

Perspective

Beyond Autophagy: ATG9A as an Emerging Membrane Repair Factor

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How To Cite: Lara Corona, M.; Claude-Taupin, A. Beyond Autophagy: ATG9A as an Emerging Membrane Repair Factor. *Ubiquitylation & Atg8ylation* **2026**, 1(1), 6.

Received: 8 July 2026

Revised: 18 August 2026

Accepted: 19 August 2026

Published: 27 August 2026

Abstract: Membrane damage occurs in all cell types, triggered by environmental cues, pathogens or intrinsic cellular processes. To survive, cells have evolved various mechanisms to repair their membranes. Among these, the autophagic protein ATG9A, initially described as a key factor in autophagy initiation, is now known to participate in multiple stages of autophagy, including phagophore expansion and closure. Moreover, ATG9A has recently been uncovered as playing a crucial role in both plasma membrane and lysosomal membrane repair. In this perspective article, we briefly overview the novel functions of ATG9A and discuss key unanswered questions, including the mechanisms by which ATG9A-containing vesicles promote repair, which may depend on the size and nature of the membrane damage.

Keywords: ATG9A; plasma membrane; lysosome; repair; damage

1. Introduction

The sole core transmembrane autophagy protein ATG9A was initially described for its role in autophagy initiation [1,2]. In this context, the lipid scramblase activity of ATG9A, in concert with the lipid transfer protein ATG2, has been shown to promote the phagophore expansion [3–6]. On top of being involved in autophagy initiation, the ATG9A protein has been recently shown to play a role in autophagosome closure by recruiting the ESCRT machinery [7].

Beyond autophagy, ATG9A plays several non-canonical functions [8], including in plasma membrane repair [9–11], lysosomal repair [12,13], lipid droplet homeostasis [14], Golgi function [15], migration [16] and inflammatory responses [17–19]. While these novel functions were initially considered unrelated, it is now becoming apparent that key roles of ATG9A in autophagy may also underlie its non-autophagic functions. In this perspective article, we explore the mechanistic parallels between the roles of ATG9A in autophagy and its non-canonical functions in membrane repair, with a particular emphasis on the role of its scramblase activity depending on contexts.

2. Full Scrambling Activity of ATG9A Needed for Autophagy Initiation

ATG9A scrambling activity was first reported in 2020 in mammalian cells and yeast by Maeda et al. [3] and Matoba et al. [4], respectively. This was subsequently confirmed by the team of Dr. Reinisch [20]. Scramblases mediate the bidirectional transport of lipids between two leaflets of a membrane, without requiring ATP. The scramblase activity of ATG9A lies on its capacity to form trimers with a central pore, which is connected to the cytosol through the cavity of each protomer. Mutations affecting the central pore of ATG9A can inhibit scrambling activity by around 50% [3]. In vitro, yeast Atg9 and mammalian ATG9A have been shown to scramble the phospholipids phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylserine (PS), as well as phosphatidylinositol-3-phosphate (PI3P) [3,4]. In both yeast and mammals, PI3P is a key phosphoinositide driving the progression of the autophagy pathway. It is initially enriched at the endoplasmic reticulum (ER), where it



promotes omegasome formation by recruiting the PI3P-binding effector DFCP1. PI3P also recruits WIPI2 to drive the transition from the omegasome to the phagophore. WIPI2, in turn, mediates the recruitment of ATG16L1, thereby promoting LC3 lipidation and membrane elongation. PI3P remains enriched on the outer membrane of the expanding phagophore before being dephosphorylated by PI3P-Phosphatase Ymr1 in yeast, or MTM1 in mammals, a step required for phagophore closure and subsequent fusion of the mature autophagosome with a lysosome to form the autolysosome [21,22]. Mutations affecting the central pore of ATG9A, when expressed in ATG9A KO cells, resulted in the accumulation of small, closed vesicles or cup/sheet-shaped membranes resembling growing phagophores, associated with an inhibition of autophagy activity of around 50%. These findings indicated that the scramblase activity of ATG9A is necessary for membrane expansion [3]. During autophagy initiation, ARFIP2 modulates the peripheral distribution of ATG9-positive vesicles to deliver PI4KIII β to the phagophore, thereby promoting synthesis of PI4P [23]. An emerging model suggests that, in parallel, ATG9A receives phospholipids from lipid transferases, such as ATG2, and distributes these lipids between the inner and outer leaflets of the growing phagophore membrane thanks to its lipid scramblase activity, thereby regulating autophagosome membrane curvature and lipid composition, which is essential for autophagy progression [24–27] (Figure 1A).

