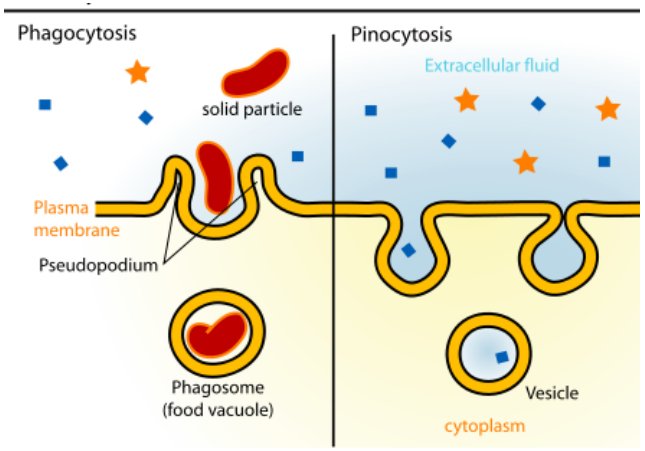
Endocitosi

VI SONO DIFFERENTI TIPI DI ENDOCITOSI

TIPO DI MATERIALE INTERNALIZZATO

FAGOCITOSI

PINOCITOSI (micro-macro)

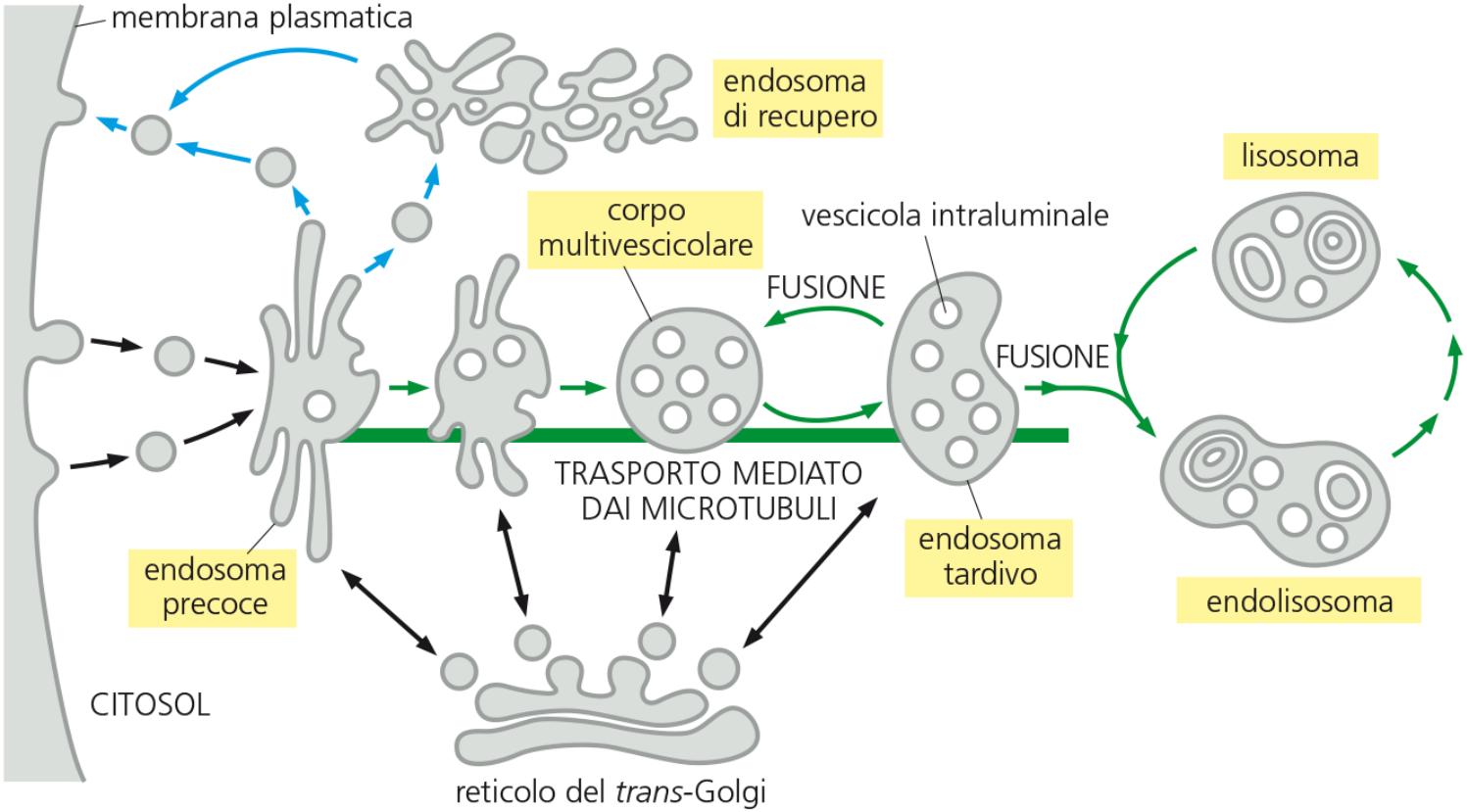


TIPO DI VESCICOLA CHE SI FORMA

ENDOCITOSI MEDIATA DA CAVEOLE (caveolina)

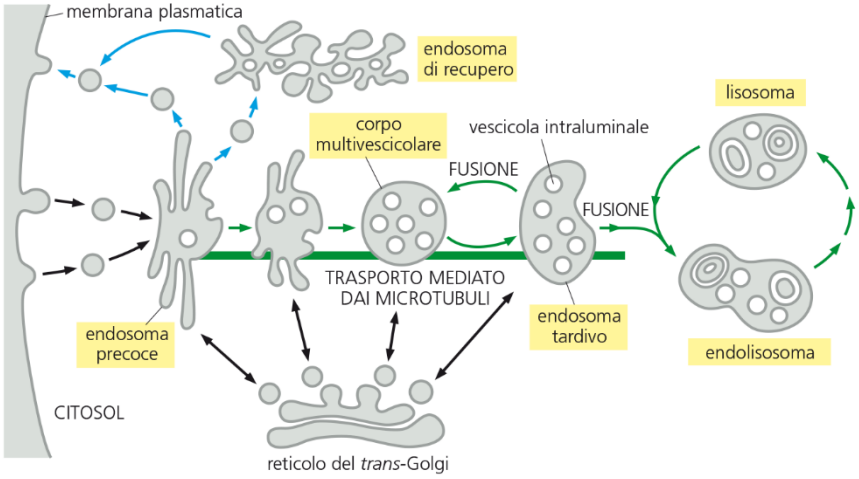
ENDOCITOSI MEDIATA DA RECETTORE (clatrina)

ENDOCITOSI E' UN MECCANISMO CON CUI LA CELLULA INTERNALIZZA 'MATERIALI' DALL'ESTERNO



Le proteine di membrana destinate alla degradazione vengono internalizzate nelle vescicole intraluminali. La trasformazione degli endosomi precoci in tardivi è accompagnata dalla perdita delle sporgenze tubulari. L'endosoma tardivo o corpo multivescicolare si muove lungom i microtubuli, verso l'interno della cellula. Gli endosomi tardivi maturi non mandano più vescicole alla membrana e si fondono tra loro e coi lisosomi per degradare il loro contenuto.
La maturazione degli endosomi è connessa per mezzo delle vescicole di trasporto al TGN, fornendo di continuo proteine lisosomiali di nuova sintesi.

Processo di maturazione degli endosomi

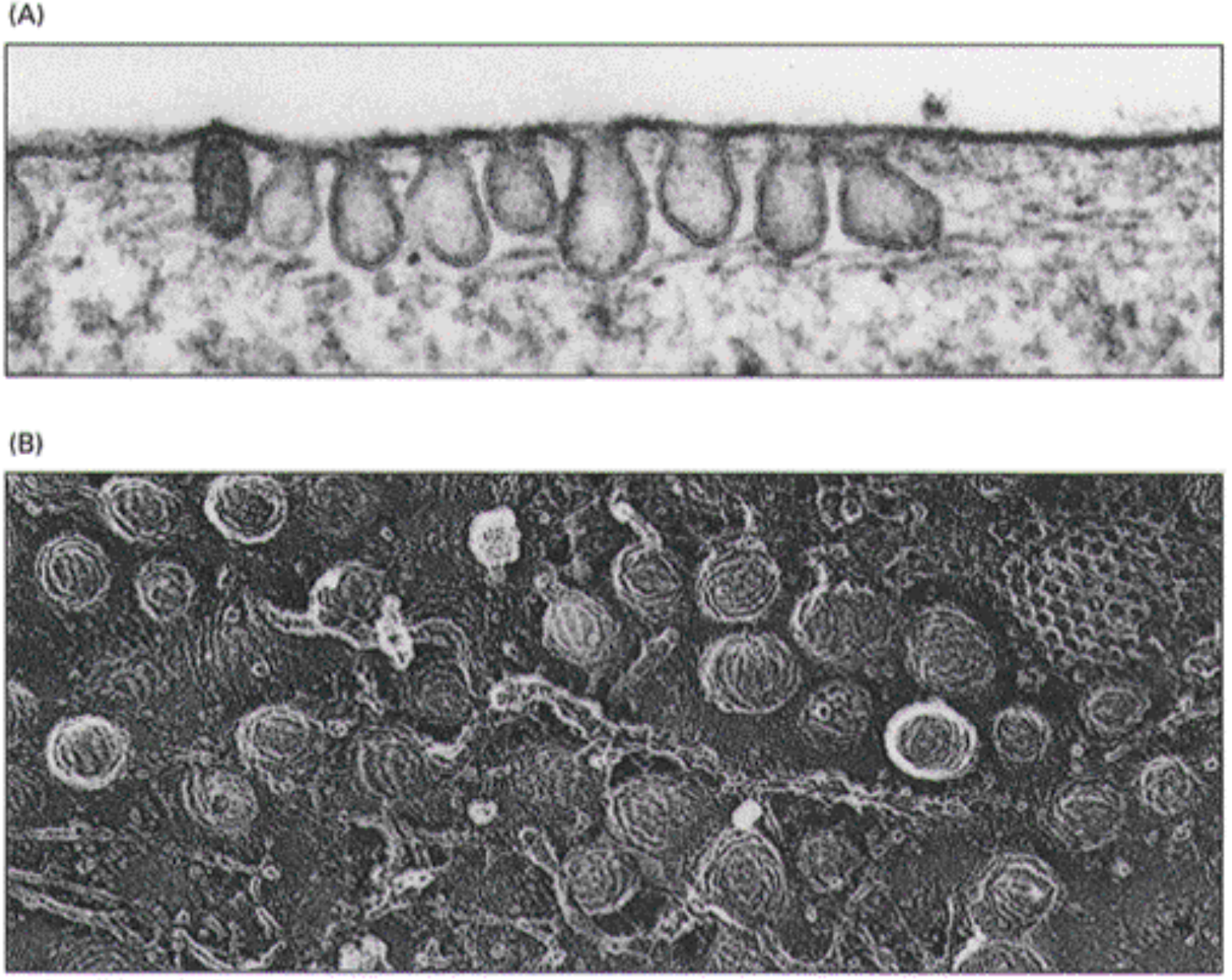


Cambiamenti durante il processo di maturazione

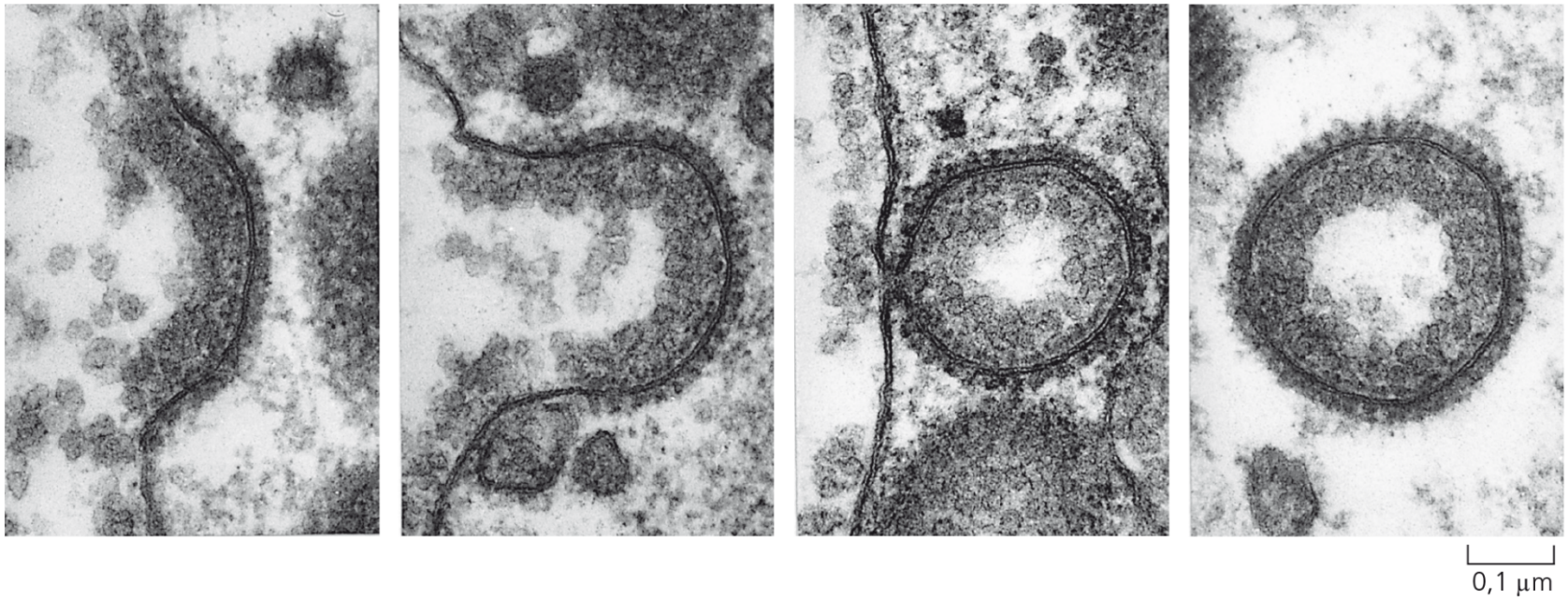
1. L'endosoma cambia forma e posizione poiché i domini tubulari vengono persi
2. Le Rab, i fosfoinositidi, le proteine SNARE e i microtubuli contribuiscono alla trasformazione del lato citosolico della membrana dell'endosoma che quindi cambia funzione
3. Una ATPasi di tipo V nella membrana dell'endosoma pompa H+ dal citosol nel lume acidificando l'organello rendendo le idrolasi lisosomiali sempre più attive
4. Le vescicole intraluminali sequestrano nell'endosoma i recettori delle vie di segnalazione endocitati, fermando la segnalazione da parte del recettore
5. Le proteine del lisosoma sono trasportate dal TGN all' endosoma in maturazione

Questi eventi avvengono gradualmente ma portano a una conpleta trasformazione dell'endosoma in endolisosoma precoce.

