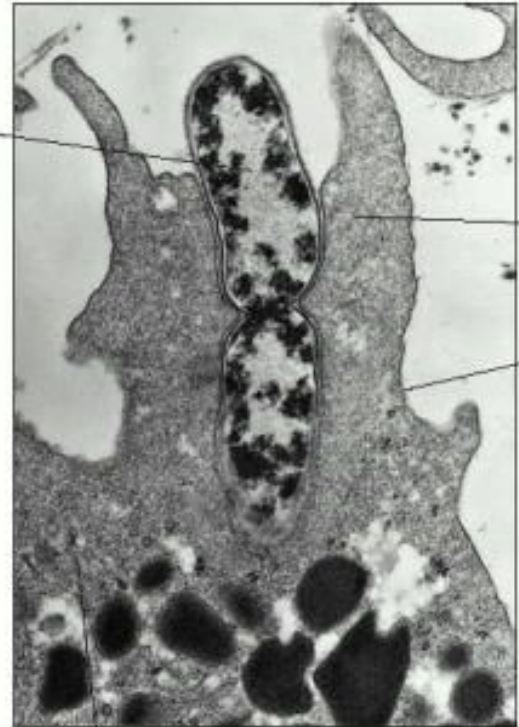


5 μm



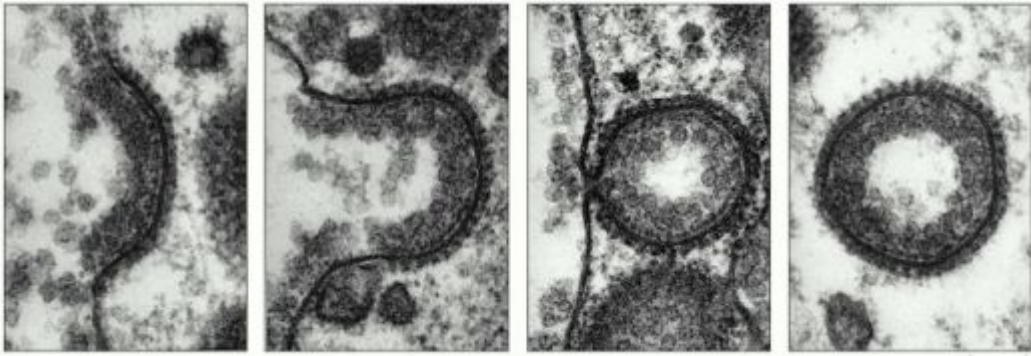
bacterium

pseudopod

plasma membrane

phagocytic white blood cell

1 μm

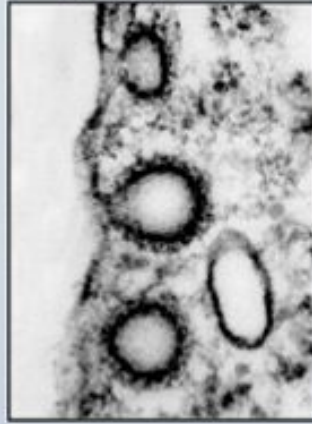


0.1 μm

A. Macropinocytosis



B. Clathrin-coated vesicle



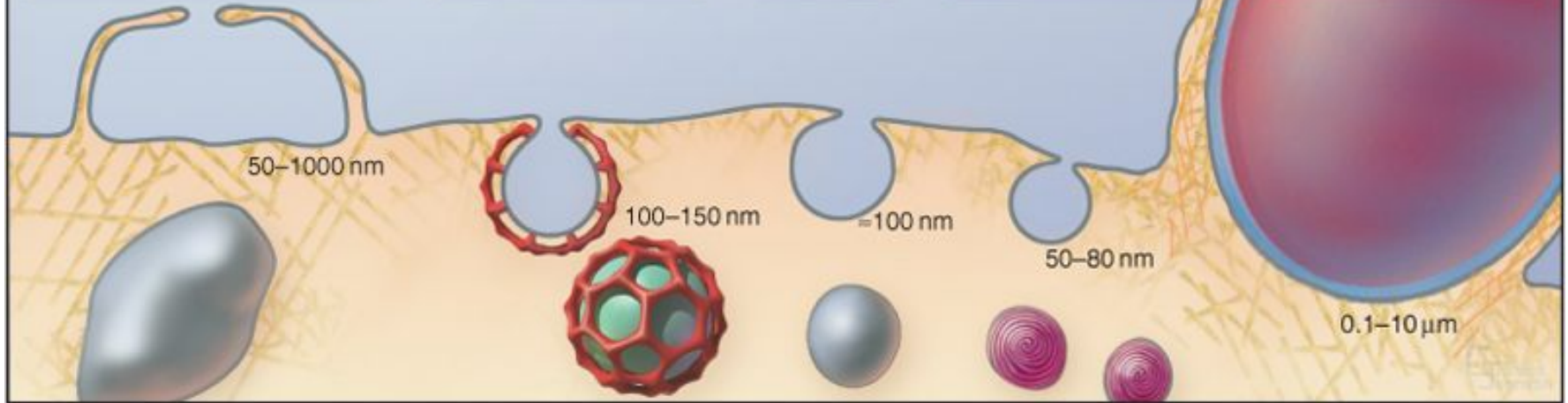
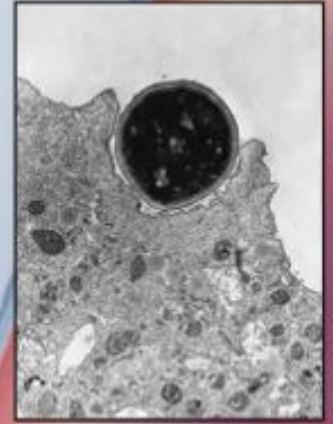
C. Noncoated vesicle

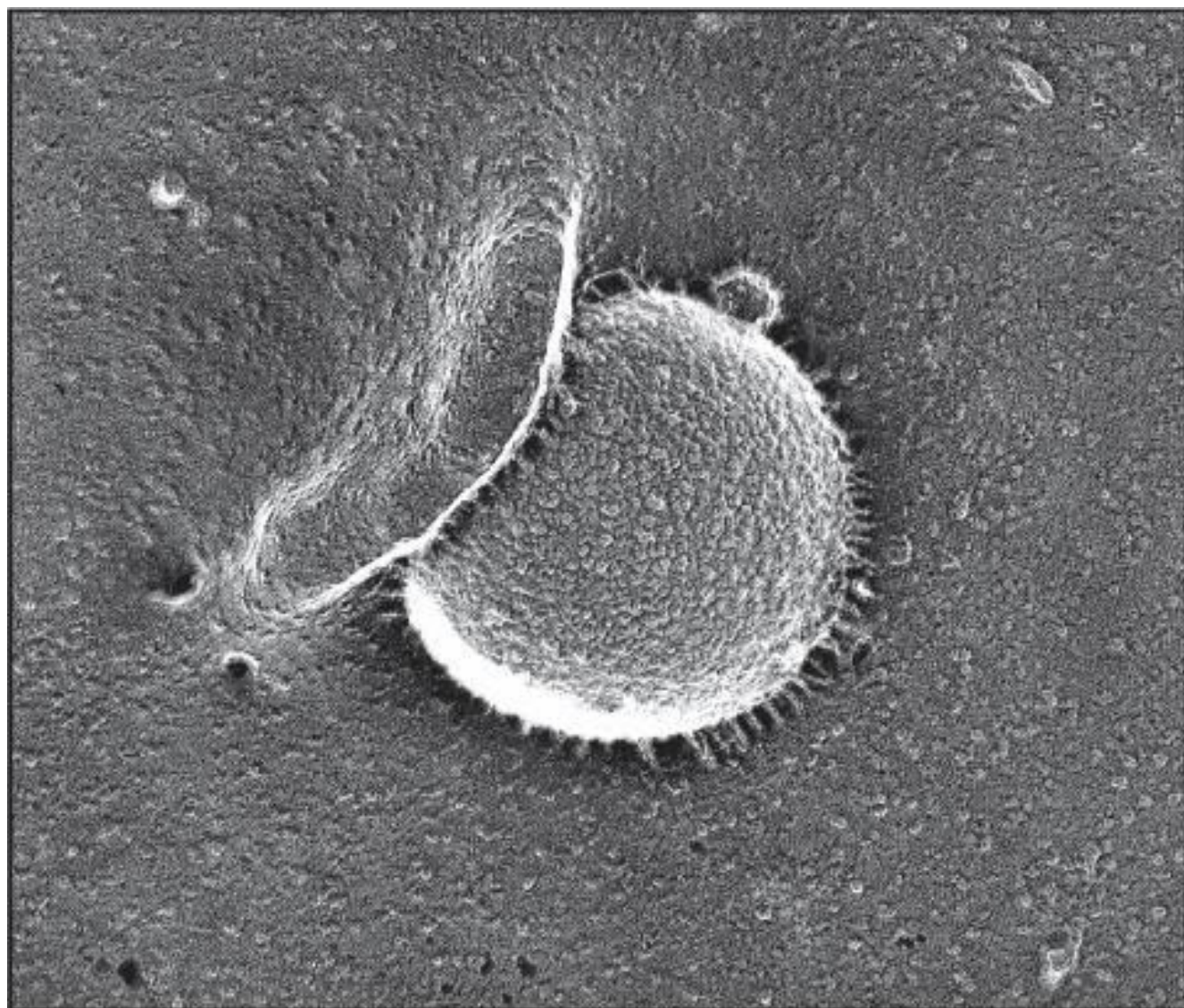


D. Caveolae



E. Phagocytosis





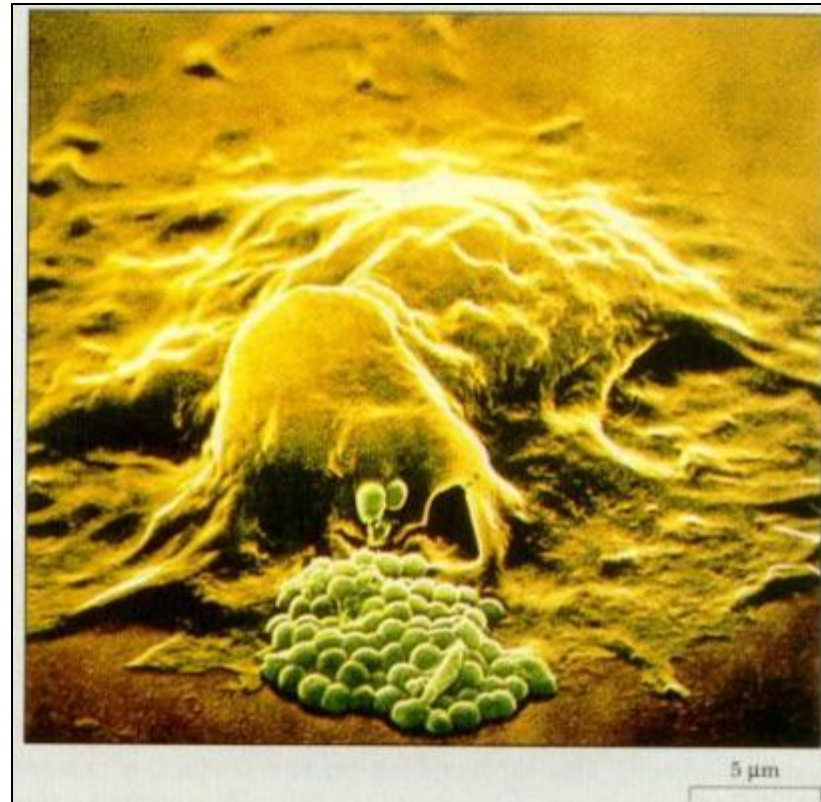
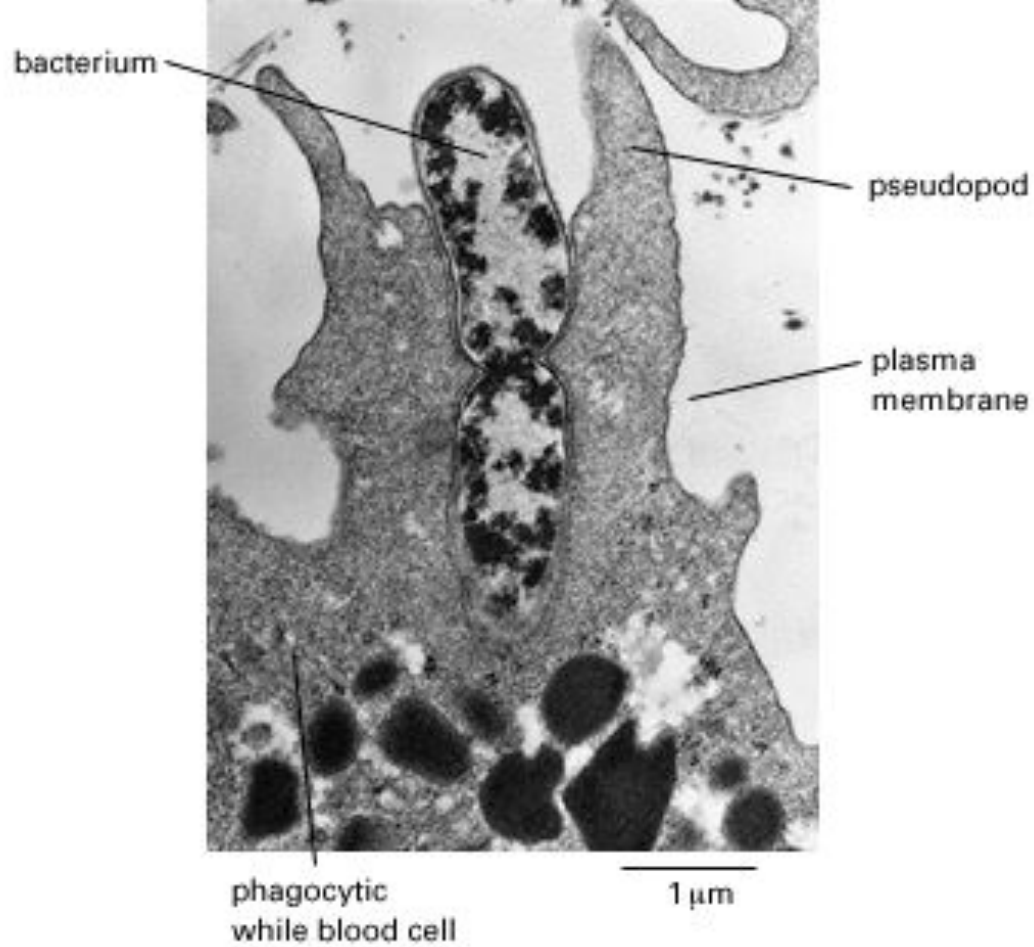
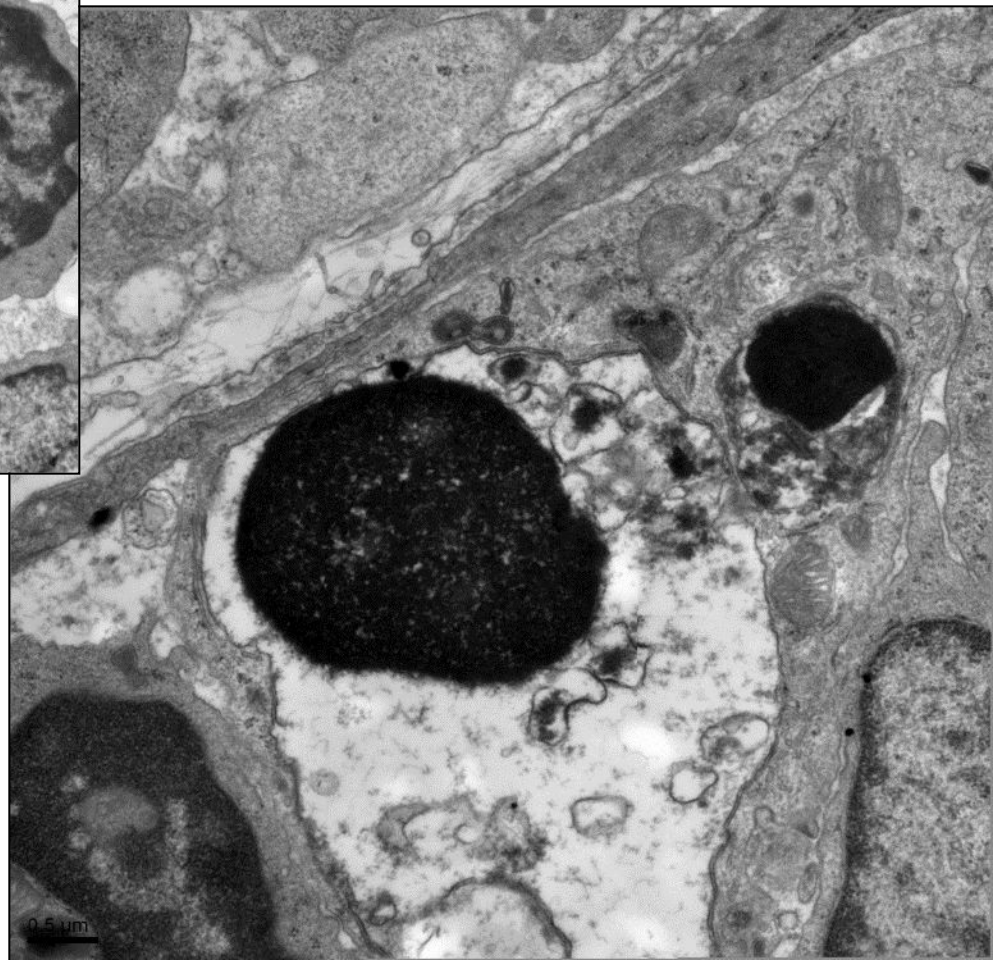
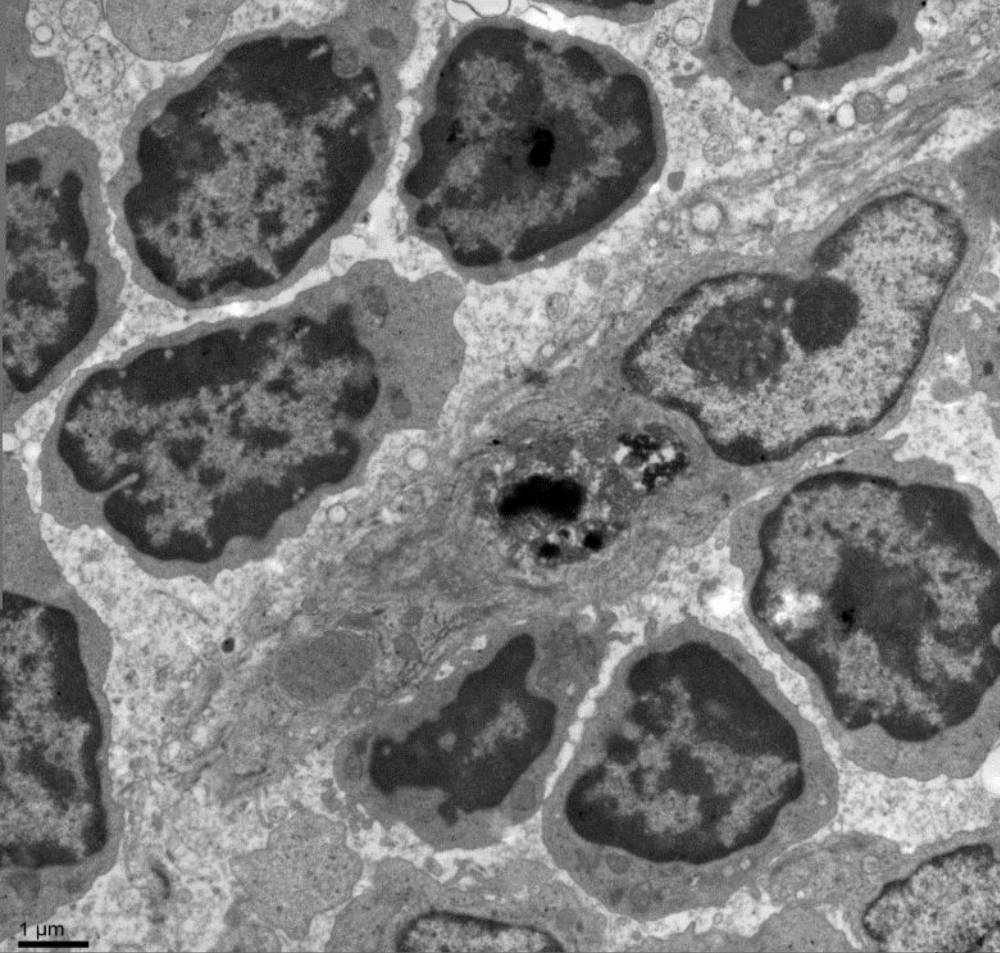


Figure 2 Pseudopods extend around the foreign microorganism. Extension requires the polymerization of actin into actin filaments. (Lennart Nilsson)



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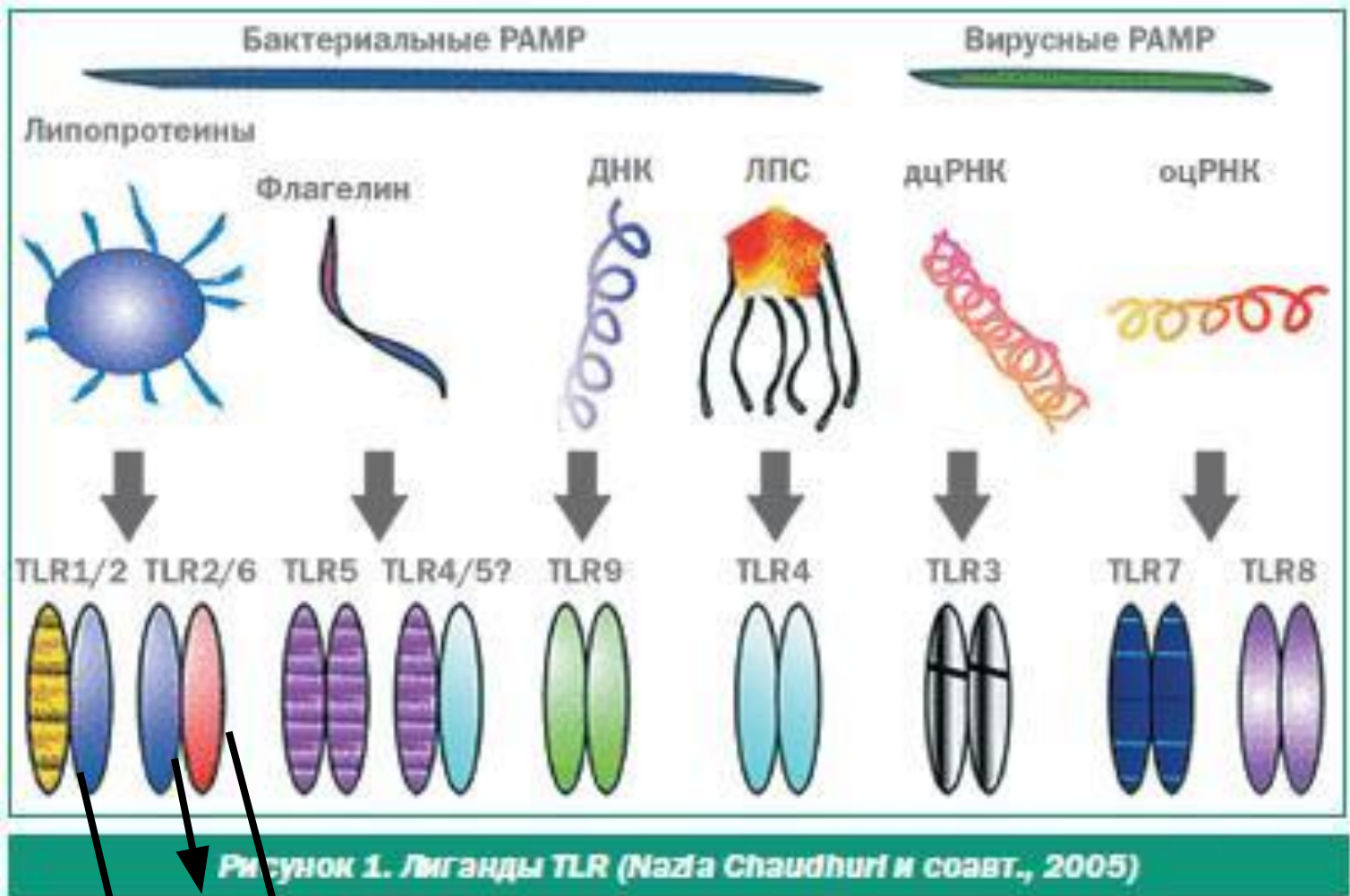
<https://www.frontiersin.org/articles/10.3389/fimmu.2020.01097/full>