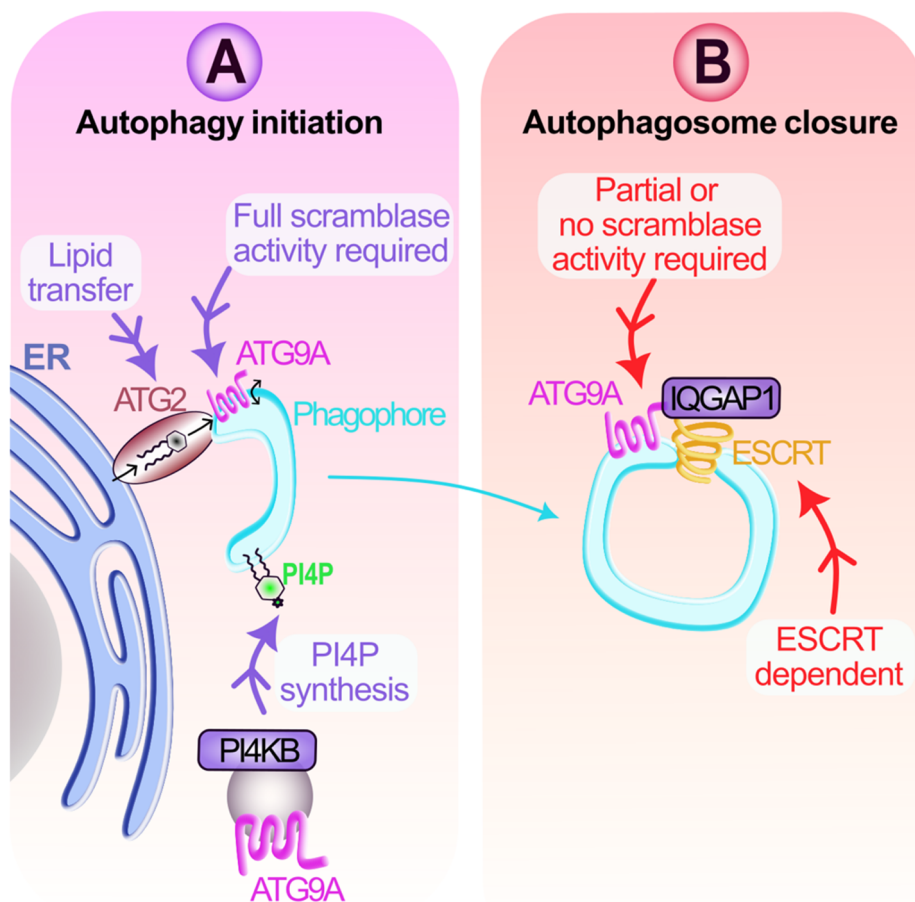


Figure 1. Roles of ATG9A in autophagy initiation and autophagosome closure. **(A)** During autophagy initiation, ATG9A vesicles deliver the lipid kinase PI4KB (also known as PI4KIIIb) to the phagophore membrane, promoting local synthesis of PI4P. In parallel, ATG9A scrambles lipids between the two membrane leaflets of the phagophore. This scramblase activity acts together with ATG2, which transfers lipids from a donor membrane toward the phagophore, thereby supporting its expansion. **(B)** ATG9A also promotes autophagosome closure through its interaction with IQGAP1 and the consequent recruitment of the ESCRT machinery, a process that requires partial or no scramblase activity. PI4P: phosphatidylinositol-4-phosphate.