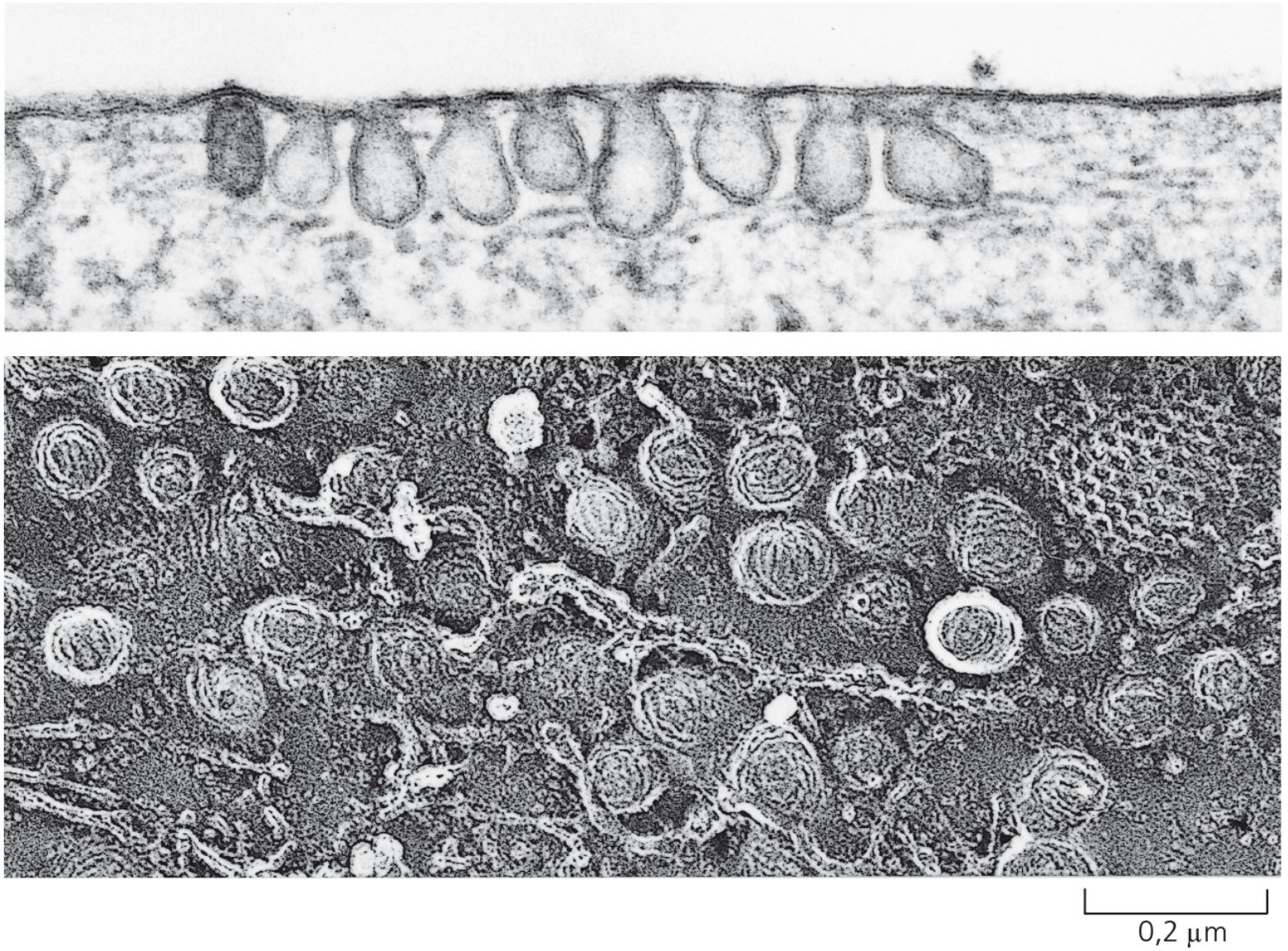
ENDOCITOSI MEDIATA DA CAVEOLINA E CLATRINA



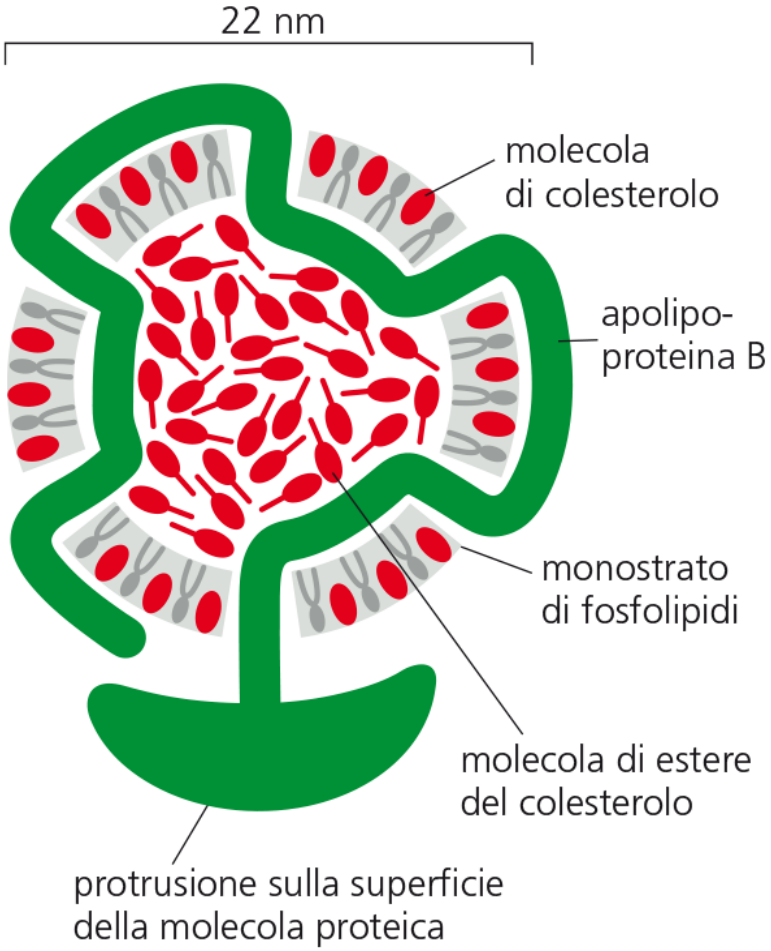
La CLATRINA promuove la formazione di vescicole di endocitosi



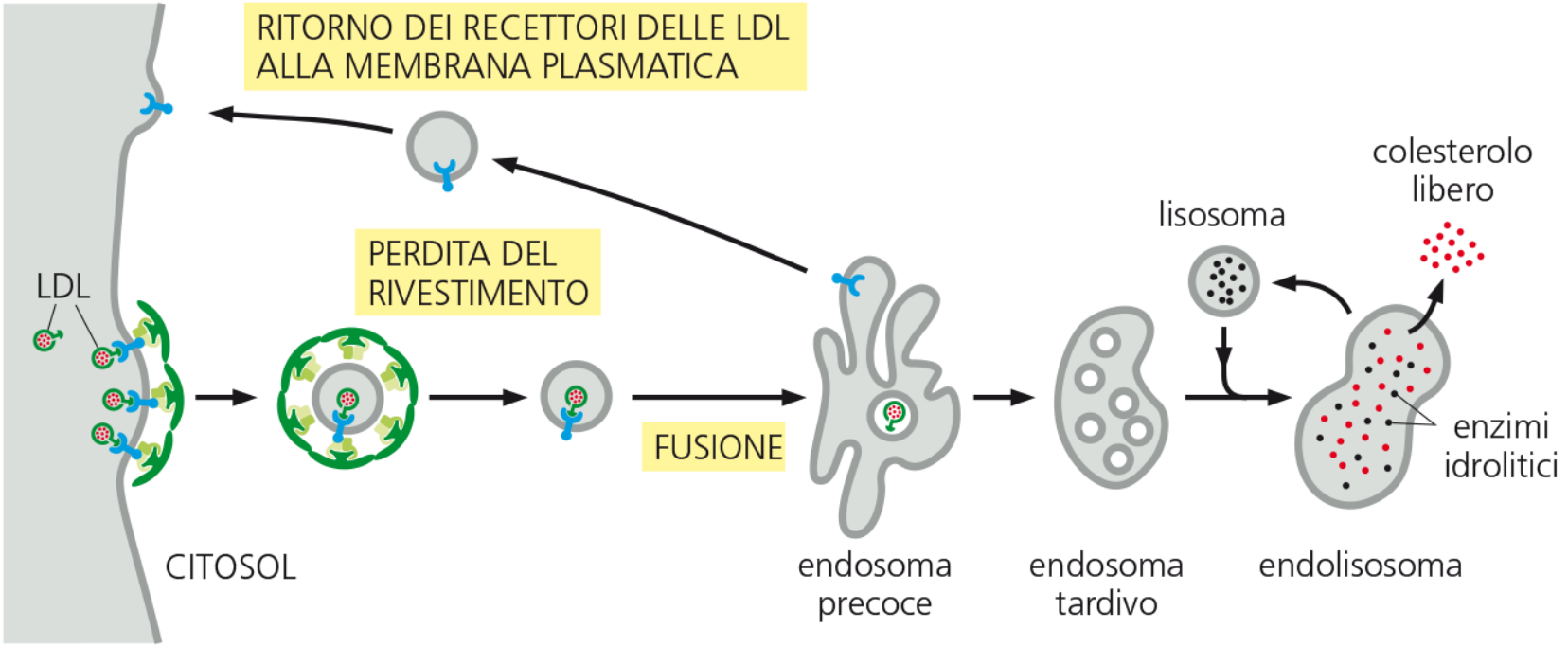
ENDOCITOSI MEDIATA DA CAVEOLINA E CLATRINA