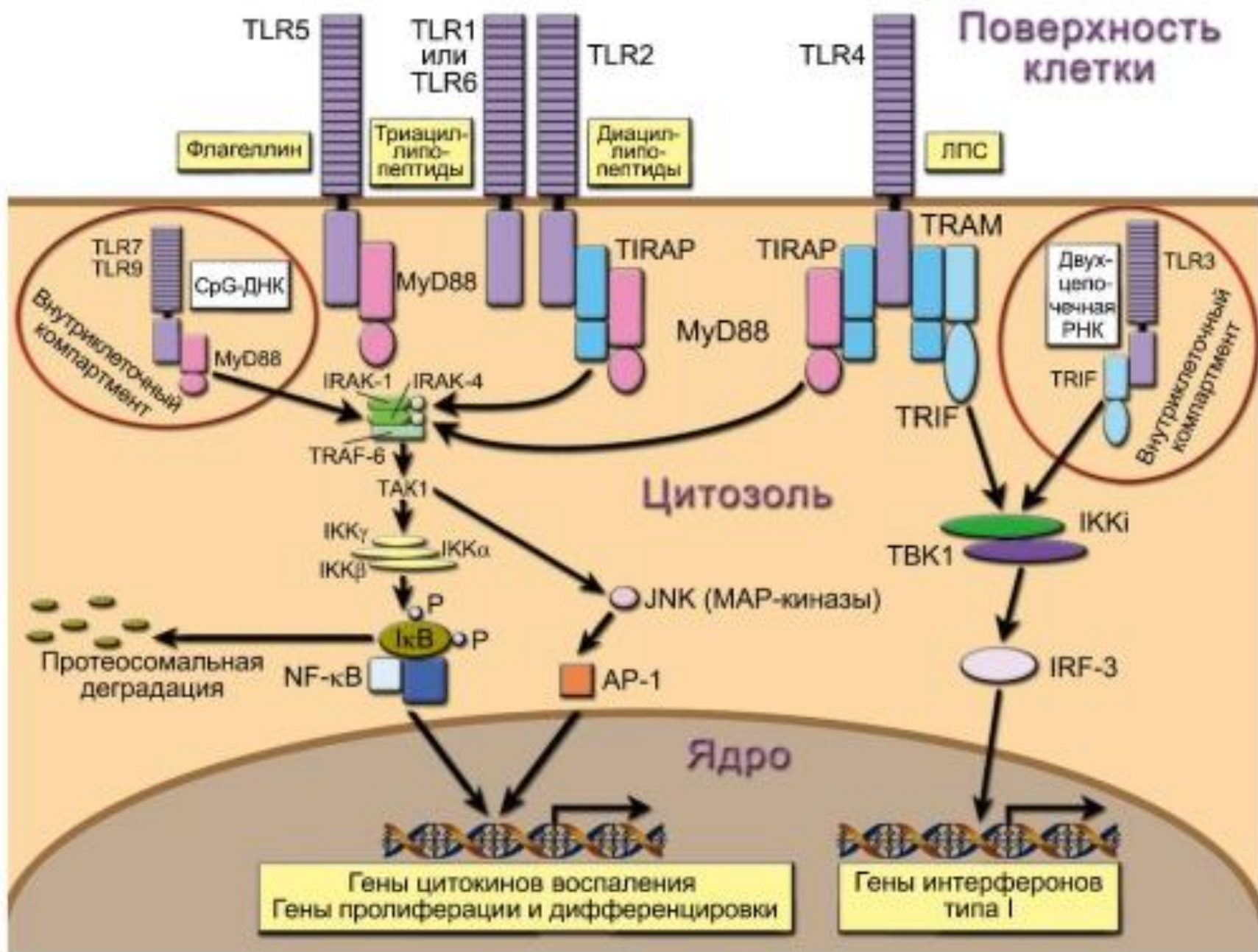
Группы хемоаттрактантов

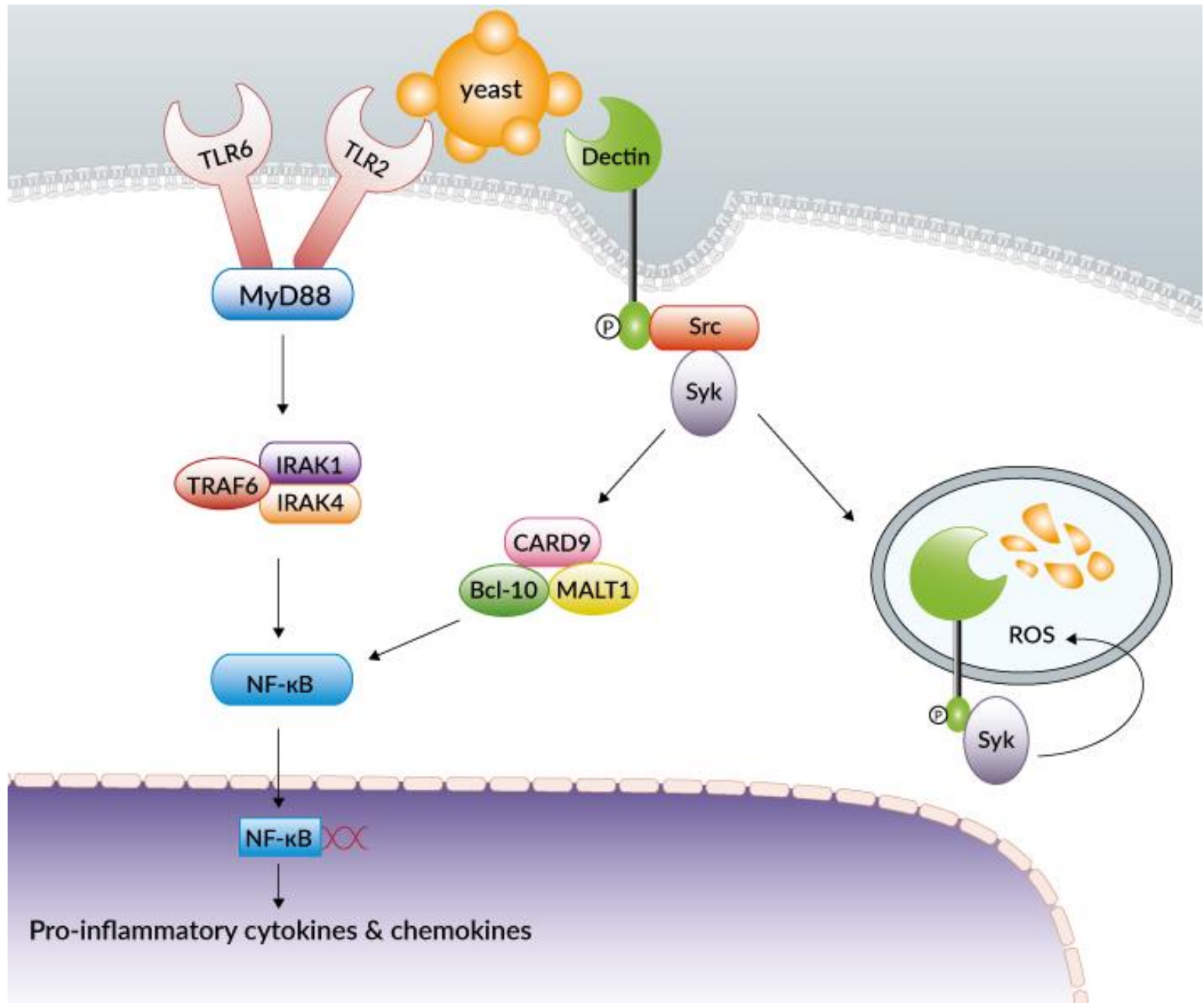
- Вещества, продуцируемые микроорганизмами (fMLP)
- Противовоспалительные факторы, образующиеся в очаге воспаления (цитокины, лейкотриены, компоненты системы комплемента)
- Вещества, попадающие в межклеточное пространство при нарушении целостности плазмолеммы

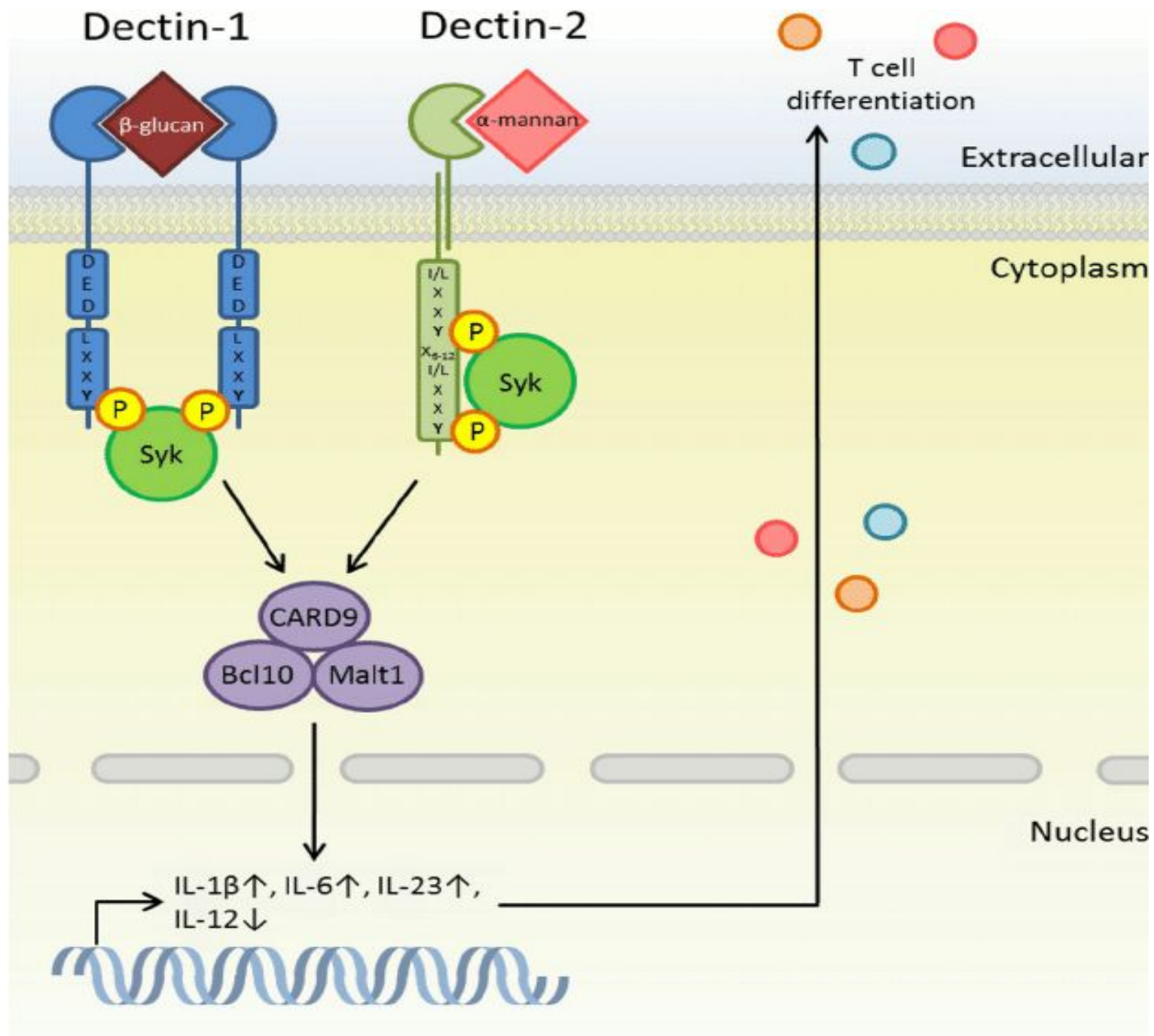
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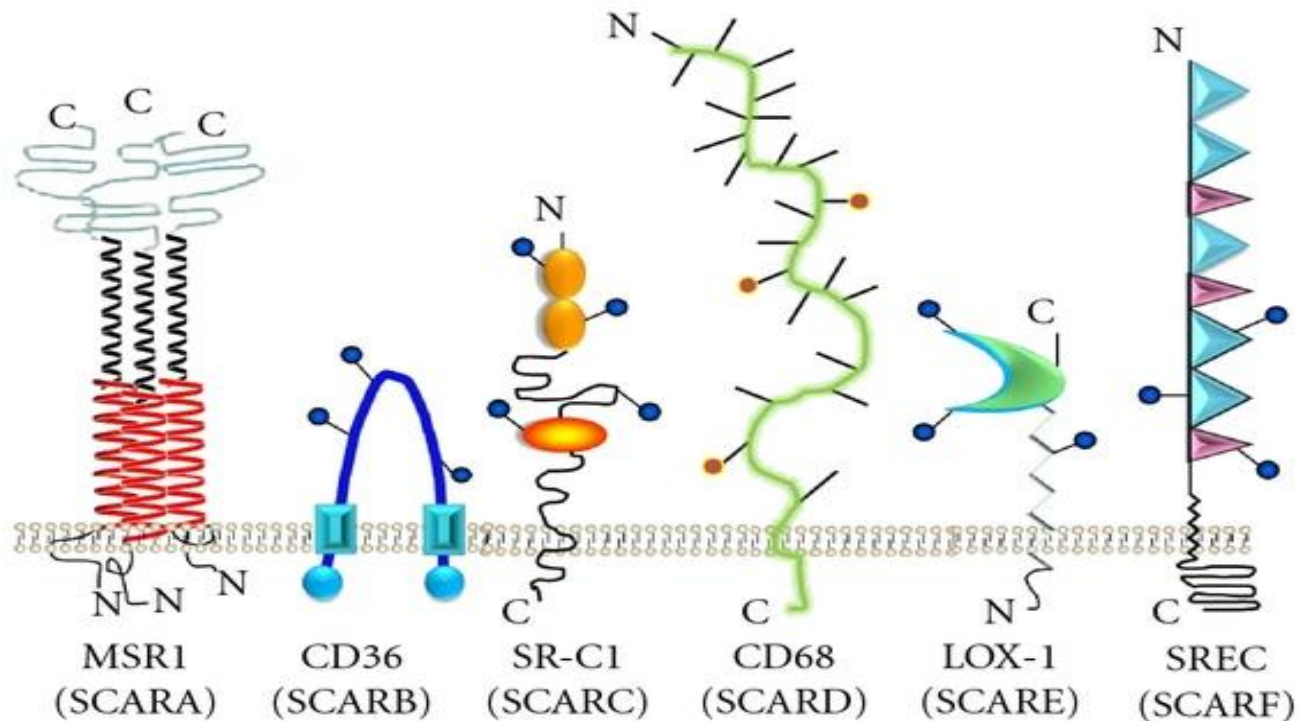








Receptors	Ligands
Pattern-recognition receptors	
Mannose receptor (CD206)	Mannan
Dectin-1 (CLEC7A)	β 1,3-glucan
CD14	Lipopolysaccharide-binding protein
Scavenger receptor A (CD204)	Lipopolysaccharide, lipoteichoic acid
CD36	<i>Plasmodium falciparum</i> -infected erythrocytes
MARCO	Bacteria



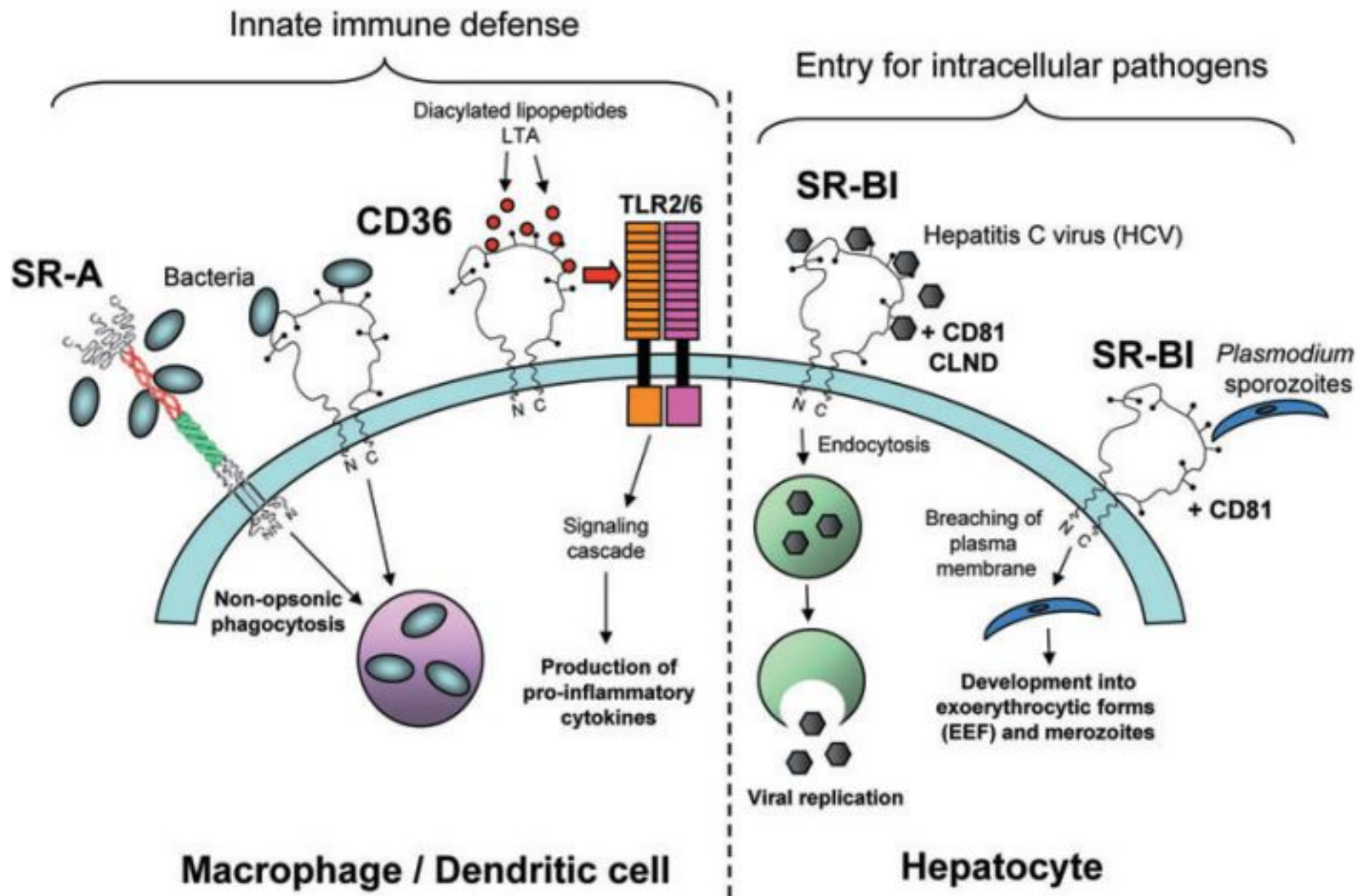
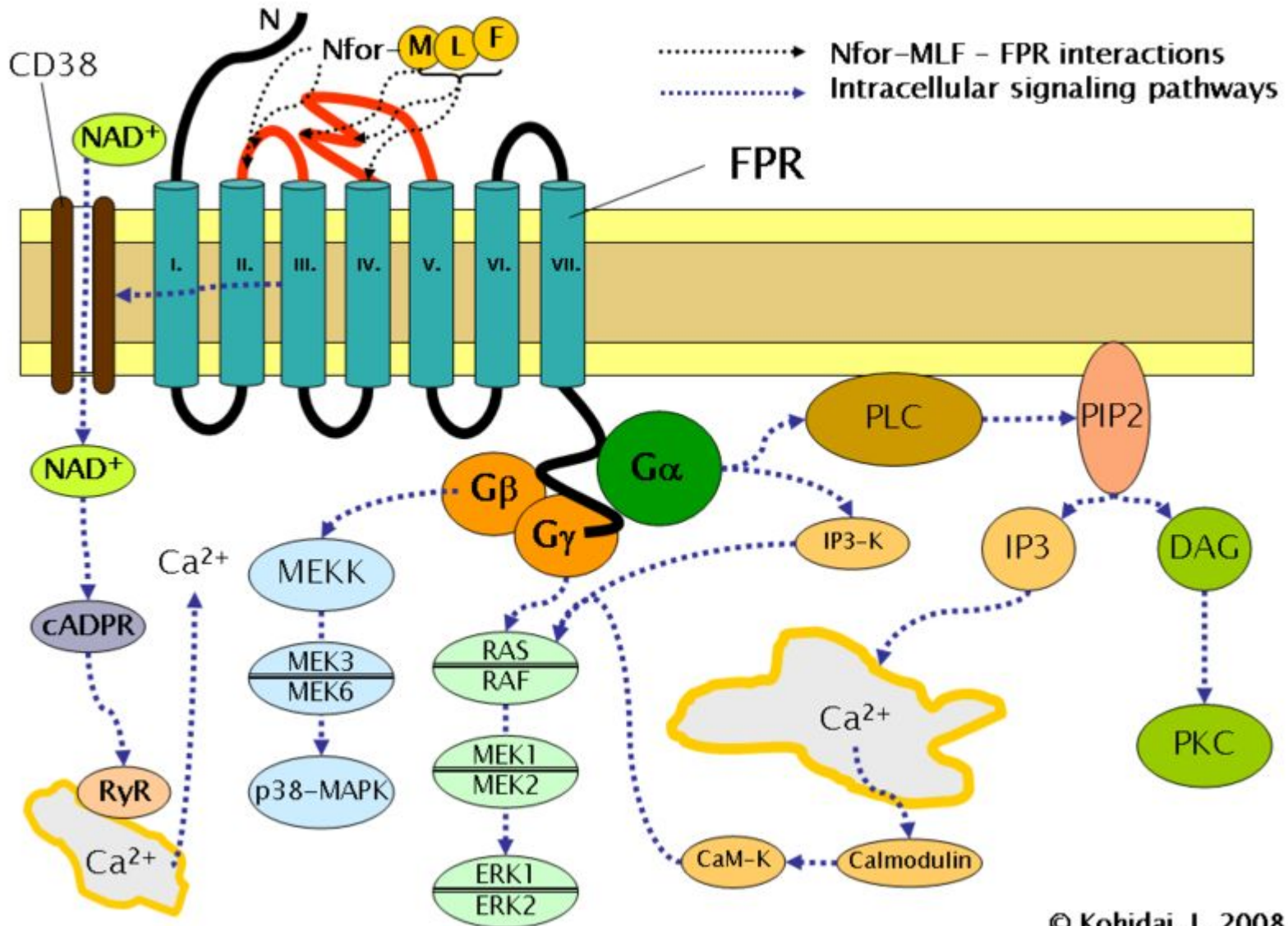


Fig. 1. Summary of the most important functions of SR in the innate immune defence and the role of SR in infections caused by intracellular pathogens such as HCV and *Plasmodium* spp. See text for details.

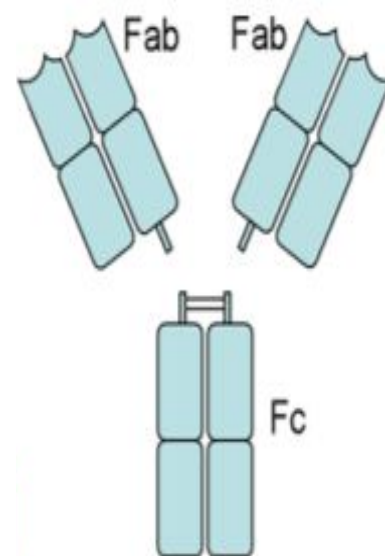
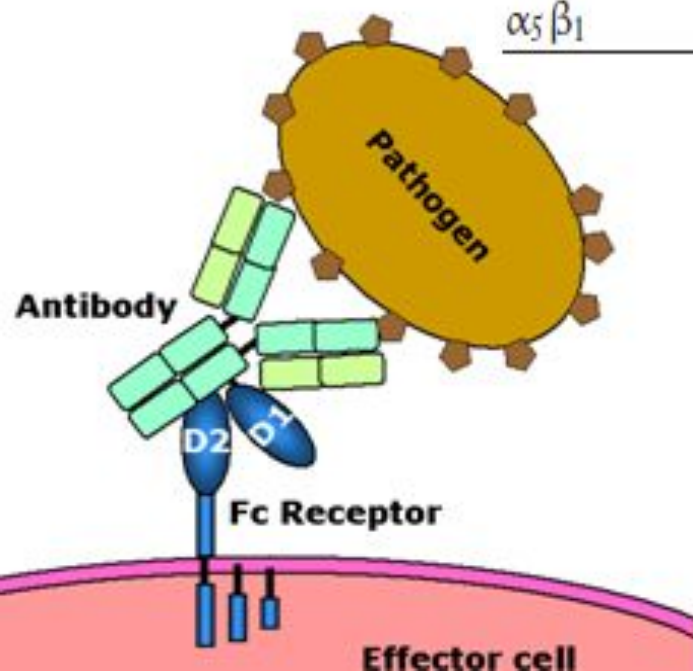
Рецептор к формилметионину

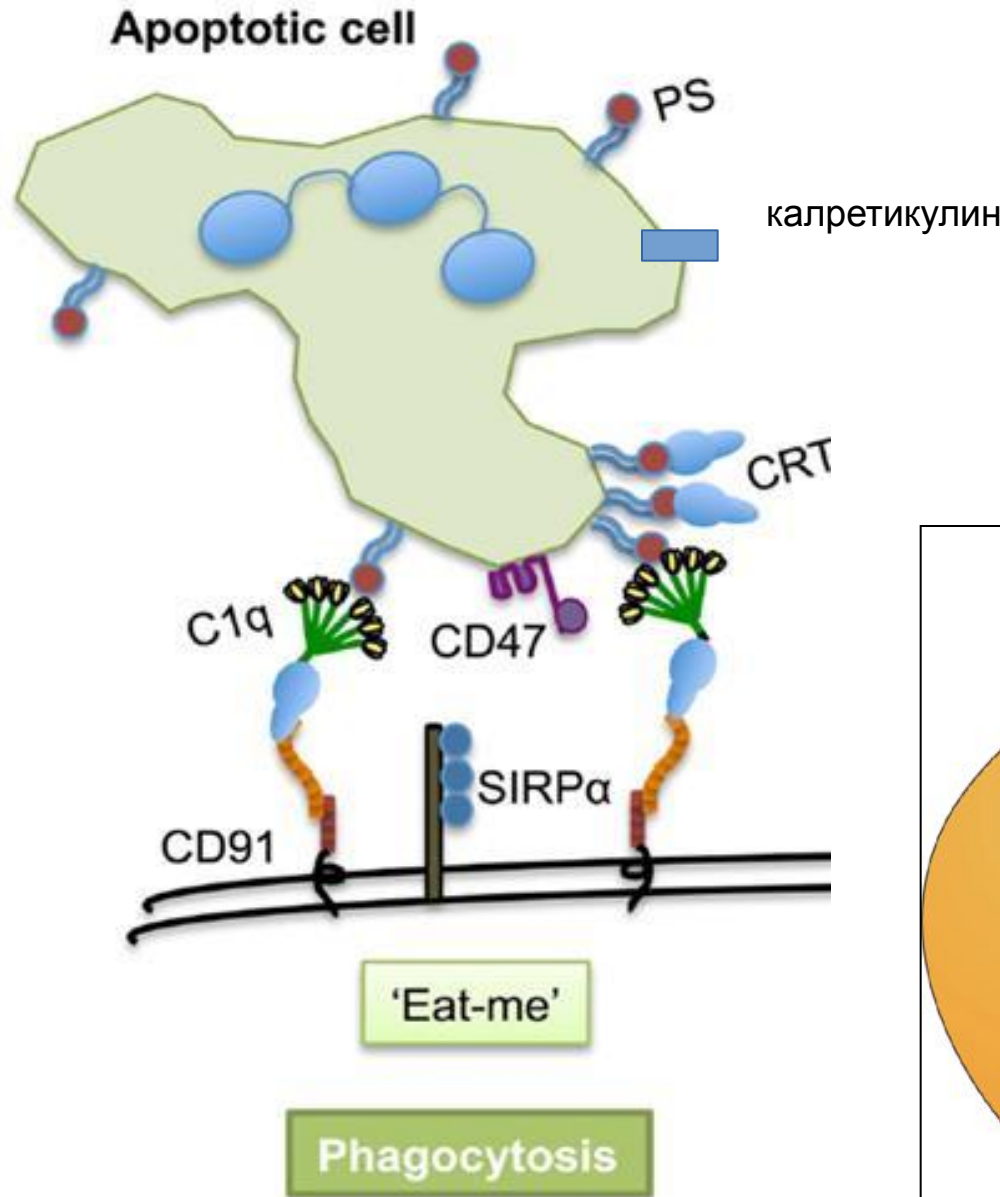


рецептор

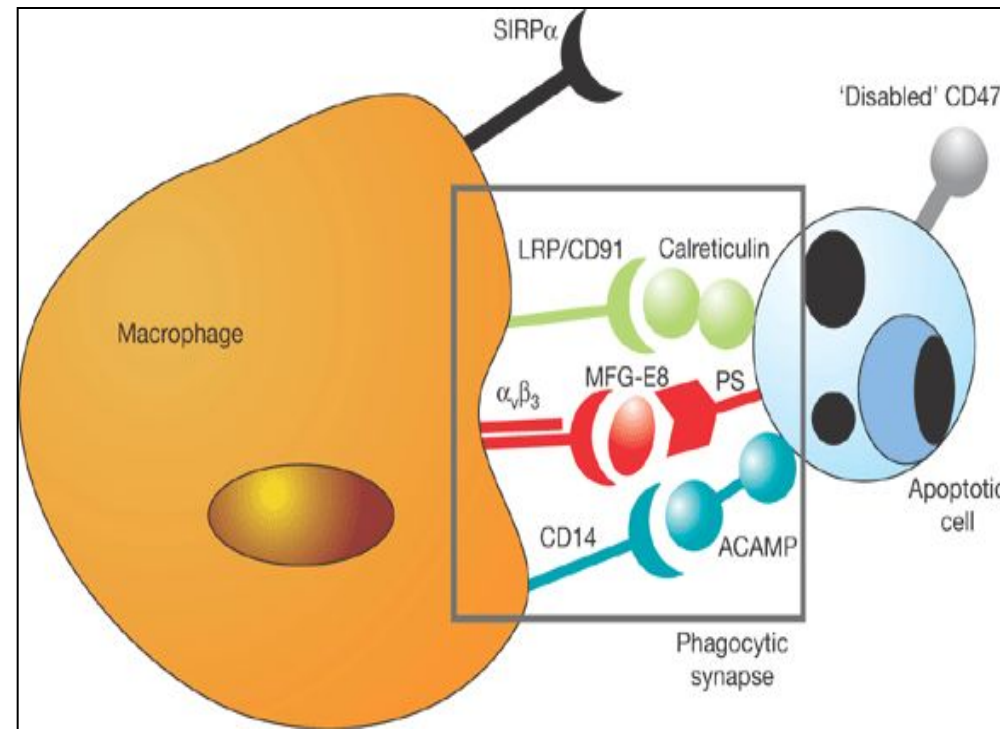
ОПСОНИН

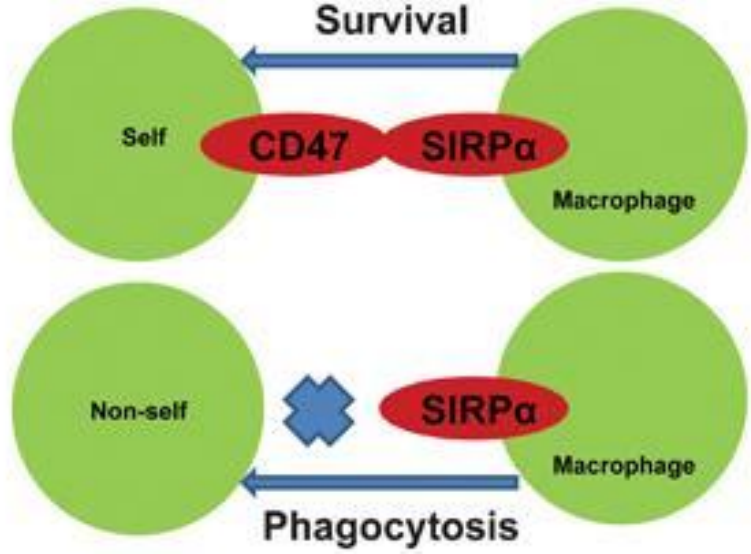
Fc γ RI (CD64)	IgG1 = IgG3 > IgG4
Fc γ RIIa (CD32a)	IgG3 \geq IgG1 = IgG2
Fc γ RIIc (CD32c)	IgG
Fc γ RIIIa (CD16a)	IgG
Fc α RI (CD89)	IgA1, IgA2
Fc ϵ RI	IgE
CR1 (CD45)	Mannan-binding lectin, C1q, C4b, C3b
CR3 ($\alpha_M\beta_2$, CD11b/CD18, Mac-1)	iC3b
CR4 ($\alpha_V\beta_2$, CD11c/CD18, gp150/95)	iC3b
$\alpha_5\beta_1$	Fibronectin, vitronectin