3. Autophagosome Closure Does Not Require Full ATG9A Scrambling Activity

Although the scramblase activity of ATG9A has been associated with autophagy initiation events, a recent study from Javed et al. reported a role for ATG9A in promoting autophagosome closure through the recruitment of the ESCRT machinery [7]. Interestingly, the M33 scrambling mutant of ATG9A was able to rescue the autophagy defects observed in ATG9A-deleted cells to levels similar to an ATG9A WT construct, suggesting that

ATG9A's role in promoting autophagosome closure may require only partial scrambling activity, or may be independent on its scramblase function (Figure 1B).

4. ATG9A-Mediated Plasma Membrane Repair via Vesicular Fusion and Delivery of Repair Factors

Beyond its autophagic functions, ATG9A has been associated with novel functions related to membrane repair events. Interestingly, some of these are dependent on the scramblase activity of ATG9A, while others may not be dependent on its scrambling activity or only partially.

The first report of the role of ATG9A in membrane repair was related to plasma membrane (PM) damage induced by chemical compounds such as digitonin, but also toxins (Streptolysin O) or pore-forming proteins such as Gasdermin D and MLKL, associated with pyroptosis and necroptosis processes, respectively [9]. In this setting, the role of ATG9A in promoting PM repair was associated with the recruitment of the ESCRT machinery at the PM through IQGAP1, prompting PM shedding and subsequent release of extracellular vesicles [28]. IQGAP1, a calcium-responsive protein was shown by GST-Pulldowns to interact with ATG9A and the ESCRT proteins TSG101 [29] and CHMP2A [9]. IQGAP1 knock-down impaired ATG9A recruitment and membrane repair, supporting a role for IQGAP1 in coordinating ATG9A-dependent PM repair; however, they do not demonstrate that IQGAP1 is the sole recruiter of ATG9A or define the precise order of recruitment between ATG9A, IQGAP1, and ESCRT components. In this context, an ATG9A scramblase mutant (M33, exhibiting around 50% of lipid scrambling activity [3], complemented the loss of ATG9A and protected cells against digitonin-induced PM damage to the same extent as an ATG9A WT construct [9]. Zhang et al. further demonstrated that ATG9A vesicular fusion with the PM was necessary to promote digitonin-induced PM repair via the STX13-SNAP23-VAMP3 SNARE complex, regulating the unconventional secretion of several galectins (galectin-9, -4, and -8) and annexin A6 [30]. In the context of PM damage, ATG9A is therefore proposed to function by mediating the fusion of ATG9A-containing vesicles, most likely derived from nanovesicles [31] or endosomal structures [32], with the PM, thereby contributing to the delivery of repair factors (Figure 2A).

