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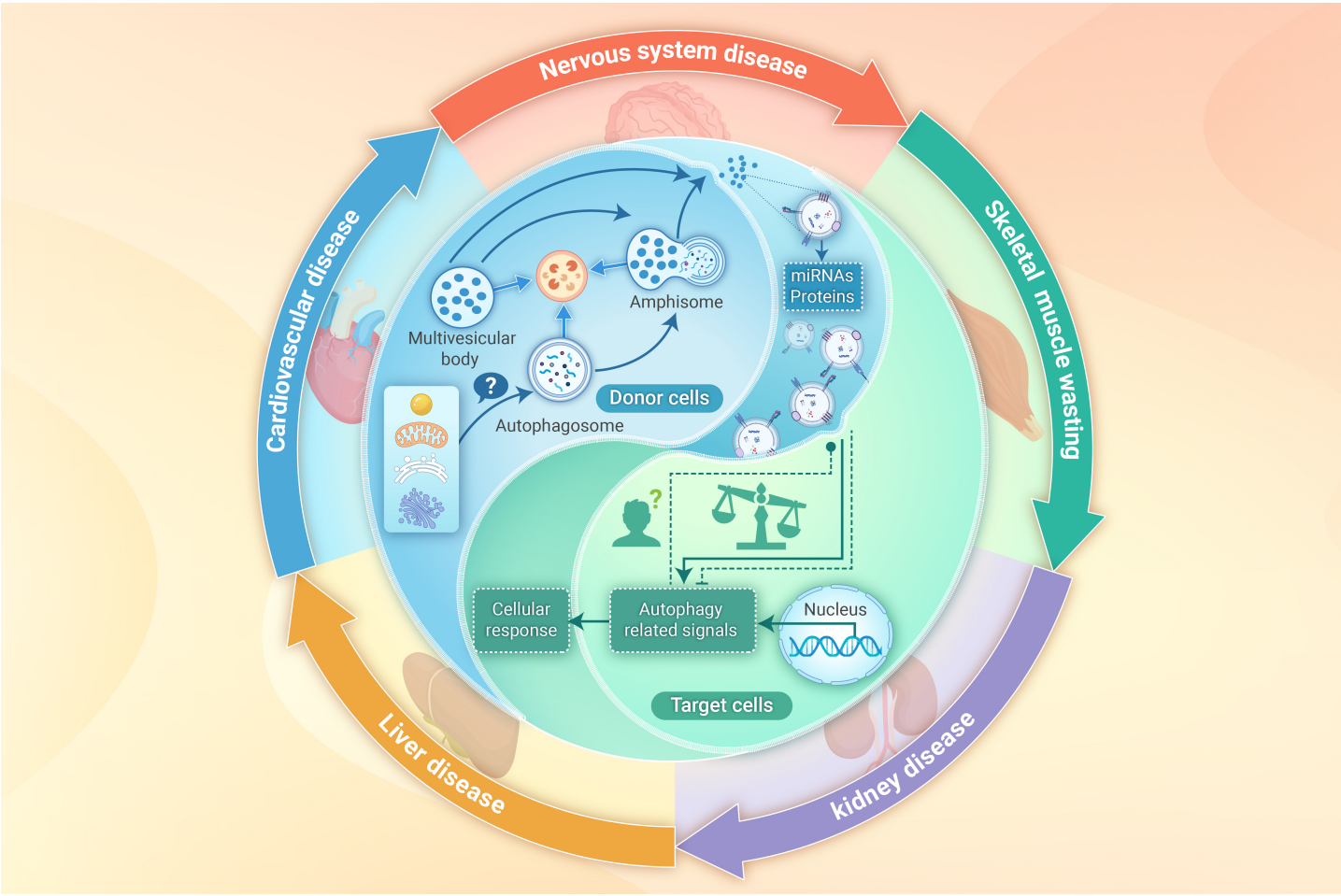
## GRAPHICAL ABSTRACT




## PUBLIC SUMMARY

- The homeostatic role between exosomes and autophagy depends on the intracellular and intercellular crosstalk.
- Their intracellular connections intersect through shared molecular machinery or organelle.
- Exosomal miRNAs and proteins activate or inhibit autophagy-related signals to mediate intercellular crosstalk.

REVIEW





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The intracellular and intercellular information exchange is the key to regulate the body function. Current studies have indicated the intracellular and intercellular crosstalk between exosomes and autophagy as two components of the eukaryotic endomembrane system. Exosomes are bilayer lipid membrane vesicles to participate in intercellular communication. Autophagy is to form autophagosome, then fuse with lysosome to degrade contents encapsulating cytoplasmic components. Exosomes and autophagy not only intersect through common molecular mechanism or organelle within cells, but also could activate intracellular autophagy-related signaling pathways to demonstrate the therapeutic potentiality of various diseases via exosomal miRNAs and proteins. The intracellular and intercellular crosstalk of them serves a homeostatic role in mitigating stress. What has become clear is that the steady state of this interaction is of great significance in physiology and pathology. If we could better understand the crosstalk from more perspectives, such as the function of exosomal lipids in regulating autophagy, the use of invertebrates as research models and the relationship between exosomes and selective autophagy of organelle-level, this represents an opportunity for treatment, especially the application of engineered exosomes.

## INTRODUCTION

The intracellular and intercellular crosstalk is particularly important for maintaining cellular homeostasis, which is also applicable for understanding the homeostatic role between exosomes and autophagy. Generally, exosomes are a subtype of extracellular vesicles (EVs) and approximately 40-160 nm in diameter.[1] Exosomes were discovered in 1983 while studying the maturation of reticulocytes into erythrocytes.[2,3] Although initially treated as cell waste, the study of exosomes has become an hotspot.[4] Exosomes are famous for physiological and disease-related events as well as serving as disease biomarkers in recent studies. Critically, there are still challenges in establishing procedures to isolate and purify exosomes, which may cause heterogeneous populations of EVs, including exosomes.[1] Therefore, some discussed findings can be attributed to the mixture of exosomes with other EVs. As for autophagy, it is an evolutionarily conserved mechanism that exists in cells to maintain their normal operation, which is regulated by a series of complex molecules.[5] The intracellular trafficking pathways control intercellular signal transduction by promoting the secretion of intracellular substances and diffusing them into the external environment to be uptaken by target cells.[6] Current studies have shown connective molecular mechanisms of exosome biogenesis and autophagy, and found that autophagy-related (ATG) signaling pathways can be activated or inhibited by the exosomal miRNAs and proteins. Therefore, we first describe the common molecular mechanisms or organelles of exosome biogenesis and autophagy in cells, and then discuss the potential implications of exosomes regulating autophagy in diseases after internalization by target cells, including engineered exosomes. As mentioned in 1966 that autophagy could be selective,[7] according to the different degradation substrates, autophagy of various organelles could be included. Several studies have reported that mitophagy drives exosome secretion[8] or engineered exosomes regulate mitophagy,[9] while little attention has been paid to lipophagy, which may be attributed to the less clear molecular mechanism of driving lipophagy. Finally, we discuss from effective molecules of exosomes, the evolution of crosstalk between exosomes and autophagy, the connection between exosomes and selective autophagy of organelle-level, and the application of engineered exosomes in regulating autophagy, looking forward to providing reference for future research.

