rubinsztein, D.C. (2012) Arf6 promotes autophagosome formation via effects on phosphatidylinositol 4,5-bisphosphate and phospholipase D. J. Cell Biol. 196 (4), 483–496.
[115] Moreau, K., Puri, C. and Rubinsztein, D.C. (2015) Methods to analyze SNARE-dependent vesicular fusion events that regulate autophagosome biogenesis. Methods 75, 19–24.
[116] Fader, C.M., Aguilera, M.O. and Colombo, M.I. (2012) ATP is released from autophagic vesicles to the extracellular space in a VAMP7-dependent manner. Autophagy 8 (12), 1741–1756.
[117] Moreau, K., Ravikumar, B., Renna, M., Puri, C. and Rubinsztein, D.C. (2011) Autophagosome precursor maturation requires homotypic fusion. Cell 146 (2), 303–317.
[118] Hager, H.A., Roberts, R.J., Cross, E.E., Proux-Gillardeaux, V. and Bader, D.M. (2010) Identification of a novel Bves function: regulation of vesicular transport. EMBO J. 29 (3), 532–545.
[119] Proux-Gillardeaux, V., Rudge, R. and Galli, T. (2005) The tetanus neurotoxin-sensitive and insensitive routes to and from the plasma membrane: fast and slow pathways? Traffic 6 (5), 366–373.
[120] Tayeb, M.A., Skalski, M., Cha, M.C., Kean, M.J., Scaife, M. and Coppolino, M.G. (2005) Inhibition of SNARE-mediated membrane traffic impairs cell migration. Exp. Cell Res. 305 (1), 63–73.
[121] Veale, K.J., Offenhäuser, C., Whittaker, S.P., Estrella, R.P. and Murray, R.Z. (2010) Recycling endosome membrane incorporation into the leading edge regulates lamellipodia formation and macrophage migration. Traffic 11 (10), 1370–1379.
[122] Bajno, L., Peng, X.R., Schreiber, A.D., Moore, H.P., Trimble, W.S. and Grinstein, S. (2000) Focal exocytosis of VAMP3-containing vesicles at sites of phagosome formation. J. Cell Biol. 149 (3), 697–705.
[123] Puri, C., Renna, M., Bento, C.F., Moreau, K. and Rubinsztein, D.C. (2013) Diverse autophagosome membrane sources coalesce in recycling endosomes. Cell 154 (6), 1285–1299.
[124] Fader, C.M. and Colombo, M.I. (2009) Autophagy and multivesicular bodies: two closely related partners. Cell Death Differ. 16 (1), 70–78.
[125] Proux-Gillardeaux, V., Raposo, G., Irinopoulou, T. and Galli, T. (2007) Expression of the Longin domain of TI-VAMP impairs lysosomal secretion and epithelial cell migration. Biol. Cell 99 (5), 261–271.
[126] Antonin, W., Riedel, D. and von Mollard, G.F. (2000) The SNARE Vti1a-beta is localized to small synaptic vesicles and participates in a novel SNARE complex. J. Neurosci. 20 (15), 5724–5732.
[127] Furuta, N., Fujita, N., Noda, T., Yoshimori, T. and Amano, A. (2010) Combinational soluble N-ethylmaleimide-sensitive factor attachment protein receptor proteins VAMP8 and Vti1b mediate fusion of antimicrobial and canonical autophagosomes with lysosomes. Mol. Biol. Cell 21 (6), 1001–1010.
[128] Itakura, E., Kishi-Itakura, C. and Mizushima, N. (2012) The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes. Cell 151 (6), 1256–1269.
[129] Takáts, S., Nagy, P., Varga, Á., Pircs, K., Kárpáti, M., Varga, K., Kovács, A.L., Hegedus, K. and Juhász, G. (2013) Autophagosomal Syntaxin17-dependent lysosomal degradation maintains neuronal function in Drosophila. J. Cell Biol. 201 (4), 531–539.
[130] Shen, H.M. and Mizushima, N. (2014) At the end of the autophagic road: an emerging understanding of lysosomal functions in autophagy. Trends Biochem. Sci. 39 (2), 61–71.
[131] Liu, R., Zhi, X. and Zhong, Q. (2015) ATG14 controls SNARE-mediated autophagosome fusion with a lysosome. Autophagy 11 (5), 847–849.
[132] Renna, M., Schaffner, C., Winslow, A.R., Menzies, F.M., Peden, A.A., Floto, R.A. and Rubinsztein, D.C. (2011) Autophagic substrate clearance requires activity of the syntaxin-5 SNARE complex. J. Cell Sci. 124 (Pt 3), 469–482.
[133] Morelli, E., Ginefra, P., Mastrodonato, V., Beznoussenko, G.V., Rusten, T.E., Bilder, D., Stenmark, H., Mironov, A.A. and Vaccari, T. (2014) Multiple functions of the SNARE protein Snap29 in autophagy, endocytic, and exocytic

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021

trafficking during epithelial formation in Drosophila. Autophagy 10 (12), 2251–2268.

[134] Cadwell, K., Liu, J.Y., Brown, S.L., Miyoshi, H., Loh, J., Lennerz, J.K., Kishi, C., Kc, W., Carrero, J.A., Hunt, S., Stone, C.D., Brunt, E.M., Xavier, R.J., Sleckman, B.P., Li, E., Mizushima, N., Stappenbeck, T.S. and Virgin, H.W. (2008) A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature 456 (7219), 259–263.

[135] DeSelm, C.J., Miller, B.C., Zou, W., Beatty, W.L., van Meel, H., Takahata, Y., Klumperman, J., Tooze, S.A., Teitelbaum, S.L. and Virgin, H.W. (2011) Autophagy proteins regulate the secretory component of osteoclastic bone resorption. Dev. Cell 21 (5), 966–974.

[136] Ushio, H., Ueno, T., Kojima, Y., Komatsu, M., Tanaka, S., Yamamoto, A., Ichimura, Y., Ezaki, J., Nishida, K., Komazawa-Sakon, S., Niyonsaba, F., Ishii, T., Yanagawa, T., Kominami, E., Ogawa, H., Okumura, K. and Nakano, H. (2011) Crucial role for autophagy in degranulation of mast cells. J. Allergy Clin. Immunol. 127 (5), 1267–1276.e6.

[137] Michaud, M., Martins, I., Sukkurwala, A.Q., Adjemian, S., Ma, Y., Pellegatti, P., Shen, S., Kepp, O., Scoazec, M., Mignot, G., Rello-Varona, S., Tailler, M., Menger, L., Vacchelli, E., Galluzzi, L., Ghiringhelli, F., di Virgilio, F., Zitvogel, L. and Kroemer, G. (2011) Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 334 (6062), 1573–1577.

[138] Bryceson, Y.T., Rudd, E., Zheng, C., Edner, J., Ma, D., Wood, S.M., Bechensteen, A.G., Boelens, J.J., Celkan, T., Farah, R.A., Hultenby, K., Winiarski, J., Roche, P.A., Nordenskjöld, M., Henter, J.I., Long, E.O. and Ljunggren, H.G. (2007) Defective cytotoxic lymphocyte degranulation in syntaxin-11-deficient familial hemophagocytic lymphohistiocytosis 4 (FHL4) patients. Blood 110 (6), 1906–1915.

[139] Dressel, R., Elsner, L., Novota, P., Kanwar, N. and Fischer von Mollard, G. (2010) The exocytosis of lytic granules is impaired in Vti1b- or Vamp8-deficient CTL leading to a reduced cytotoxic activity following antigen-specific activation. J. Immunol. 185 (2), 1005–1014.

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021