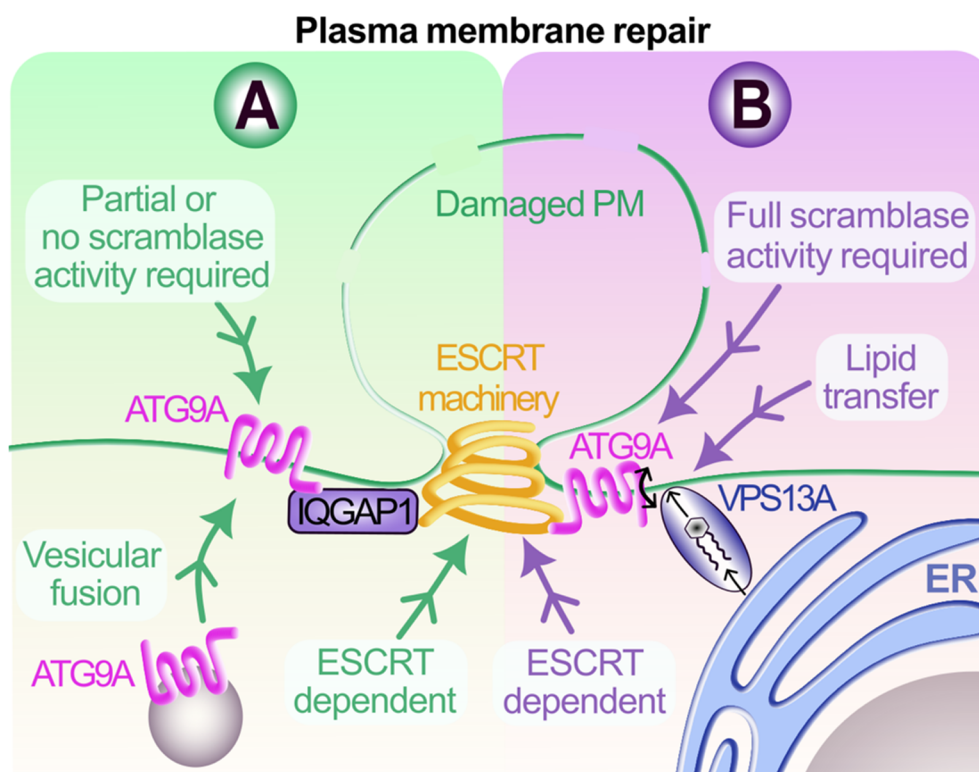


Figure 2. Roles of ATG9A in plasma membrane repair. (A) IQGAP1 recruitment of ATG9A vesicles to the plasma membrane, via vesicular fusion, promotes ESCRT assembly and the shedding of damaged membrane. In this context, the ATG9A scramblase mutant M33 is still able to support PM repair, suggesting that this process requires partial or no scramblase activity. (B) ATG9A promotes the recruitment of a donor membrane, such as the endoplasmic reticulum (ER), to the plasma membrane via VPS13A. Full ATG9A scramblase activity may then enable lipid transfer from the donor membrane to the plasma membrane, supporting membrane remodeling and/or ESCRT-dependent repair.

5. ATG9A-Mediated Lysosomal Repair through PI4P Delivery and Lipid Scrambling

As demonstrated by the laboratories of Sharon Tooze [12] and Hong Zhang [13], ATG9A is also playing a role in protecting the lysosomal membrane from damage. De Tito et al. have shown that brief induction of lysosomal damage using the lysosomotropic agent L-leucyl-L-leucine methyl ester (LLOMe) led to the recruitment of ATG9A to lysosomes, thereby promoting phosphatidylinositol-4-phosphate (PI4P) production at the site of damage through the delivery of the kinase PI4K2A. In this context, ATG9A scramblase mutants (M8 and M33, each exhibiting a 50% decrease in scrambling activity and reduced autophagic activity by 20% and 50%, respectively [3] were not able to contribute to lysosomal repair in ATG9A KO cells [12]. The proposed model suggests that, upon lysosomal damage, ATG9A-containing vesicles relocate to lysosomes to deliver PI4K2A, thereby promoting PI4P production at the lysosomal membrane. This, in turn, facilitates the exchange of PI4P for phosphatidylserine (PS) at endoplasmic reticulum (ER)-lysosome membrane contact sites, ultimately promoting lysosomal repair. In this context, the lipid scramblase activity of ATG9A may increase lipid accessibility, thereby facilitating lipid transfer at ER-lysosome contact sites. Alternatively, or in addition, ATG9A may interact with lipid transfer proteins involved in lysosomal repair, such as VPS13 [33] or ATG2 [34], the latter of which has been reported to function as a PS effector during lysosomal repair (Figure 3A).