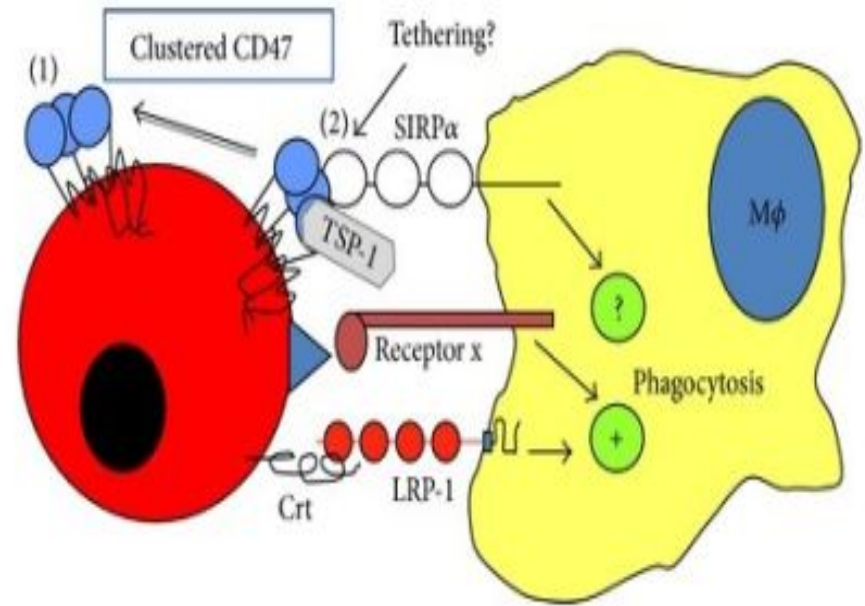


TIM-1	Phosphatidylserine
TIM-4	Phosphatidylserine
BAI1	Phosphatidylserine
Stabilin-2	Phosphatidylserine
Mer	Gas6, protein S
$\alpha_V \beta_3$	MFG-E8 <small>Секретируется макрофагами</small>
$\alpha_V \beta_5$	Apoptotic cells
CD36	Oxidized lipids

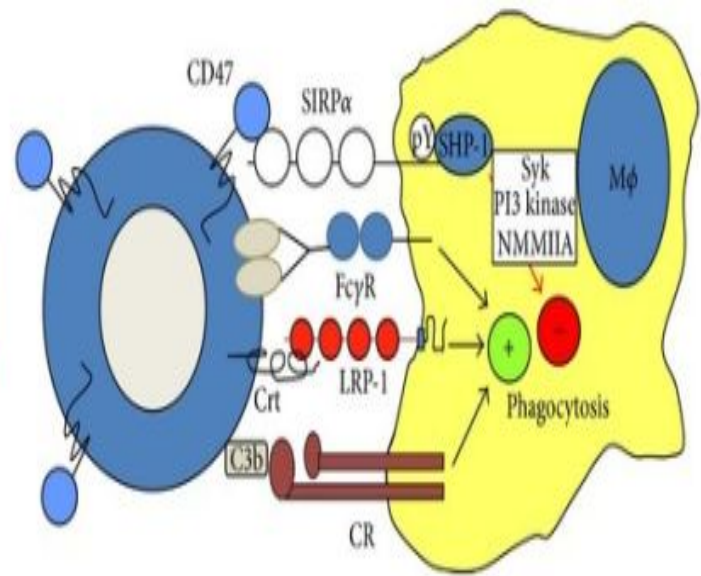




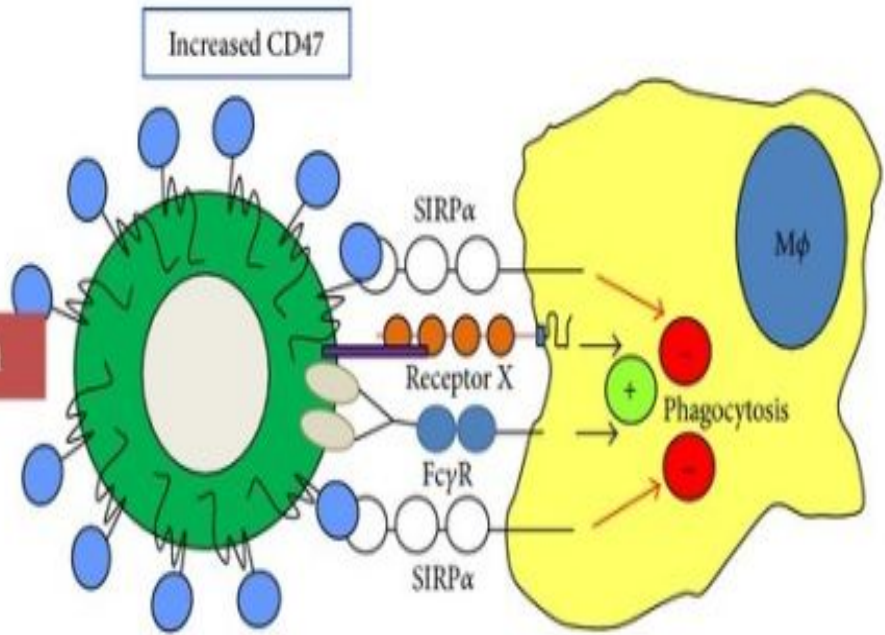
Apoptotic host cell



Viable host cell



Cancer cell



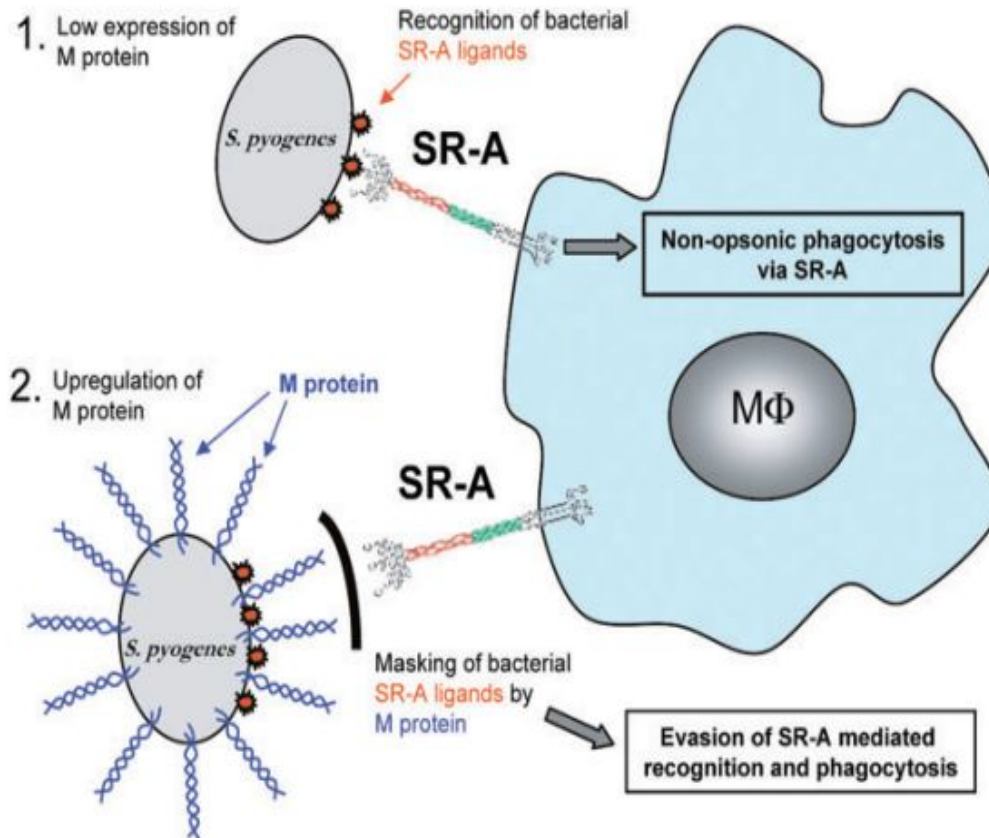
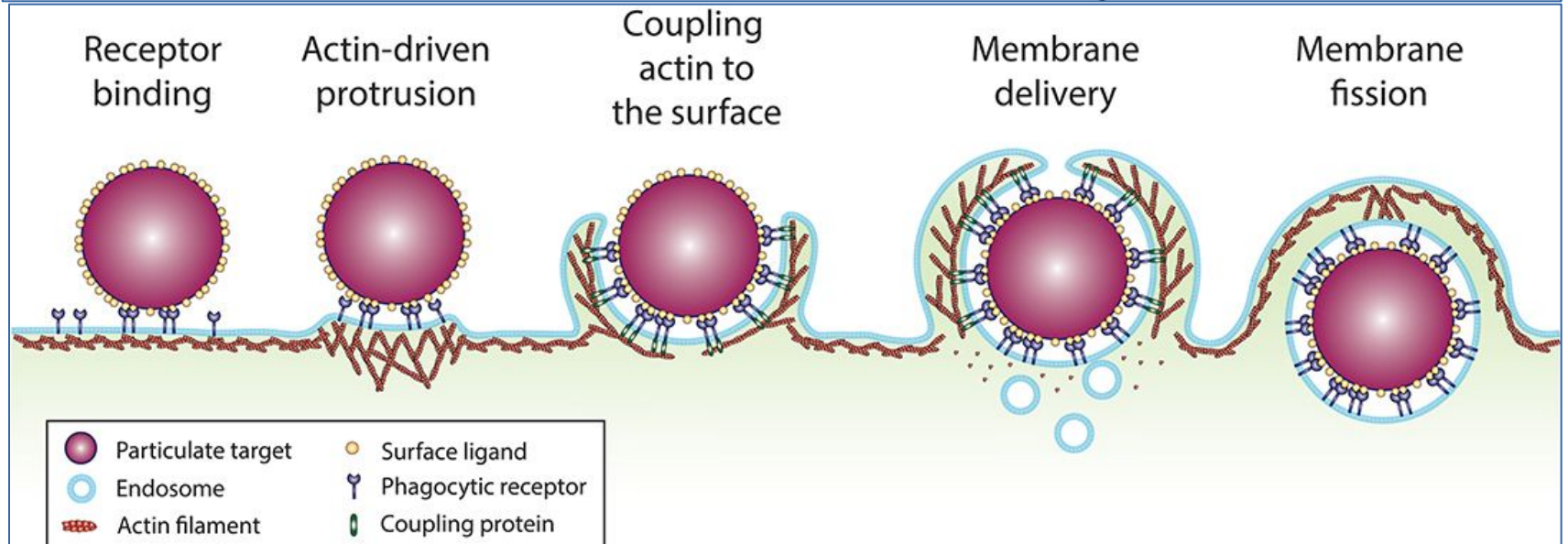
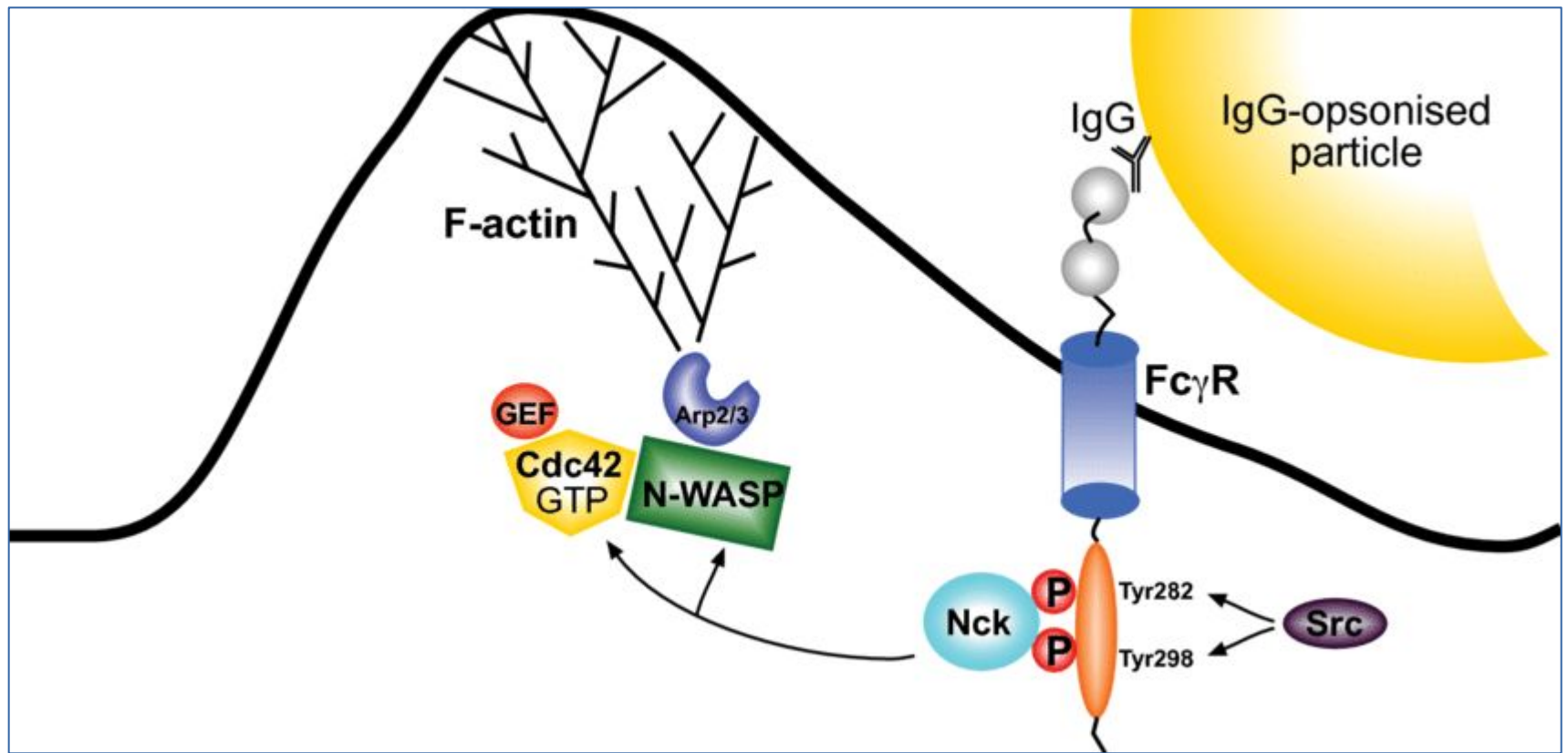
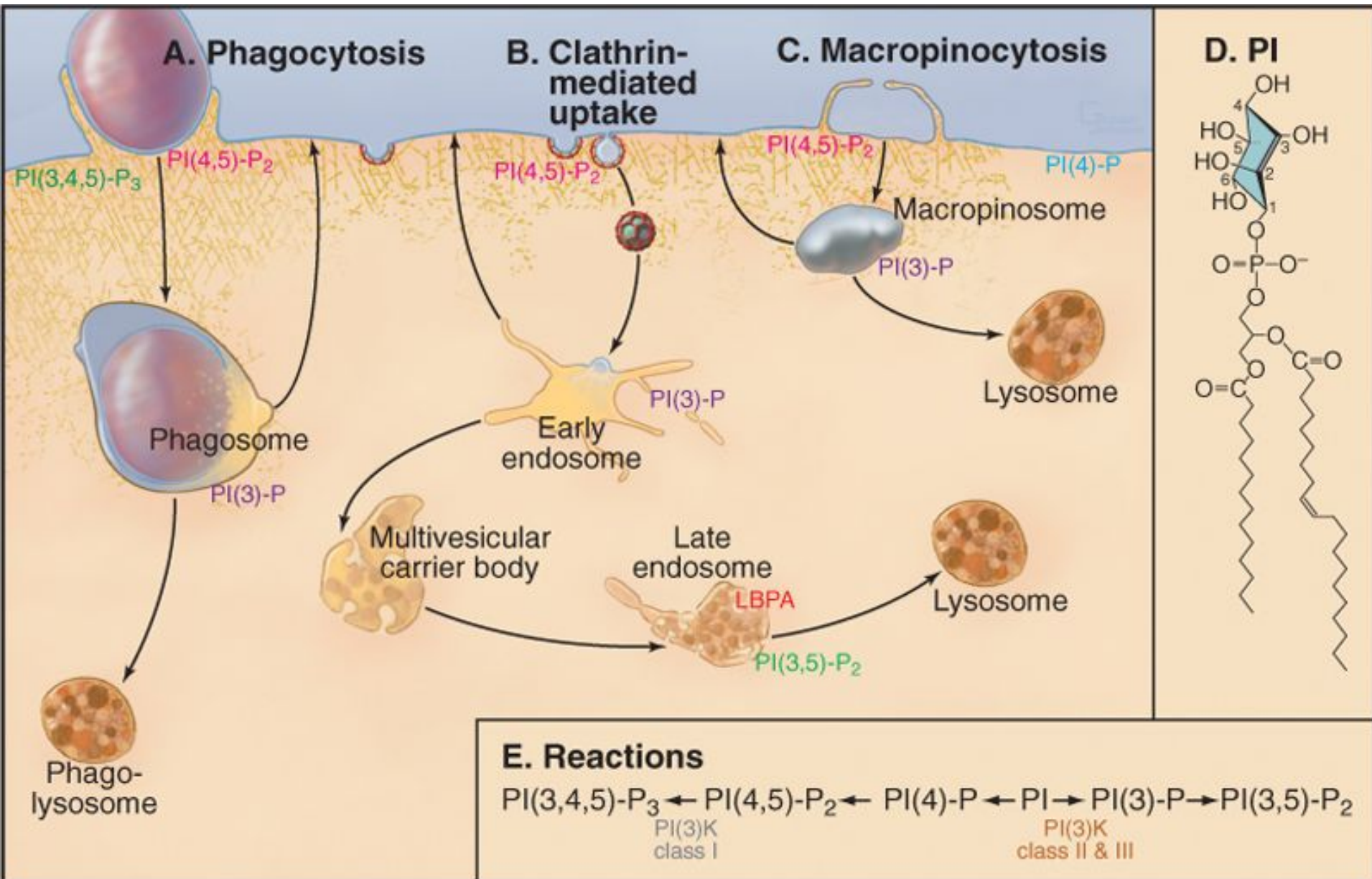


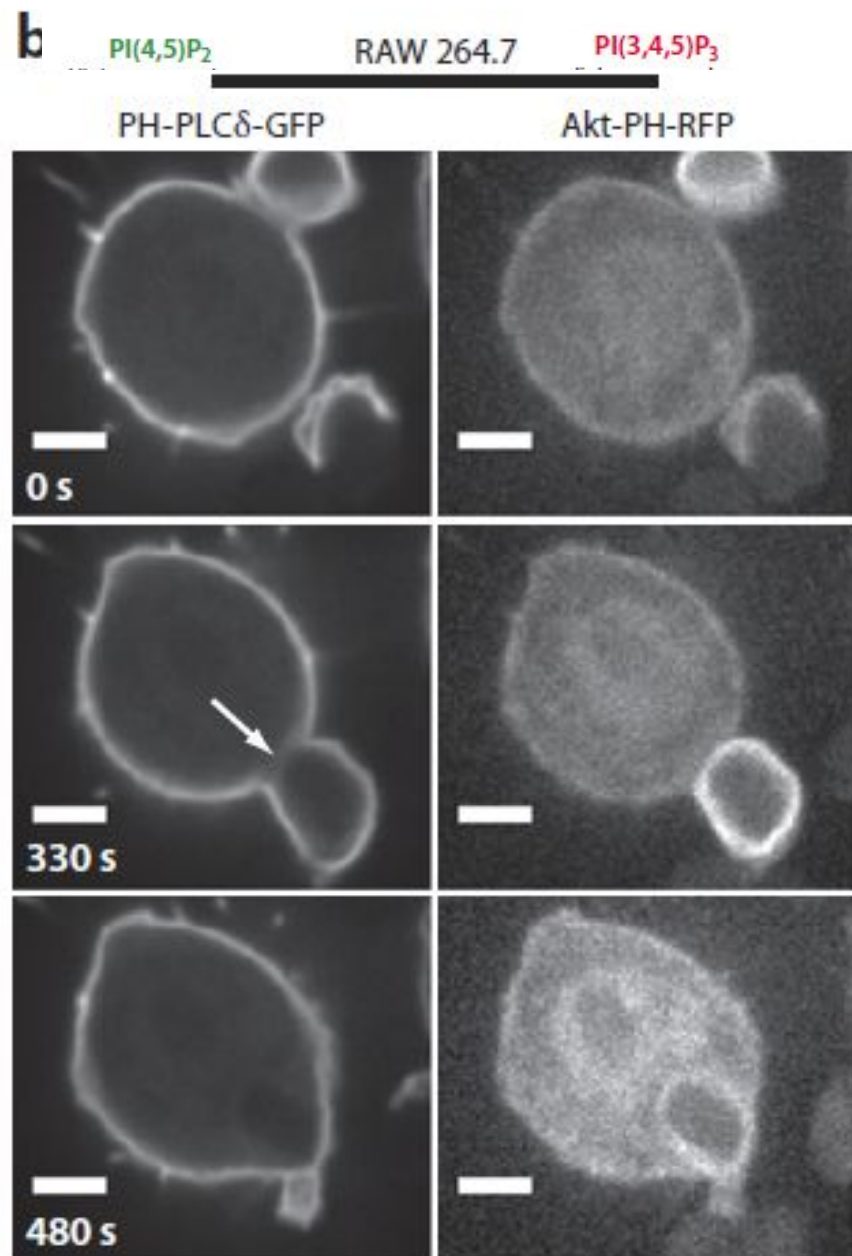
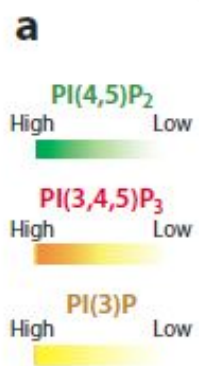
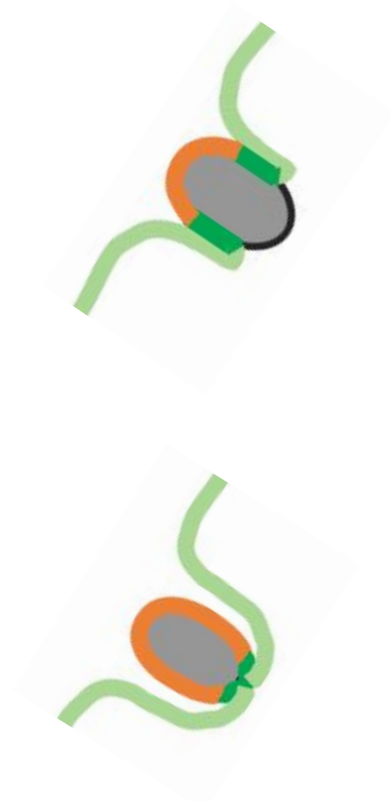
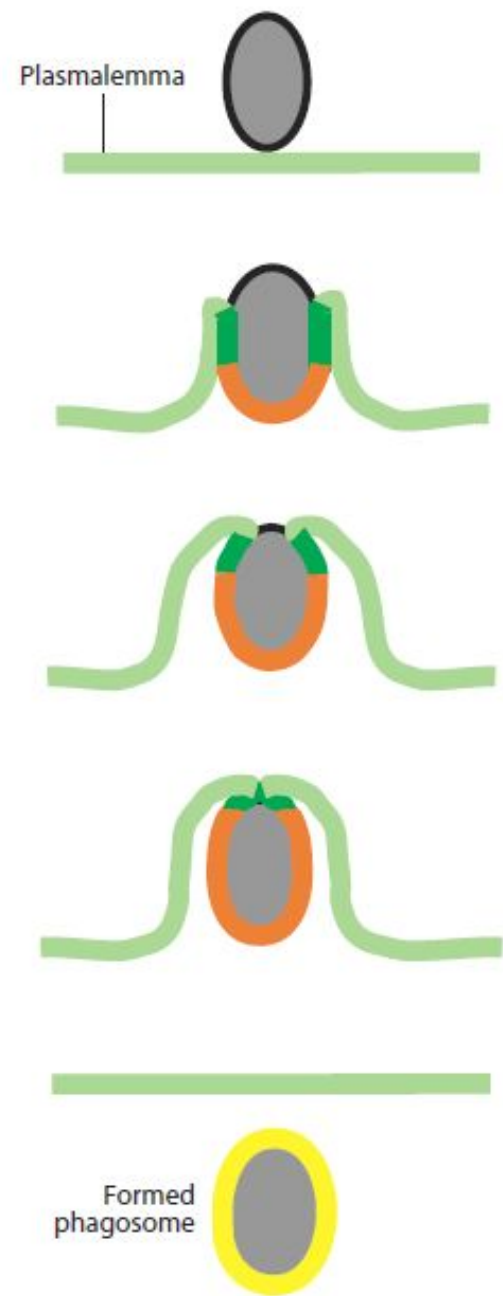
Fig. 2. Model of evasion mechanism in *Streptococcus pyogenes* to avoid SR-A-mediated recognition and non-opsonic phagocytosis by MΦ. (1) At low expression of the surface M protein, the SR-A ligand(s) at the bacterial surface are exposed, resulting in SR-A-mediated recognition and phagocytosis. (2) When M protein is expressed at high levels, it prevents SR-A-mediated phagocytosis of *S. pyogenes* by masking the ligand(s) for SR-A at the bacterial surface. See text for references.