## INTRACELLULAR CONNECTIONS BETWEEN EXOSOMES AND AUTOPHAGY

### Classical and non-classical exosome biogenesis

Exosome biogenesis includes classical and non-classical pathways (Figure 1). Generally, canonical exosome secretion is characterized by double invaginations of the plasma membrane (PM) and multivesicular bodies (MVBs) formation. The first deformation of PM is facilitated by multimeric proteins like caveolae[10,11] and clathrin,[12,13] then undergoes dynamin[14] or endosomal sorting complexes required for transport (ESCRT)[15]-dependent fission to form early sorting endosomes (ESEs), integrating with already existing ESEs to mature late sorting endosomes (LSEs) facilitated by the trans-Golgi network (TGN) and endoplasmic reticulum (ER).[16-18] The second step involves that LSEs eventually generate MVBs containing several intraluminal vesicles (ILVs).[1,19-21] ESCRT is not necessary for this step. Specifically, some studies have shown that it is dependent on ESCRT,[12,20,22] but the generations of ceramide activated by neutral sphingomyelinase 2,[23-25] phosphatidic acid activated via phospholipase D2[26] and lipid-raft with a Ras-like protein in brain 31 (Rab31)-flotillin-dependent way[27] facilitate the ESCRT-independent pathway. MVB-docking proteins assist in transporting MVBs to the PM, which results in releasing exosomes by the following exocytosis.[1,28]

Additionally, membrane budding from diverse organelles and the nuclear envelope can trigger unconventional pathways for exosome biogenesis.[19] Compared with late endosomal exosomes, Rab11-positive exosomes increase via downregulating mTORC1 signal.[29] Additionally, the existence of lysosome-associated membrane protein 1 and Rab7 in apoptotic exosome-like vesicles secreted from early apoptotic cells suggests the role of endolysosomal transport pathway.[30-32] Moreover, leukotriene $B_4$ ($LTB_4$) and its synthetase secreted from neutrophils are packaged in MVBs.[33,34] The biogenesis of MVBs containing $LTB_4$ originates from the nuclear membrane, in which there is the $LTB_4$ synthesis mechanism.[35] Mitochondria-derived vesicles also release their internal vesicles as exosomes via fusing with canonical MVBs.[19] The latest finding reveals that the cation channel protein encoded by the SARS-CoV-2 envelope (2-E) is closely associated with Golgi fragmentation and the production of 2-E-enriched exosomes,[36] proposing a novel type of extracellular vesicle of Golgi origin. The above two exosome synthesis pathways together reveal that MVBs from different cell types and internal origins affect the type of components inside and outer layer of exosomes.

### Core mechanisms of autophagy

Three categories of autophagy in mammals are usually divided into microautophagy, macroautophagy and chaperone-mediated autophagy (CMA) according to the ways entering in lysosome (Figure 2).[37] Among them, microautophagy is directly engulfed and degraded by the deformation of lysosome or vacuole surface,[38,39] while CMA is to degrade the target protein

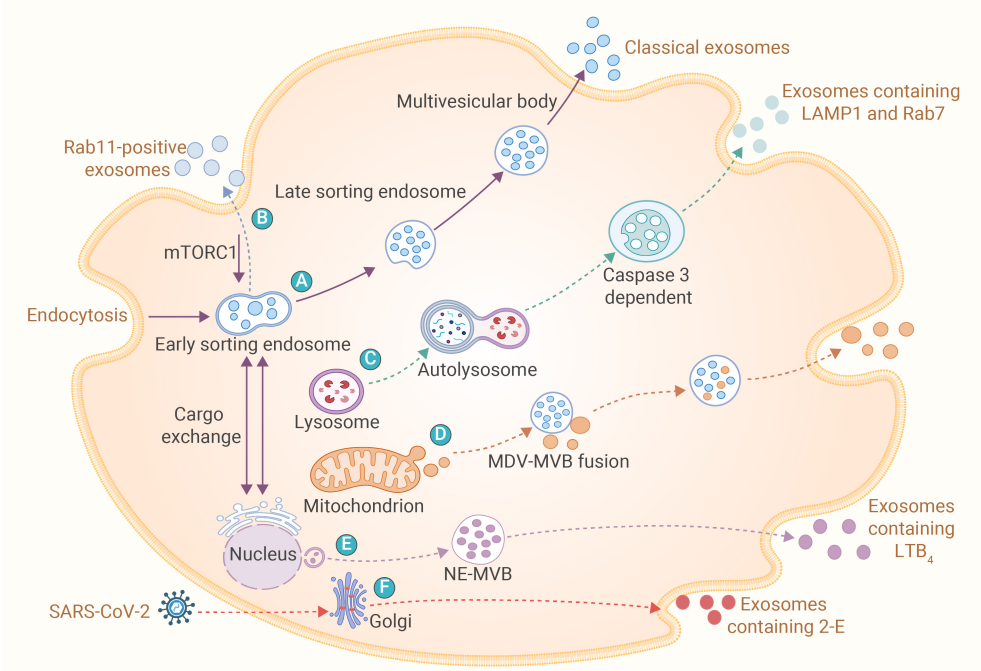


**Figure 1. Classical and non-classical exosome biogenesis** (A) The classical exosome biogenesis begins with endocytosis at the plasma membrane (PM), sequentially followed by the formation of early sorting endosome, late sorting endosome and multivesicular body (MVB), finally fusing with the PM to secrete exosomes. (B) Ras-like protein in brain 11 (Rab11)-positive exosomes originate from glutamine deprivation-induced the decrease of mTORC1 signal and such exosomes lack canonical exosomal markers. (C) Early apoptotic cell secretes apoptotic exosome-like vesicles containing lysosome associated membrane protein 1 (LAMP1) and Rab7. (D) Mitochondria-derived vesicle (MDV) fuses with canonical MVB to secrete exosomes. (E) Nucleus envelope-derived MVB (NE-MVB) in the activated neutrophil secretes exosomes containing leukotriene $B_4$ ($LTB_4$). (F) The cation channel protein encoded by the SARS-CoV-2 envelope (2-E) is closely associated with Golgi fragmentation and the production of 2-E-enriched exosomes. This figure was created by using BioRender, the same below.

bearing a Lys-Phe-Glu-Arg-Gln (KFERQ)-like motif directly across the lysosome membrane,[40] neither of which involve autophagosomes.[41] Therefore, we mainly summarize the core molecular mechanisms of macroautophagy focusing on the changes of autophagosomes in this part.

***Initiation.*** The initiation of autophagy can be divided into two stages including induction and nucleation. The occurrence of autophagy can be induced by a variety of intracellular and extracellular signals, including nutrient deficiency, stress, abnormal protein aggregates, damaged organelles and infectious microorganisms. This induction process is mainly mediated by the unc-51-like kinase (ULK) complex.[42,43] The ULK complex is the earliest ATG protein that targets the membrane structure formed by autophagosome precursors. The initiation of autophagosome formation requires the assembly of multiple ULK complexes, which in turn serve as a recruitment platform for other ATG proteins.[44] Studies have also shown that ULK complex components may be directly associated with the membrane, because a domain that binds to membrane lipids is predicted in the ULK1 protein.[45] There is also a possible lipid binding region in ATG13, which is linked to negatively charged membrane phospholipids through arginine/lysine residues at the N-terminus of the protein.[46] Moreover, the ULK complex is also a positive regulatory factor in the phagophore expansion and autophagosome containing a specific double membrane structure.[47]

After autophagy is induced, multiple core ATG proteins in the cytoplasm are recruited to the site of autophagosome biogenesis, interacting with the membrane source here to generate autophagosome precursor/isolation membrane.[48-50] This process is also known as membrane nucleation, which is facilitated by phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3KC3) complex.[42,43] This PI3KC3 complex can also convene the ATG12-ATG5-ATG16L1 complex and microtubule-associated protein light chain 3 (LC3) to promote the expansion of the phagocytic vesicle membrane.

***Elongation and closure.*** After the formation of autophagosome precursors, the phagocytic vesicle membrane will continue to expand until the contents are completely wrapped. The above process also needs the participation of two ATG7-catalyzed ubiquitin-like coupling pathways.[47] The first ubiquitin-like system leads to coupling ATG5 with ATG12 and then forms a polycomplex with ATG16L1, this polycomplex interacts with the outer membrane of extended phagocytic vesicles.[51-53] The second system causes LC3 to be processed via encoding the mammalian homologous gene of yeast ATG8. Upon induction of autophagy, ATG4 protein cleaves pre-LC3 to generate LC3-I coupling with phosphatidylethanolamine in the membrane to form the lipid form of LC3 attaching to the autophagosome membrane.[54] LC3-II is recruited to the growing phagosome, and its integration depends on ATG5-ATG12.[55,56] Following the formation of autophagosome, LC3-II on the outer membrane recycles into the cytoplasm, which allows it to be used to assess cellular autophagy levels.[5,57]

***Fusion and degradation.*** The fusion of autophagosomes and endosomes/lysosomes requires the synergy of multiple membrane dynamics regulators, which includes soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), tethers and Rab7, as well as the mutual transport of autophagosome and lysosome.[58,59] This fusion process is mainly mediated by two SNARE complexes comprising syntaxin 17 (STX17), synaptosome associated protein 29 (SNAP29) and vesicle-associated membrane protein 8 (VAMP8), as well as YKT6, SNAP29 and STX7.[60,61] Different complexes may play a role in different steps of this fusion or drive autophagosomes to fuse with different late endosomes/lysosomes. The fused SNARE will decompose and revert to their donor compartments to uphold the characteristics of the inner membrane and prepare for subsequent fusion.[62]