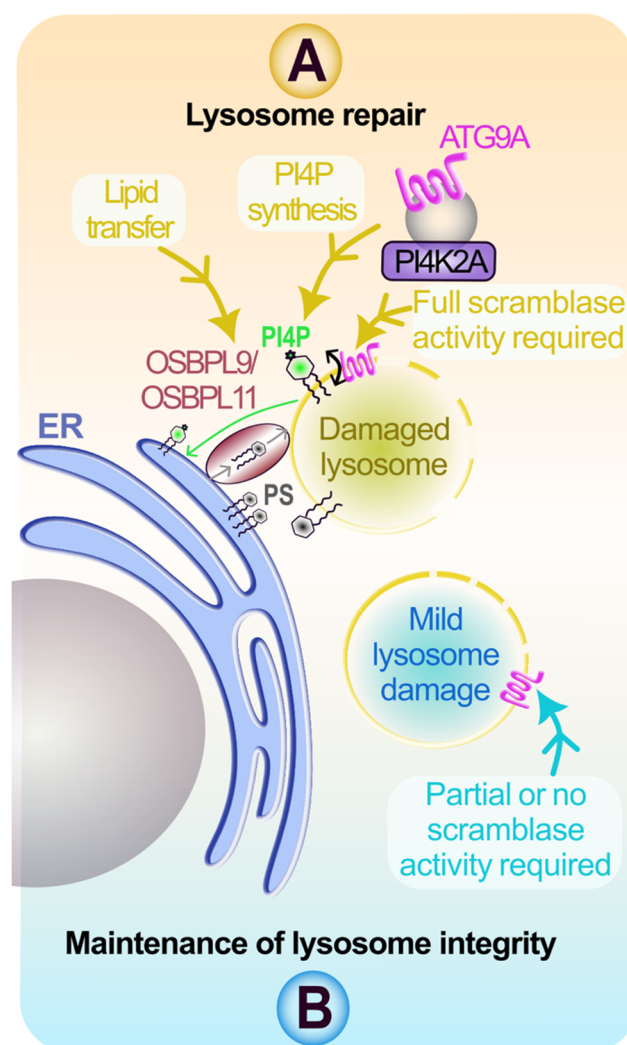


Figure 3. Roles of ATG9A in lysosomal repair and maintenance of lysosome integrity. **(A)** Upon LLOMe-induced damage, ATG9A vesicles deliver the kinase PI4K2A to the lysosomal membrane, leading to increased local PI4P synthesis. Oxysterol-binding protein-like proteins (OSBPLs) then exchange PI4P for phosphatidylserine (PS) at ER-lysosome contact sites, mediating lysosomal repair. In this context, the extent of lysosomal repair positively correlates with ATG9A's full scramblase activity. **(B)** In *C. elegans* Epg-5 mutants, which accumulate damaged lysosomes, ATG9A limits this accumulation and thereby maintains lysosomal integrity. In this process, mildly damaged lysosomes co-distribute with ATG9A, and partial or no scramblase activity appears sufficient to limit the accumulation of damaged lysosomes in this context. PI4K2A: phosphatidylinositol-4-kinase-2a; PI4P: phosphatidylinositol-4-phosphate.

6. ATG9A in the Maintenance of Lysosomal Integrity

In *C. elegans*, Wang et al. showed that ATG-9 facilitates the maintenance of lysosome integrity in Epg-5 mutants, in which non-degradative autolysosomes with a damaged membrane accumulate [35]. In this context, ATG-9 surrounded only mildly damaged lysosomes, which were not labeled with Galectin-3 but did show defective lysosomal acidification. Interestingly, mutations attenuating the lipid scrambling activity of ATG9A (C475F, located within the central pore of the ATG-9 homotrimer) were able to rescue lysosomal damage [13]. As mentioned earlier, the scramblase mutants used in these studies only show a partial reduction in scrambling activity (up to 50%). These findings suggest that ATG-9 maintains lysosomal integrity in Epg-5 mutants through a mechanism that may be independent of its lipid scrambling activity, for example by recruiting membrane repair factors, such as the ESCRT machinery, as it has been proposed during PM repair [9,11] (Figure 3B). Alternatively, maintaining lysosomal integrity in this context may require only partial scramblase activity. Accordingly, the authors proposed a model in which ATG-9 promotes lysosomal repair by altering membrane curvature and/or tension through lipid redistribution, potentially by regulating phosphatidylethanolamine (PE) levels. Consistent with this model, reducing PE levels, but not those of other phospholipids such as phosphatidylserine (PS) or phosphatidylcholine (PC), rescued the accumulation of damaged lysosomes and promoted lysosomal biogenesis in Epg-5 mutants [13]. ATG-9 may also function at membrane contact sites between lysosomes and other organelles, such as the ER, where it could recruit lipid transfer proteins that remodel the lysosomal membrane to preserve its integrity and limit damage [34,36–40]. Such mechanisms could explain why lysosomal integrity is maintained and why mildly damaged lysosomes would remain repairable in cells expressing an ATG9A mutant with attenuated scrambling activity.