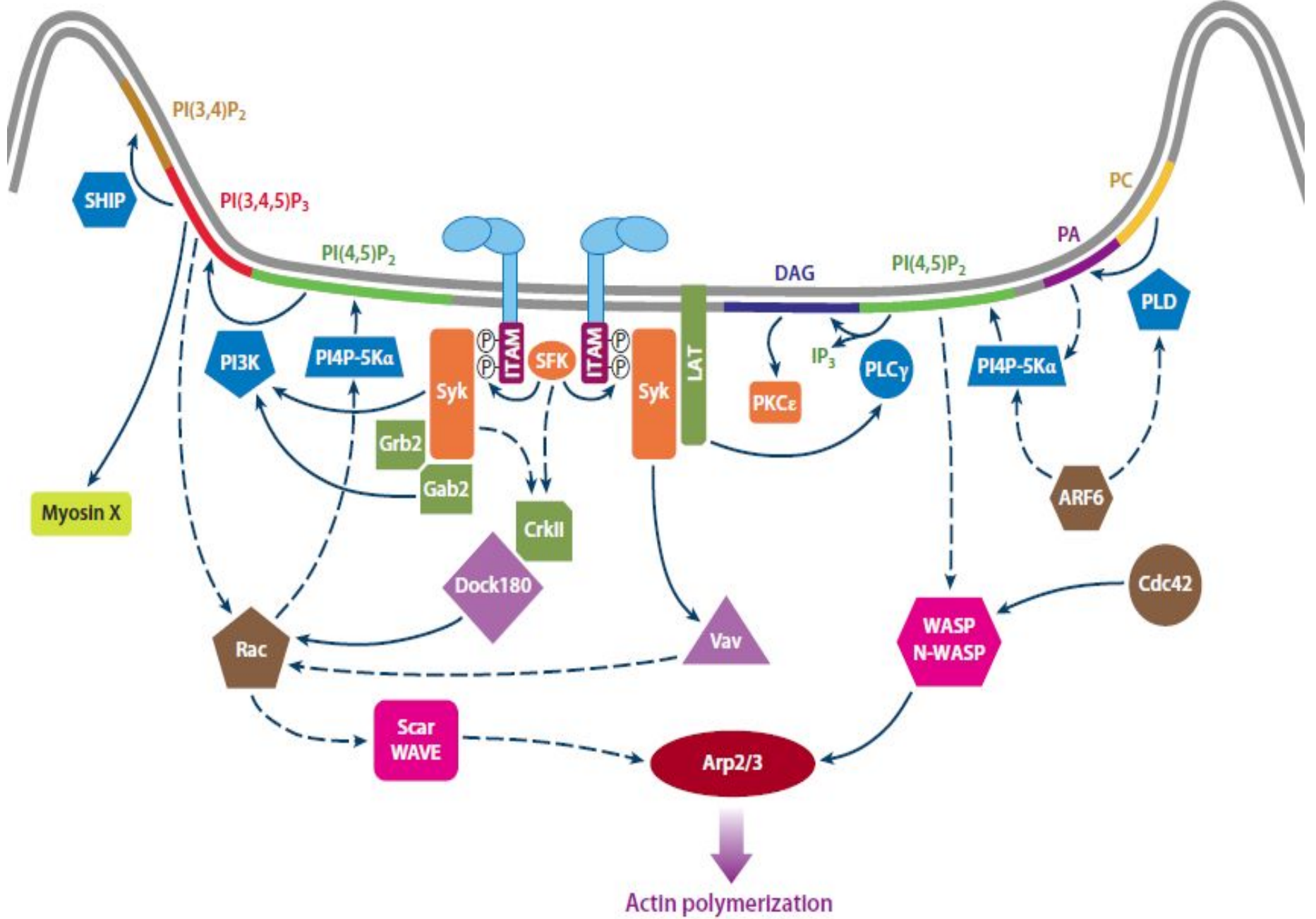
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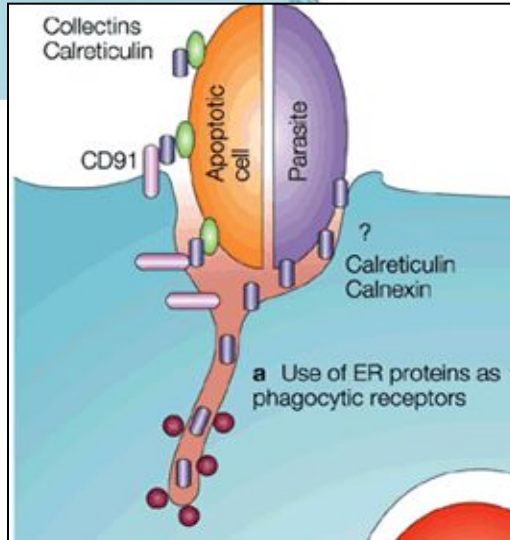
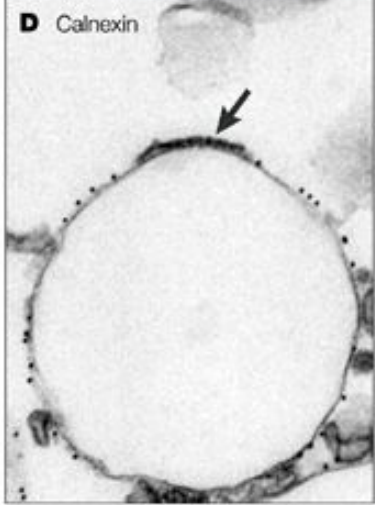
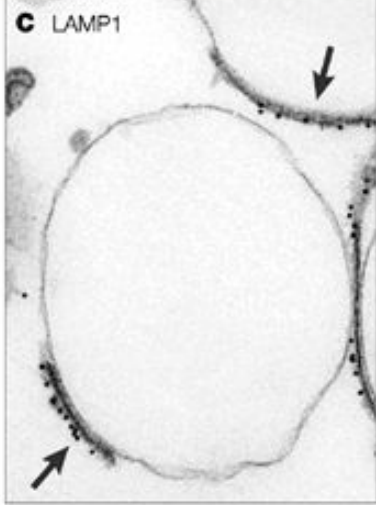
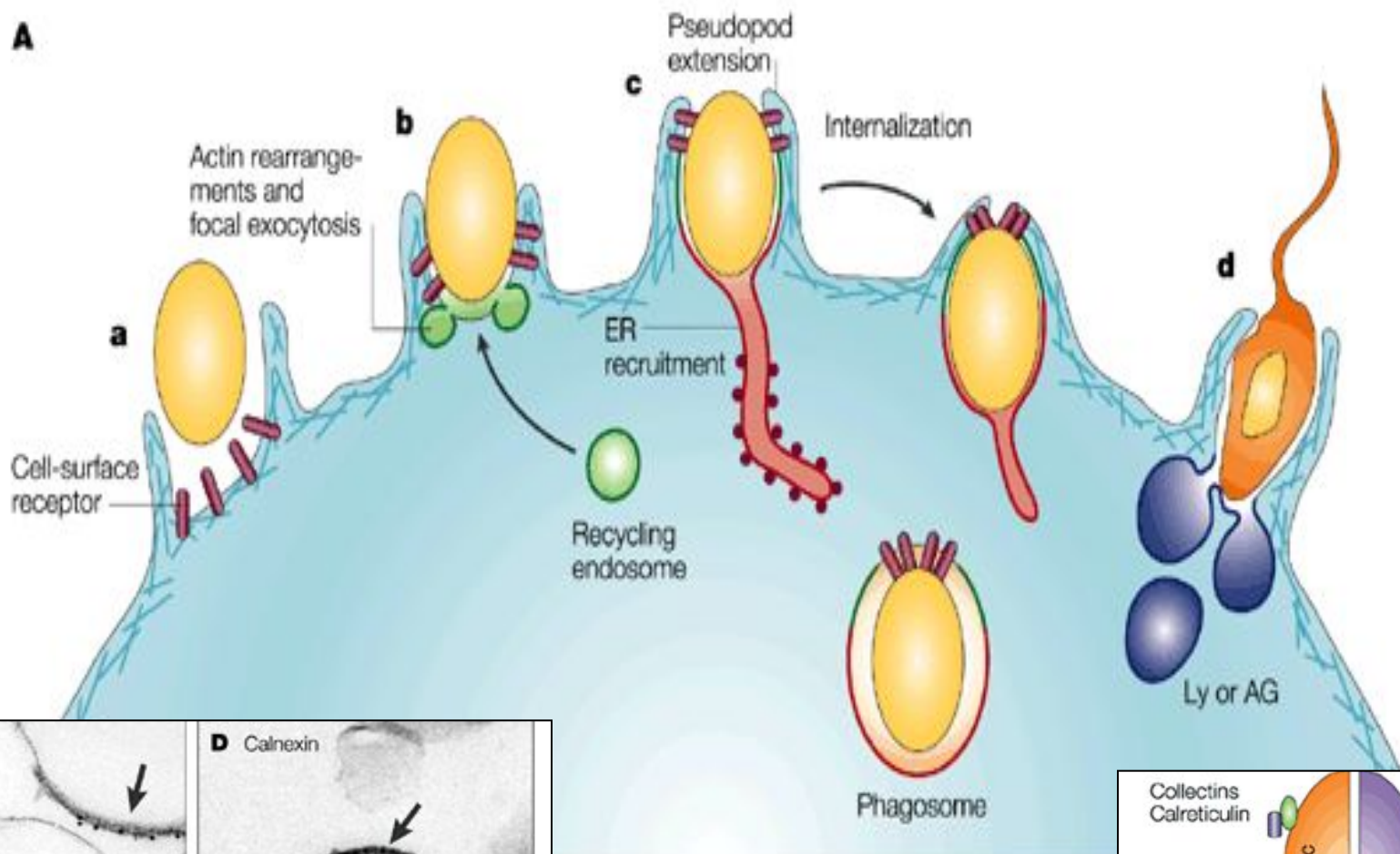


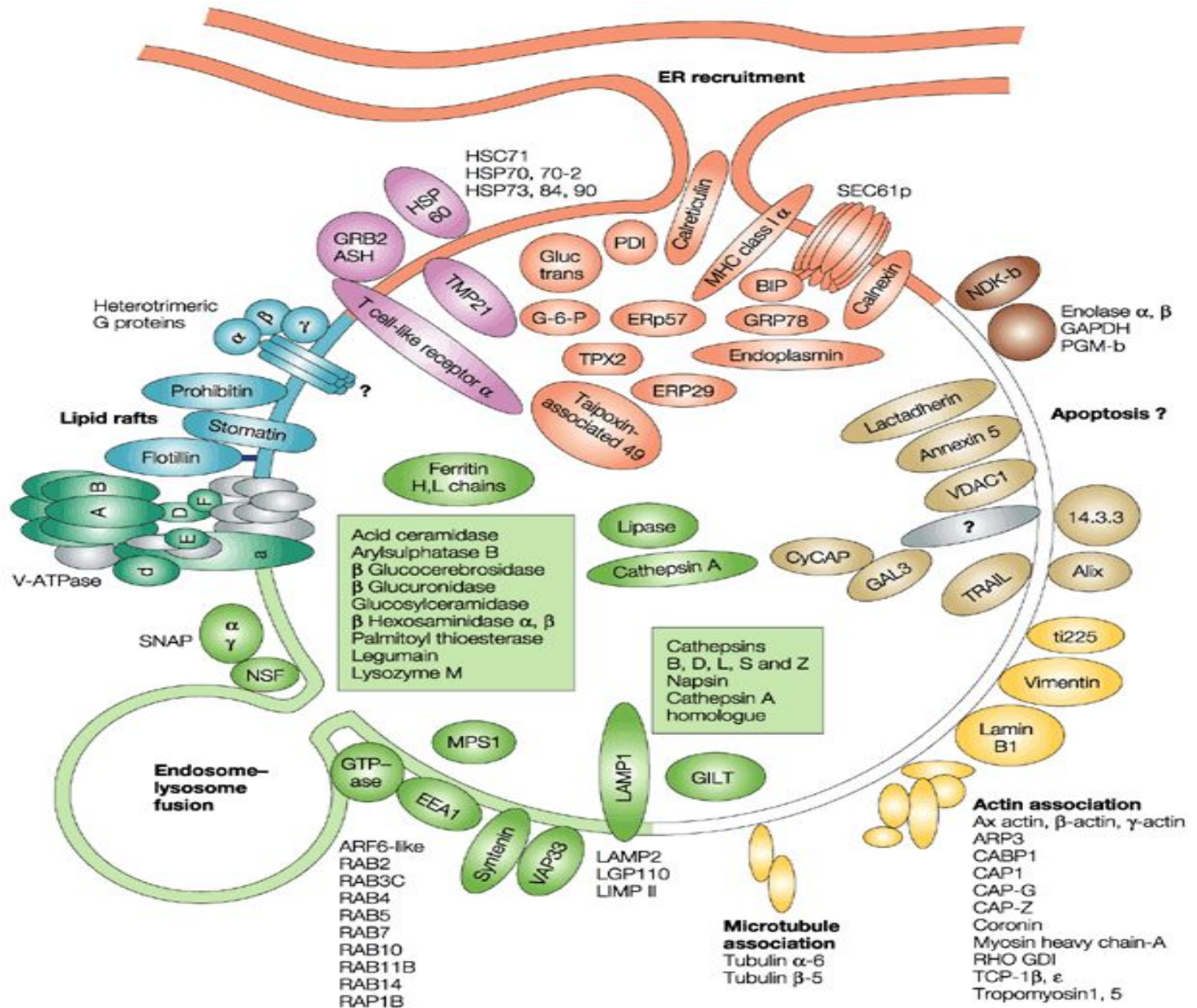


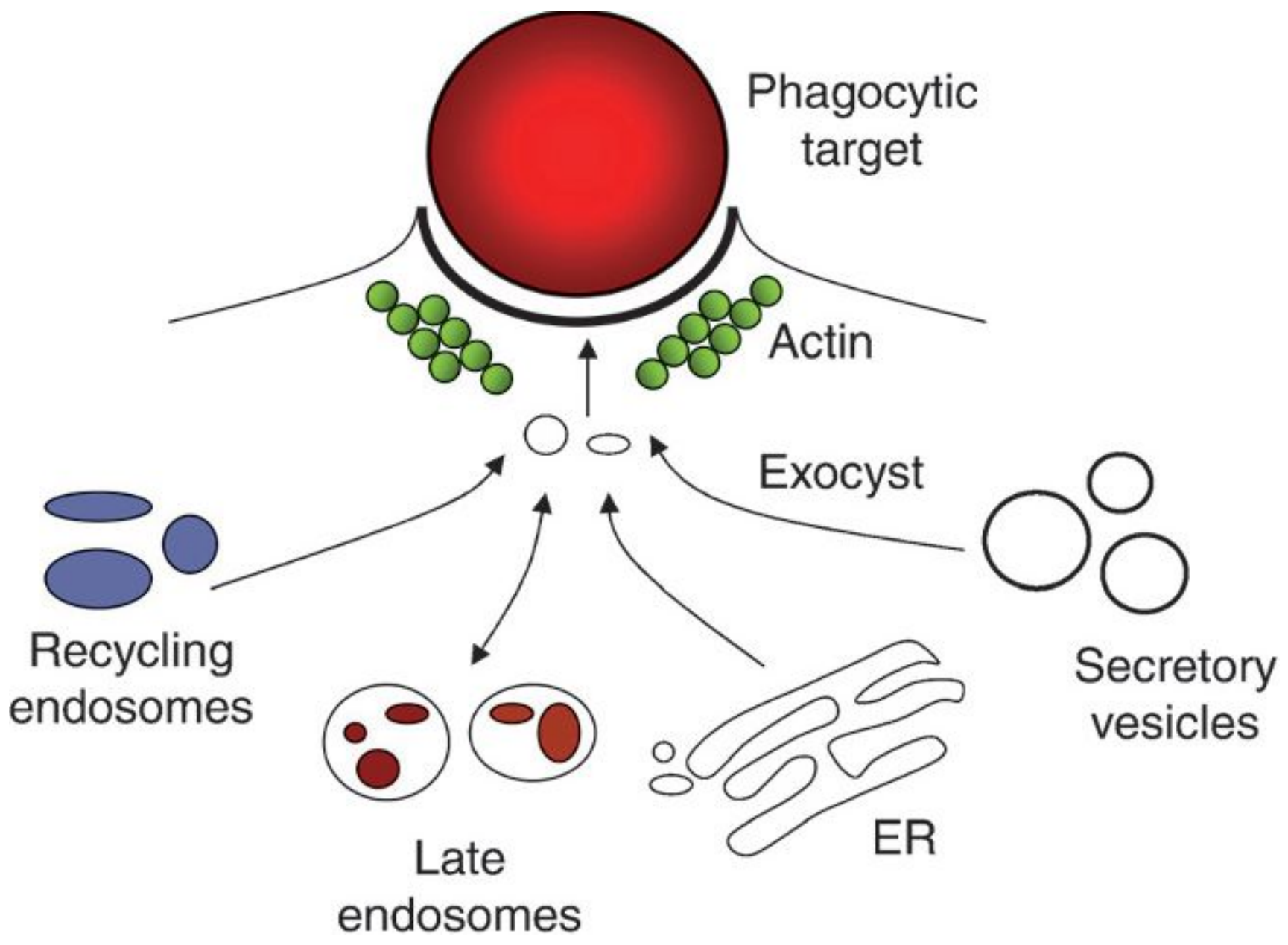




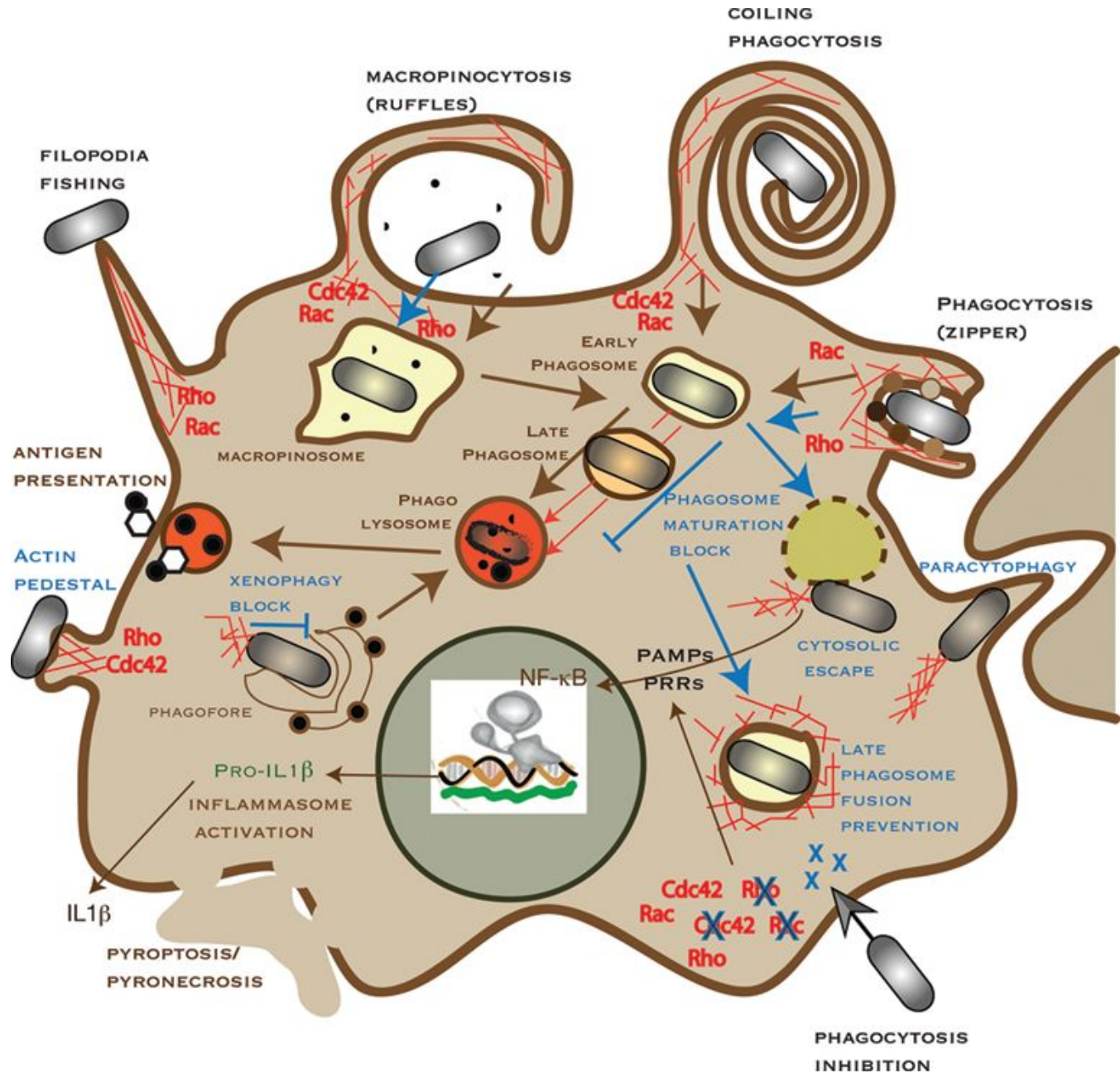
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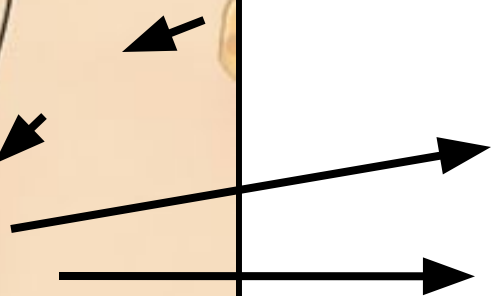
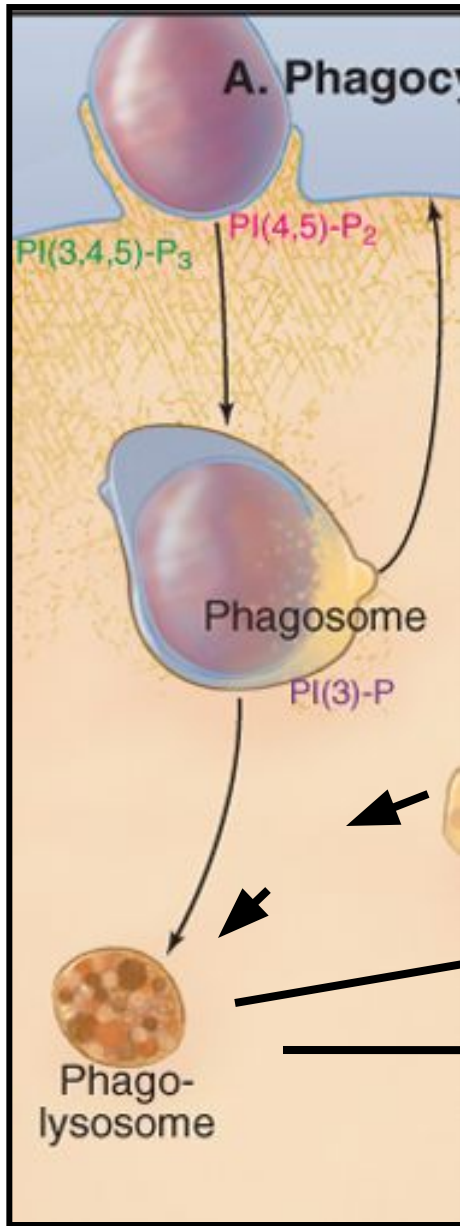