Particella lipoproteica a bassa densità

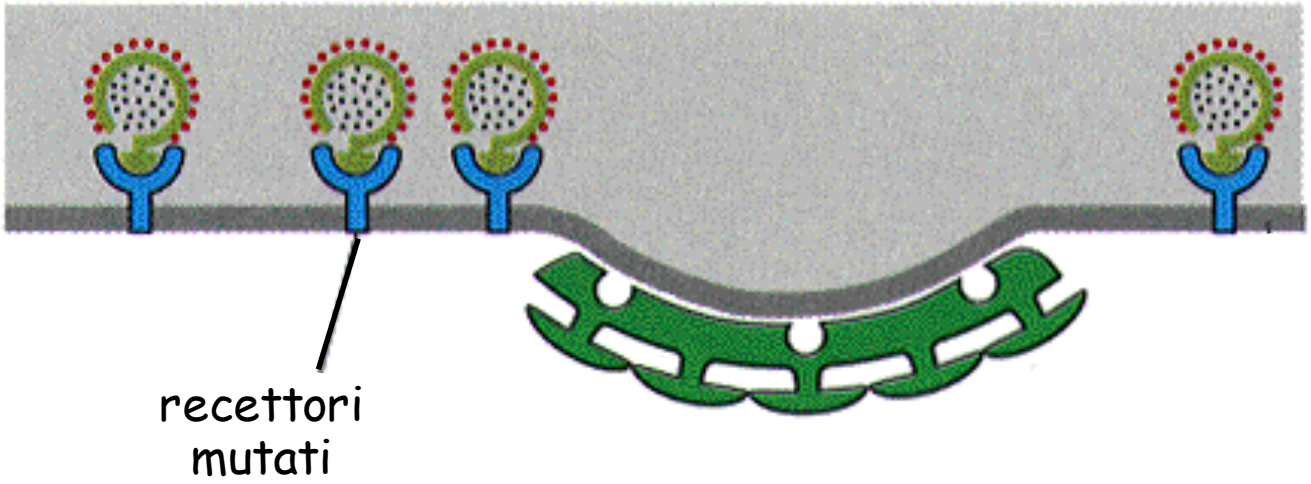


Endocitosi mediata da recettore

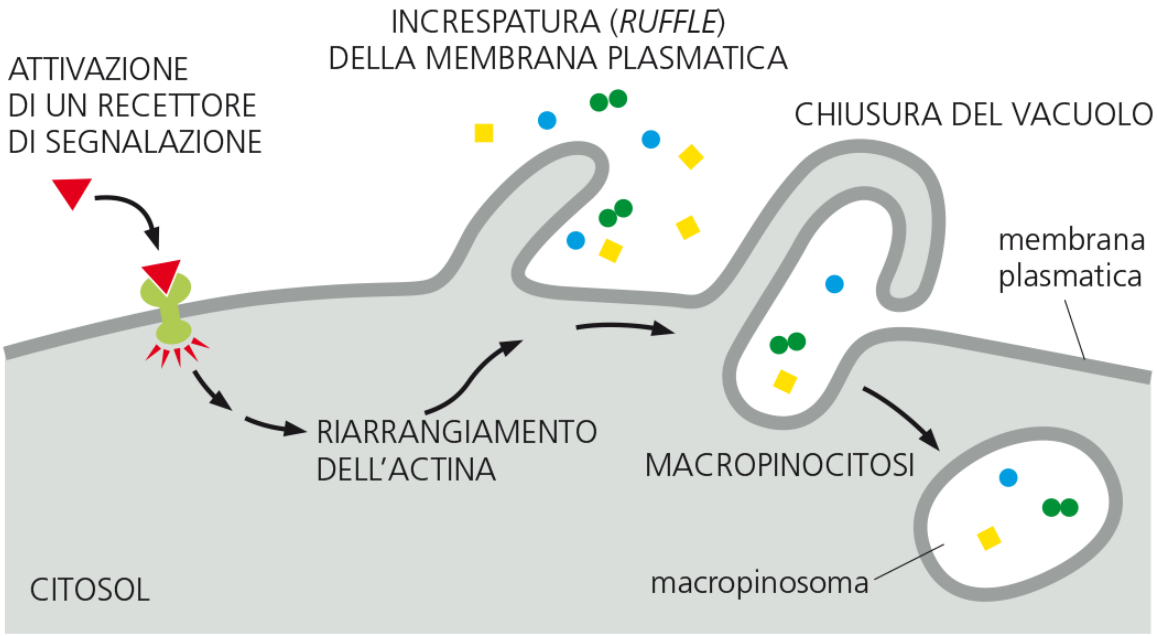


Un segnale per l'endocitosi nella coda citosolica del recettore lega AP2 in seguito al cambio conformazionale indotto da PI(4,5)P2 sulla membrana, AP2 recluta poi la clatrina per l'internalizzazione

IPERCOLESTEROLEMIA FAMILIARE

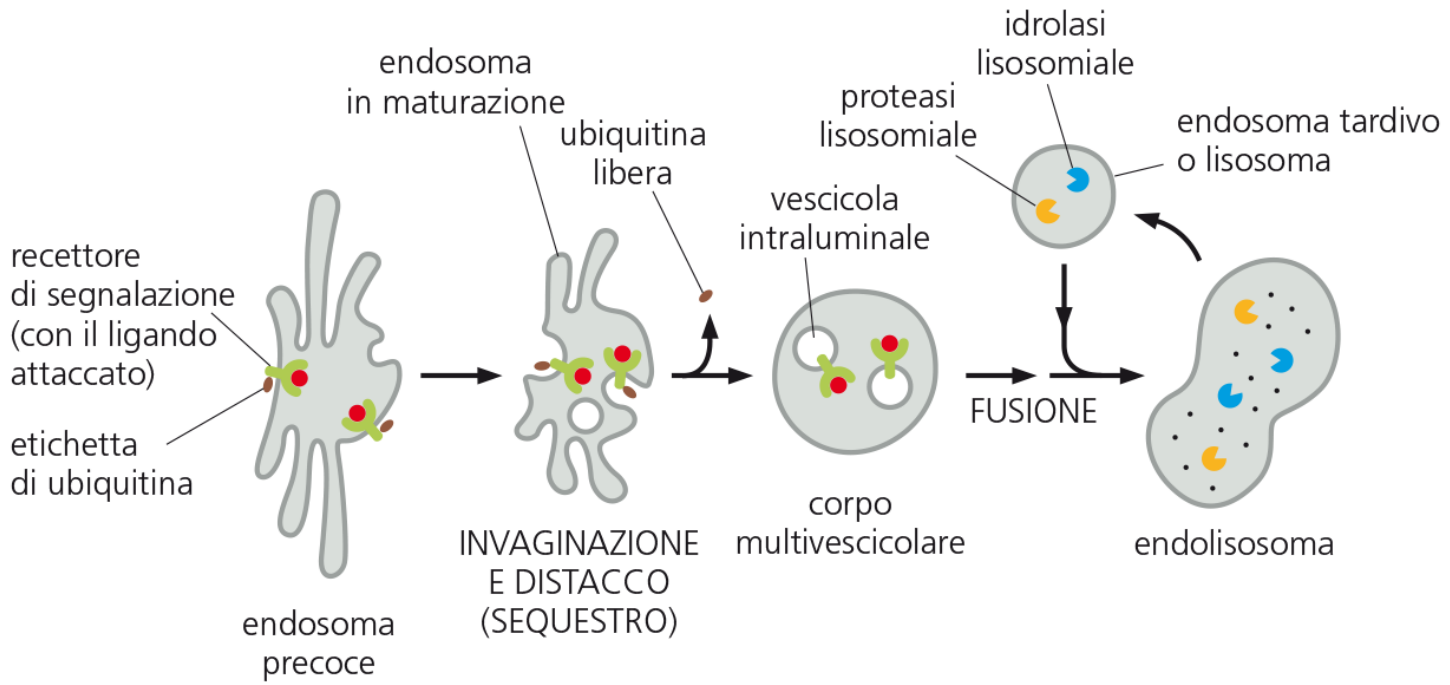


La macropinocitosi avviene indipendentemente dalla clatrina

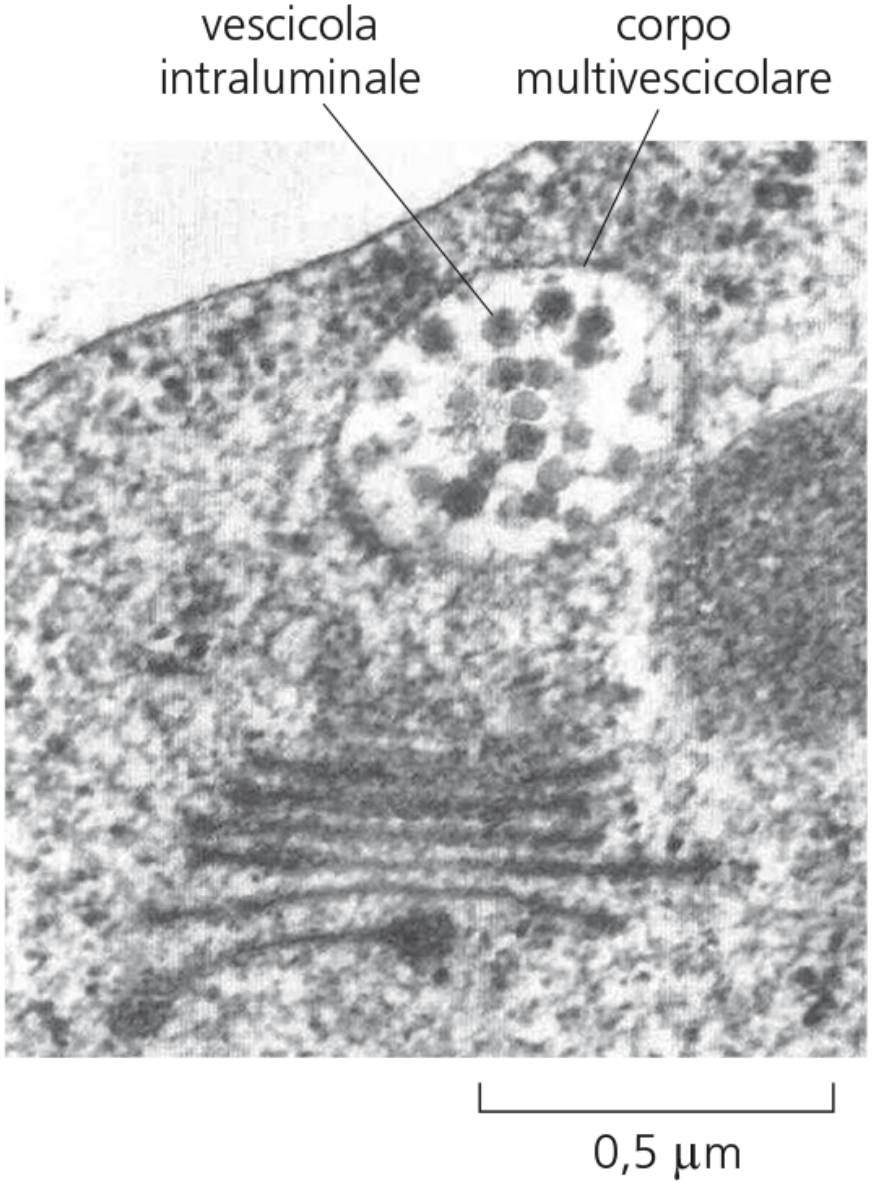


La macropinocitosi avviene solo in caso di attivazione di un recettore di superficie (da parte di ligandi come fattori di crescita, ligandi delle integrine) che porta al riarrangiamento dell'actina e formazione di ruffles sulla membrana. I macropinosomi si fondono poi coi lisosomi senza riciclare alla membrana.

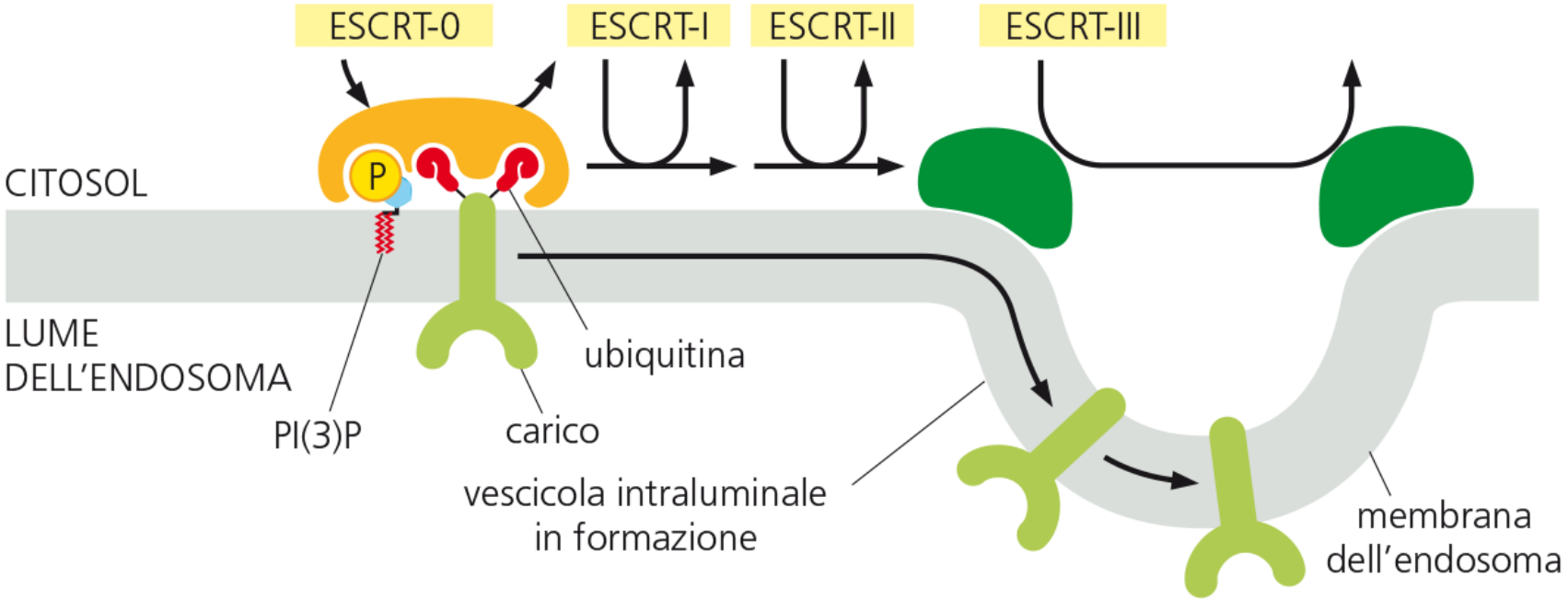
Sequestro di proteine endocitate in corpi multivescicolari



Le proteine di membrana ubiquitinate vengono separate in domini sulla membrana dell'endosoma che si invagina e si distacca in vescicole intraluminali che sono necessarie per una degradazione completa delle proteine di membrana endocitate.