7. ATG9A-Mediated Plasma Membrane Repair Dependent on Lipid Delivery and Full Scramblase Activity

More recently, a study from Muskat et al. deciphered a novel mechanism by which ATG9A repairs the PM following damage with digitonin [11]. In this context, ATG9A partners with the lipid transfer protein VPS13A, previously involved in the autophagy pathway through an interaction with ATG9A [41]. During PM damage, the authors observed that ATG9A co-immunoprecipitated with the lipid transfer protein VPS13A, which had previously been shown to transfer lipids from the ER to the PM through ER–PM contact sites [42,43]. The co-distribution of VPS13A with the PM was shown to depend on ATG9A during PM damage, thereby placing ATG9A redistribution at the PM as an initial event promoting PM repair. Consistent with this, overexpression of ATG9A in VPS13A-depleted cells failed to rescue PM repair. Interestingly, the M33 scramblase mutant also failed to rescue PM damage. It is therefore plausible that the VPS13A–ATG9A partnership promotes lipid transfer from a donor membrane toward the PM, with ATG9A's scramblase activity facilitating this process and thereby allowing membrane growth and/or repair (Figure 2B).

Even though Muskat et al. [11] used similar conditions of damage and the same scramblase mutant as the original study by Claude-Taupin et al., the study from Muskat et al. appears to have induced lower levels of PM damage, based on a comparison of propidium iodide incorporation into nuclei, an indirect marker of PM damage. If similar to the functions of ATG9A in repairing the lysosomal membrane, the full scramblase activity of ATG9A may be needed for mildly damaged PM or may only require partial scrambling efficiency for higher levels of damage. Interestingly, the study by Muskat et al. compared the levels of PM damage in cells following knockdown of VPS13A or TSG101 and observed increased damage in siTSG101 cells compared to siVPS13A, thereby positioning the ESCRT machinery as an essential factor in promoting PM repair through the recruitment of ATG9A. We propose a model in which two mechanisms could act in parallel. First, ATG9A–VPS13A (or possibly other lipid transfer proteins) may promote lipid transfer from the ER, and potentially other organelles, to the PM, repairing mild PM damage as observed in the context of lysosomal repair. In this context, ATG9A may, similarly to its proposed role in lysosomal membrane repair, promote PI4P production at the PM, thereby facilitating the exchange of PI4P for PS through lipid transfer proteins. Consistent with this hypothesis, a recent study has shown that PI4P accumulates at sites of PM damage, followed by PS enrichment in a manner dependent on the lipid transfer protein ORP9 [44]. Second, ATG9A–VPS13A could promote membrane growth, favoring PM curvature prior to ESCRT-dependent budding, or scramble lipids at the PM following repair in order to restore PM composition. PM growth might be promoted by contact sites between donor membranes and the PM. As suggested by Muskat et al., the ER could be an ideal candidate for this role, with VPS13A potentially transporting lipids such as PE toward the PM [45]. Interestingly, a VPS13-like lipid transfer protein, BLTP2, was recently shown to transfer PE toward the PM, thereby regulating PM fluidity [46], a key factor required for PM remodeling and completion of the repair process [47]. Alternatively, VPS13A has been shown to associate with endosomes [48], in which ATG9A also traffics [49], raising the possibility of a functional link between the two. In yeast, Vps13 has been

shown to transfer lipids from the ER to endosomes, a process supporting efficient ESCRT-mediated intraluminal vesicle formation [50]. Although this remains speculative, it is tempting to hypothesize that ATG9A-positive endosomes, in contact with VPS13-donor membranes, could similarly participate in membrane growth and/or remodeling, potentially contributing to ESCRT function at the PM to promote repair. Whether lipid transfer, lipid scrambling, and ESCRT-dependent remodeling occur sequentially or in parallel remains to be defined and addressing this question will be essential to understanding how ATG9A might coordinate plasma membrane repair.