Механизмы захвата



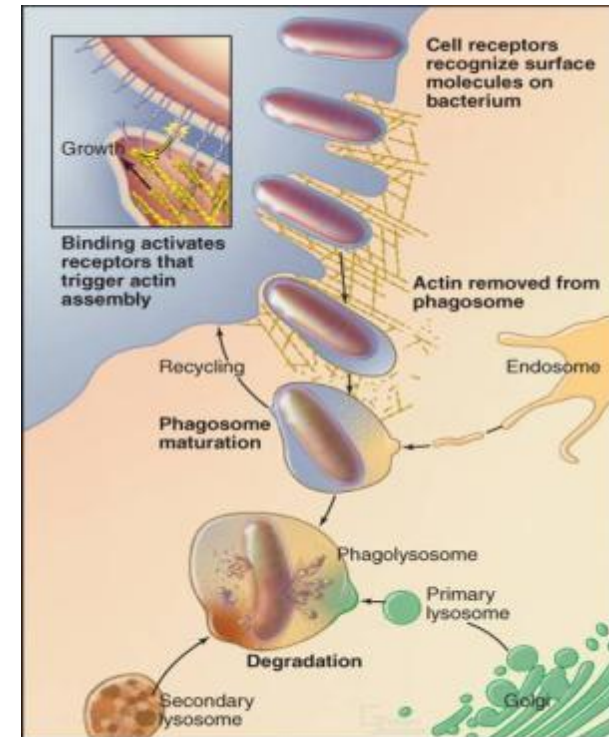
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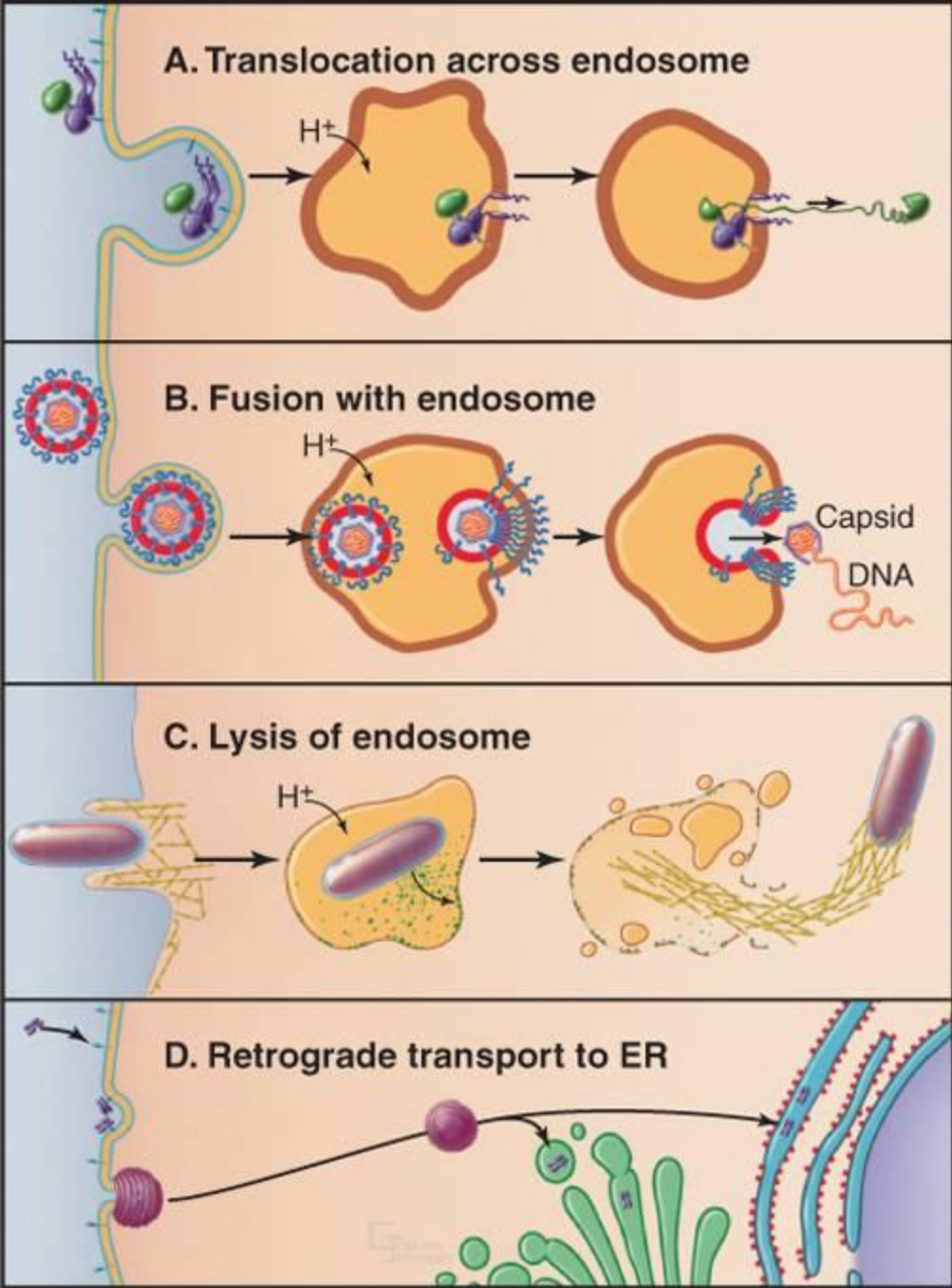


Расщепление содержимого фаголизосом

- Активные формы кислорода (NADPH-оксидаза)
- Галоидсодержащие соединения (миелопероксидаза)
- Азотистые метаболиты (NO-синтаза)
- Катионные белки (лизоцим, серпроцидины, лактоферрин, ВРІ-протеины)
- Бактерицидные пептиды (дефензины, кателицидины)
- Факторами, обеспечивающие локальное закисление (V-АТФаза)
- Другие ферменты

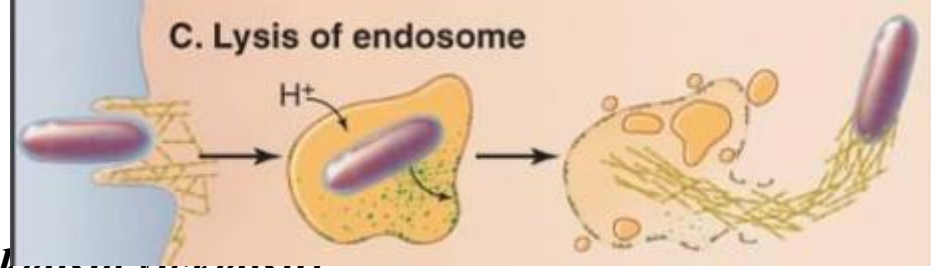


Способы выживания



"Escape "

Секреция токсинов, которые разрушают мембрану фагосом (*Shigella flexneri*, *Listeria monocytogenes*, *Rickettsia rickettsii*)



"Dodge"

Вход в клетку через альтернативный, патоген-специфичный путь (*Salmonella typhimurium*, *Legionella pneumophila*, *Chlamydia trachomatis*)

Ингибирование слияния фагосомы с лизосомами (*S. typhimurium*, *Mycobacterium tuberculosis*)

Ингибирование закисления фаголизосомы (*Mycobacterium* species)

"Stand and Fight"

Репликация при низком рН (*Coxiella burnetii*, *S. typhimurium*)

Усиление репарации ДНК – выживание при оксидативном стрессе (*S. typhimurium*)

Защита с помощью патогенспецифичных факторов (*C. burnetii*, *S. typhimurium*)

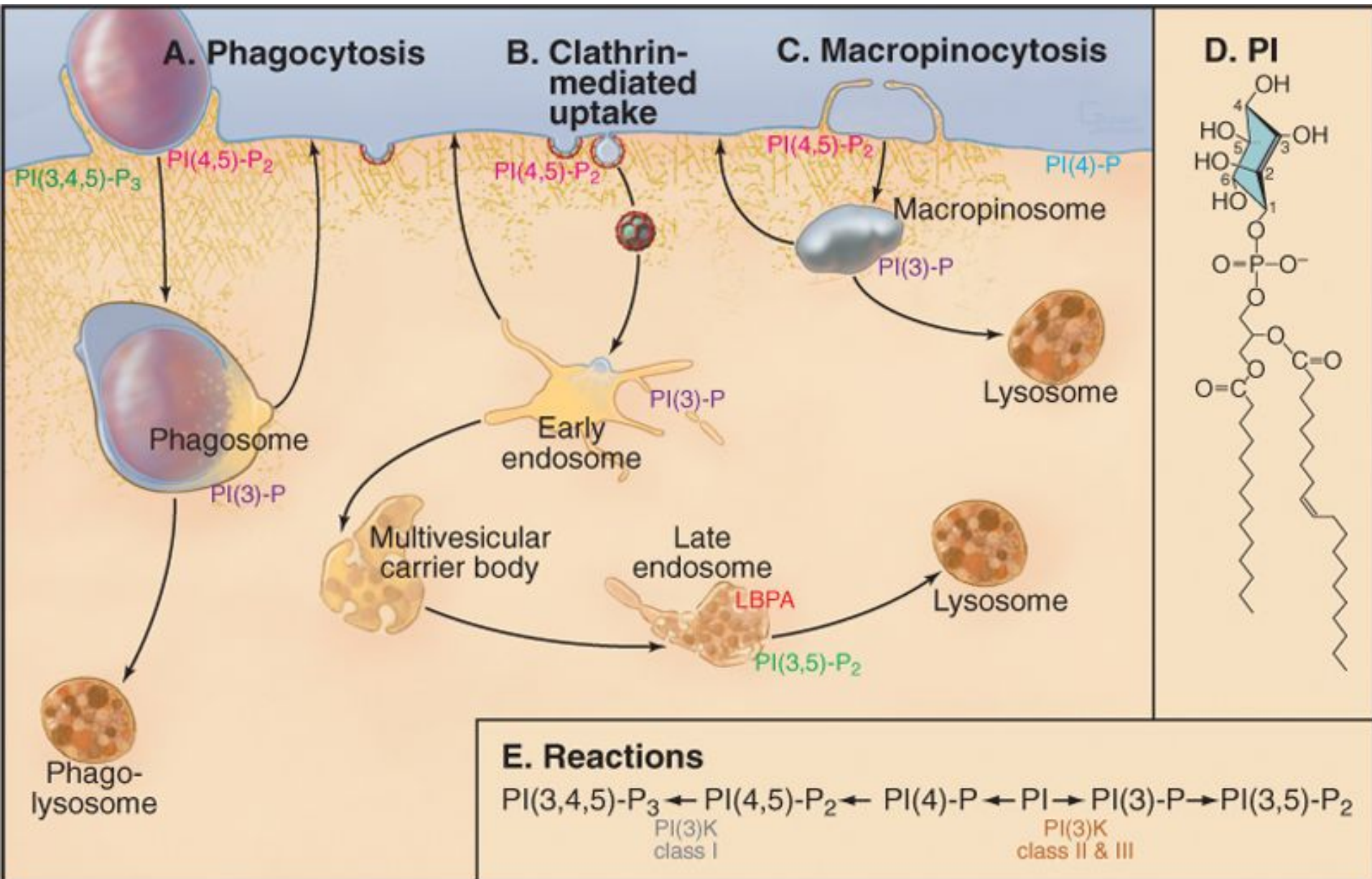
Нарушение процессинга и презентации бактериальных антигенов (*S. typhimurium*)

Effectors	Functions	Species
Inhibition of attachment		
Protein A	Binds Fc region, preventing normal interaction with Fc γ R	<i>Staphylococcus aureus</i>
Capsule	Prevents complement deposition	<i>Cryptococcus neoformans</i> , <i>Streptococcus pneumoniae</i> , <i>Escherichia coli</i> K1, <i>Klebsiella pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>S. aureus</i> , <i>Haemophilus influenzae</i> , <i>Treponema pallidum</i>
M proteins	Prevents binding to CRs	<i>Streptococcus pyogenes</i>
YadA	Prevents deposition of C3b	<i>Yersinia enterocolitica</i>
Inhibition of signaling		
YopH	Tyrosine phosphatase for Cas, Fyb, SKAP-HOM, paxillin, and FAK	<i>Yersinia</i> sp.
YopE	GAP for RhoA, Rac, and Cdc42	<i>Yersinia</i> sp.
YopT	Cysteine protease of Rho, Rac, and Cdc42	<i>Yersinia</i> sp.
YpkA (YopO)	Serine/threonine kinase of actin, RhoA, and Rac	<i>Yersinia</i> sp.
ExoT	GAP for RhoA, Rac, and Cdc42	<i>Pseudomonas aeruginosa</i>
ExoS	GAP for RhoA, Rac, and Cdc42	<i>Pseudomonas aeruginosa</i>
EspJ	Inhibits Fc γ R- and CR3-mediated phagocytosis	<i>Escherichia coli</i>
EspB	Inhibits myosin-actin interactions	<i>Escherichia coli</i>
EspH	Inactivates Rho GEFs	<i>Escherichia coli</i>
T4SS	Delays phagocytosis	<i>Helicobacter pylori</i>
LspA1 and -2	Inhibit Src-family kinases	<i>Haemophilus ducreyi</i>
Nef	Inhibits membrane delivery to the phagosome	HIV-1

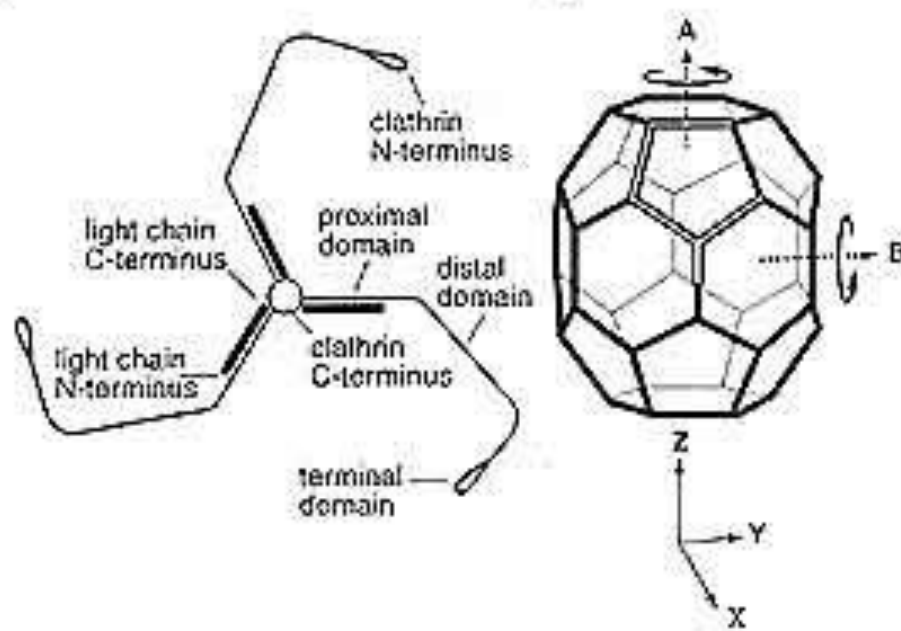
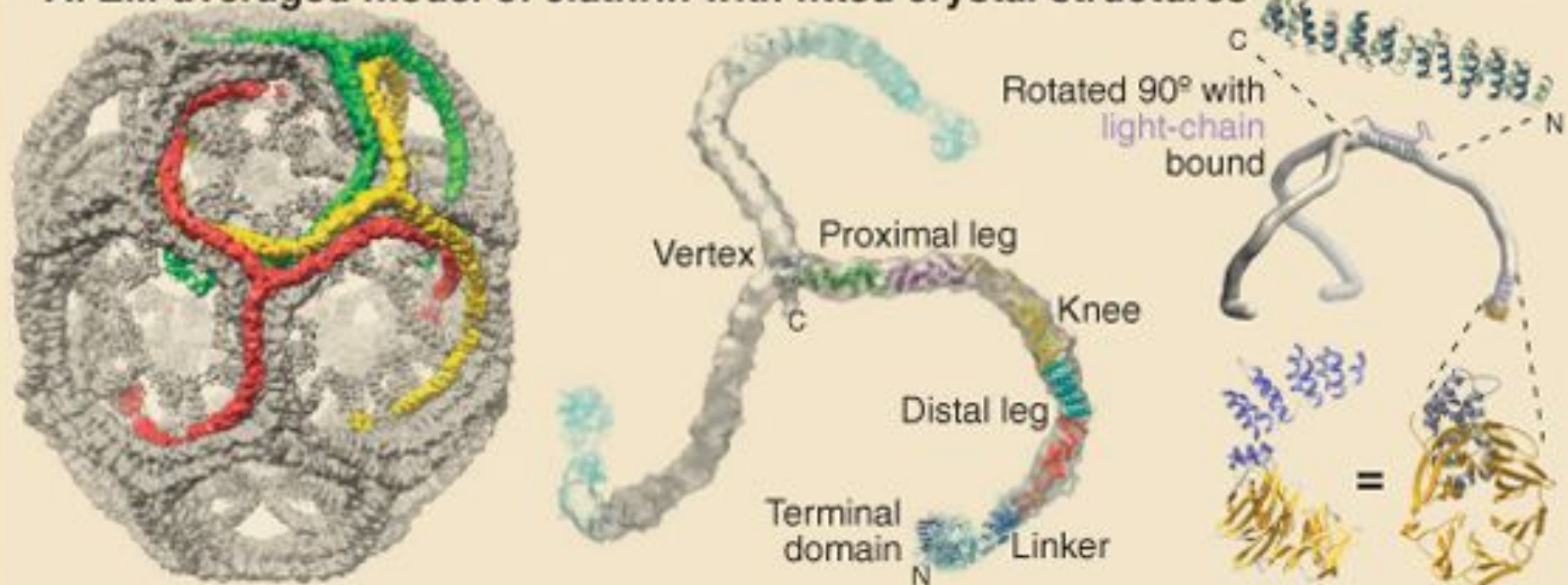
Table 3 Representative human pathogens and the biochemical properties of pathogen-containing phagosome

Strategy	Organism	Mechanisms of survival and phagosome properties
Altered phagosome maturation	<i>Mycobacterium tuberculosis</i>	Phagosome is mildly acidic and continuously interacts with recycling endosomes bearing the TfRs that provide the bacteria with iron <i>M. tuberculosis</i> -containing phagosomes are Rab5 positive but devoid of PI(3)P and EEA1
		Maturation arrest is mediated by the expression of numerous effector proteins (e.g., SapM and PknG) and lipids (e.g., lipoarabinomannan)
	<i>Burkholderia cenocepacia</i>	Delay maturation of their vacuole
		<i>B. cenocepacia</i> -containing phagosomes acquire early markers [i.e., Rab5, PI(3)P, and EEA1], but Rab7 activation and phagosome acidification are perturbed
		LAMP proteins are eventually acquired, indicating lysosomal fusion Require the expression of unknown bacterial effectors secreted through type IV and/or type VI secretion systems
	<i>Coxiella burnetii</i>	Internalized <i>C. burnetii</i> transit through Rab5- and Rab7-positive compartments Ultimately reside within an acidic lysosome-like compartment Bacteria-containing vacuole acquires markers of autophagy (e.g., LC3), indicating intersection with autophagosomes, ostensibly for nutrient acquisition
<i>Histoplasma capsulatum</i>	Evade formation of late phagosomes and phagolysosome fusion Perturb V-ATPase activity, blocking acidification, which prevents vesicular fusion and the acquisition of lysosomal markers (i.e., LAMP-2)	
<i>Leishmania donovani</i> and <i>L. major</i>	<i>Leishmania</i> spp. impair phagosome maturation by blocking the fusion of late endosomes and lysosomes The blockade in maturation requires the expression of a unique surface glycolipid, LPG F-actin accumulation around the parasite-containing phagosome also occurs in an LPG-dependent manner, ostensibly to form a cage that blocks fusion of late endosomes and lysosomes	

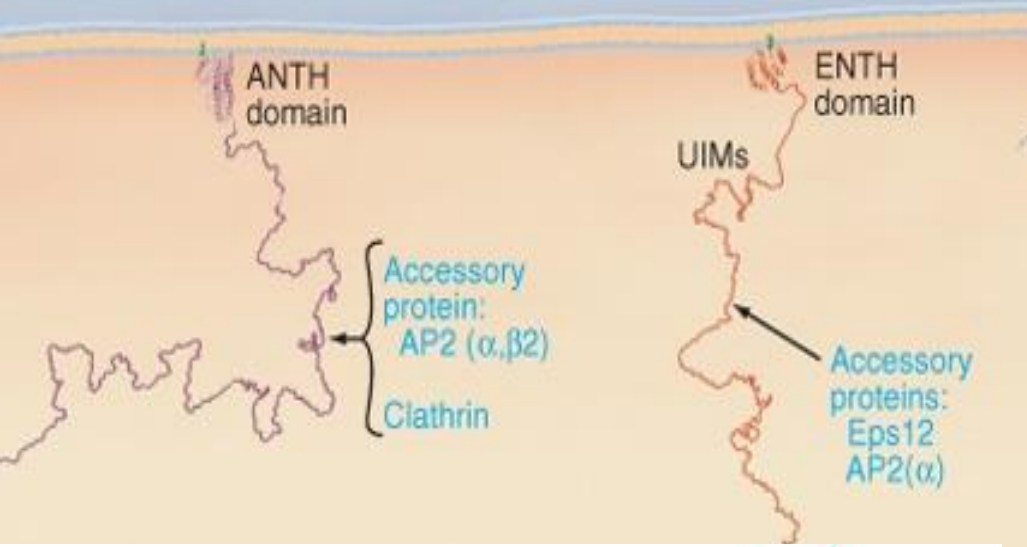
Strategy	Organism	Mechanisms of survival and phagosome properties
	<i>Theileria parva</i>	Rapidly escape phagosomes through an unknown mechanism and replicate in the cytosol Induce uncontrolled proliferation of infected cells, and through the expression of the protein TaSE, attach to host cell microtubules to disseminate between daughter cells
Genesis of a unique vacuole	<i>Cblamydia trachomatis</i>	Upon phagocytosis, <i>C. trachomatis</i> construct a unique vacuole, termed the inclusion, in which the bacteria replicate Inclusion is devoid of early and late phagosome markers (Rab5 and Rab7, respectively) and does not resemble a proper phagosome
		Many effector proteins (e.g., IncA) are required for <i>C. trachomatis</i> to usurp host cell functions and to construct its inclusion
	<i>Toxoplasma gondii</i>	Invade phagocytes and reside in a unique vacuole that, although derived from the host cell plasma membrane, is largely devoid of host transmembrane proteins The vacuole does not acidify, and <i>T. gondii</i> induces the formation of a pore in its vacuole to gain access to diffusible nutrients from the host Host cell microfilaments and vimentin associate with the <i>T. gondii</i> -containing vacuole, ostensibly to dock it in proximity
Phagosome lysis	<i>Listeria monocytogenes</i>	Express a pore-forming toxin, LLO, that in conjunction with various lipases solubilizes the limiting membrane of the phagosome Maturation of the phagosome is rapidly prevented by LLO-dependent pore formation and perturbation of luminal H ⁺ and Ca ²⁺ concentrations
	<i>Sbigella flexneri</i>	Lyse phagosomes in which they reside, entering the cytosol and disseminating via actin-based motility Phagosome escape requires the function of the Mxi-Spa type III secretion system and the secreted effector proteins IpaB, IpaC, and IpaD



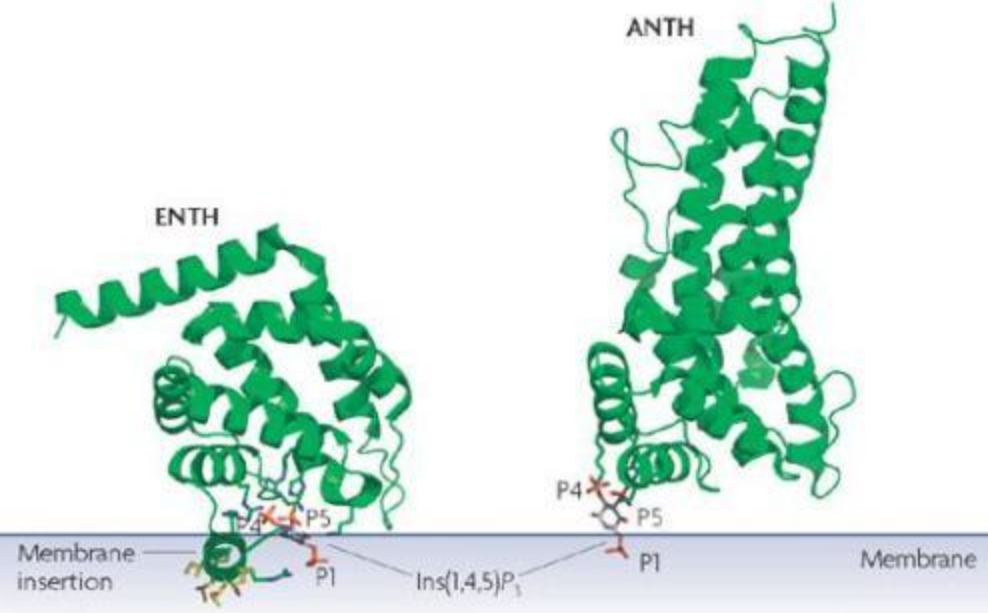
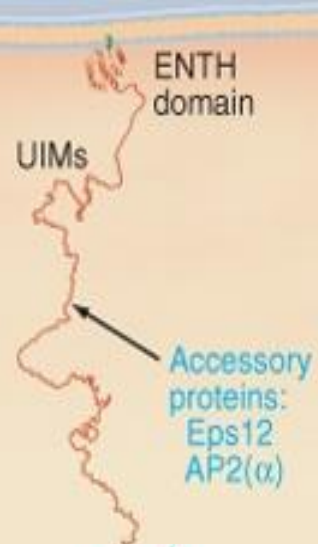
A. EM-averaged model of clathrin with fitted crystal structures