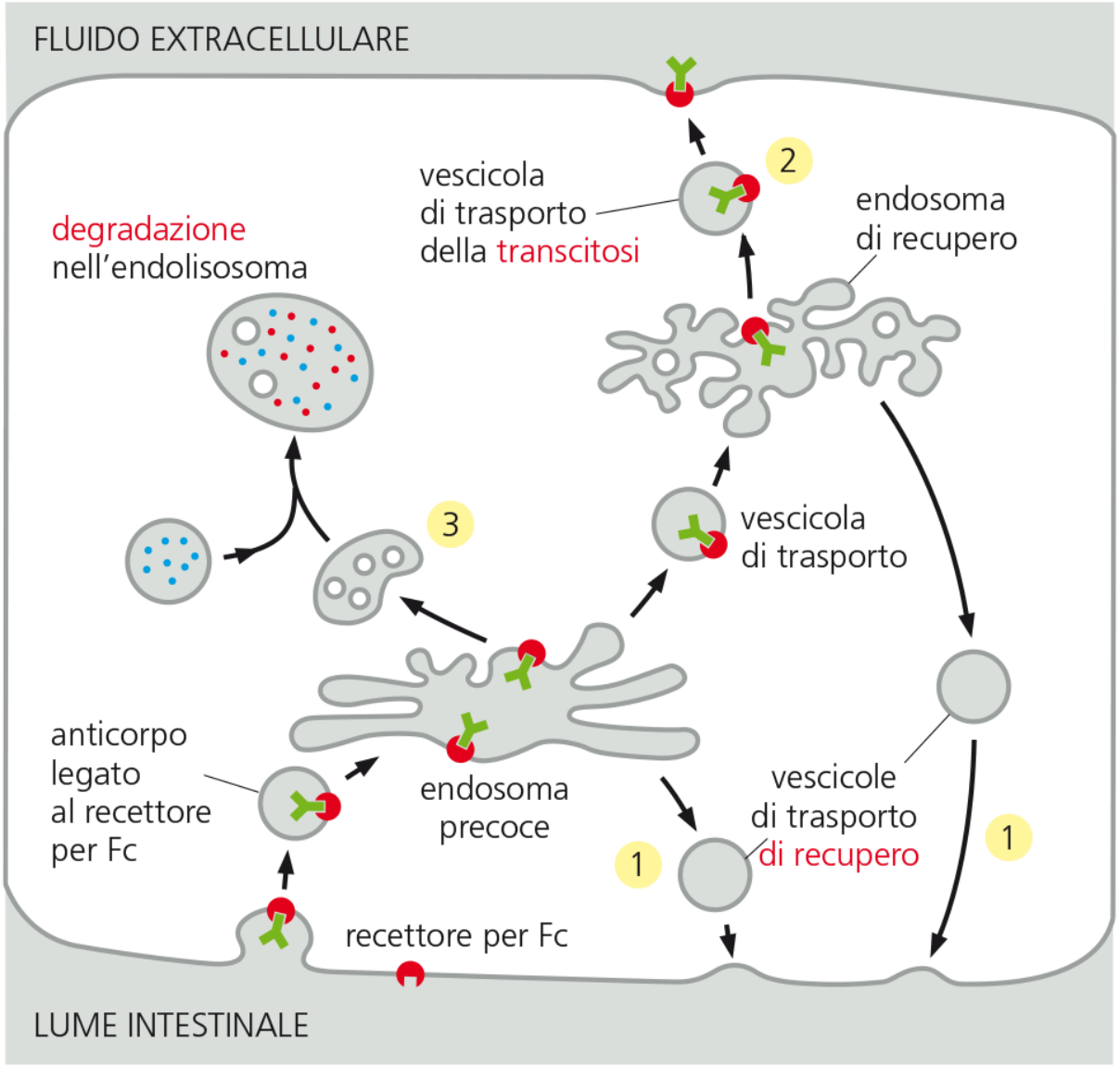


Come si forma un corpo multivescicolare

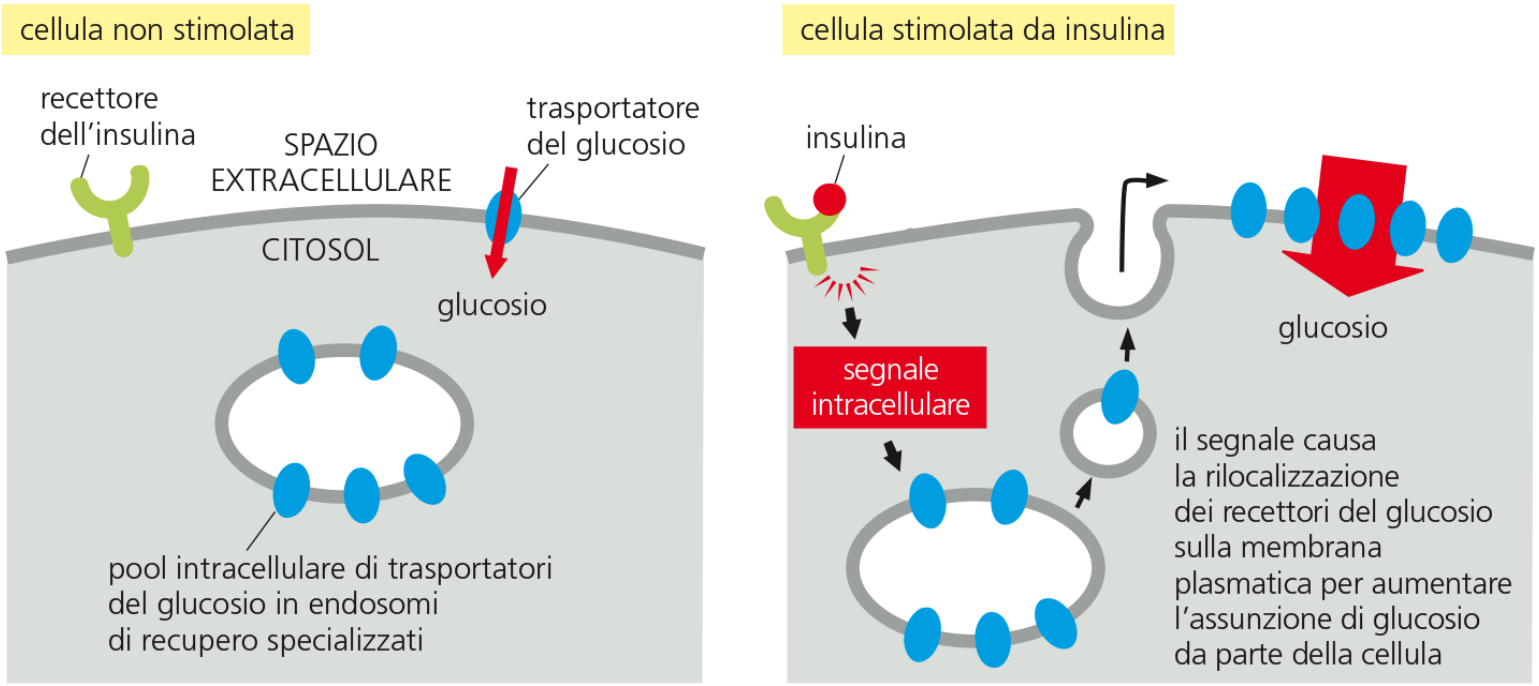


I complessi ESCRT sono solubili nel citosol e evengono reclutati sulla membrana dell'endosoma solo quando è necessario e sono poi rilasciati nel citosol quando la vescicola si distacca

Destino dei recettori endocitati

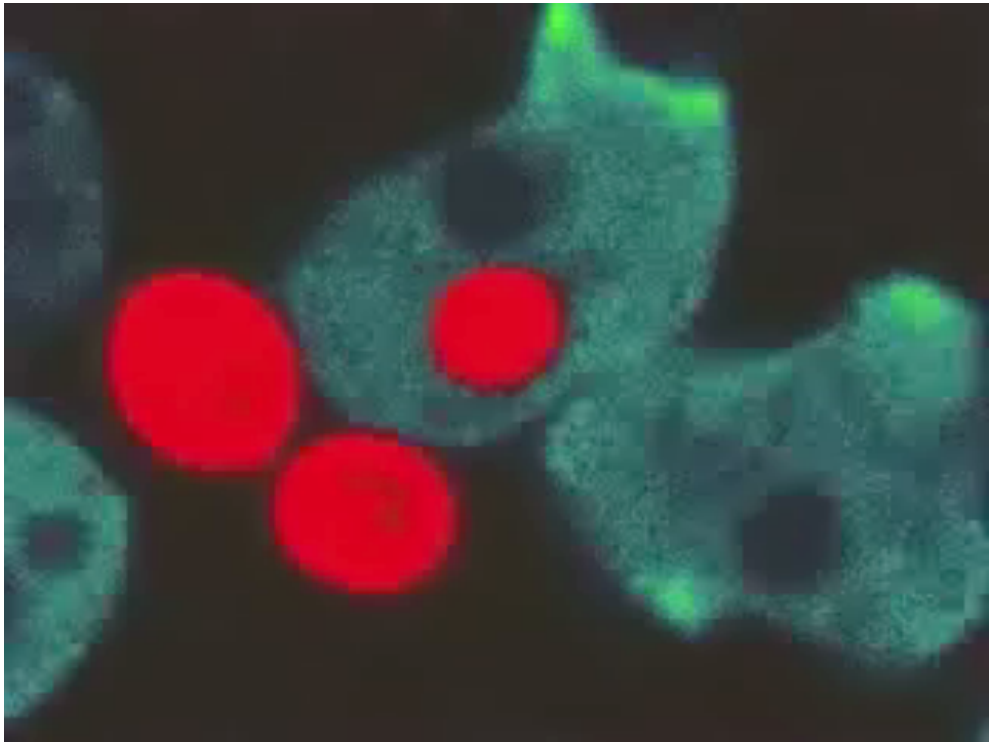


Proteine della membrana plasmatica in endosomi di recupero

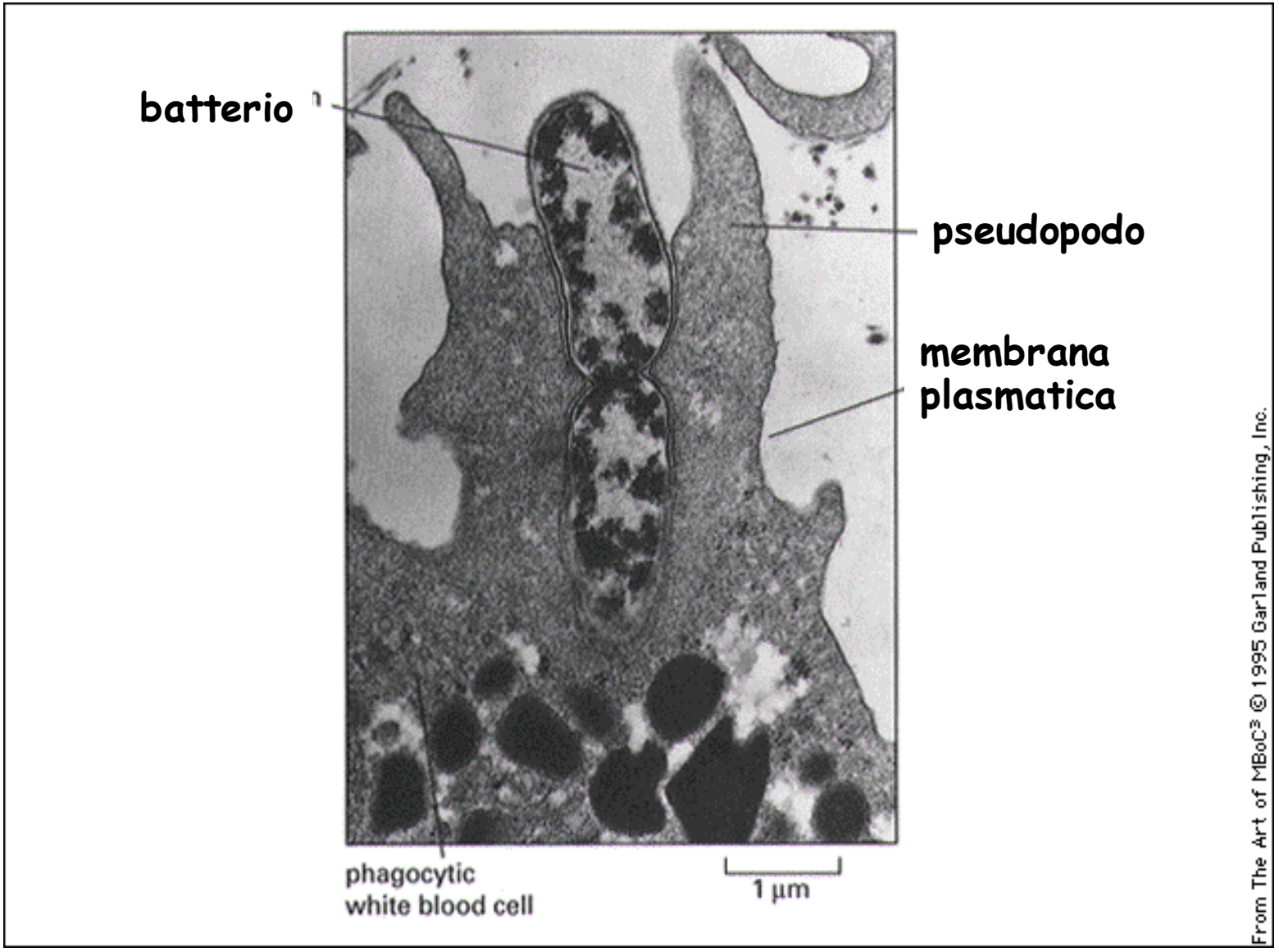


Gli endosomi di recupero posdsono servire da sito di deposito di proteine spacializzate della membrana plasmatica permettendo di mobilizzarle quando necessario.