Additionally, tethered proteins like homotypic fusion and vacuole protein sorting complex (HOPS), ectopic PGL-granule 5 (EPG5) , pleckstrin homology and RUN domain containing M1 (PLEKHM1) and tectonin β-propeller repeat containing 1 (TECPR1), also perform a crucial role in the capture of autophagosomes, promoting their fusion efficiency and specificity with lysosomes.[58] Specifically, HOPS, as the molecular chaperone of SNARE, binds to Rab7 and phosphatidylinositol to form a complex that targets autophagosomes or late endosomes/lysosomes.[63-65] EPG5 is a tethered protein that serves a crucial function in the fusion of autophagosomes obtained in the genetic screening of *C.elegans*.[66] As a Rab 7 effector, EPG5 transfers from the cytoplasm to the lysosome via interacting with Rab7 and VAMP8. During the fusion of autophagosomes and endosomes/lysosomes, EPG5 interacts with LC3 to capture autophagosomes/endosomes and enhances the STX17-SNAP29-VAMP8 complex. EPG5 deficiency leads to the accumulation of autophagosomes, amphisome and non-degradable autolysosomes.[67,68] The β-propeller proteins WD repeat domain 45 (WDR45) and WDR45B interact with EPG5 and mediate its target of lysosomes in neural cells. Additionally, the tethered protein PLEKHM1 is also an effector of Rab7.[69] As for TECPR1, it is localized to lysosome via binding to phosphatidylinositol 4-phosphate, and selectively binds to LC3C and ATG5-ATG12 on the autophagosome.[70,71] After autolysosome has formed, the inner substances of autophagosomes are degraded by a series of acid hydrolases including lipases and proteases and recycled by cells.[72] Collectively, the fusion of autophagosomes and endosomes/lysosomes involves multiple membrane fusions and is regulated by multiple factors. Therefore, the systematic analysis of these processes is crucial for understanding the entire autophagic process.

## Connective molecular machinery of exosome biogenesis and autophagy

Besides the interaction between autophagy and endocytosis,[73] recent studies suggest the exosome biogenesis is closely related to autophagy through common molecular machinery or organelle inside the cell,[74-77] pointing that

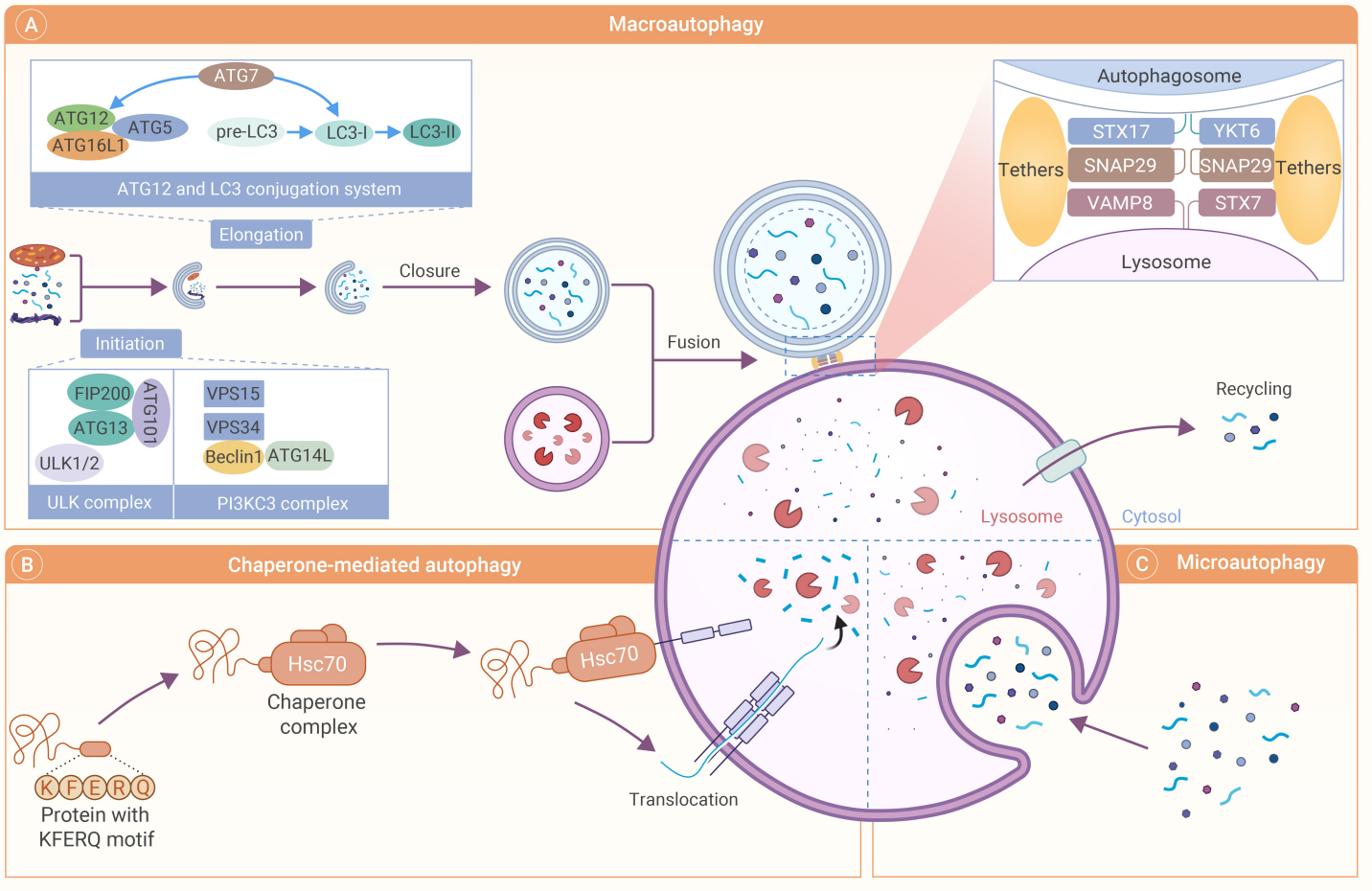


**Figure 2. Three categories of autophagy** (A) Macroautophagy is the pathway by which cytoplasmic components are degraded by the processes of initiation, elongation, closure, fusion and degradation. (B) Chaperone-mediated autophagy is an autophagic process that delivers proteins containing the pentapeptide sequence Lys-Phe-Glu-Arg-Gln (KFERQ) recognized by heat shock cognate protein 70 (Hsc70) for degradation in lysosome. (C) Microautophagy is able to degrade small amounts of cytoplasmic contents by delivering its targets to lysosome through lysosomal membrane invagination. PI3KC3: phosphatidylinositol 3-kinase catalytic subunit type 3; VPS: vacuolar protein sorting; FIP200: focal adhesion kinase family interacting protein of 200 kDa; ULK: unc-51 like kinase; ATG16L1: autophagy-related protein (ATG) 16 like 1; STX: syntaxin; LC3: microtubule-associated protein light chain 3; SNAP29: synaptosome associated protein 29; VAMP8: vesicle-associated membrane protein 8.

we should pay more attention to the regulatory mechanisms of intracellular organelle fate and the cargo transport of ATG proteins (Figure 3).

***Degradative autophagy and secretory autophagy.*** Although autophagy is classically viewed as degradative autophagy mediated by lysosome,[52] the core autophagy mechanism has now been involved in the termed secretory autophagy including conventional secretion of inflammatory cytokines,[78] secretory lysosomal efflux,[79] release of exosomes,[76,80] extracellular release of lysozyme[81] and unconventional secretion of proteins lacking N-terminal signal peptides.[82-84] Mostly, the secretory autophagy focuses on the last one through various mechanisms.[85,86] The identification of autophagy-related substance degradation and unconventional secretion paves the way for a major breakthrough in linking autophagy to a variety of physiological processes and disease conditions. However, the mechanisms for coordinating these two pathways are still elusive. Here, we mainly discuss the fate regulation mechanisms of MVBs and autophagosomes to understand the intracellular connection between exosomes and autophagy.