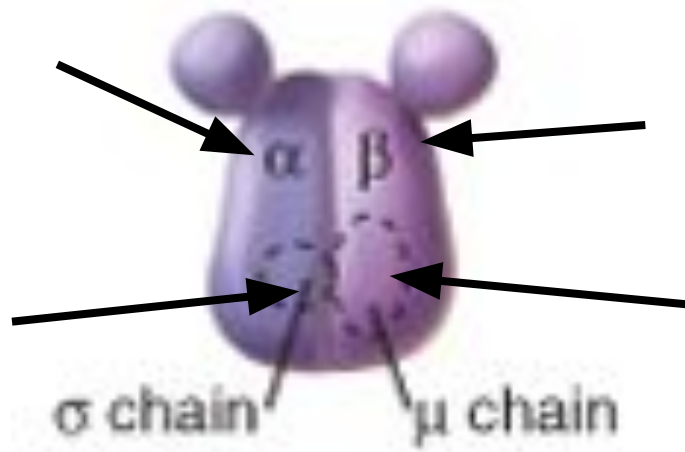


C. AP180/CALM and potential binders

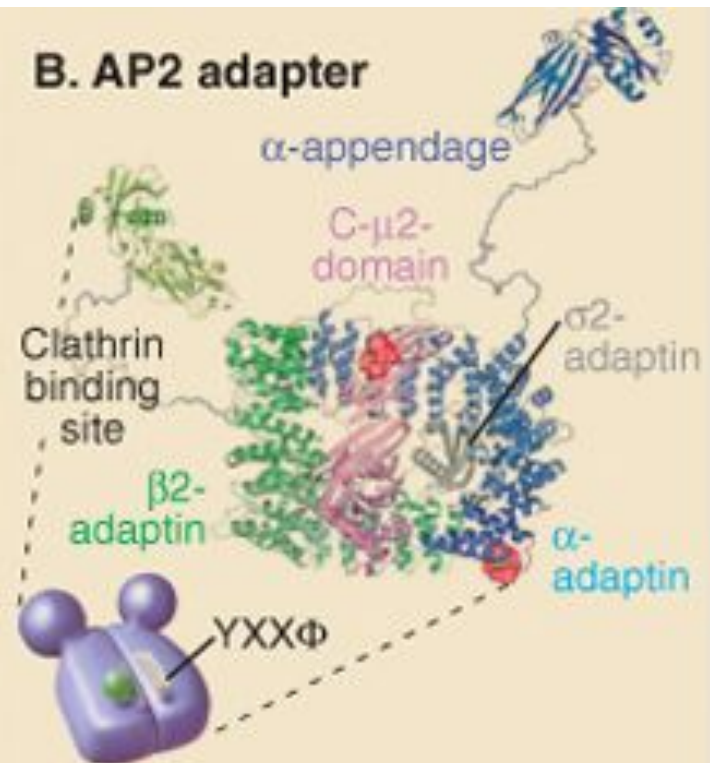


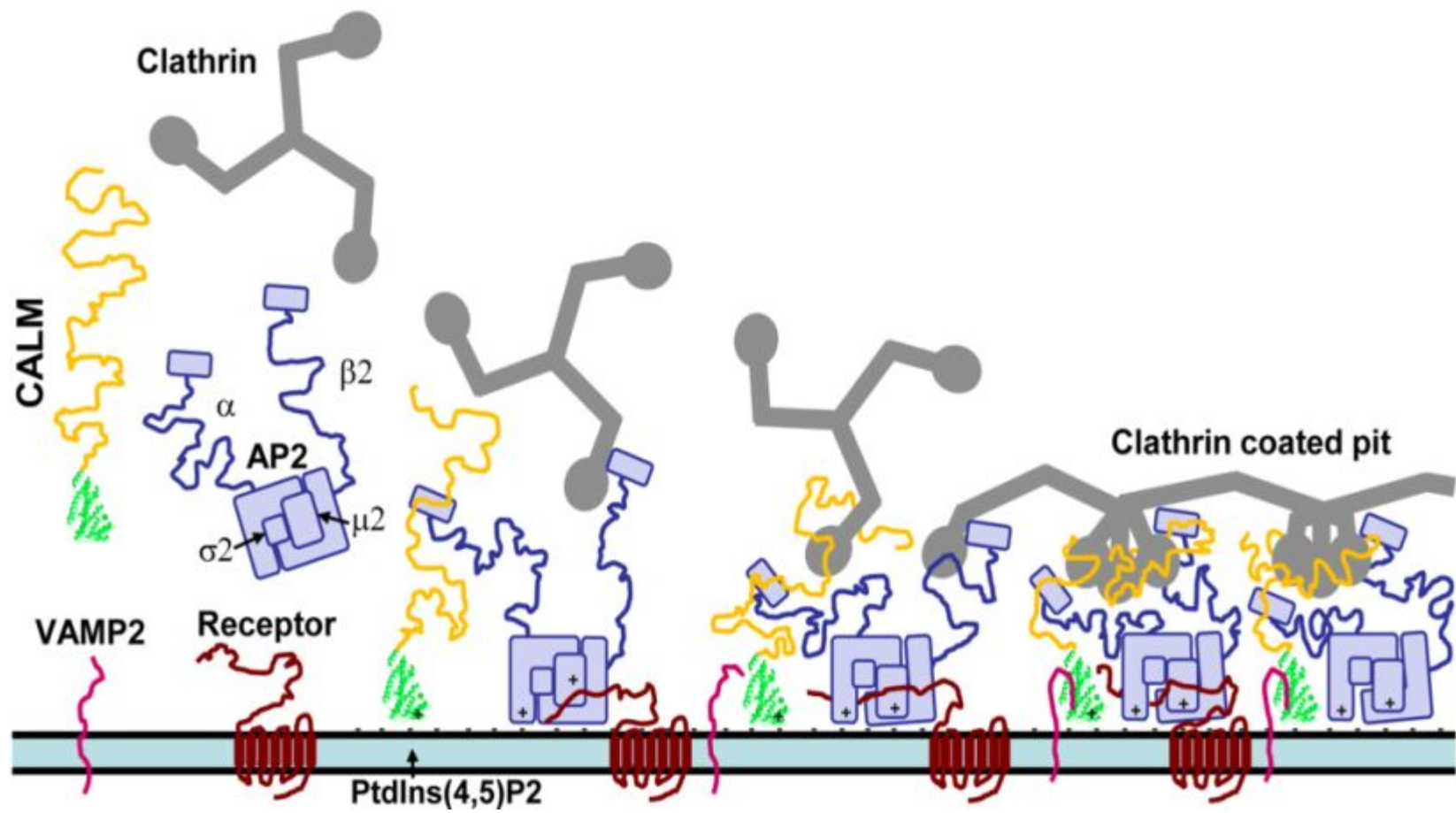
D. Epsin and potential binders

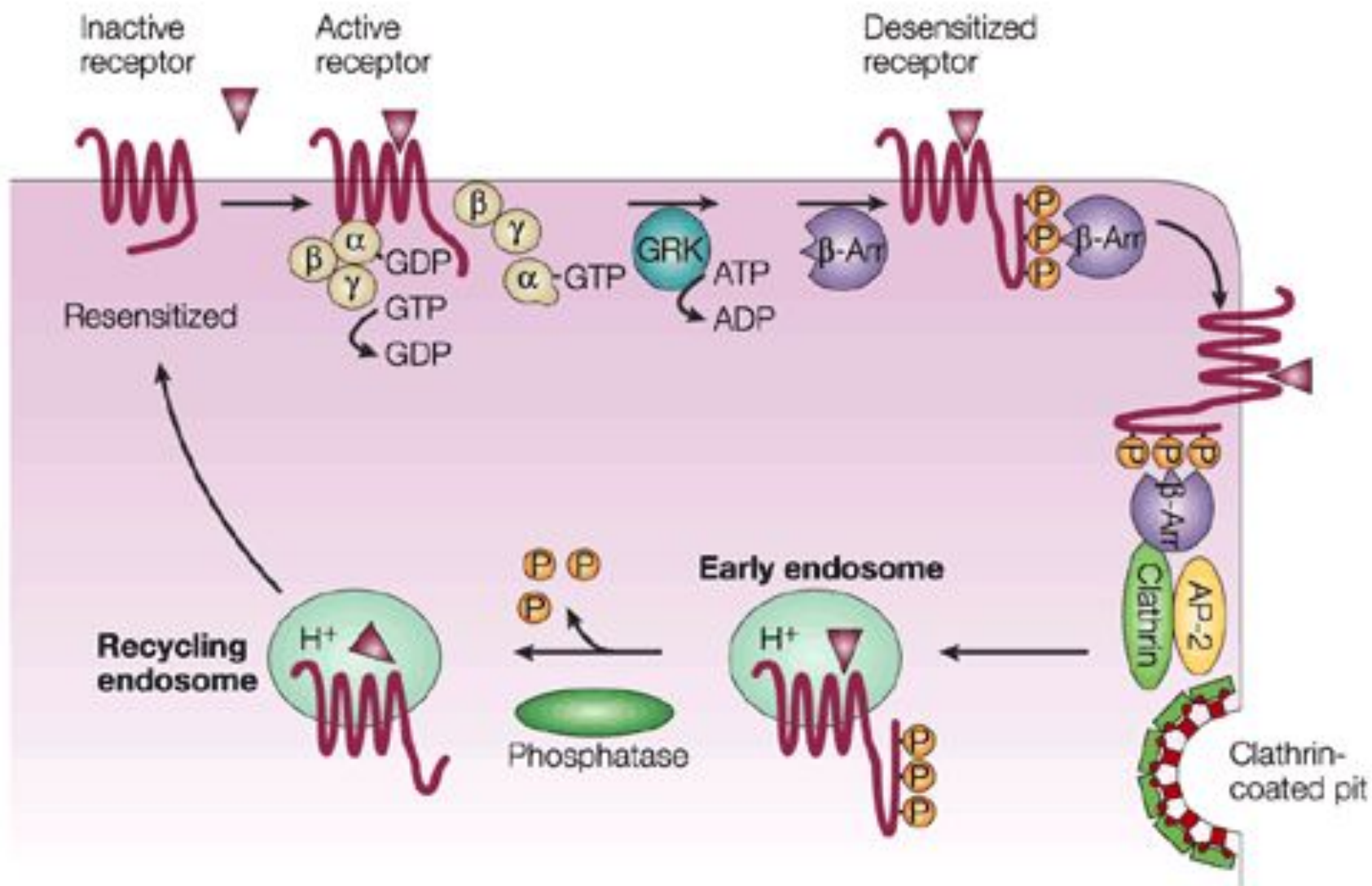


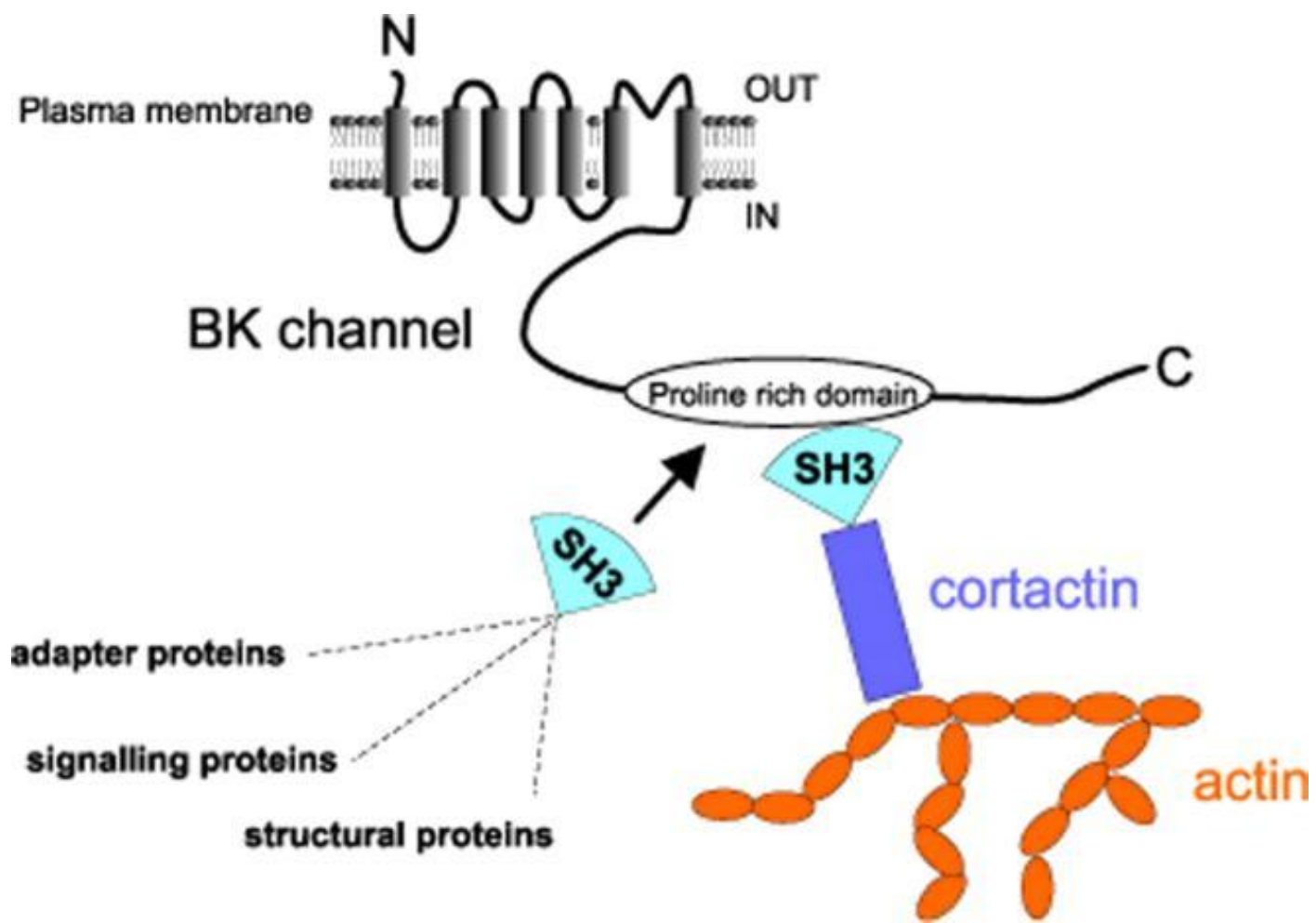


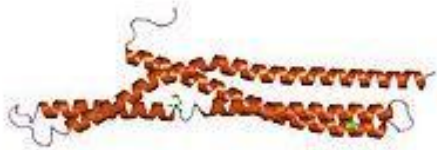
B. AP2 adapter





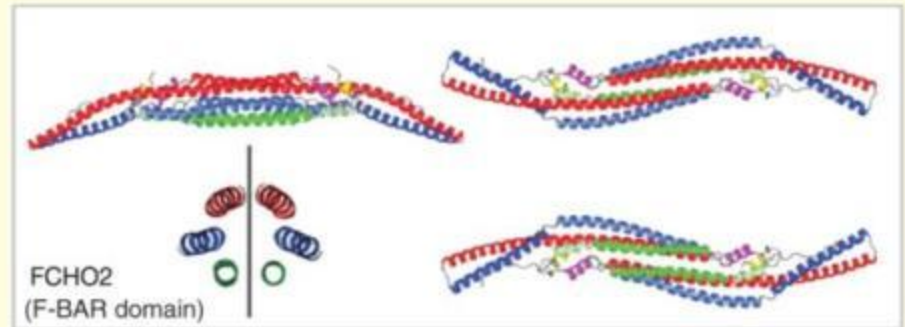
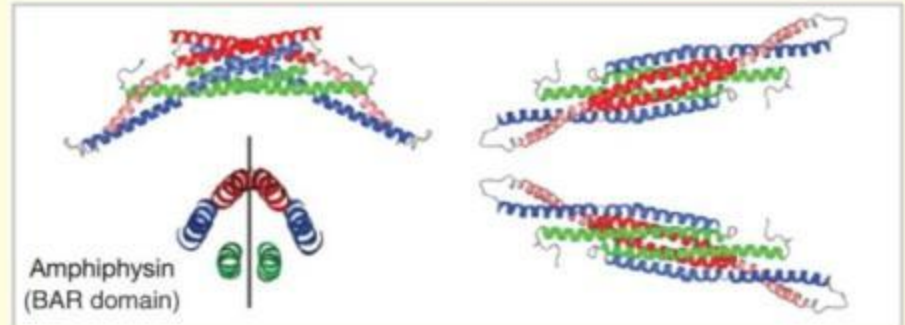






SH3 domains	Amphiphysin, endophilin
N-BAR	Amphiphysin, endophilin, BRAP1/bin2, nadrin
F-BAR	Syndapin/pacsin

Crystal structure

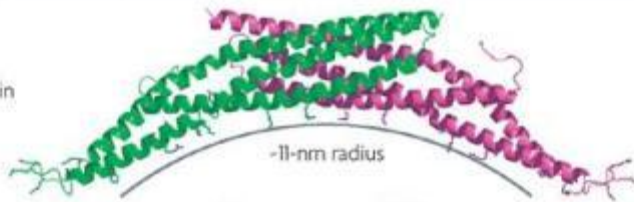


(from Henne et al., 2007)

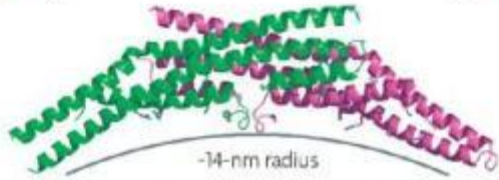
- F-BAR domains curve less sharply than BAR domains, correlating with the formation of broader membrane tubules
- Thus different BAR domain relatives might bind to and shape different parts of budding vesicles

b

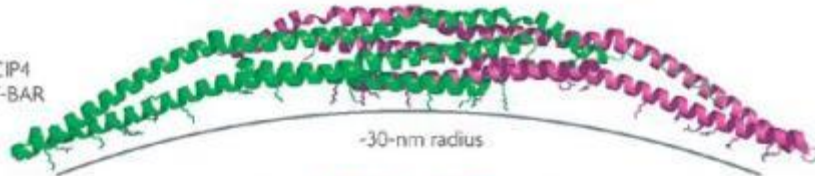
Amphiphysin
N-BAR



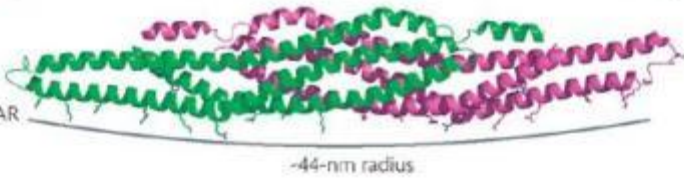
Endophilin-A1
N-BAR



CIP4
F-BAR



IRSp53
IMD/I-BAR



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PSTPIP subfamily



- Associated with tyrosine phosphatases
- Bind to WASP and might induce filopodia

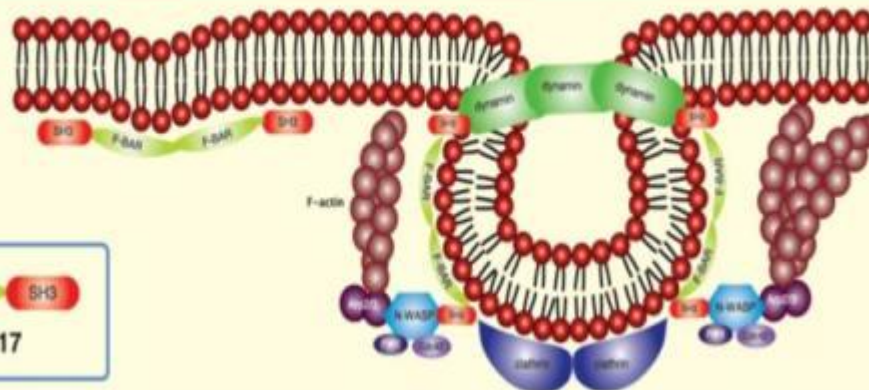


Filopodium
induced
by PSTPIP2

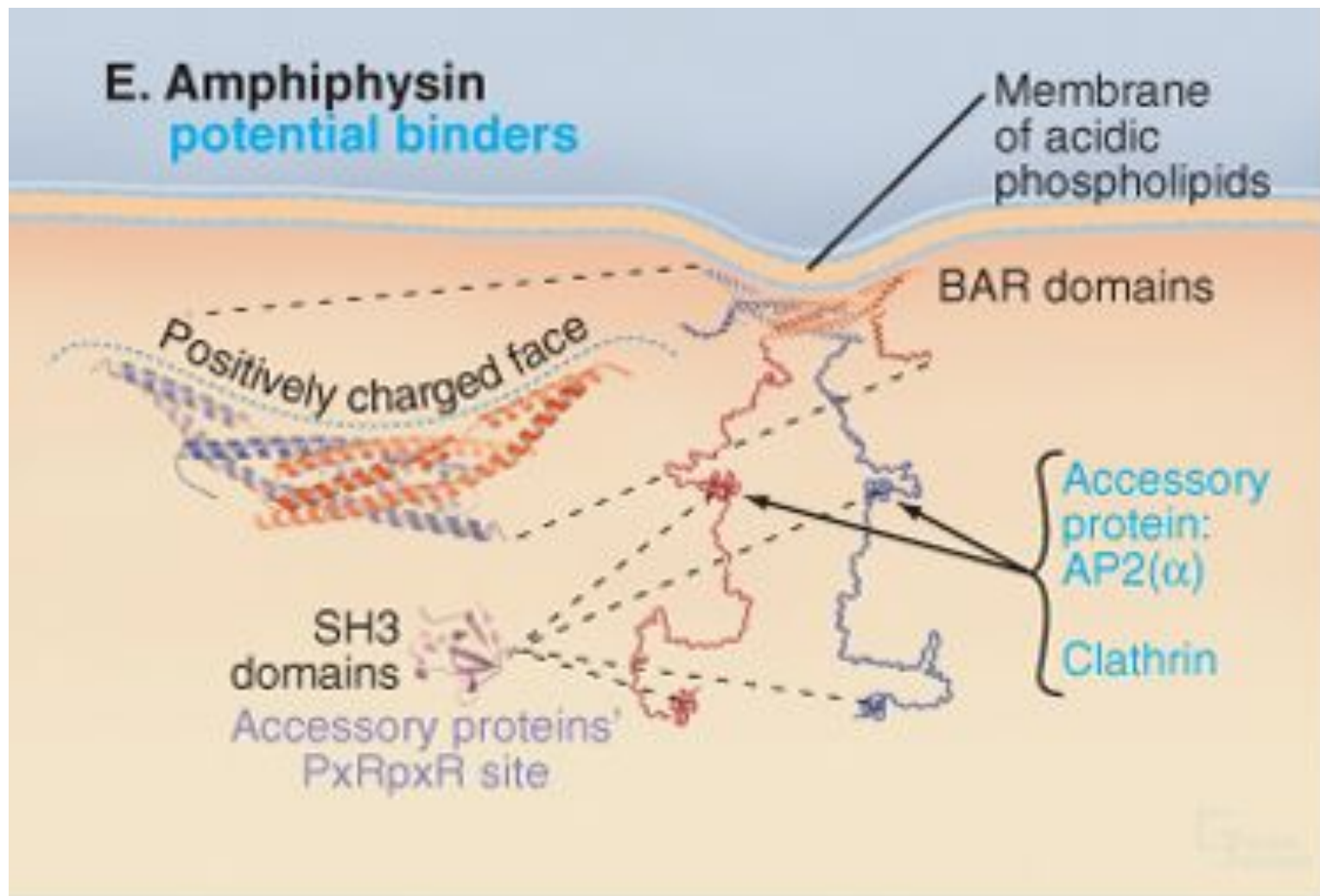
F-actin

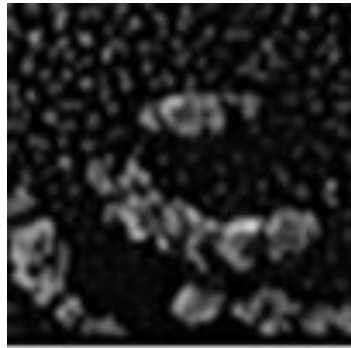
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FBP17-mediated endocytosis

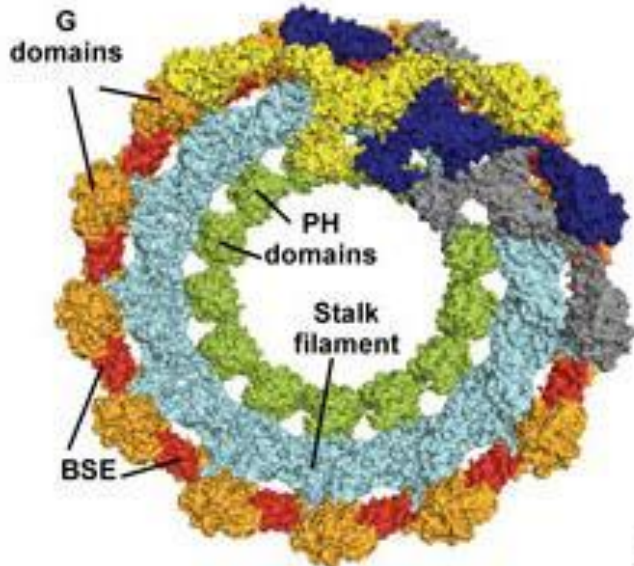
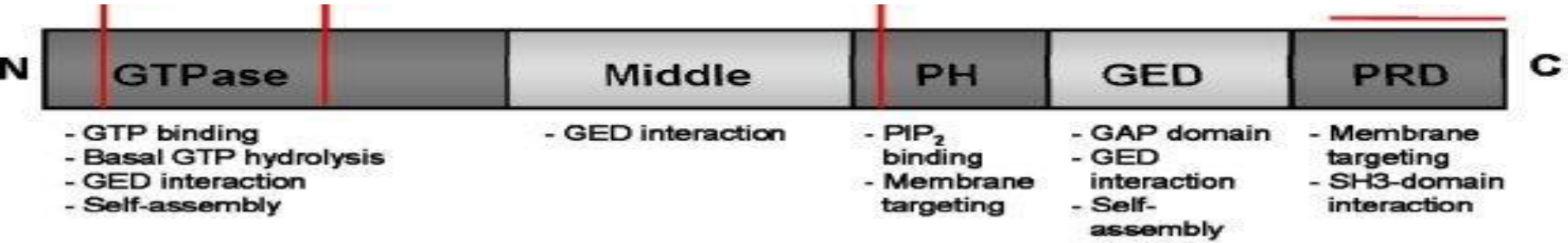
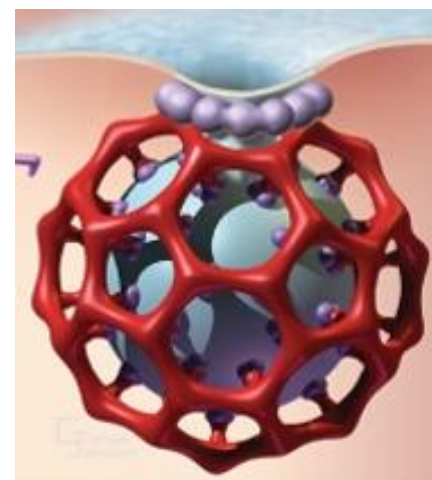
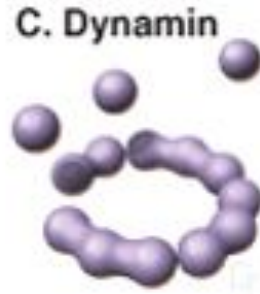