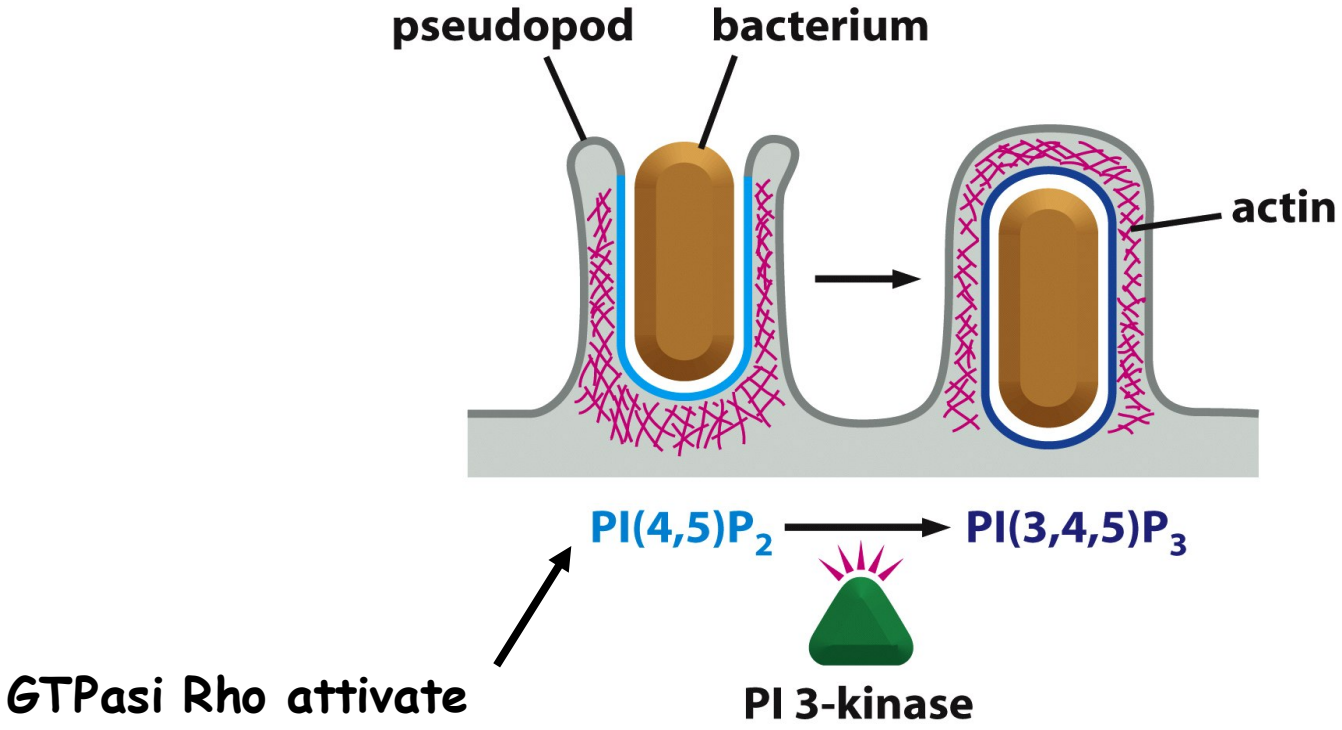
FAGOCITOSI



FAGOCITOSI


batterio
pseudopodo
membrana plasmatica
phagocytic white blood cell
1 µm
From The Art of MBoC3 © 1995 Garland Publishing, Inc.

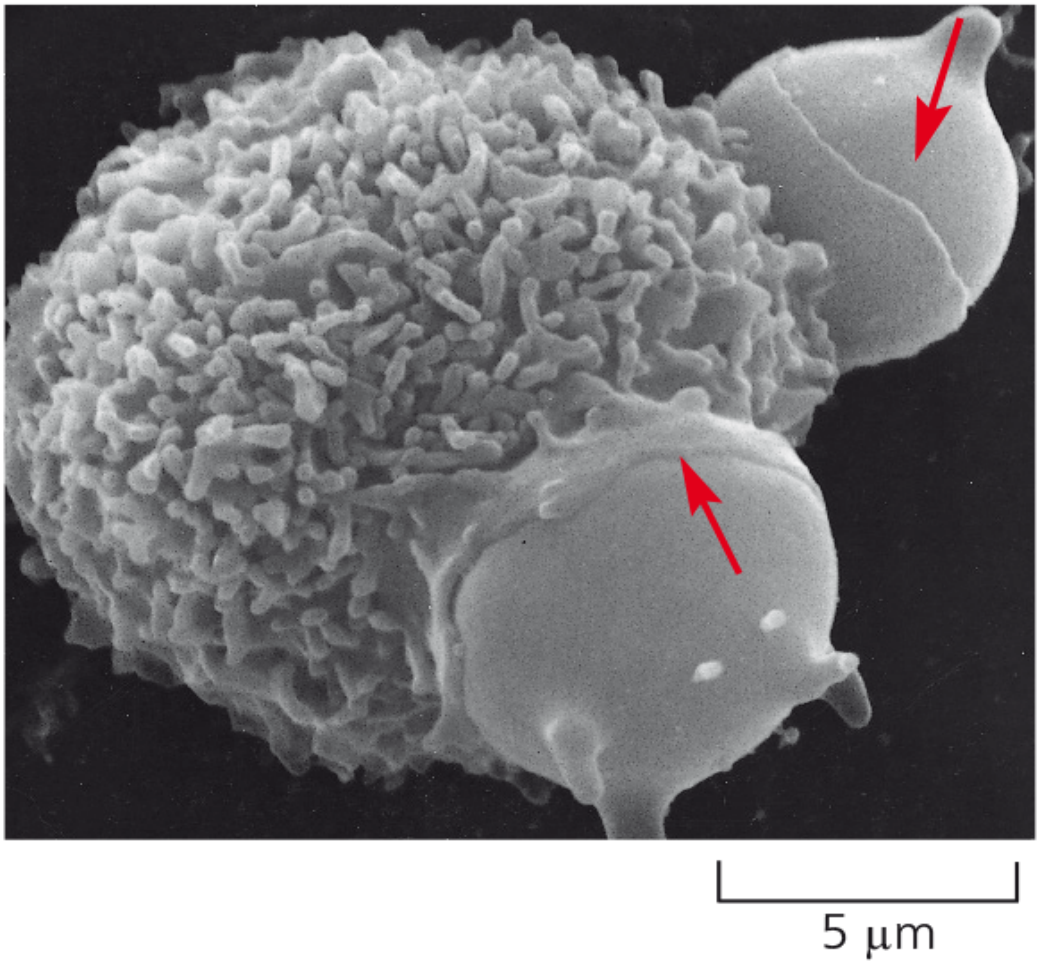
Rimodellamento della membrana plasmatica durante la fagocitosi



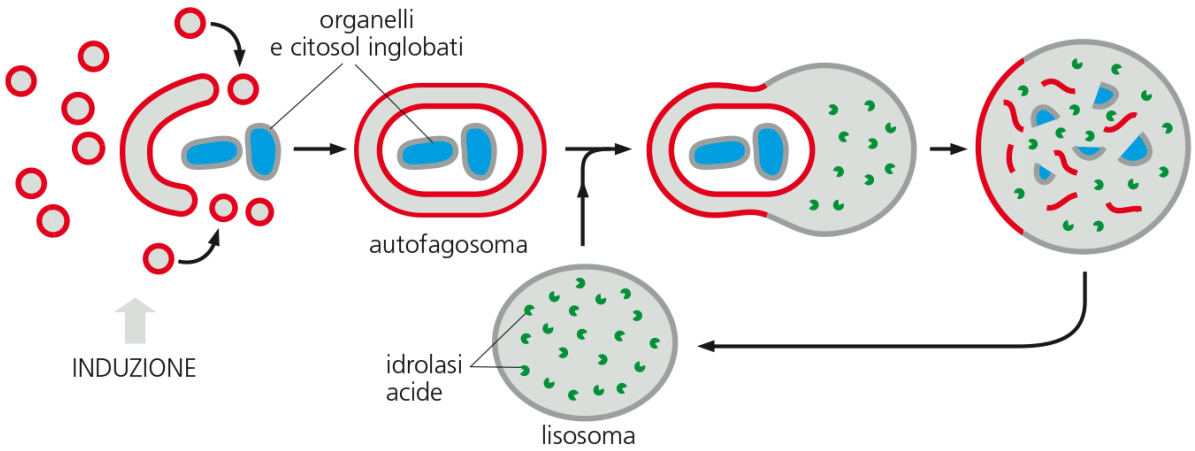
La fagocitosi è un processo indotto dal carico: è attivata da recettori sulla superficie dei fagociti per mezzo di segnali di attivazione dati da anticorpi che sono secreti dalla cellula fagocitica e attaccano il patogeno.
La polimerizzazione di actina per la organizzazione degli pseudopodi è indotta da una GTPasi della famiglia Rho e da Rho-GEF che le attivano.

Figure 13-47b *Molecular Biology of the Cell* (© Garland Science 2008)

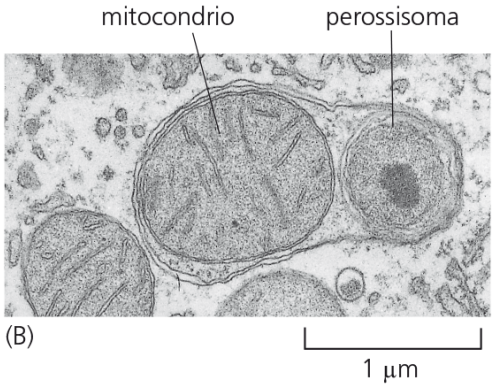
Fagocitosi da parte di un macrofago



Autofagy



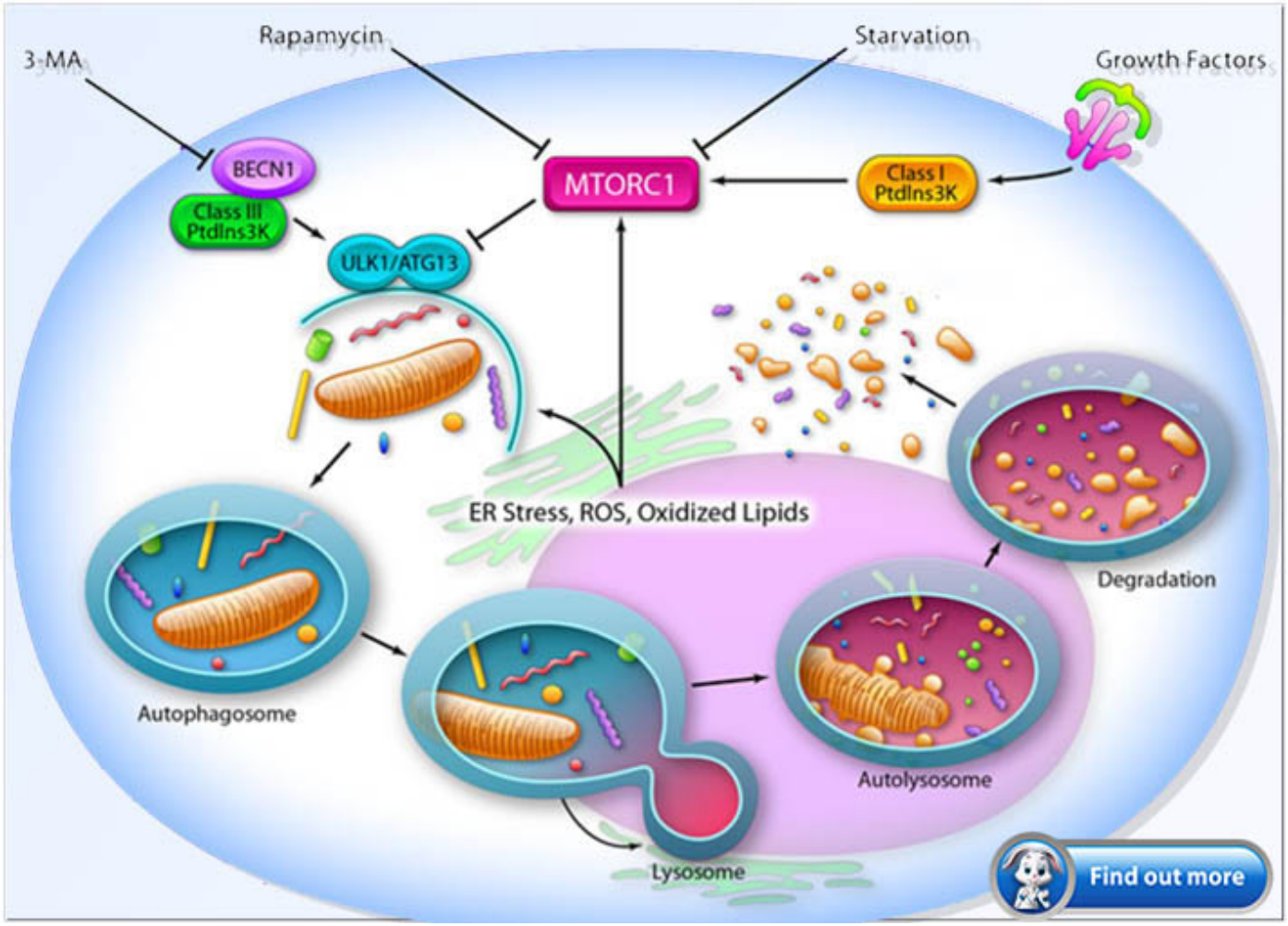
(A)