(1) The fate regulation of MVBs

Factually, in addition to fusing with the PM during classical exosome biogenesis, mature MVBs interacting with the ER are sorted to another destination known as lysosomes,[87,88] suggesting that MVBs can play the function of degradation or secretion. Evidently, starvation induced autophagy of erythroleukemia cell line K562 assists the fusion of autophagosome-MVB and reduces exosome release,[89] hypothesizing that the inability of exosome release causes MVBs to enter the degradative autophagy pathway. Furthermore, protein kinase C δ, a novel PKC subtype, regulates the fusion of MVB induced by T cell receptor with the PM at the immune synapse for the secretion of pro-apoptotic exosomes.[90] Post translational modification is also involved in sorting specific proteins into exosomes. For instance, as a ubiquitin-like modification, ISGylation induction decreases the number of MVBs and exosome secretion.[91]

Moreover, Rab11, a small GTPase regulating the transmembrane receptors of PM, promotes the docking of MVBs and PM with a calcium-dependent way.[92] However, the mutation of Rab11 and Rab4 leads to decreased exosomal cargo levels and intracellular cargo accumulation.[93] Further, heat shock protein 90 (Hsp90), as an effector protein of Rab11, allows exosome release through evolutionarily conserved amphiphilic helices.[94] Another small GTPase Rab35, promotes the fusion of MVB-PM in an adaptor protein $CD_2AP$ -dependent manner.[95,96] Furthermore, activated Akt linking stiff extracellular matrix promotes GTP loading to Rab8, driving exosome secretion.[97] Rab27 is the best-known as the regulator of exosome release by transporting MVBs.[98] Reportedly, two Rab27 isoforms, Rab27a and Rab27b, correspondingly affect the size and distribution of MVBs, revealing different roles in the exosomal pathway.[99] As a close relative of Rab27, Rab37 is additionally involved in the secretion of apical exosomes when Rab39 acts as a specific regulator of basolateral exosome release.[98] These studies have shown that endosomal recycling mechanisms, especially the small GTPase Rab family, act as a crucial role in the secretory fate of MVBs.

Additionally, ER membrane contact sites have been investigated to convert the fate of MVBs from secretion to degradation,[100] suggesting that the interaction between organelles may decide the fate of MVBs, especially the dynamics of membrane lipids. Moreover, another activated secretory autophagy pathway uses hydroxychloroquine to inhibit lysosome by increas-

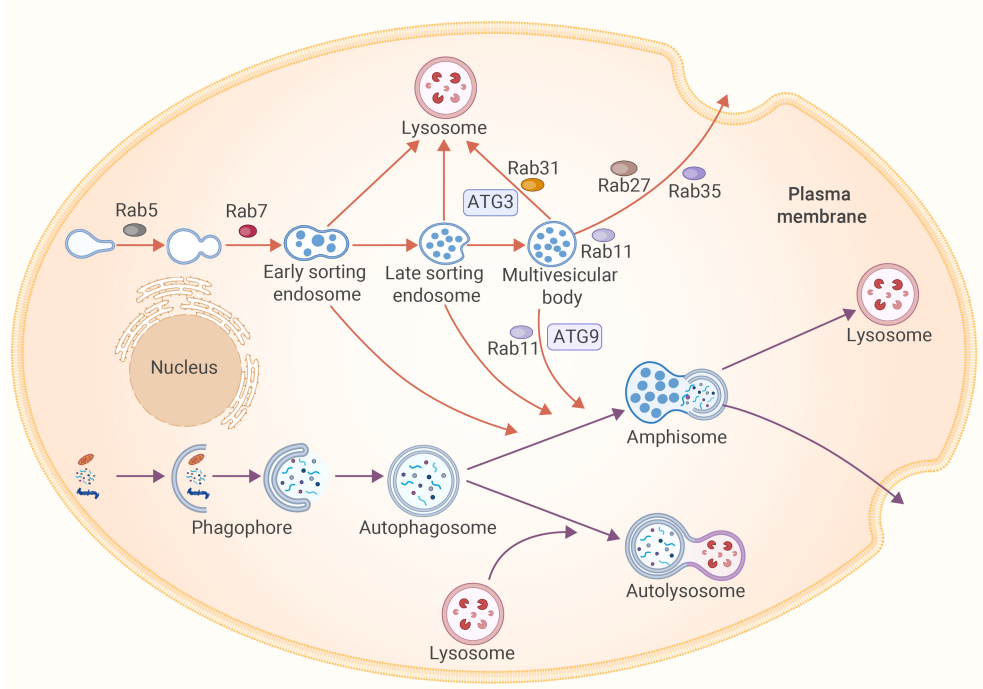


**Figure 3. The intracellular intersection of exosome biogenesis and autophagy** It mainly involves the fate of multivesicular bodies (MVBs) and autophagosomes. MVBs can directly secrete exosomes, and also fuse with lysosomes, while autophagosomes can bind to lysosomes to form autolysosomes. The intracellular intersection is that autophagosomes bind to different endosomes or MVBs to form amphisomes, which will be degraded or secreted.

ing lysosomal pH,[101] pointing the crucial function of pH in deciding the fate of MVBs. Additionally, several studies have been reported that pharmacological inhibition of lysosomes can induce strong extracellular release of autophagic cargoes through the secretion of exosomes.[102-104] These studies indicate the link between autophagic regulators and endolysosomal changes in unconventional secretion, suggesting that the fate of intracellular MVBs can be intervened by exogenous lysosomal inhibitors or nutrient treatment.

(2) The fate determination of autophagosomes

Similarly, except for fusing with lysosomes, nascent autophagosomes also directly fuse with LSEs, ESEs or MVBs to generate amphisomes, and lysosomes subsequently degrade their contents.[105,106] Conversely, amphisomes also perform a secretory function in lung epithelial cells, in which the treatment of interferon-γ leads to the co-localization of LC3B, annexin A2 and CD63 on the amphisome, indicating that the autophagosome formation and the amphisome fusing with PM are critical.[107] As for CD63, it is required for the endosomal cargo sorting latent membrane protein 1, but CD63-dependent vesicular protein secretion directly antagonizes the intracellular signaling activation of mTOR-related proteins under the condition of Epstein-Barr virus infection, providing a perspective for the complex intersection about secretion and degradation.[108] This fate switch of secretion and degradation has also been demonstrated to be controlled by protein tyrosine phosphatase 1B[109] or presenilins,[110] but these depend on the specific cellular microenvironment.

Additionally, interleukin-1β (IL-1β), an identified target of secretory autophagy in mammals, is integrated into the space between the inner and outer membrane of autophagosome intermediates to be transported to the PM for secretion.[111,112] However, it should be emphasized that autophagy-dependent unconventional secretion and exosome secretion are carefully discriminated. Specifically, when the secretion of IL-1β with an autophagy-dependent manner requires MVBs, the formation of amphisomes is necessary.[112,113] Intriguingly, a recent study reveals the closed-loop effect of mitophagy-mediated exosome[8], pointing that the balance between selective autophagy of organelles and exosomes deserves our attention. Overall, elucidating the function of autophagy-dependent secretion, especially for selective autophagy at the organelle level, is an important area for understanding exosome biogenesis in future study.

***Vesicular transport of ATG proteins.*** The role and mechanism of ATG proteins in regulating autophagy have been widely explored. However, more and more studies have shown that ATG proteins play non-autophagic functions to regulate different biological processes without affecting autophagy.[114-116] For instance, kinesin heavy chain adaptor protein unorded 76 is bound to and phosphorylated by ATG1, which increases its affinity with synaptotagmin 1 to promote the transport of axonal guidance molecules in *Drosophila melanogaster*.[117,118] Similarly, ATG6 has been reported to be essential for vesicular transport in *Drosophila melanogaster*,[119] the endocytosis of ATG6-deleted pupal wing cells is severely damaged and the late endosome formation is abnormal along with dense vesicle bodies containing multilayer bodies.[120] Moreover, ATG9 and ATG16 may participate in phagocytosis with an autophagy-independent way.[121] Furthermore, ATG9 is involved in the formation of ILVs as the only transmembrane protein and the knockdown of ATG9 impairs autophagic flux and reduces ILVs in the amphisomes and autolysosomes under the basal state.[122] Apart from regulating the lipidation of LC3 and autophagosome formation, ATG16L1 also repairs PM mediated by lysosome, which does not depend on its role in autophagy.[123,124] The deletion of ATG5 enhances the phagocytosis of dendritic cells,[125] and ATG5 and ATG16L1 have been indicated the secretory function of exosome biogenesis.[80] Specifically, the dissociation of vacuolar proton pump from MVBs is mediated by ATG5, allowing MVB-PM fusion to release exosome instead of the acidification of MVBs,[80] evidence points that ATG proteins participate in the fate of MVBs between degradation and secretion. Other ATG proteins like ATG3, ATG4B, and ATG7, are related to non-autophagic phagocytosis.[126] ATG8 family proteins take part in LC3-associated phagocytosis (LAP) and endocytosis (LANDO) except for regulating autophagy.[127] Similarly, subsequent studies further reveal these processes of LAP[128] and LAP-like LC3 conjugation on endosomes,[129] LANDO,[130] LC3 - dependent EV loading and secretion.[131] Additionally, the phosphatidylinositol 3-kinase (PI3K) complex is connective between endocytosis and autophagy, and its function depends upon binding different regulatory proteins. For example, the PI3K complex binds to ATG14L to mediate the expansion of autophagosome, while binding to UV radiation resistance-associated gene promoting endosomal maturation.[132,133] The instability of PI3K complex after inhibiting beclin1 would reduce the exosome release and autophagic flux of chronic myeloid leukemia cells.[134] Taken together, we mainly summarize and discuss the cargo sorting and phagocytosis of ATG proteins to understand their roles in exosome biogenesis.