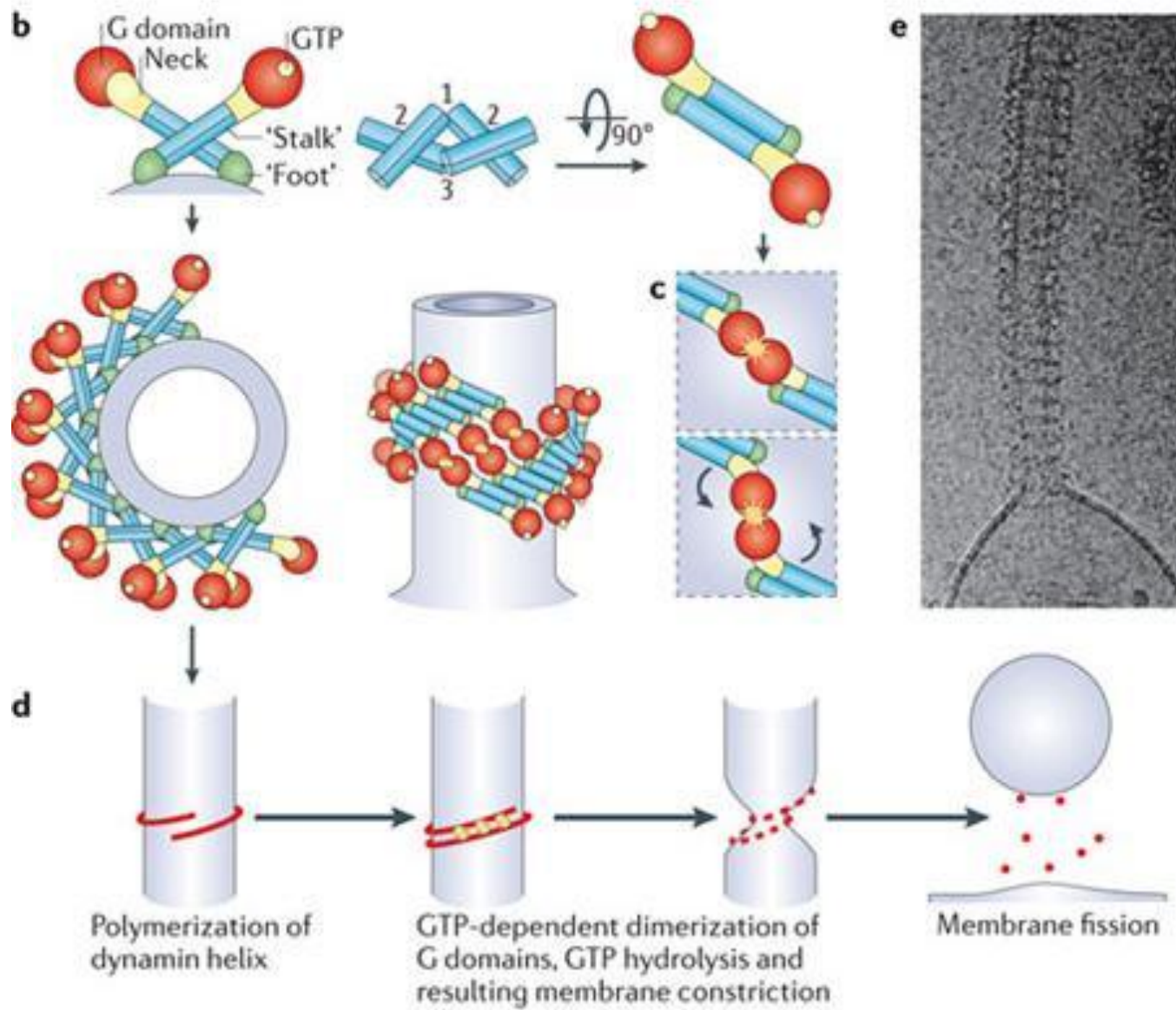
FBP17

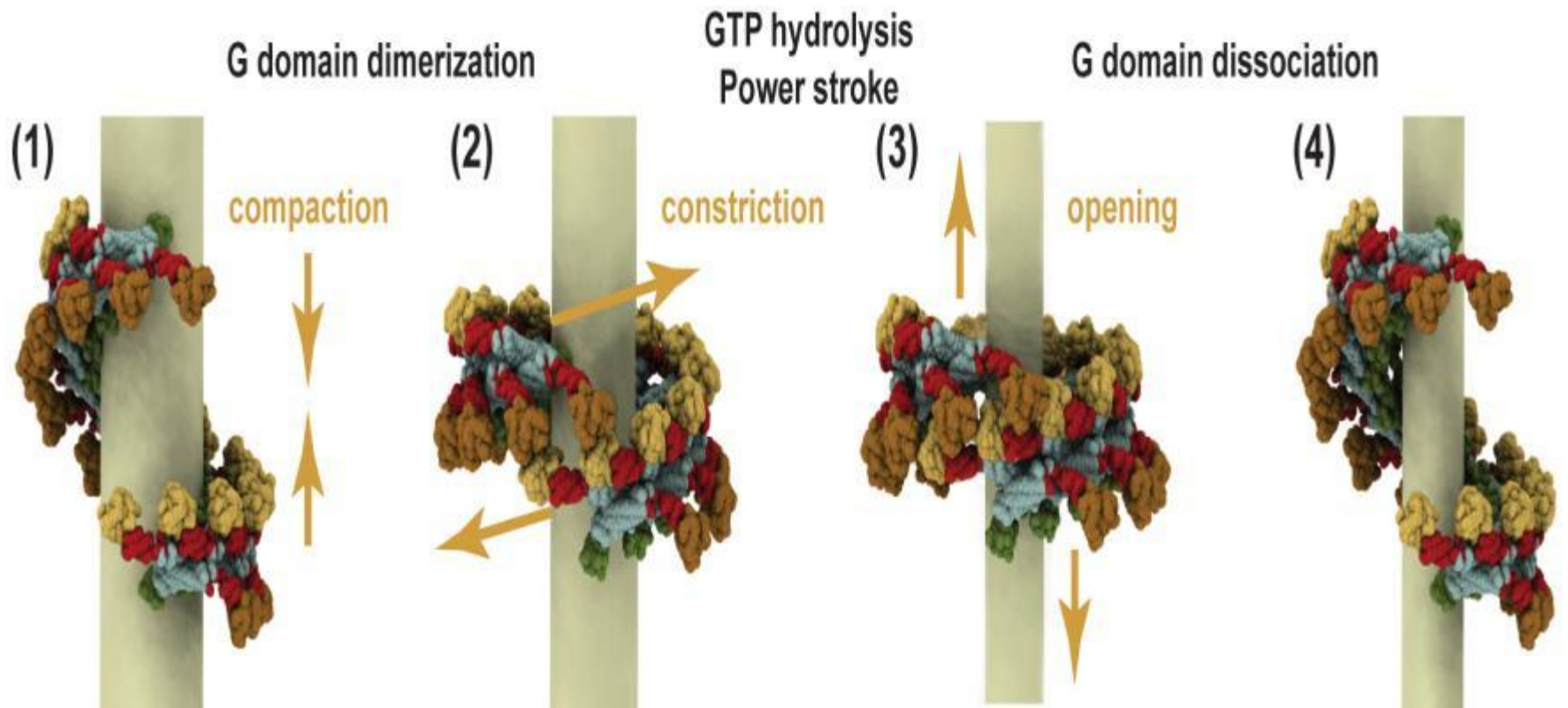




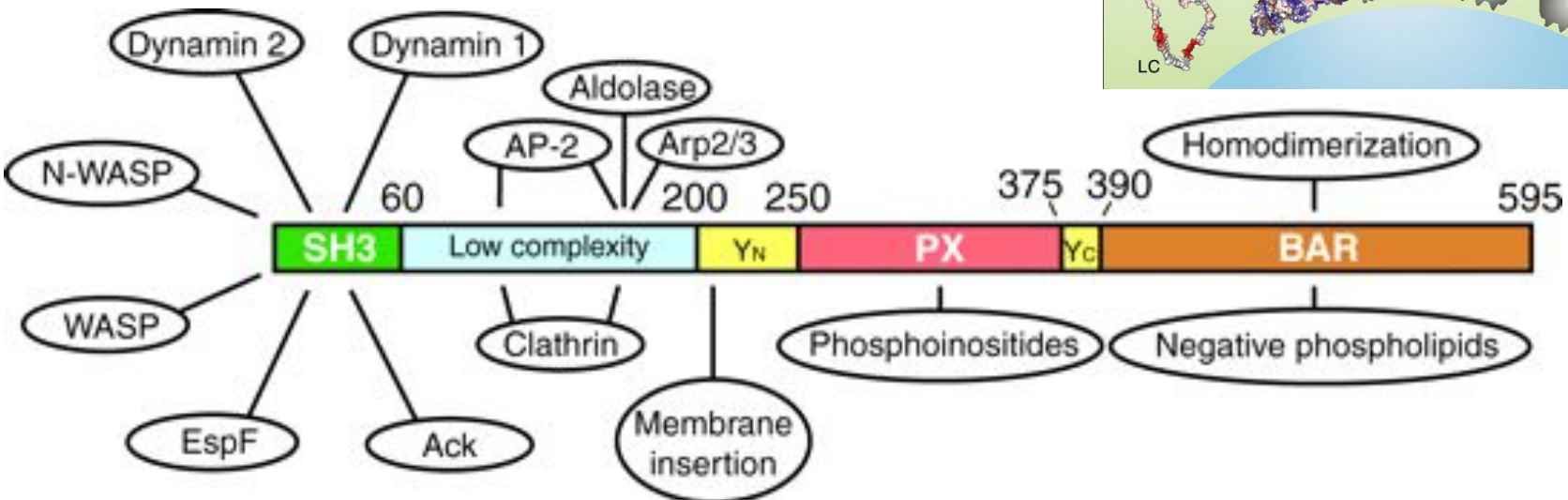
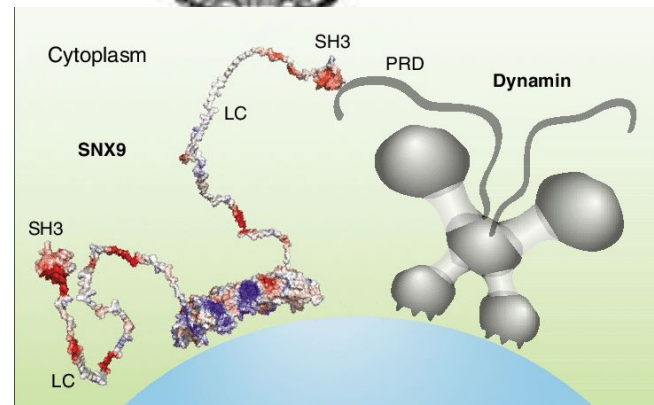
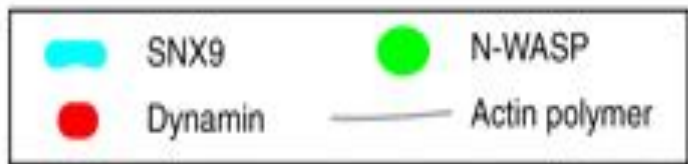
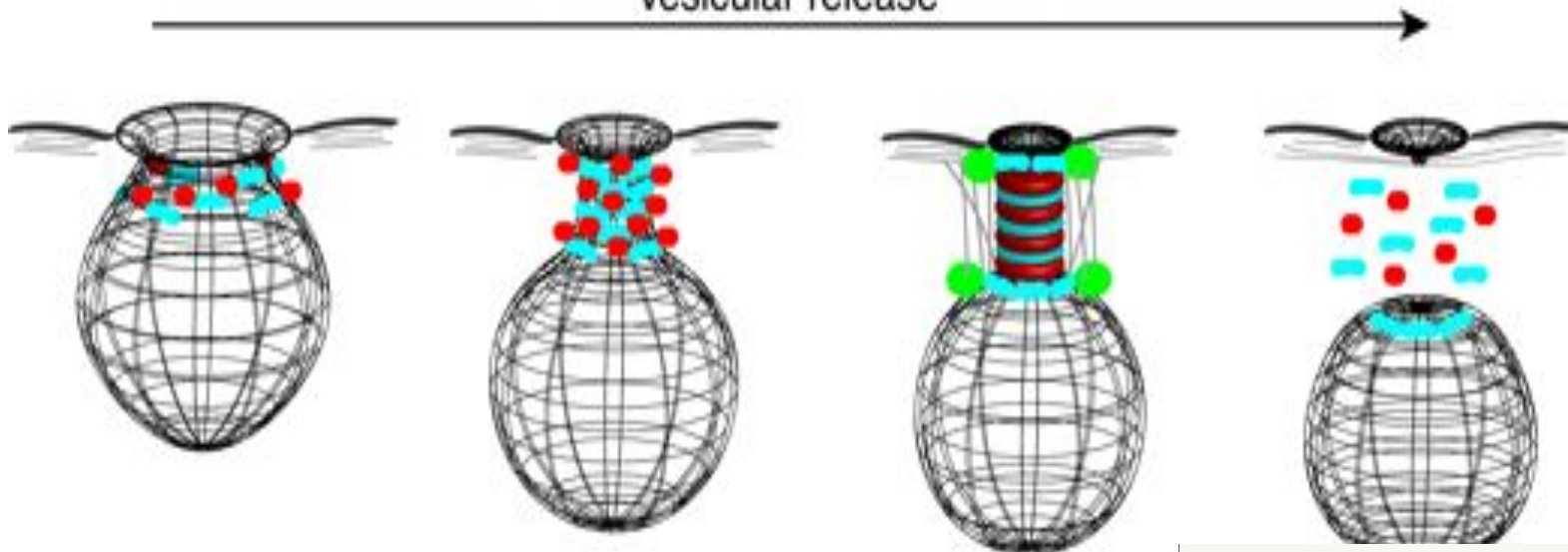
C. Dynamin

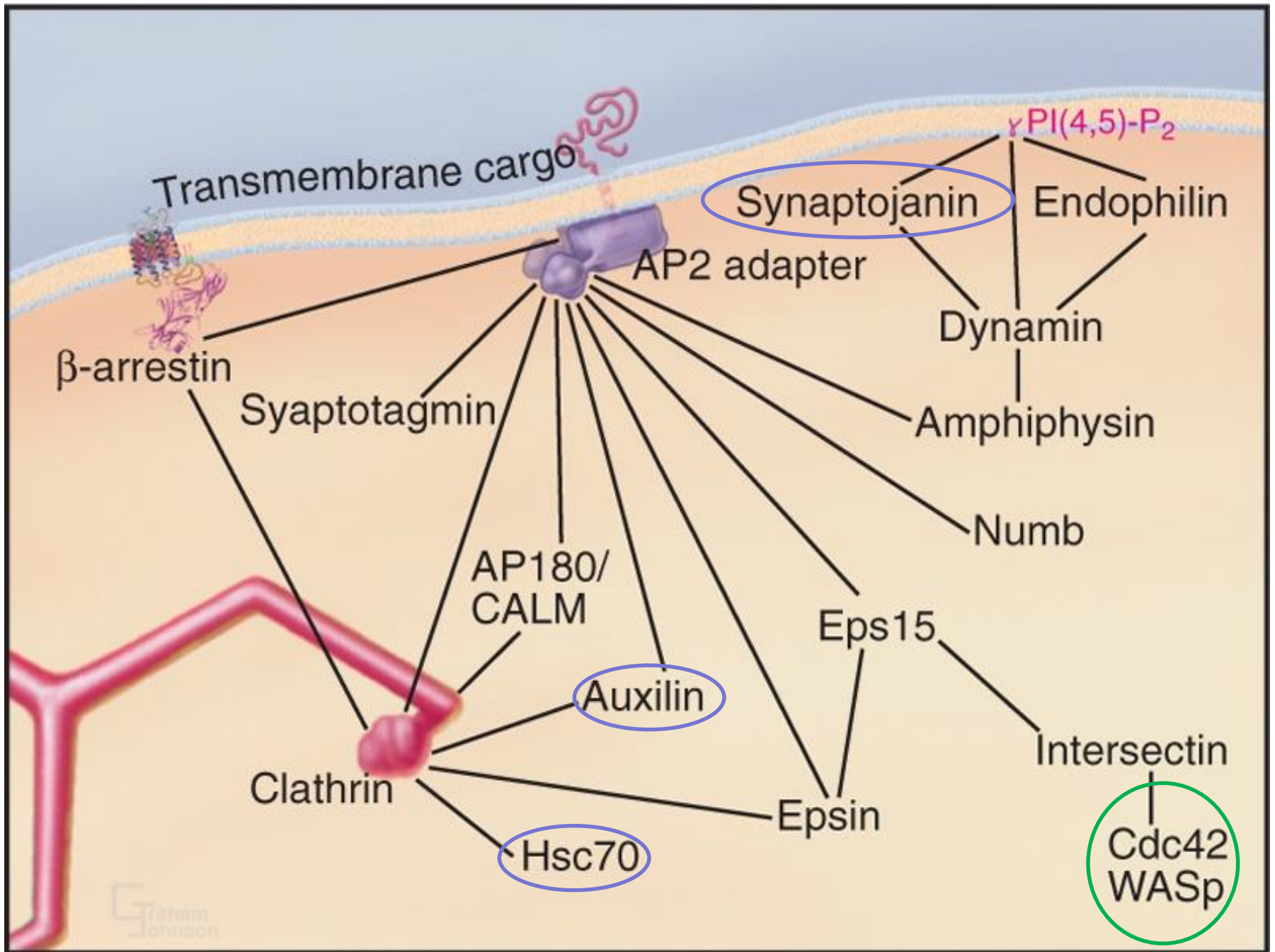


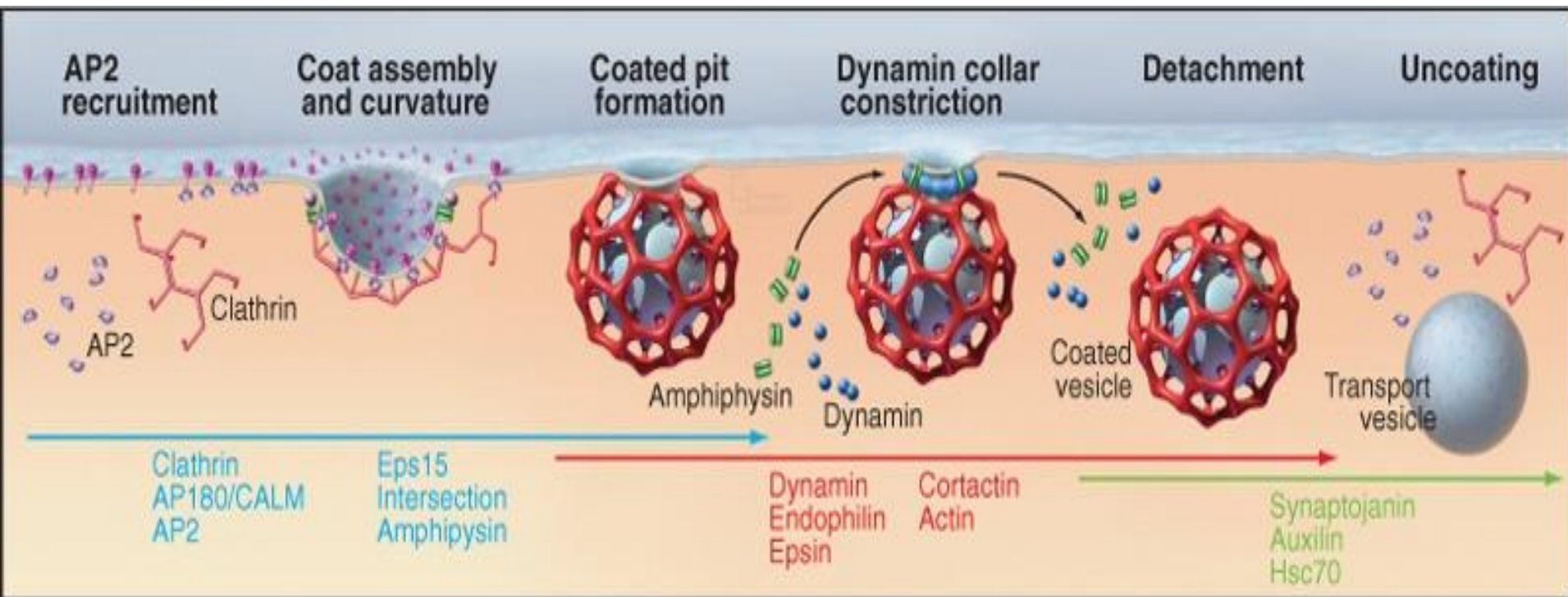




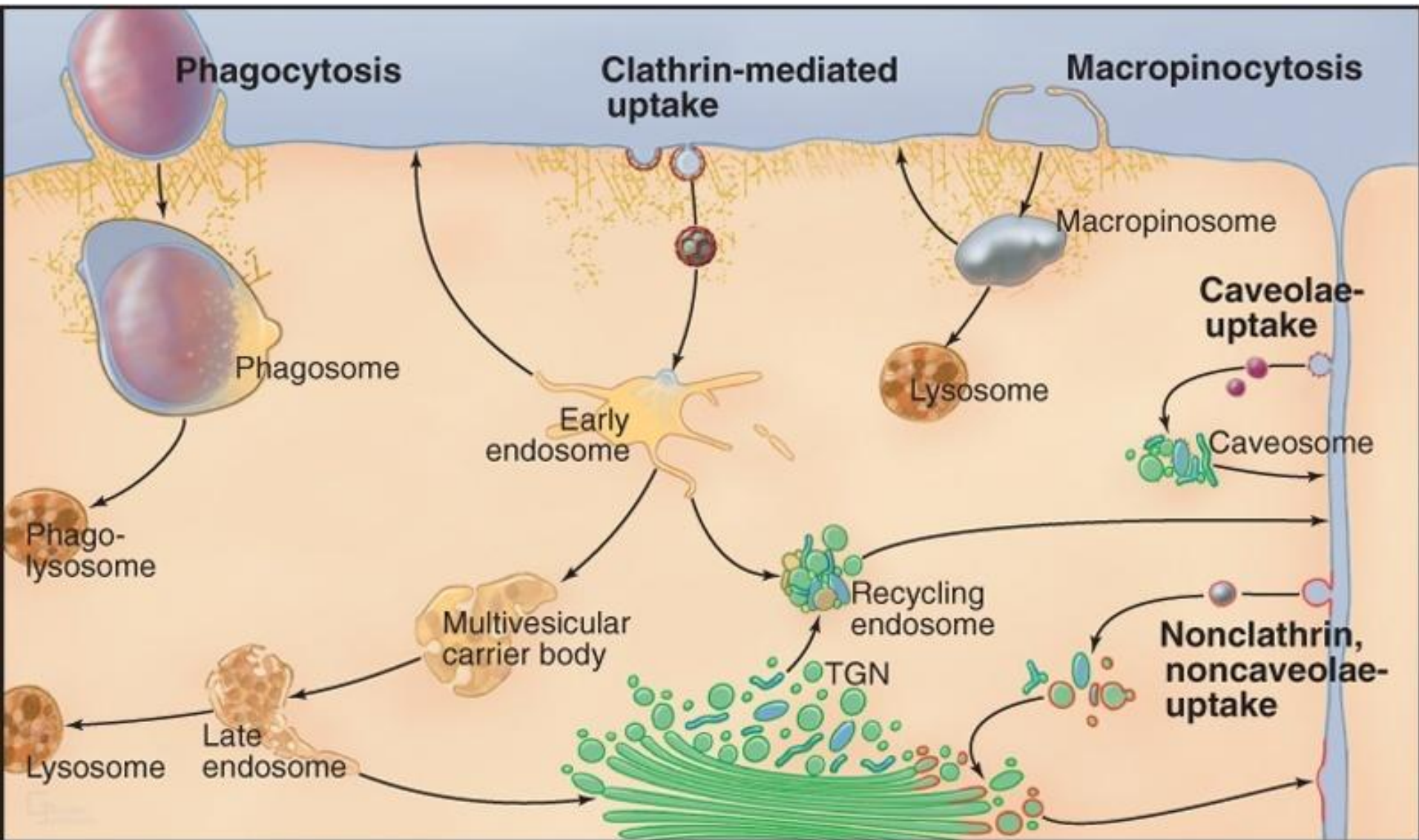
Vesicular release



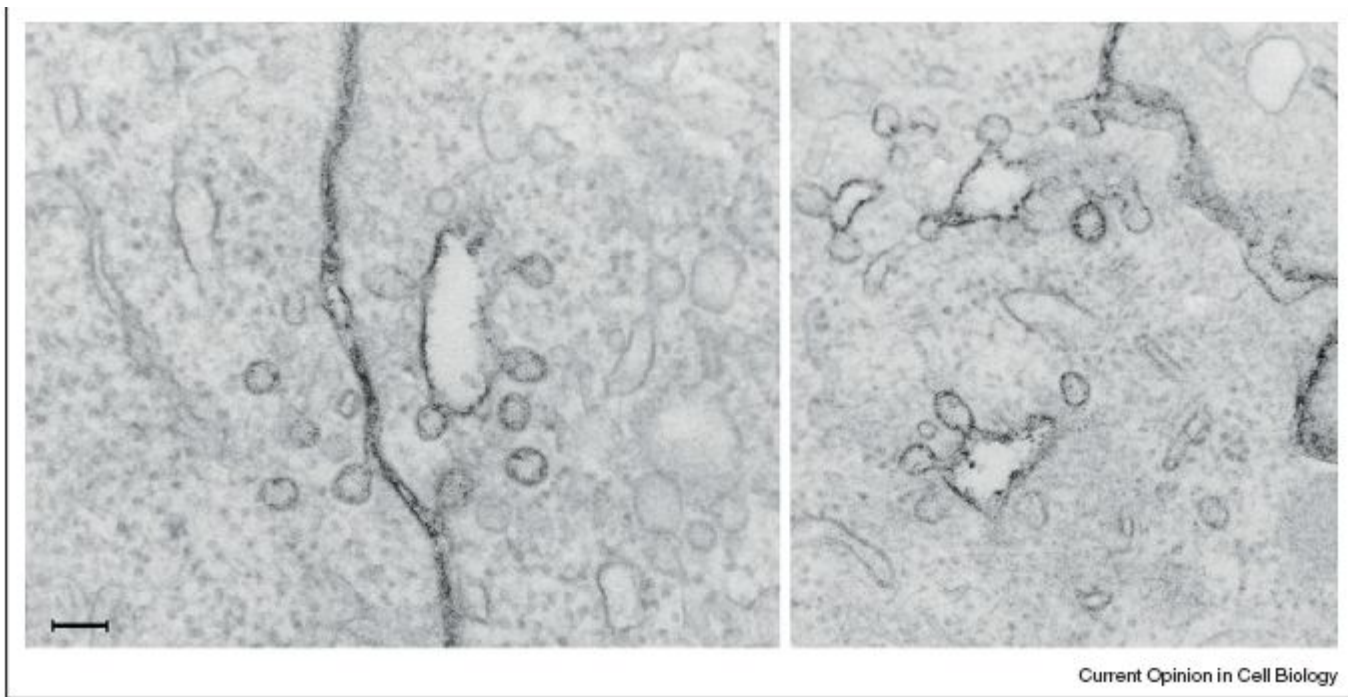




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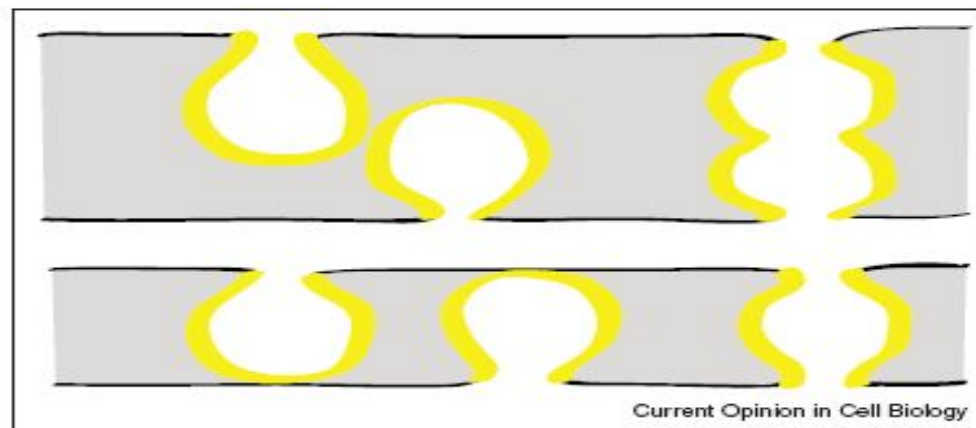