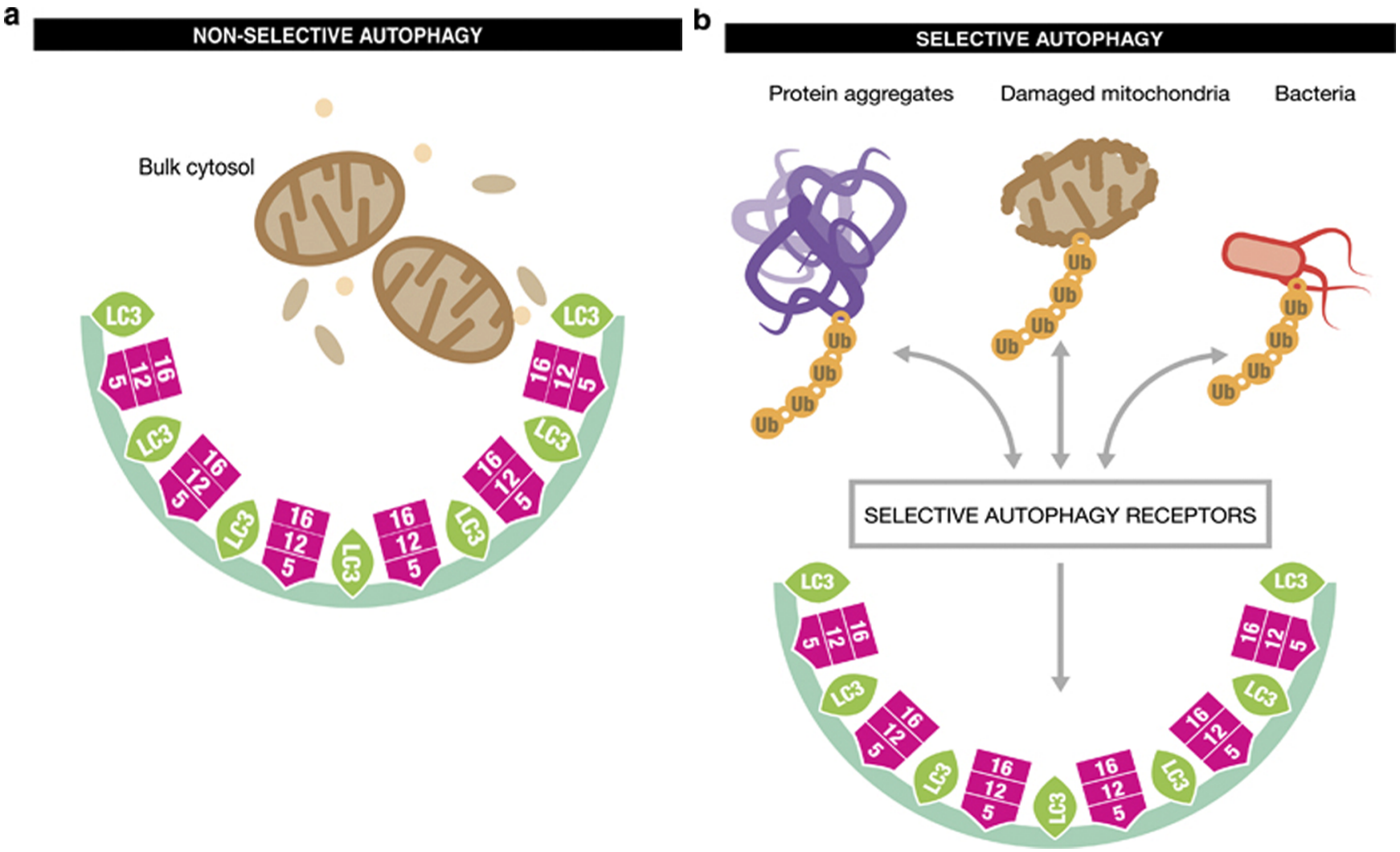
Il Nobel per la medicina 2016 alle scoperte sulla "pulizia cellulare"

Il Nobel per la medicina 2016 è stato assegnato a Yoshinori Ohsumi per le sue scoperte sui meccanismi dell'autofagia, un processo fondamentale di "pulizia cellulare", che ha un ruolo importante in molte patologie, da quelle neurodegenerative a malattie da accumulo lisosomiale a varie forme di tumore

Autophagy Processes

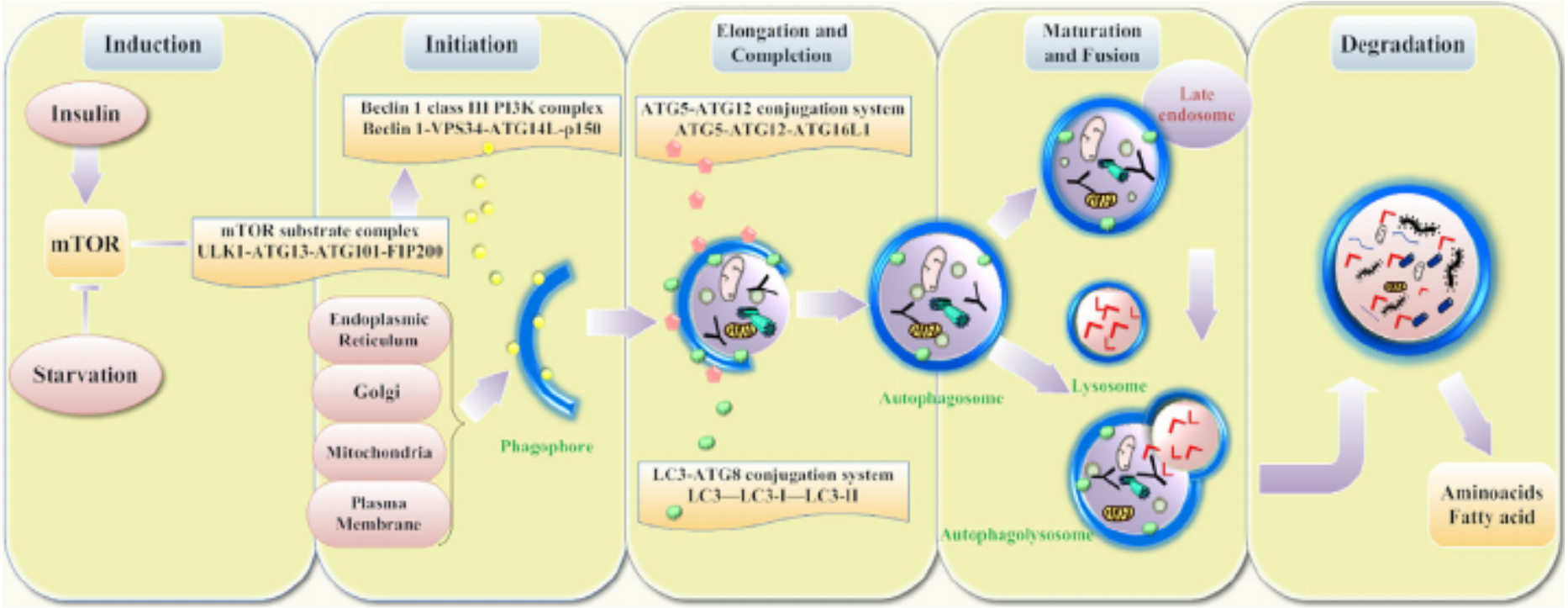


Non-selective and selective Autophagy



(a) Upon nutrient deprivation, autophagy catabolizes cytoplasmic components nonselectively into autophagosome and mediates recycling and global turnover of cytoplasmic materials. (b) In selective autophagy particular substrate are targeted into the autophagosome by selective autophagy receptors. The targeted cargo includes protein aggregates, damaged mitochondria or pathogens such as bacteria. ATG 16/12/5 complex; LC3, mammalian LC3 modifier including all LC3 and GABARAP family protein; Ub ubiquitin

Autophagy Processes



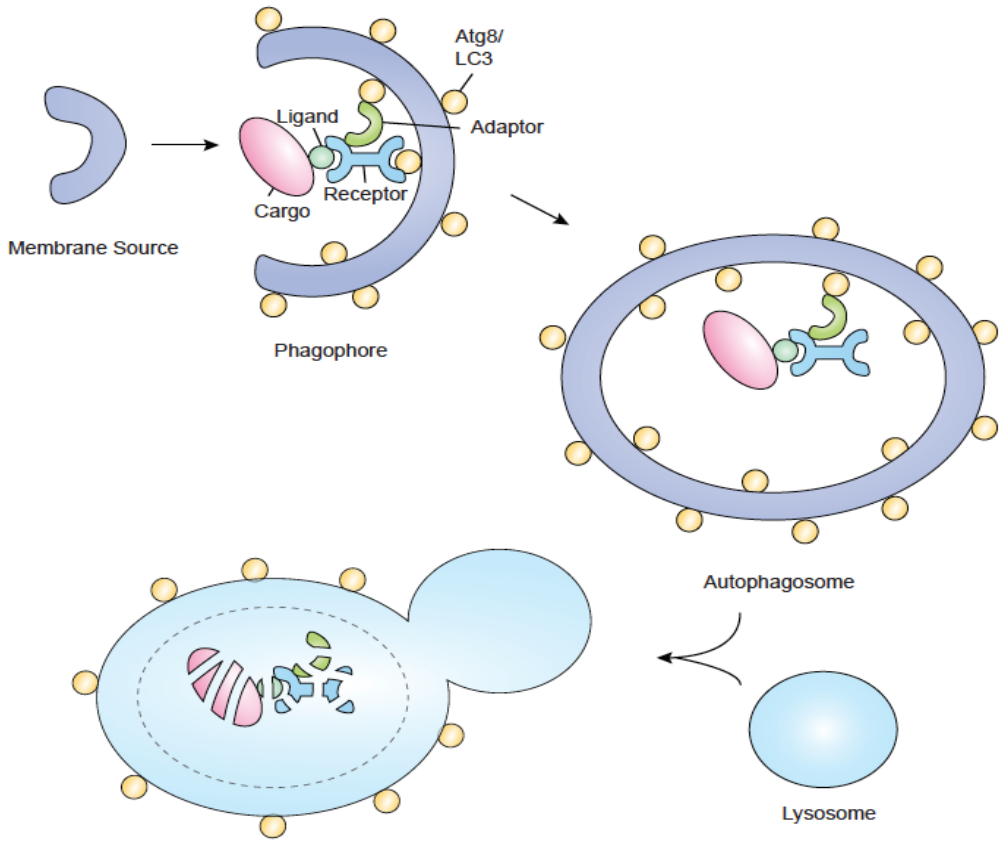
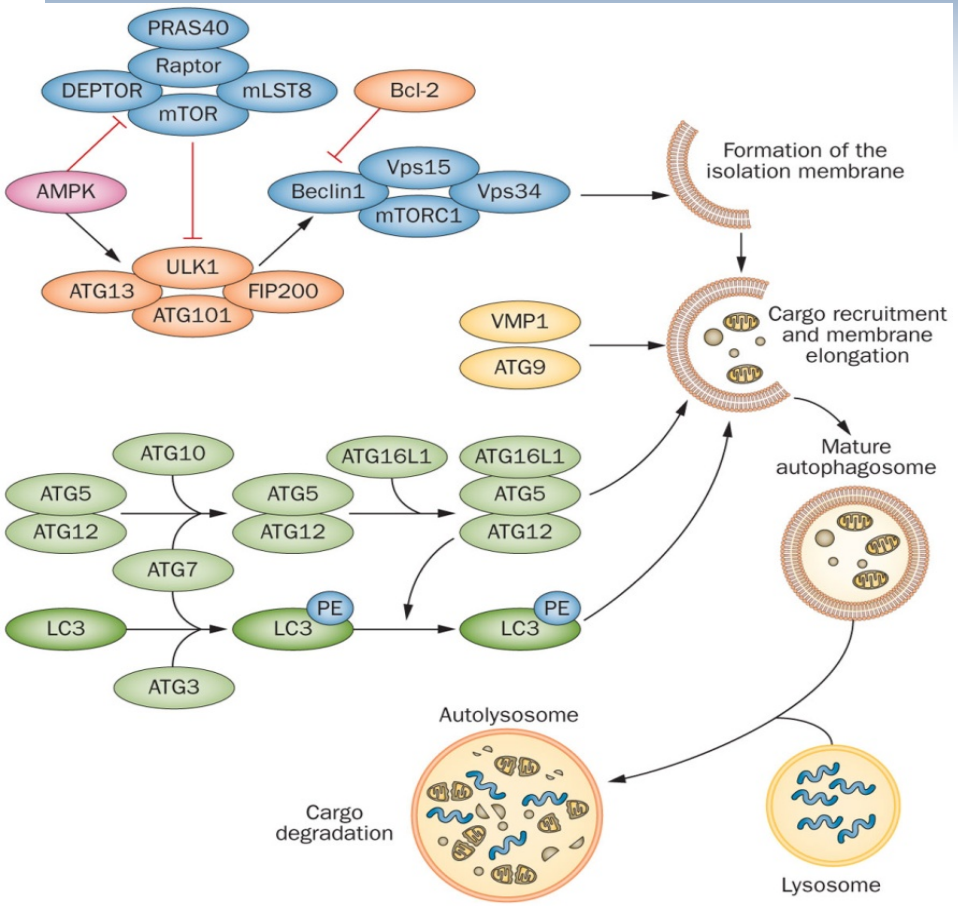


Figure 1. Selective Autophagy

In selective autophagy, cargo, such as organelles, is degraded by the autophagolysosome. Cargo is often tagged with ligands such as ubiquitin, enabling it to interact with receptor proteins that can then interact with the autophagosomal membrane. This interaction occurs by binding to Atg proteins such as Atg8/LC3 or through interaction with adaptor proteins. After the cargo is brought to the phagophore, formation of the autophagosome occurs and this structure can then fuse with the lysosome to form the autophagolysosome, degrading the cargo.