## INTERCELLULAR RELATIONSHIPS BETWEEN EXOSOMES AND AUTOPHAGY

### Exosome internalization

Exosomal diverse components could reflect its parental cell.[4] After exosome secretion, exosomal cargoes are often released into the extracellular environment through various mechanisms, which include transmembrane channel-mediated active transport or exosome destruction by secreted lipases,[135,136] providing a mechanism to ensure effective intercellular communication by regulating exosomal cargoes. When exosomes reach the recipient cells, they are internalized along with binding to the cell surface and activating signaling cascades.[137] Generally, these two steps involve the interactive mode between exosomes and recipient cells and the intracellular transport pathway, the uptake of exosomes is often selective.

***Membrane surface receptor-ligand interaction.*** The manner in which exosomes bind to the cell surface through their surface proteins has been

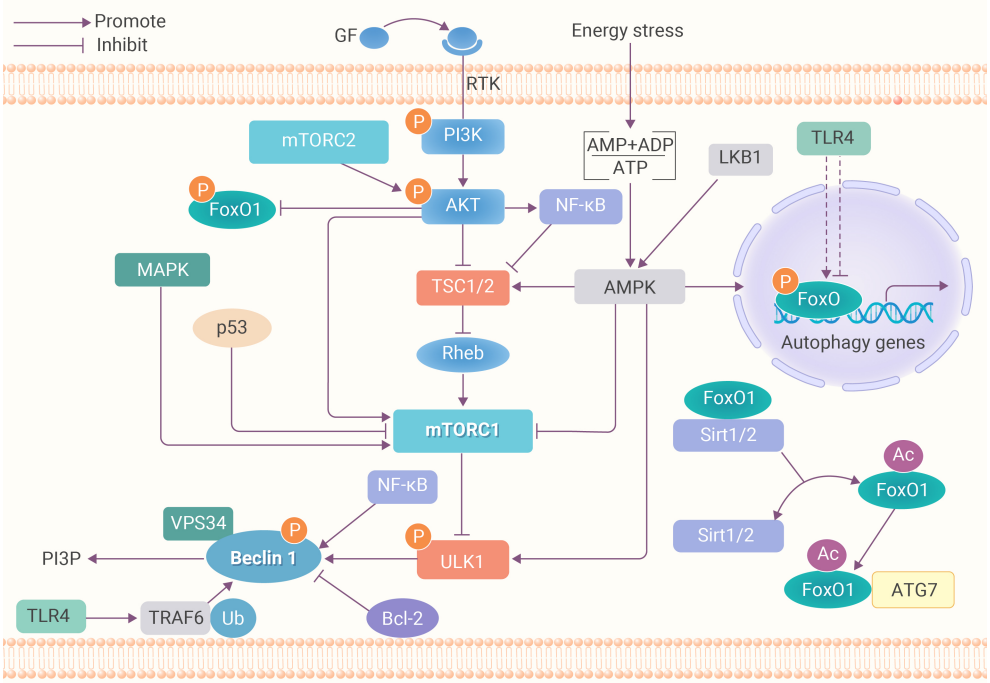


**Figure 4. Autophagy-related signals** Beclin-1 and mTORC1 are the hubs of autophagy-related signals. Growth factors (GF) activate phosphatidylinositol 3-kinase (PI3K) by binding to receptor tyrosine kinase (RTK), thereby phosphorylating protein kinase B (AKT). Activation of AKT inhibits tuberous sclerosis complex 1/2 (TSC1/2) complex, releasing Ras homolog enriched in brain (Rheb) to activate mTORC1. It will phosphorylate unc-51-like kinase 1 (ULK1) to inhibit its activity, which prevents autophagy initiation. Mitogen-activated protein kinase (MAPK) is a positive regulator of mTORC1, while tumor protein 53 (p53) in the cytoplasm and adenosine 5'-monophosphate-activated protein kinase (AMPK) are negative regulators. The activation of Beclin-1 will form a complex with vacuolar protein sorting 34 (VPS34) to produce phosphatidylinositol 3-phosphate (PI3P). P: phosphorylation; Ac: acetylation; Ub: ubiquitin; Bcl-2: B-cell lymphoma-2; NF-κB: nuclear factor kappa-B; LKB1: liver kinase B1; TRL4: toll-like receptor 4; FoxO: forkhead box protein O; Sirt1/2: silent information regulator 2 homologue 1/2; TRAF6: tumor necrosis factor receptor associated factor 6.

demonstrated by reduced uptake of recipient cells due to the degradation of these surface proteins.[138,139] Another study reports CD9 is the cell surface glycoprotein and tetraspanin of EVs from cancer-associated stromal fibroblast containing abundant annexin A6 to mediate tumor-stroma crosstalk.[140] Similarly, vimentin-contained exosomes secreted from colorectal cancer cells could be internalization by macrophages through receptor-mediated recognition.[141] These above studies have revealed the crucial function of proteins in exosome internalization. In addition, there are also reported examples of ligand-receptor binding, such as integrin-tetraspanin complex,[142,143] exosomal ephrin receptor binding to ephrin expressed on the cell membrane of recipient cells[144-146] and the receptor bearing collagenous structure mediating exosome internalization in macrophage.[147] In addition, the proteome of parental cell effects the surface proteins of exosomes, so these studies indicate that the membranal components of exosomes could be dynamic according to different physiological states of cells. The glycosylation modification of protein also affects the uptake of exosomes in target cells,[148] suggesting that we need to pay attention to the mechanism of other modifications of proteins in exosome internalization.

***Endocytosis.*** Moreover, endocytosis including macropinocytosis[149] and phagocytosis[150,151] is one of the mechanisms of exosome internalization promoted by clathrin, caveolae, dynamin and cholesterol.[152-155] Likewise, endocytosis without clathrin operates with the requirement of caveolin 1, small GTP binding proteins of the Rho family and specific lipids.[156] Additionally, enzymatic knockout of heparan sulfate proteoglycans (HSPGs) could significantly reduce the uptake of exosomes.[157] The integrin ITGB3 interacts with HSPGs, allowing their endocytosis-mediated exosome internalization[158] and hypoxia-mediated exosome uptake is dependent on the increased HSPGs, which preferentially follow the lipid-raft pathway.[159] These processes have a certain bias to the target cells. Furthermore, exosomes secreted from oligodendrocytes could be internalized in microglia, which is achieved through a macropinocytotic mechanism that is not accompanied by an inflammatory response.[160] Epidermal growth factor receptors significantly enhance exosome uptake by actively inducing macropinocytosis.[161] These macropinocytosis-mediated exosome internalizations have also been reported in other studies.[162,163] Additionally, the uptake of exosomes by phagocytes occurs through phagocytosis to understand the exosome-cell interaction,[150,151] but it may represent a selective clearance compared with non-phagocytic cells.[150] Once secreted exosomes are internalized inside target cells, they could be delivered to regulate the phenotype and function of recipient cells.[164,165]

***Membrane fusion.*** During the fusion of exosomes with the cell surface membrane, two different lipid bilayers approach each other to form a hemifusion stalk, which facilitates the mixing of the two hydrophobic cores.[152] For instance, specifically, exosomal α-synuclein is released into the recipient cell through direct fusion with PM.[166] Whether the exosomal lipid components participate in this fusion process is an important research topic for the future.