8. ATG9A Scramblase Activity and Other Non-Canonical Functions

Beyond repair mechanisms, ATG9A can protect cells against TNF-induced apoptosis, associated with the assembly of a cytoplasmic complex, called “complex IIa”, upon TNF sensing [17]. This process also depends on other autophagy-related proteins, such as FIP200, ATG2A/B, and VPS34, but does not depend on components of the ATG8 lipidation machinery, such as ATG5, ATG7, and ATG16L1. The ATG9A scramblase activity mutants (M8, M28 and M33 [3]) cannot rescue TNF-induced apoptosis. Hence, ATG9A may protect cells from cell death through a mechanism similar to that involved in autophagy initiation, requiring its full scramblase activity. In this context, ATG9A may facilitate the formation of a vesicular compartment that sequesters the cytosolic complex IIa, potentially promoting the growth of an autophagosomal-related structure through cooperation with lipid transfer proteins. Following fusion with lysosomes, the contents of this compartment will be degraded, hence limiting cell death associated with the accumulation of cytosolic complex IIa (Figure 4).

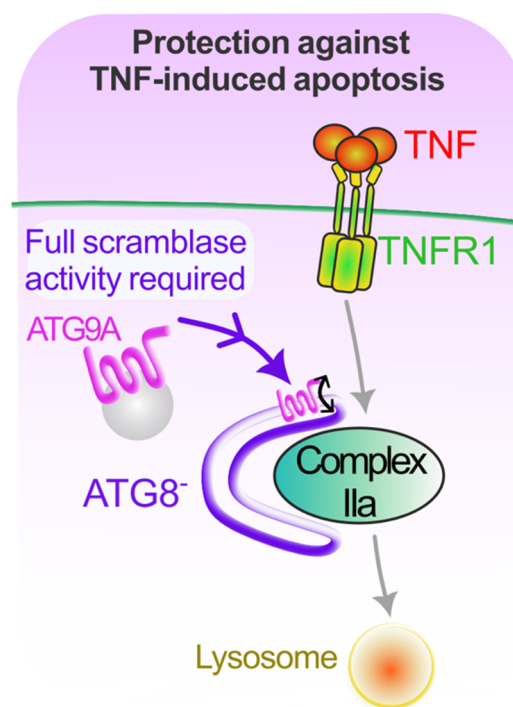


Figure 4. ATG9A-dependent protection against TNF-induced apoptosis. Upon TNF stimulation, the TNF receptor TNFR1 induces the accumulation of cytosolic complex IIa, leading to apoptosis. ATG9A counteracts this process by promoting the sequestration of complex IIa and its subsequent lysosomal degradation, a process that depends on ATG9A’s full scramblase activity but is independent of the ATG8 lipidation machinery. TNF: tumor necrosis factor; TNFR1: tumor necrosis factor receptor 1.

ATG9A can also support the growth of *Chlamydia trachomatis* with an unknown mechanism [51]. In this study, the authors were able to rescue the growth of *Chlamydia trachomatis* with WT and an ATG9A scramblase mutant (M33 [3]). Interestingly, it was previously shown that *Chlamydia trachomatis* can induce the rupture of its inclusion membrane through proteases [52] using a mechanism comparable to cytokinesis, which is dependent on the ESCRT machinery [53]. It is therefore tempting to hypothesize that, in the context of *Chlamydia trachomatis* infection, ATG9A could repair the inclusion membrane following protease-induced damage, hence delaying the release of new bacteria in the cytosol and promoting the growth of *Chlamydia trachomatis*. Alternatively, as the M33 scramblase shows only a 50% decrease in scramblase activity, the low levels of scramblase activity could be sufficient to help growing the inclusion membrane and promote the growth of *Chlamydia trachomatis*.