The molecular biology of autophagy



Fougeray, S. & Pallet, N. (2014) Mechanisms and biological functions of autophagy in diseased and ageing kidneys *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.201

nature REVIEWS NEPHROLOGY

Activation of AMPK in response to low cellular energy status inhibits mTOR and activates ULK1 via phosphorylation. Coordinated activation of the ULK1–ATG13–ATG101–FIP200 complex (which is inhibited by mTORC1) and the lipid kinase Vps34–Beclin 1 complex (which is inactivated by Bcl-2), drives the formation of the isolation membrane. The transmembrane proteins ATG9 and VMP1 participate in the recruitment of lipids from endosomes and the Golgi to the isolation membrane. The ATG5–ATG12–ATG16L1 complex and LC3–PE system also have roles in cargo recruitment, membrane elongation and maturation. ATG7 and ATG10 catalyse the conjugation of ATG12 to ATG5, whereas ATG7 and ATG3 catalyse conjugation of PE to LC3. The ATG5–ATG12–ATG16L1 complex covalently links PE to LC3, which becomes lipidated and associates with autophagosomes. SNARE proteins mediate fusion between autophagosomes and lysosomes and various lysosomal enzymes hydrolyze proteins, lipids and nucleic acids. Abbreviations: AMPK, AMP-activated protein kinase; ATG, autophagy-related protein; ATG16L1, Autophagy-related protein 16-1; DEPTOR, DEP domain-containing mTOR-interacting protein; FIP200, FAK family kinase-interacting protein of 200 kDa; LC3, microtubule-associated protein 1 light chain 3; mLST8, target of rapamycin complex subunit LST8; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PE, phosphatidyl ethanolamine; PRAS40, proline-rich AKT1 substrate 1; Raptor, regulatory-associated protein of mTOR; SNARE, soluble NSF attachment protein receptor; ULK1, serine/threonine-protein kinase ULK1; VMP1, vacuole membrane protein 1; Vps, vacuolar protein sorting.

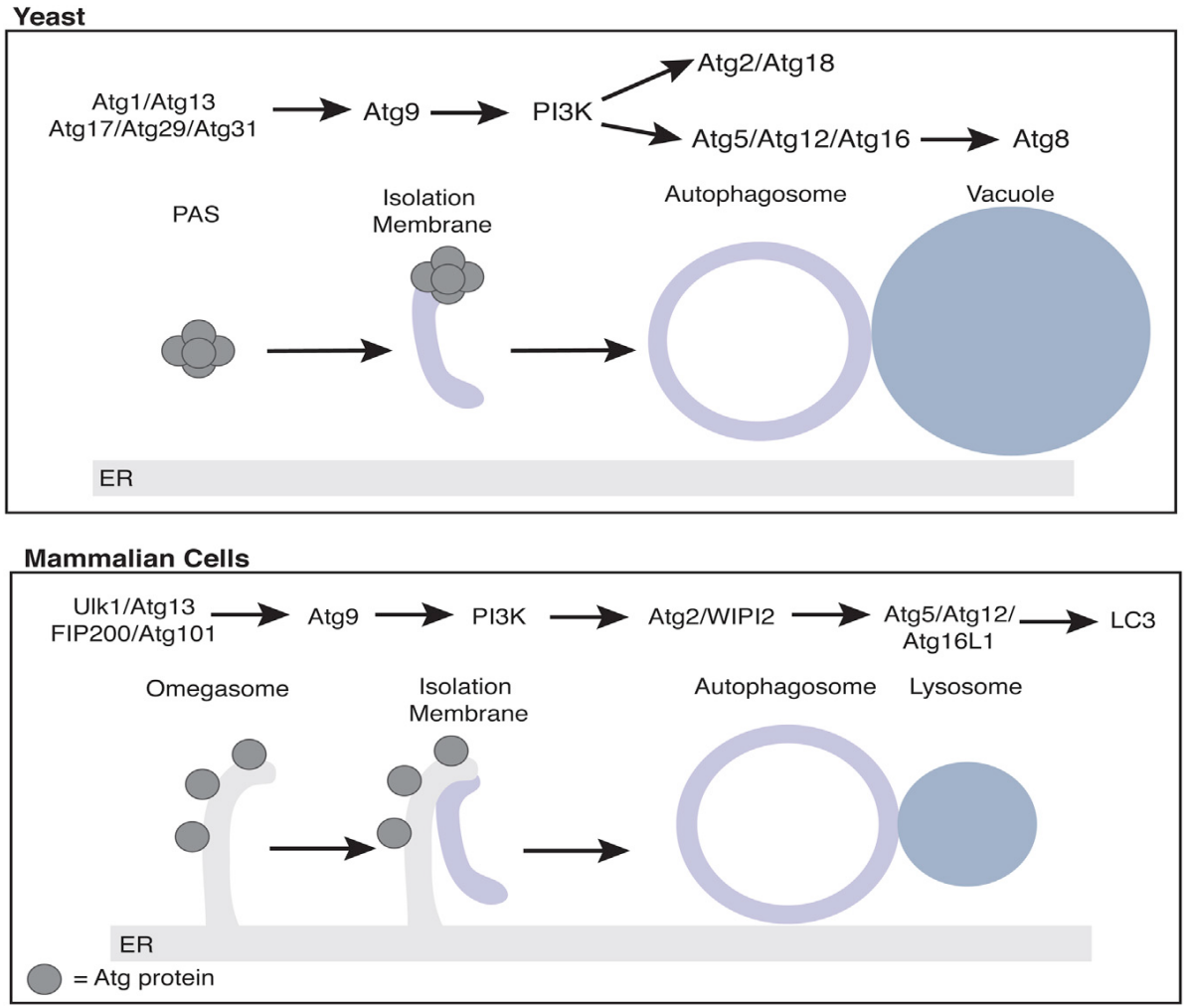
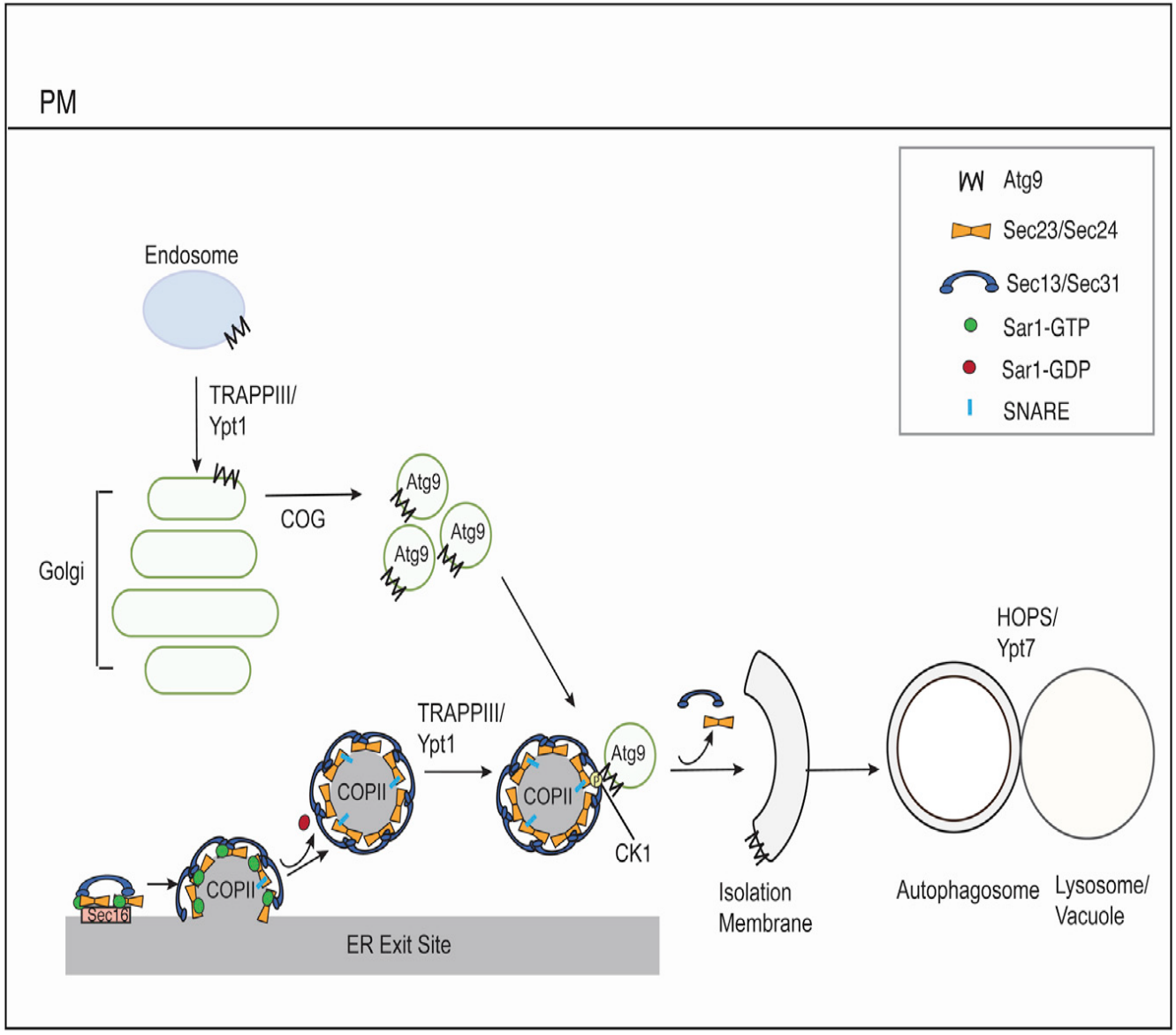


Figure 1. Overview of Autophagosome Formation

The Atg proteins, which form six major groups, recruited in a hierarchical manner to the PAS in yeast (top) or the omegasome in mammals (bott A double-membrane track called the isolation membrane forms. The isolation membrane expands and then seals to form an autophagoson before it fuses with the vacuole in yeast or lysosome in mammals to release its contents for degradation.

COPII Vesicles, Tethers, and Other Factors in Autophagy



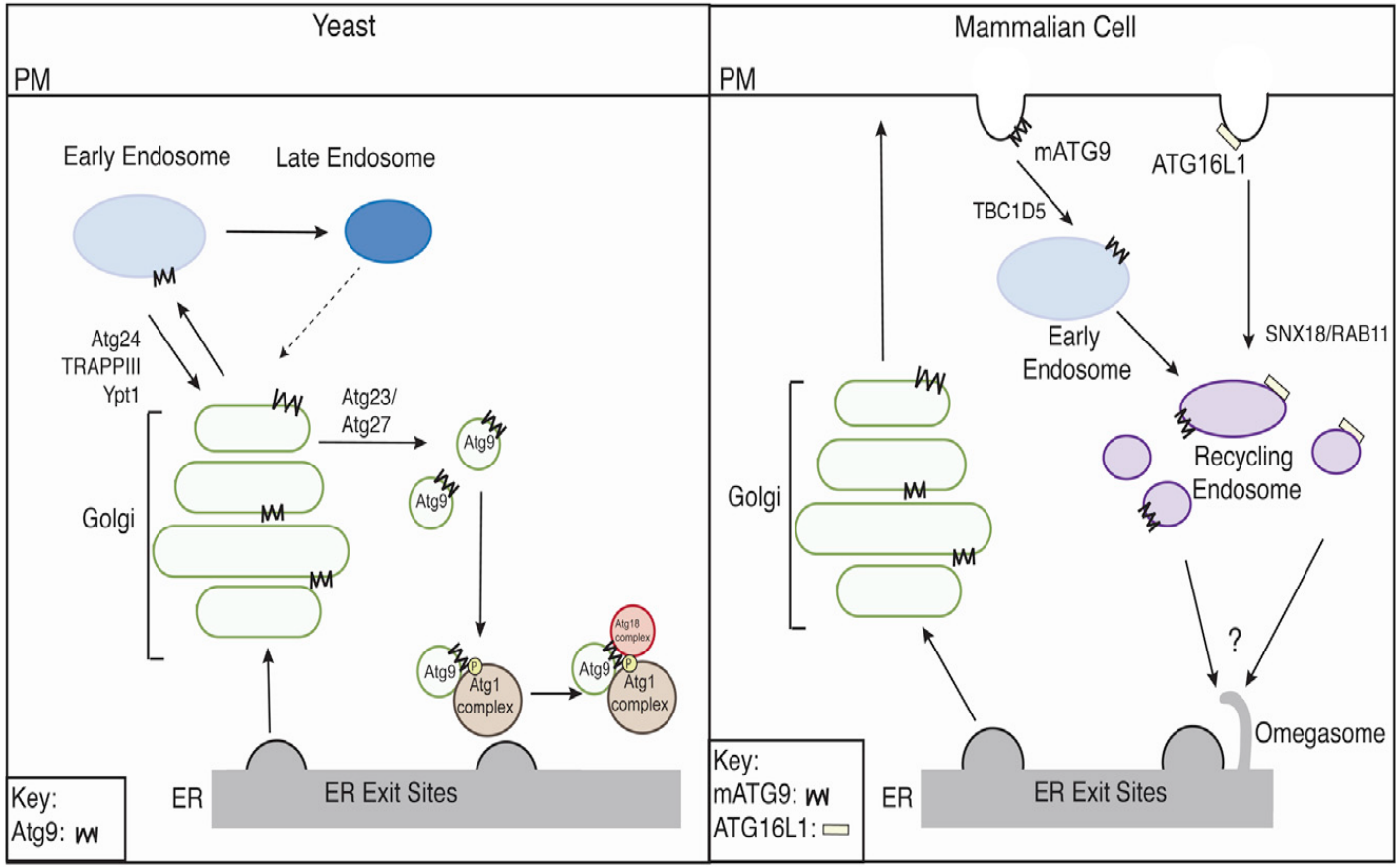
COPII Vesicles, Tethers, and Other Factors in Autophagy

Formation of the COPII coat is initiated at ERES by the GEF Sec12. Sec16 at ERES facilitates coat assembly. Sec12 activates Sar1 and recruits the Sec23/Sec24 complex, which is followed by recruitment of the Sec13/Sec31 complex. After the coat has formed, Sar1 is released from the vesicle, and the coat remains on the vesicle to aid in intracellular targeting. CK1 phosphorylates Sec24, which enhances its interaction with Atg9.