## Autophagy-related signals

As previously mentioned in the mechanisms of autophagy, this process involves the regulation of a complex set of molecules and proteins. Multiple signals are key factors in regulating autophagy (Figure 4).

***mTORC1.*** mTOR is the target protein of rapamycin including mTORC1 and mTORC2.[167] Specifically, under the condition of nutritional deficiency or after treatment with mTOR inhibitors, mTORC1 is dissociated from the ULK complex to ultimately induce autophagosome formation, but the opposite results are observed under the sufficient nutrition condition.[168] The phosphorylation of ULK1 gives rise to inhibiting its own activity, thereby suppressing autophagic initiation. Moreover, phosphorylation of mTORC1-dependent ATG13 also inhibits ULK1 activity and prevents the complex from recruiting to the site of autophagic initiation.[169] These suggest that mTORC1 could attenuate the occurrence of autophagy upon activation. However, it has also been found that simultaneous inhibition of mTORC1 and mTORC2 activity may enhance autophagic induction.[170] In particular, celastrol known as a triterpene compound, triggers apoptosis and autophagy via blocking Akt/mTOR signaling pathway.[171] Activated Akt activates mTORC1 to inhibit autophagy and also phosphorylates the tuberous sclerosis complex (TSC) 1/2, enriching the small GTPase Ras homologue enriched in brain (Rheb) to activate mTORC1.[172,173] Interestingly, Rheb is anchored on the outer surface of lysosome,[174] suggesting that Rheb could activate mTORC1 via interacting with it when mTORC1 is attached to the outer surface of lysosome.[175]

Additionally, isoliquiritigenin inhibits the development of pancreatic cancer via blocking autophagy through direct targeting p38 MAPK signaling pathway.[176] AMPK is activated when the cellular energy state is destroyed.[177] Activated AMPK could directly catalyze the multisite phosphorylation of serine in ULK1 to block the interaction between ULK1 and AMPK[178] or phosphorylate the raptor in mTORC1, thereby inactivating mTORC1 to induce autophagy.[179-181] These studies suggest that activation of AMPK could upregulate autophagy to degrade proteins as an alternative source of nutrients. As for p53, it plays dual significantly different roles in regulating autophagy. While p53 in the nucleus could activate autophagy, p53 in the cytoplasm could inhibit autophagy, but its mechanism remains to be studied.[182] Therefore, it can be seen that the function of p53 on autophagy hinges on its subcellular localization. Generally, Akt and MAPK signaling pathways inhibit autophagy upon activation of mTORC1 pathways, and negative regulation of mTORC1 pathway like AMPK signaling pathway promotes autophagy.

***Beclin-1.*** Beclin-1 is mainly located in the TGN, ER and mitochondria to

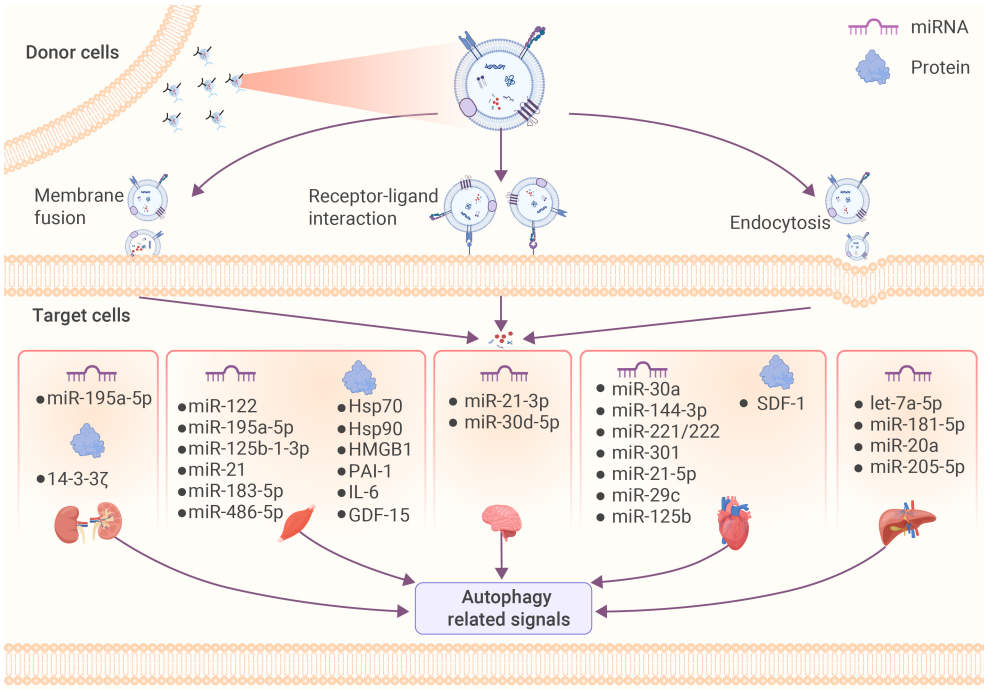


**Figure 5. Exosomal cargoes regulate autophagy-related diseases** Donor cells-derived exosomes are internalized by target cells in the brain, muscle, heart, kidney and liver through the three ways. The encapsulated miRNAs and proteins can regulate autophagy-related signals to affect the occurrence and development of diseases. Hsp: heat shock protein; PAI-1: plasminogen activator inhibitor-1; IL-6: interleukin 6; GDF-15: growth differentiation factor 15; HMGB1: high mobility group box protein B1; SDF-1: stromal-derived factor 1.

initiate autophagy,[183] which controls autophagy via regulating the production of phosphatidylinositol-3-phosphate.[184-186] Detailly, vesicular protein sorting 34 combines with Beclin-1, recruiting ATG14L to promote autophagosome fusion.[187,188] However, B-cell lymphoma-2 (Bcl-2) binds to the Bcl-2-homology-3 domain of Beclin-1 to inhibit Beclin-1-dependent autophagy,[188] suggesting that the relative number of Bcl-2 and Beclin 1 binding to each other in cells determines the level of autophagy.

***Forkhead box Os (FoxOs).*** The FoxO family of mammals is widely expressed in vivo and has a positive regulatory effect on autophagy-related and lysosomal genes.[189,190] FoxO1 and FoxO3 are identified as major triggers of autophagy, which could depend on specific context.[191-193] The genetic regulation of FoxO is associated with significant variations in the expression of some autophagic genes related to the processes of autophagic initiation, autophagosome formation and fusion.[191,192,194-197] In addition to the above typical function as transcription factors, FoxOs may also regulate autophagy by directly coupling with ATG7 in the cytoplasm with a transcriptional-regulation-independent manner.[198-201] Additionally, FoxOs also control autophagy activity via epigenetic mechanisms,[202-204] but this is still in its infancy. Furthermore, the turnover of FoxO protein is regulated by autophagy.[205,206] These studies have basically determined the regulatory pathway of FoxO on autophagy, and whether autophagy will regulate upstream of FoxO still needs to be studied, that is the balance of FoxO-autophagy axis further studies are concerned with.

***Nuclear factor kappa-B (NF-κB).*** NF-κB serves a momentous role in regulating cell death by inducing transcription of genes encoding apoptosis and autophagy. It exists in the form of dimers and participates in various diseases.[207] The involvement of this signaling in autophagy has been observed to be dependent based on environmental factors.[208] Activated NF-κB is enough to stimulate the expression of *BECN*1 and Bcl-2-associated athanogene 3-HspB8 complex.[207,209,210] Contrarily, the NF-κB signaling pathway may promote the expression of autophagic inhibitors like Bcl-2 family members and Beclin-1 binding partners and restrain autophagy inducers such as p53.[210-212]

***Toll-like receptors (TLRs).*** TLRs are a class of transmembrane proteins composed of extracellular, transmembrane and intracellular signal domains. There are more and more studies linking TLRs with autophagy, especially TLR4 and TLR7.[213-215] Specifically, there may be autophagy-related signals downstream of TLR4. TLR4 initiates the recruitment of myeloid differentiation factor 88 and activates tumor necrosis factor receptor associated factor 6 (TRAF6). The polyubiquitination of TRAF6 activates Beclin-1 to promote autophagy.[216,217] However, activated TLR4 suppresses autophagy through inhibiting FoxO3 in microglia, the opposite response is observed in macrophages,[218] suggesting that the function of TLR4 may be affected by cell type. As for TLR7, it pitches in imiquimod-induced cell death characterized by autophagosome formation.[219] These studies have shown the function of TLRs in immune cells. Future studies are supposed to explore the intersection between more different TLRs and autophagy.