9. Conclusions and Perspectives

In this perspective article, we discussed the novel functions of ATG9A in membrane repair, highlighting the importance of its scramblase activity in several contexts, which seem to be related to the level of damage. As stated earlier, the ATG9A scramblase mutants used in these studies [9,11–13] showed a 50% decrease in scramblase activity, which correlates with 20–50% autophagy defects [3]. Even though this has not yet been clearly established, the reported roles of ATG9A scramblase activity in promoting membrane repair seem to be linked to low levels of damage. Based on the available evidence, we propose that dependence on ATG9A full scramblase activity may scale inversely with damage severity, being most important when low-level damage requires membrane remodeling and growth for repair. This model remains speculative and awaits direct experimental validation. When the levels of damage are more substantial and require the ESCRT machinery to induce repair, scrambling mutants were still able to rescue the defects induced by ATG9A deletion. This could mean either that ATG9A-dependent membrane repair does not always require the full scrambling activity of ATG9A, or that ATG9A plays pleiotropic roles in remodeling membranes, including through scrambling-independent processes—notably, for example, through the recruitment of the ESCRT machinery. During limited lysosomal damage, the recruitment of the ESCRT machinery favors the repair of the lysosomal membrane [54]. In the same context, the ATG9A scrambling activity could be necessary to repair damaged lysosomes, thereby reducing the likelihood of extensive damage.

Several non-canonical functions of ATG9A have been described before the discovery of the scramblase activity of ATG9A. It will be interesting in the future to evaluate how the scramblase activity of the protein is related to these functions. For example, could the scramblase activity of ATG9A be important to promote Golgi fragmentation and/or to limit type I IFN production upon dsDNA activation? Another point to determine is the importance of calcium in the recruitment of ATG9A for its canonical and non-canonical functions. Although some of the downstream functions of ATG9A differ between autophagy, plasma membrane repair and lysosomal repair, each process is initiated by conditions that generate localized calcium signals [12,55–58]. This raises the possibility that a conserved function of ATG9A might be its mobilization to sites of membrane stress in response to calcium. Once recruited, ATG9A could engage distinct partners including lipid transfer proteins, components of the ESCRT complex or other membrane-remodeling factors, depending on the identity of the damaged organelle and the magnitude of membrane remodeling needed. In line with this, the recruitment of ATG9A to damaged lysosomes has been shown to depend on calcium [12], similarly to PM damage [9]. During PM damage events, Claude-Taupin et al. reported that the binding of ATG9A with the protein IQGAP1, responding to calcium fluxes, allows the fast recruitment of ATG9A to the damaged area [9]. During the late autophagy steps, Javed et al. [7] have shown that IQGAP1 also participates to the recruitment of ATG9A to promote autophagosome closure, even though a role for calcium in this context has not been explored. Whether calcium-dependent recruitment via IQGAP1 represents a general mechanism for ATG9A mobilization, rather than a feature specific to PM repair and autophagosome closure, remains to be determined. Addressing this question could help clarify whether a common molecular logic governs ATG9A's diverse functions.

Altogether, the recent findings position ATG9A as a central hub coordinating membrane homeostasis across multiple compartments, with its scramblase activity acting as one of several tools it could deploy, depending on the severity of the stress. Clarifying how calcium signaling links these activities, from PM repair to lysosomal damage, autophagy initiation and closure, will be a key step toward understanding ATG9A as a unifying sensor and effector of membrane integrity.

Author Contributions

M.L.C.: Visualization and writing—original draft, review, and editing. A.C.-T.: conceptualization, funding acquisition, and writing—original draft, review, and editing. All authors have read and agreed to the published version of the manuscript.

Funding

The authors received financial support from INSERM (Institut National pour la Santé et la Recherche Médicale), CNRS (Centre National pour la Recherche Scientifique), Université Paris Cité, French National Research Agency (ANR-24-CE14-0097 to AC-T) and a French Government grant from University Paris Cité, Emergence Plan d'Investissement France 2030 (ANR-18-IDEX-0001 to AC-T).

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No data were generated or deposited for this Perspective.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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