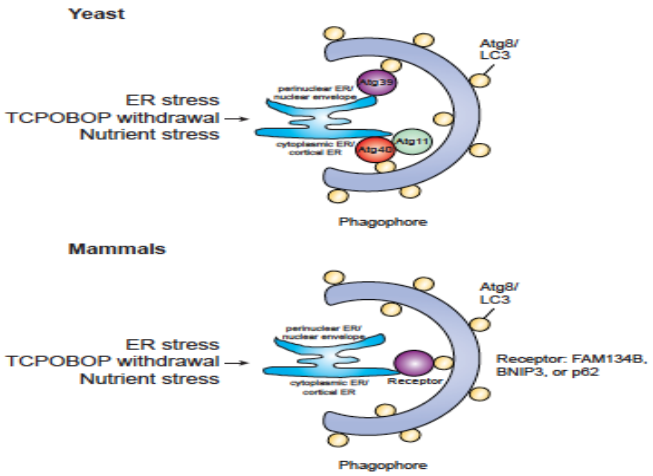
Atg9 vesicles are found at the growing edge of the isolation membrane that faces the ERES. Constitutive Atg9 trafficking requires the TRAPPIII complex, for transport from the early endosome to Golgi in yeast or endocytic to Golgi traffic in mammalian cells. Intra-Golgi transport requires COG, which is needed for the trafficking of Atg9 vesicles to sites of autophagosome formation.

TRAPPIII also binds the COPII coat and activates the GTPase Rab1, which participates in autophagosome

The Golgi and Endosomal System in Autophagy



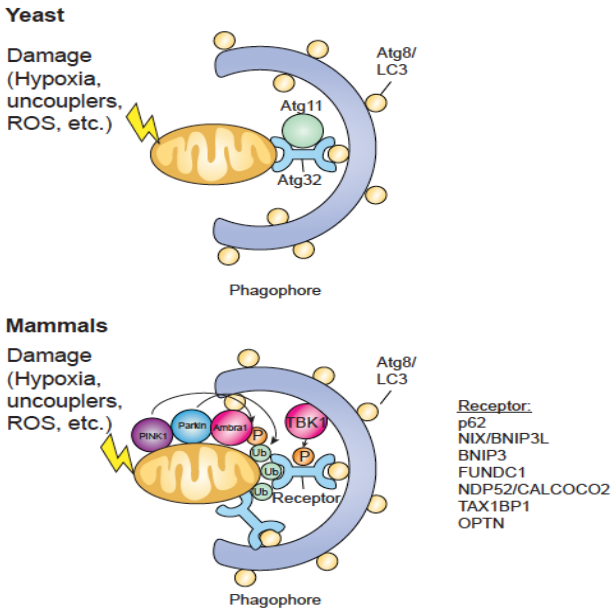
(Left) In yeast, Atg9 traffics through the secretory pathway before it localizes to the early endosome. During starvation, TRAPPII traffics Atg9 from the early endosome to the late Golgi where Atg23 and Atg27 mediate the biogenesis of Atg9 vesicles that translocate to the PAS. Late endosome trafficking bypass pathways may also exist during starvation (dashed arrow). (Right) at the plasma membrane (PM) in mammals, mATG9 and ATG16L1 are packaged into separate clathrin-coated vesicles. The interaction of mATG9 with RAPGAP TBC1D5 and AP2 facilitates its transport from the PM to the early endosome before it traffics to the recycling endosome, where it meets ATG16L1. ATG16L1 is recruited to the recycling endosome by SNX18/RAB11. The



ER-phagy/Reticulophagy

ER stress, TCPOBOP withdrawal, and nutrient stress are all stimuli that can lead to the induction of ER-phagy. In yeast, both Atg39 and Atg40 have been shown to mediate ER-phagy, localizing to distinct subdomains of the ER and interacting with Atg8. In mammals, the functional counterpart of Atg40 is FAM134B. Both BNIP3/Nix and p62 have also been implicated in ER-phagy.

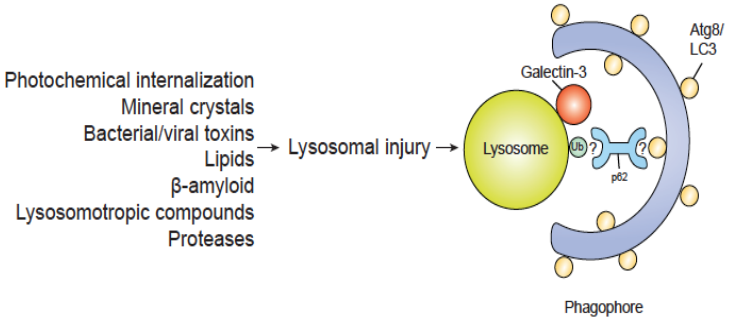
Developmental Cell
Review



Mitophagy

Mitophagy can be triggered by various stimuli, such as hypoxia, uncouplers, or reactive oxygen species (ROS), which cause damage to mitochondria. In yeast, Atg32 acts as the mitophagy receptor, binding the adaptor protein Atg11 and interacting with Atg8 on the inner membrane of autophagosomes. In mammals, Pink1 phosphorylates various targets, including ubiquitin (Ub), and recruits Parkin, which can then amplify the signal by ubiquitinating mitochondrial surface proteins. These ubiquitinated proteins can then be recognized by cargo receptor proteins that bring the mitochondria to forming autophagosomes for degradation.

Mitochondrial surface receptor proteins can also recognize LC3 to facilitate recruitment to the phagophore. AMBRA1 also localizes to damaged mitochondria through LIR motif-dependent interactions with LC3, promoting both canonical PARKIN-dependent and -independent mitochondrial clearance. In addition, TBK1 phosphorylates autophagy receptors to create a signal amplification loop in mitophagy.



Lysophagy

Lysophagy can be induced by a variety of stimuli that can lead to lysosome damage. Upon lysosomal injury, galectin-3 and LC3 are recruited to the injured lysosome. Lysosomal membranes are ubiquitinated and co-localize with p62, suggesting that ubiquitination and subsequent recruitment of p62 are involved in this process. However, the exact mechanisms of lysophagy regulation are still unclear.
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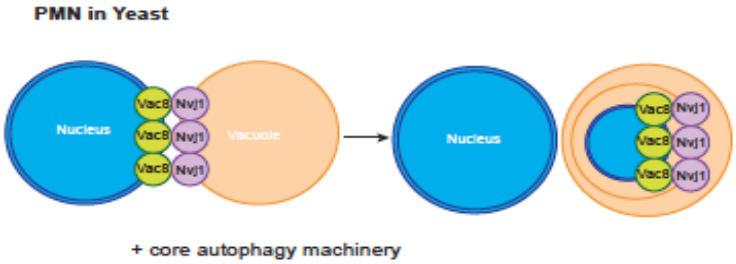
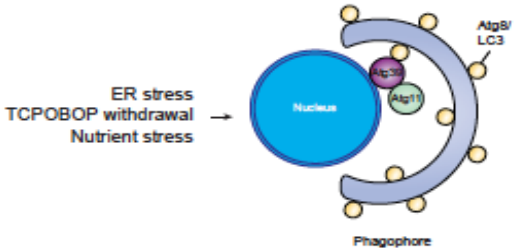
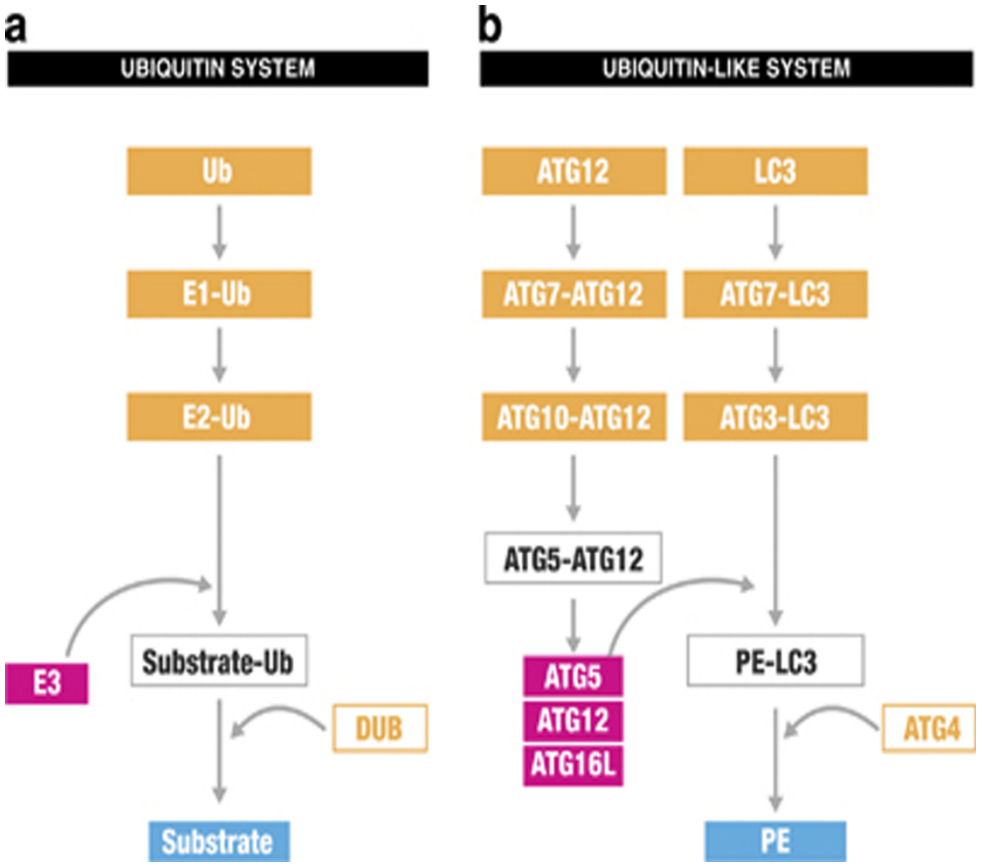




Nucleophagy

Nucleophagy is the clearance of nuclear contents by autophagy using either piecemeal micronucleophagy (PMN) or the involvement of the cargo receptor Atg39. In yeast, PMN involves the formation of a junction between the nucleus and the vacuole generated by two key proteins, Vac8 and Nvi1. These junctions bulge into the vacuole, a piece of the nucleus buds off, and this vesicle is released into the vacuole where it is degraded by vacuolar hydrolases. This process involves much of the core autophagy machinery. The nucleophagy receptor Atg39 was also shown to localize to the yeast perinuclear ER/nuclear envelope and lead to degradation of nuclear components. Less is known about the mechanism behind nucleophagy in mammals.



Two UBL are required for autophagy. (a) In the ubiquitin system, ubiquitination takes part in three steps. First, the enzymes E1 leads to activation of ubiquitin followed by a conjugation step, which is catalysed by E2 enzyme. Finally, a ubiquitin E3-ligase process tagging of ubiquitin to a protein. Removal of ubiquitin is performed by DUB. (b) The UBLs ATG12 and LC3 have functional similarities to the ubiquitin system. Both systems utilise a E1-like enzyme (Atg7) in the first activation step. Then, the E2-like enzyme Atg10 conjugates Atg12 to Atg5 to form a complex with Atg16L, which assists as a E3 ubiquitin ligase in the ligation of PE to LC3 by Atg3 (E2-like enzyme). The corresponding deubiquitinating enzyme (DUB) ATG4 removes LC3 from PE. LC3, mammalian LC3 modifier including all LC3 and GABARAP family protein; Ub, ubiquitin