## The applications of native exosomes regulating autophagy in diseases

Native exosomes are extracted from cell supernatants under physiological or pathological conditions.[220] The internalization of exosomes into various tissues indicates that specific signals could be transmitted to key metabolic tissues through the exosome pathway.[4] Previous reviews mainly emphasis on the function of exosomal miRNAs and proteins under physiological or pathological conditions,[221,222] this is also paid the similar attention to understand the application of exosomal contents in regulating autophagy. However, this does not mean ignoring the role of other cargoes in exosomes. In this section, we summarized the most recent studies on the diverse pathological processes involving native exosomal miRNAs and proteins (Figure 5).

***Skeletal muscle wasting.*** The ubiquitin-proteasome and autophagy-lysosome systems are two important mechanisms to degrade muscle protein.[223,224] These two systems recognize ubiquitination through different mechanisms and are dynamic interactions between degraded signals and systems, which are interdependent in the development of skeletal muscle wasting under diverse conditions.[225] Multiple inflammatory cytokines could activate these two pathways, such as tumor necrosis factor-α, IL-6, IL-1α and interferon-γ.[226-228] Importantly, exosome-associated miRNAs and proteins activate multiple signaling pathways to promote or inhibit autophagy.[229] Specifically, breast cancer cell-derived exosomes encapsulate miR-122 to target O-linked N-acetylglucosamine(O-GlcNAc) transferase and mediate its down-regulation, promoting O-GlcNAc glycosylation of ryanodine receptor (RYR1), thereby reducing its ubiquitination to degrade. Accumulated RYR1 leads to increasing the levels of intracellular $Ca^{2+}$ and activating calpain proteases to induce the cleavage of muscle protein,[230] indicating that the non-ubiquitination modification of the receptor causes its accumulation to affect the skeletal muscle proteolysis. Another study reports that the loss of muscle mass is owing to the oxidation of RYR1 induced by TGF-β in mouse bone metastasis.[231] Moreover, miR-195a-5p and miR-125b-1-3p from colon cancer cells-derived exosomes could activate the apoptosis signaling pathway via downregulating the level of Bcl-2.[232] Tumor-derived exosomal miR-21 induces apoptosis through TLR7 signaling.[233] These studies reveal that the apoptotic pathway also contributes to muscle proteolysis. Similarly, another exosomal miR-183-5p secreted from aforementioned cells could also induce the degradation of myotube protein.[234] In addition to the promotive role, bone marrow mesenchymal stem cell (BMMSC)-derived exosomal miR-486-5p suppresses muscle atrophy by downregulating the nuclear translocation of FoxO1.[235] These studies indicate that exosomal miRNAs could perform an anti-wasting function.

Similarly, exosomal proteins could be also internalized by skeletal muscle cells to activate downstream signaling pathways related to muscle atrophy.

For instance, tumor-released exosomes induce muscle catabolism by triggering TLR4-p38-MAPK signaling pathway, which is manifested as the upregulation of LC3 via loading with Hsp70 and Hsp90.[236] Another study also demonstrates that exosomes containing Hsp70 and Hsp90 upregulate F-box protein 32 and ubiquitin ligase E3 α II in myotubes by activating p38 MAPK, resulting in muscle loss.[237] High mobility group box protein B1-encapsulated exosomes cause muscle atrophy via activating the TLR4/NF-κB signaling pathway.[238] Exosome-enveloped plasminogen activator inhibitor-1 could promote the phosphorylation of signal transducers and activators of transcription 3 (STAT3) ,[239] which facilitates the dephosphorylation of FoxO1 and FoxO3 to enter the nucleus to promote autophagy.[240] Additionally, IL-6, known as a pro-inflammatory factor in skeletal muscle wasting,[241-243] is loaded into Lewis lung carcinoma cell-derived exosome to degrade the protein of C2C12 myotubes via triggering the STAT3 signaling pathway.[244] Additionally, tumor-derived exosomes containing growth differentiation factor 15 could regulate Bcl-2/caspase-3 pathways to induce muscle atrophy.[245] These studies have shown that exosomal proteins can activate different signal cascades with intersections depending on their components and targets. Overall, we may be concerned that different proteins and miRNAs in exosomes are uptaken by target cells to trigger the same downstream signaling pathways. Future research should pay more attention to exosomes as a whole functional unit, rather than just the role of individual molecules inside.

***Nervous system disease.*** The cerebral cortex of fetal rats is isolated to culture in vitro, and it is found for the first time that neurons could secrete exosomes.[246] The activity of vesicles is closely related to synaptic activity.[247-249] Similarly, exosomes from different sources treat neurological diseases by regulating autophagy. For example, miR-21-3p from human umbilical vein endothelial cell-derived exosomes suppress apoptosis of neural cells, which depends on the restored function of ATG12.[250] Adipose-derived mesenchymal stem cells (ADSCs)-derived exosomes bearing miR-30d-5p counteract brain injury via promoting M2 microglial/macrophage polarization.[251] Additionally, human umbilical cord mesenchymal stem cells (hucMSCs)-derived exosomes repair a Parkinson's disease (PD) via activating autophagy.[252] Furthermore, neural stem cell-derived exosomes increase the expression of LC3 and Beclin-1, and accelerate autophagosome formation, which may promote autophagy to reduce neuronal apoptosis inhibiting neuroinflammation at the early stage.[253] These studies suggest the therapeutic potentiality of exosomes regulating autophagy in nervous system diseases.

***Cardiovascular disease.*** Dysregulation of autophagy in cardiomyocytes and endothelial cells is associated with cardiac hypertrophy, atherosclerosis, myocardial infarction and heart failure.[254] Inhibiting the release of exosome containing overexpressed miR-30a can upregulate the expression of ATG proteins and ensure that cardiomyocytes maintain the necessary autophagy level after hypoxia,[255] because miR-30a can directly attaching to the 3'-UTR of BECN 1 to facilitate its degradation.[256] Exosomes released by BMMSCs carry miR-144-3p into cardiomyocytes to inhibit ischemia-reperfusion(I/R)-induced cardiomyocyte apoptosis and autophagy.[257] Exosome-mediated autophagy could represent a novel regulatory mechanism for I/R injury, and targeting this pathway might offer an innovative therapy for ischemic heart disease. MiR-221/222 is significantly expressed in exosomes from human aortic smooth muscle cells, which inhibits autophagy after co-cultured with human umbilical vein endothelial cell lines, thereby affecting the development and progression of Atheromatosis.[258] Additionally, some studies have reported that exosomal cargoes, such as miR-301,[259] miR-21-5p,[260] miR-29c,[261] miR-125b,[262] stromal-derived factor 1,[263] regulate autophagy to participate in cardiovascular diseases. However, other studies still need to elucidate the specific molecules of exosomes, providing targets for intervention.

***Liver disease.*** Exosomes could perform a fundamental role in the liver disease by their functional substances. Increasing evidence shows that exosomes derived from hepatocytes or extrahepatic mesenchymal stem cells (MSCs) inhibit the development of liver failure and promote the repair and regeneration of damaged hepatocytes by regulating the damaged liver microenvironment.

For instance, bone marrow stromal cell-derived exosomes are internalized by hepatocytes, which increases the expression of LC3 and Beclin-1 to promote the formation of autophagosomes, but apoptosis is significantly increased after intervention with autophagy inhibitors,[264] indicating that these exosomes may exert a protective effect on hepatocytes by activating autophagy to inhibit hepatocyte apoptosis. MSCs-derived exosomes are enriched with let-7a-5p, which activates autophagy by targeting mitogen-activated protein kinase kinase kinase kinase 3 (MAP4K3) to reduce the phosphorylation of transcription factor EB. Blocking the MAP4K3 pathway can weaken the activation effect of let-7a-5p on autophagy,[265] confirming that the liver protection of MSCs may be partially due to the autophagy repair mediated by let-7a-5p in exosomes. The exosomes extracted from MSCs-induced differentiated hepatocyte-like cells are injected into the mouse model of I/R liver injury, showing that these exosomes could reduce I/R-related liver injury by enhancing autophagy and inhibiting hepatocyte apoptosis.[266] MiR-181-5p from exosomes derived from ADSCs attenuates liver fibrosis by activating autophagy via STAT3/Bcl-2/Beclin-1 axis in mouse hepatic stellate cells.[267] Additionally, miR-20a from umbilical cord mesenchymal stem cell-derived exosomes is clarified to attach to the 3'-UTR of BECN 1 to exert an inhibitory effect on its expression.[268] In addition to miRNAs, exosomes containing circTGFBR2 are delivered into hepatocellular carcinoma cells to interact with miR-205-5p to promote the expression of ATG5.[269] Moreover, quercetin activates autophagy and reduces exosome release by regulating lysosomal function to alleviate ethanol-induced hepatocyte injury,[270] suggesting that this holds substantial importance for the application of quercetin in treating alcoholic liver disease. The above studies have shown that exosome-mediated autophagy activation can effectively alleviate liver cell damage and play a protective role in liver failure. Upcoming studies also need to explore the function of exosomal proteins in regulating autophagy for liver disease therapies.

***Kidney disease.*** Exosomes could regulate kidney diseases through autophagy, which include diabetic nephropathy (DN) and renal injury. Specifically, DN is a serious kidney-related complication, which is along with overnutrition and obvious inhibition of renal cell autophagy.[271-273] Exosomes from mesenchymal stem cell-derived improved DN by downregulating the mTOR signaling pathway.[274] Another study reports exosomes secreted from ADSCs attenuate DN via promoting autophagic flux and inhibiting apoptosis in podocytes.[275] Additionally, 14-3-3zeta delivered by hucMSC-exosomes may upregulate the autophagic level via modulation of ATG16L, repressing the injury of cisplatin in human renal tubular epithelial cell lines HK-2.[276,277] Moreover, hucMSC-exosomes can also activate the downstream autophagy pathway, thereby improving the level of apoptosis and promoting the renal repair.[278] BMMSC-exosomes improve lipopolysaccharide-induced renal injury in rats via enhancing the expression of LC3 II/I and p-AMPK and reducing the expression of p62 and p-mTOR.[279] Another study has revealed that autophagy-deficient macrophages aggravate kidney injury via exosomal miR-195a-5p-SIRT3 axis,[280] suggesting that macrophage autophagy has become a potential therapeutic target for acute kidney injury and other inflammation-related diseases. These studies have shown the autophagy regulation and therapeutic potential of MSC-exosomes in kidney disease.

## The applications of engineered exosomes regulating autophagy in diseases

There are many limitations in the clinical application of native exosomes, so engineered exosomes have garnered widespread interests as potential delivery tools due to their ability to target receptor ligands for surface modification and their efficient uptake by target cells across various barriers.

The therapeutic potentiality of engineered exosomal miRNAs in skeletal muscle wasting has made great progress. For instance, miR-26a is essential for the development of skeletal muscle.[281] The prepared miR-26a overexpressed exosomes containing muscle-specific targeting peptides contribute to its selective delivery to limit skeletal muscle wasting.[282] Engineered exosomal proteins are also investigated to serve different roles in skeletal muscle loss. For instance, Hsp60 could induce the expression of peroxisome proliferators activated receptor γ coactivator α1 (PGC-1α).[283] The C2C12 cell line is genetically modified with Hsp60 overexpression plasmid to produce exosomes containing Hsp60, which activate the expression of PGC-1α isoform 1 to inhibit muscle atrophy.[284] Another study constructs exosomes bearing IL-6 signal transducer decoy receptors, which selectively attenuate the IL-6 trans-signaling pathway to effectively decrease the phosphorylation

level of STAT3.[285] Collectively, their different roles may depend on cell types and specific targets.

In addition, the application of engineered exosomes has also been reported in nervous system diseases. For instance, Fe65-engineered exosomes encapsulating a natural autophagy inducer named as corynoxine-B could enter neuronal cells through amyloid-β precursor protein receptor-dependent endocytosis to induce autophagy, thereby alleviating Alzheimer's disease (AD) pathology via improving cognitive behavior,[286] suggesting that exosomes loading autophagy inducer is a feasible way by targeting the process of autophagy. Furthermore, exosomes secreted by nano-mesenchymal stem cells with high expression of tyrosine phosphatase-2 are delivered to the brain, which greatly enhance mitophagy in neurons, leading to a reduction in neuronal apoptosis and neuroinflammation to rescue synaptic loss in AD mouse models.[287] Similarly, an engineered cell vector delivers exosomal miR-138-5p to enhance mitophagy and protect hypoxic-damaged neurons,[288] the above studies imply that the relationship between exosomes and selective autophagy needs further attention. Furthermore, coupling dopamine to the surface of EVs can effectively target dopaminergic neurons in the PD brain to induce autophagy.[289] This finding paves the way for the use of dopamine-EVs as a new and selective disease modifier for the treatment of PD.

Moreover, the applications of engineered exosomes in other diseases have also been reported. For common spine and joint degenerative diseases, the use of pro-inflammatory cytokine TNF-α pretreatment increases the production of exosomes from infrapatellar fat pad-derived mesenchymal stem cells[290] and the chondrocyte-targeted FoxO3 gene editing hybrid exosome based on CRISPR/Cas9 technology is innovatively developed,[291] which enhance their own efficacy on osteoarthritis. A threaded microneedle that matches the structure of the annulus fibrosus can be loaded with exosomes derived from BMMSCs to encapsulate miR-378 that regulates mitophagy to repair intervertebral disc degeneration.[9]

Existing studies have designed engineered exosomes in different ways and link them with autophagy, especially at the organelle level, achieving synergy between yield and efficacy, showing the significant advantages of engineered exosomes, but more clinical studies are needed to evaluate its long-term safety.

## CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In summary, the intracellular connection between exosomes and autophagy mainly depends on the fate of MVBs and the vesicular trafficking of ATG proteins in addition to the classical autophagy function. Numerous studies have clarified the function of Rab family and SNARE complex in exosome secretion, and one study has shown that MVBs are localized to the PM for exosome secretion, which is controlled by phosphatidylinositol.[292] However, the molecular mechanism by which ILVs are released into exosomes rather than fused with lysosomes for degradation still remains unclear. Although they would show functional redundancy, they could also compensate for each other, indicating the intracellular balance to provide the possibility of external intervention. The intercellular relationship of them is based on the uptake of different cells-derived exosome to regulate ATG molecules to change their target cell status. However, the effect of target cell autophagy on internalizing exosome is rarely reported, meaning that the intercellular balance between exosomes and autophagy is neglected. Additionally, most studies mainly emphasis on the function of exosomal miRNAs and proteins. Indeed, the cellular homeostasis relies on the communication of different organelles, which is mediated by interorganelle membrane contact sites, pointing the importance of membrane lipid dynamics.[293] In particular, the processes of autophagy involve the extension of membrane, thus the function of exosomal lipids in regulating autophagy remains to be studied in the future.

Furthermore, several studies clarify the relationship between ATG molecules and vesicle trafficking or focus on a single study of autophagy-related diseases using invertebrates like *Drosophila melanogaster* and *C.elegans*, suggesting that there is little interaction between exosomes and autophagy. Collectively, we elaborate more on the intersection between exosomes and non-selective autophagy in this review, while the connection with selective autophagy at the organelle level has rarely been reported, which occasionally points to few studies on mitophagy and exosomes. The key step in the selective autophagy of organelles is the specific recognition and encapsulation of damaged or unwanted organelles via the autophagic membrane, which requires the presence of specific proteins on the organelles to act as receptors. Successive studies have shown that spartin,[294] oxysterol-binding protein-related protein 8[295] and ATG14[296] could be used as receptors to mediate lipophagy. It is evident that the dynamic and context-specific interactions have significant implications for between normal physiology and various diseases, offering therapeutic opportunities if we could better comprehend them, especially at the organelle level.

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## AUTHOR CONTRIBUTIONS

Q. L. drafted the manuscript, F. L. and Y. Y. supervised the manuscript, and other authors critically revised the manuscript. All authors were responsible for the content of the manuscript and approved the final version for submission.

## DECLARATION OF INTERESTS

Yulong Yin is an Editorial Board member of The Innovation Life. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare that they have no conflicts of interest.

## ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

## DATA AND CODE AVAILABILITY

Not applicable.