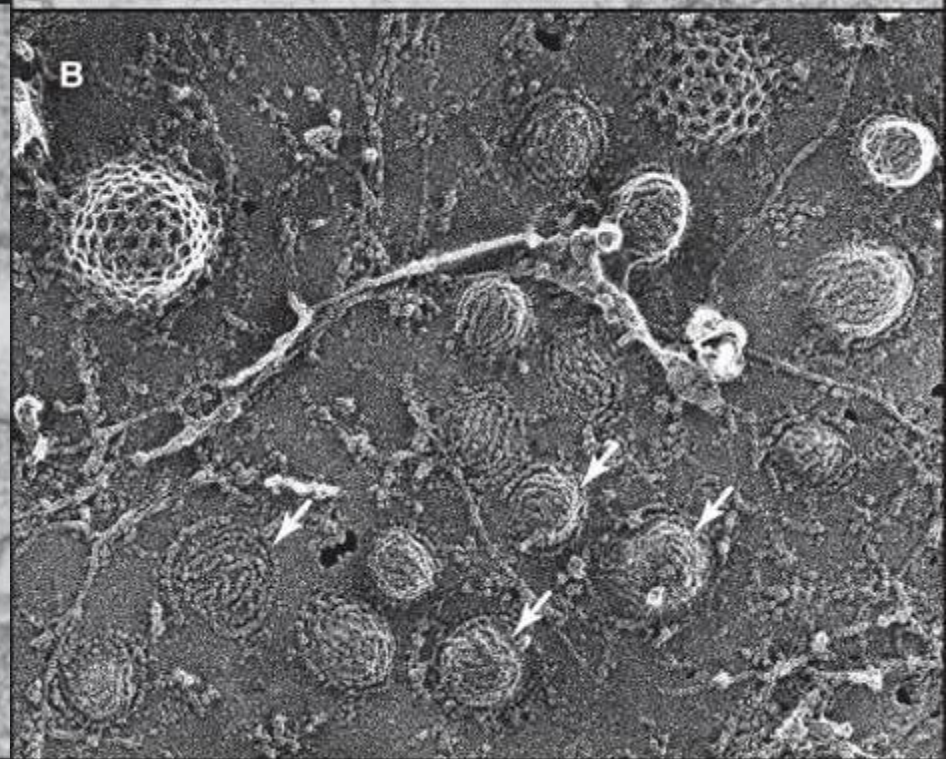
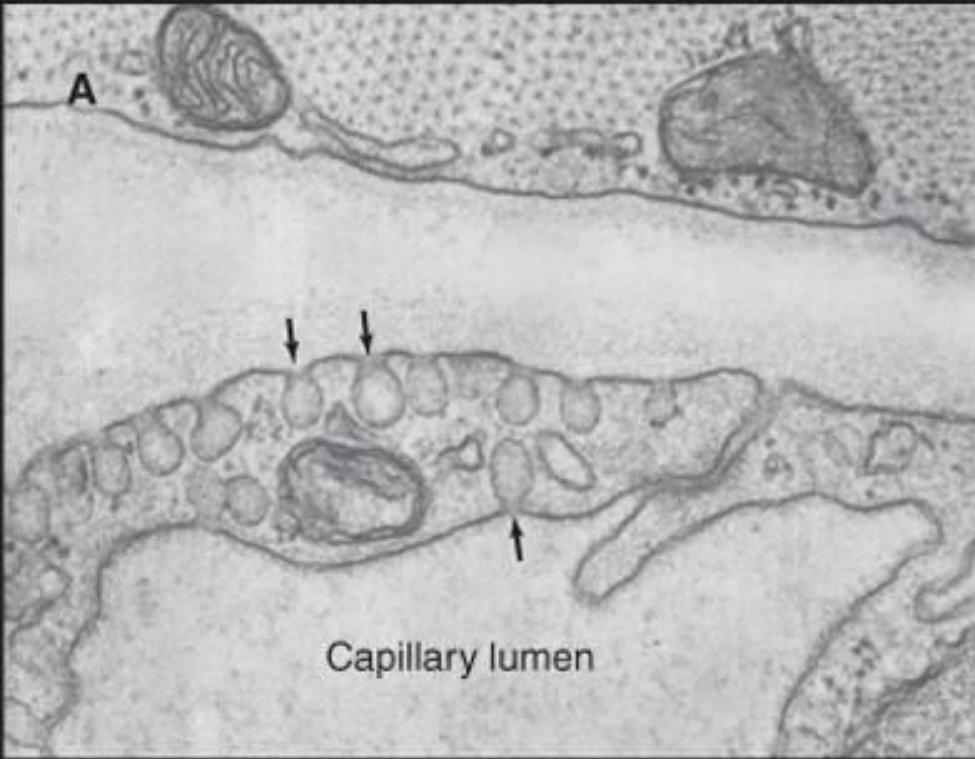




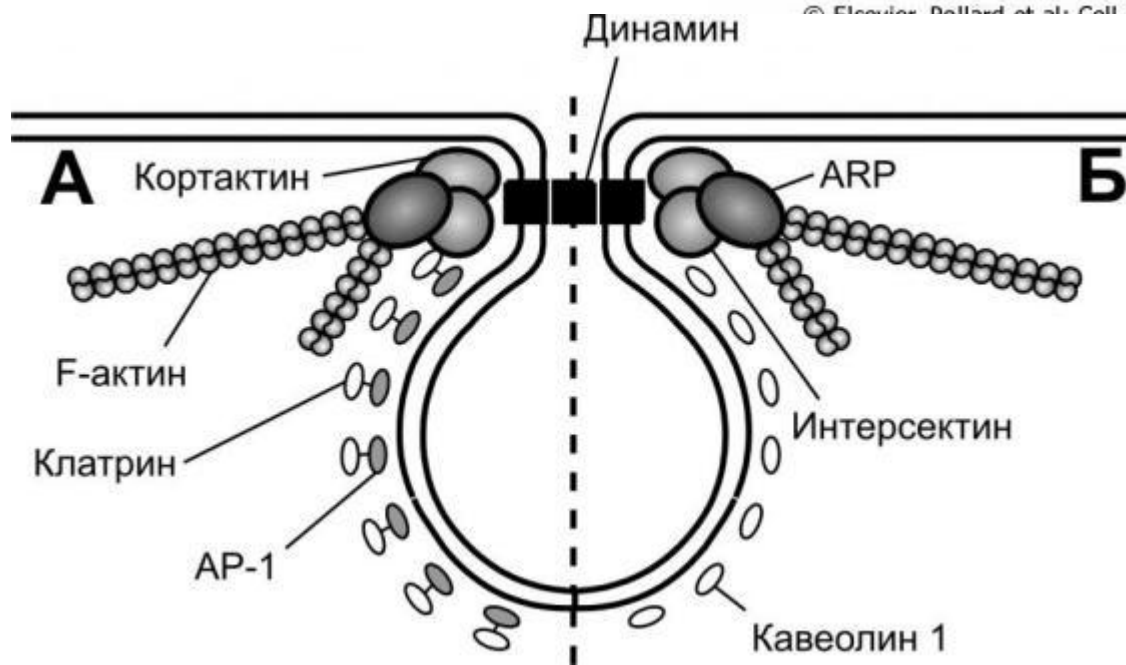
The vacuolar structures with associated caveolae apparently freely localized in the cytoplasm could easily be interpreted as special caveolar endosomes, or caveosomes. However, fixation in the presence of the surface marker ruthenium red clearly shows that the structures are surface-connected, for example, invaginations of the plasma membrane with associated caveolae, and have nothing to do with internalization of caveolae. Bar, 100 nm.

Figure 3

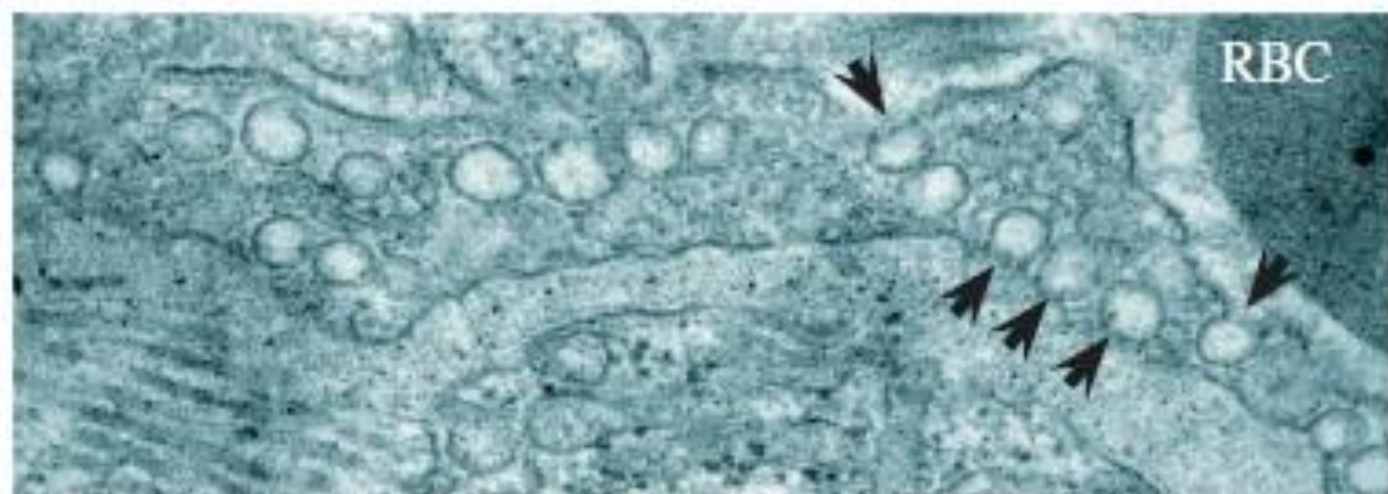




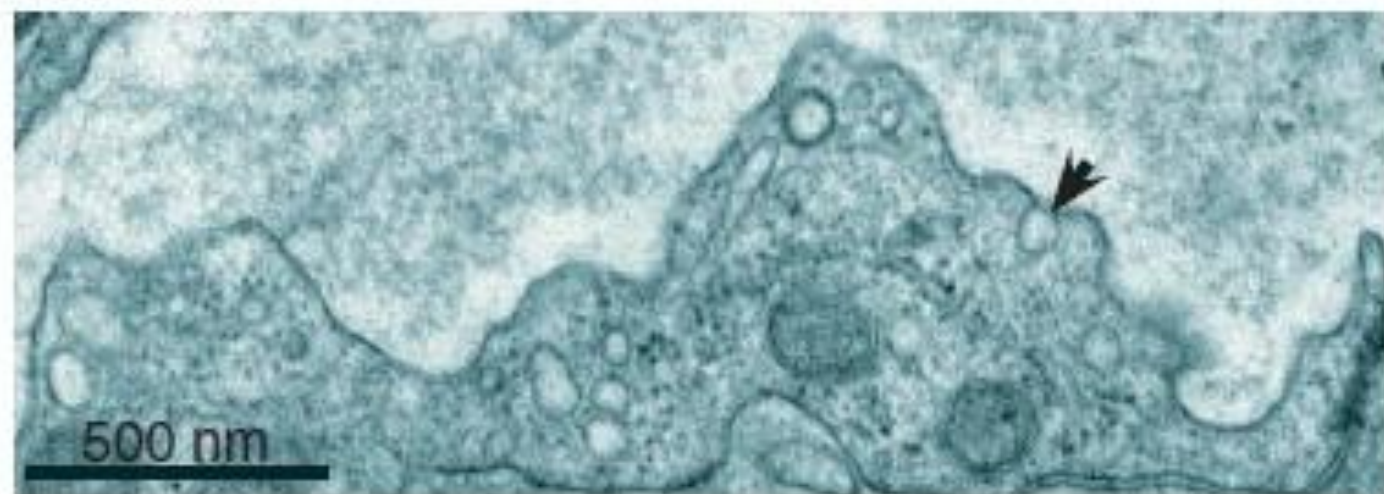
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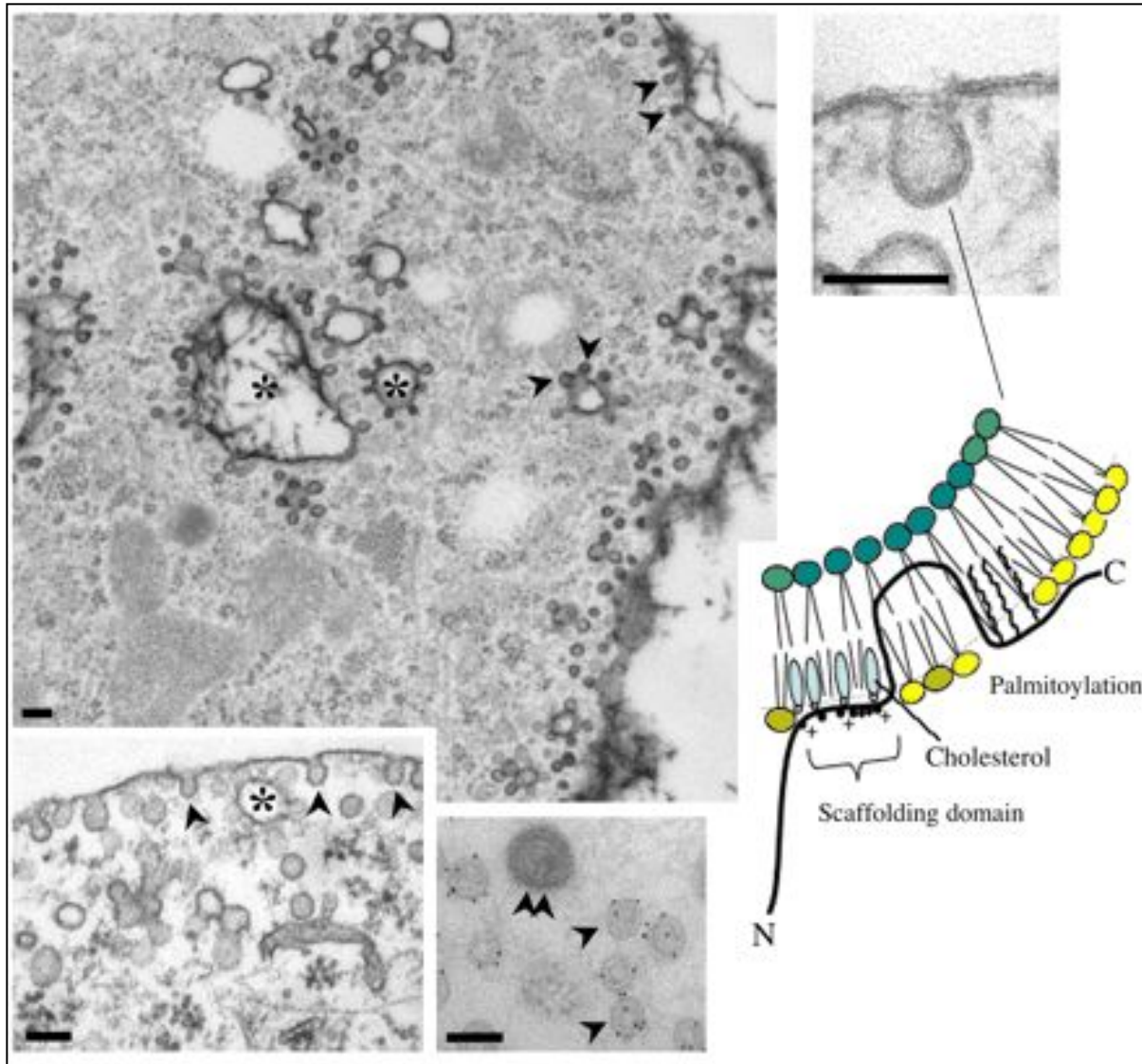


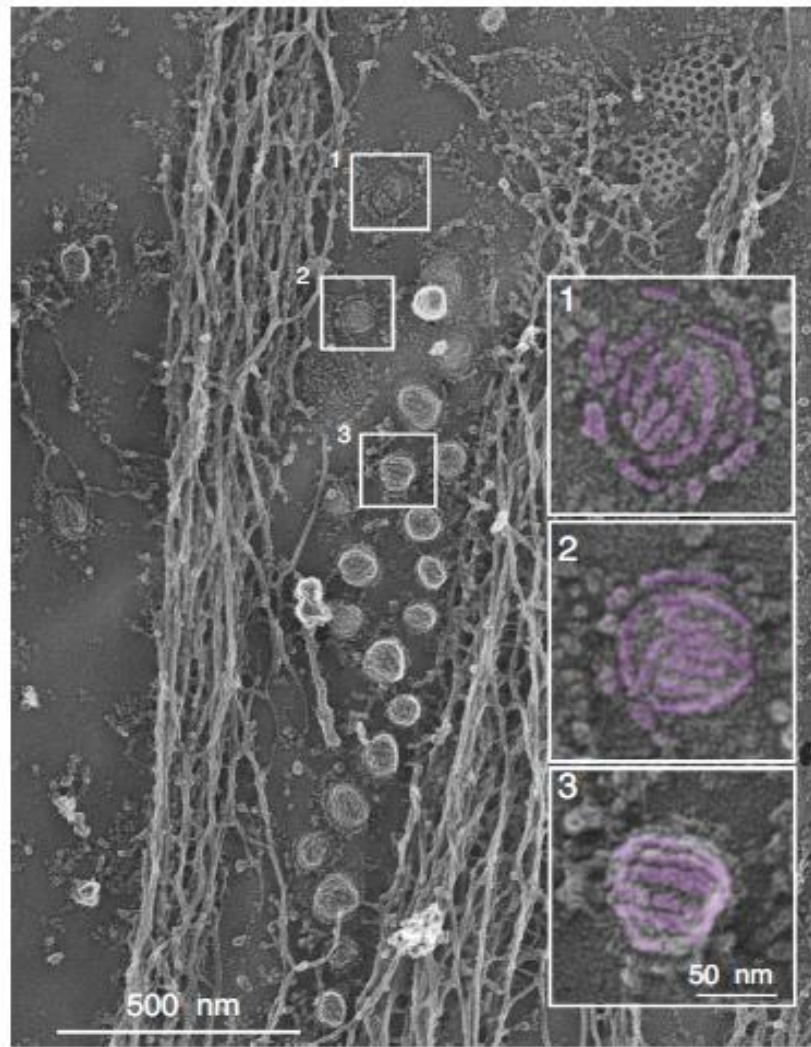
caveolin 1^{+/+}



caveolin 1^{-/-}

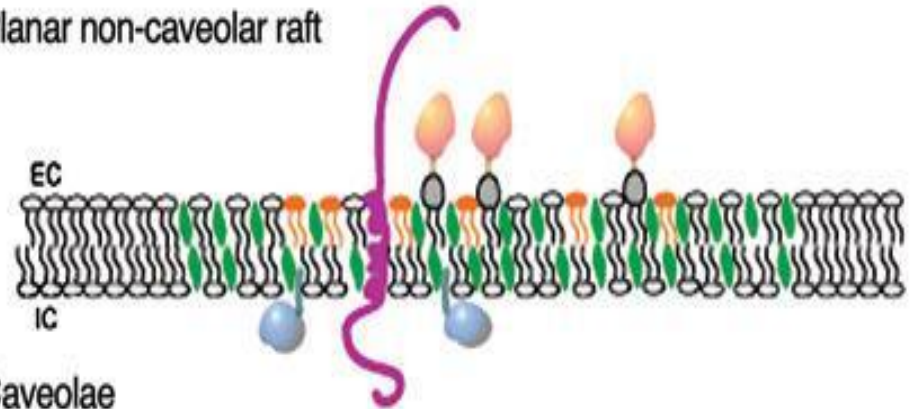




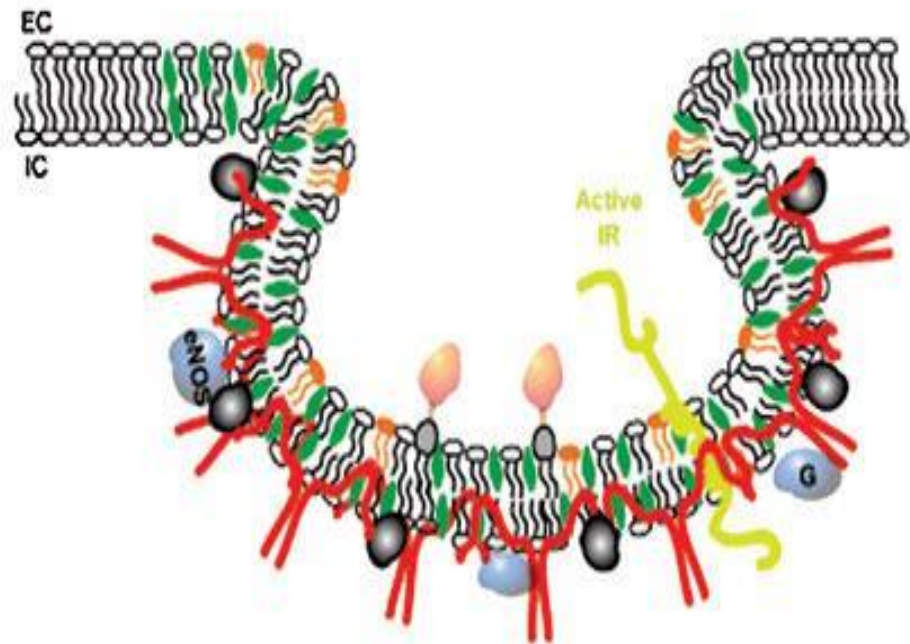


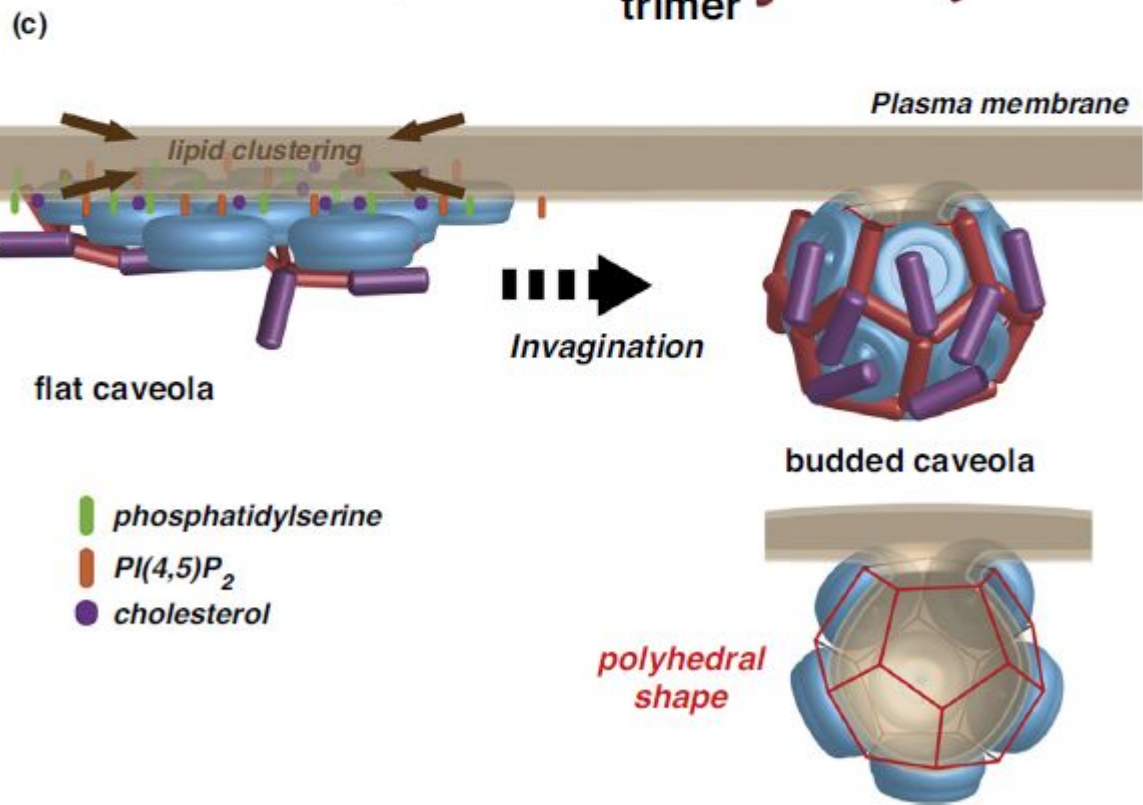
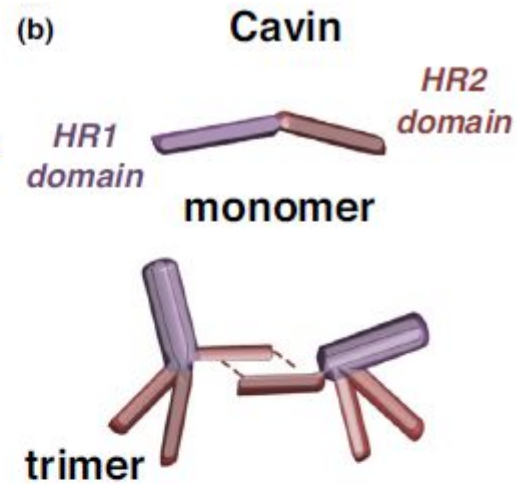
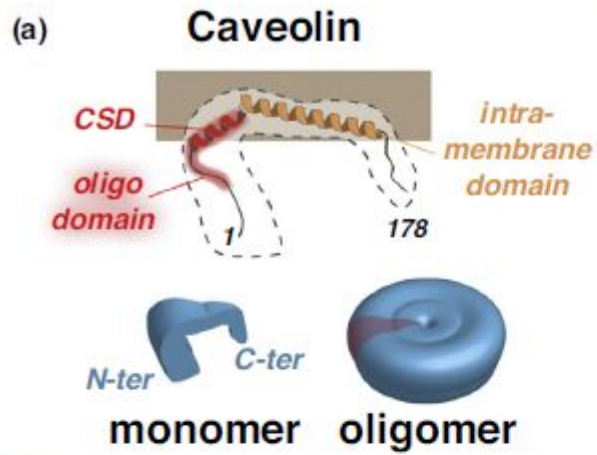
Current Opinion in Cell Biology

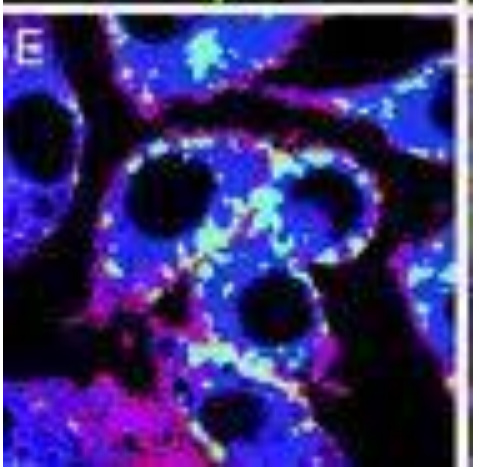
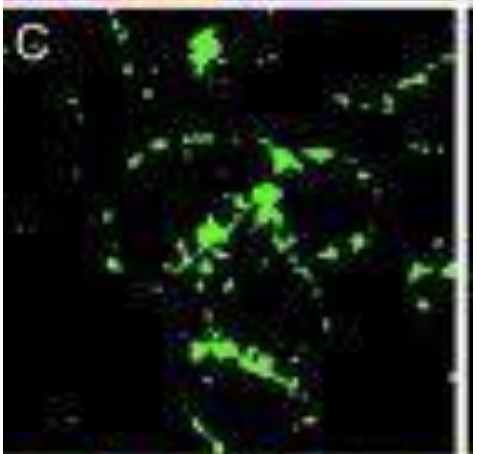
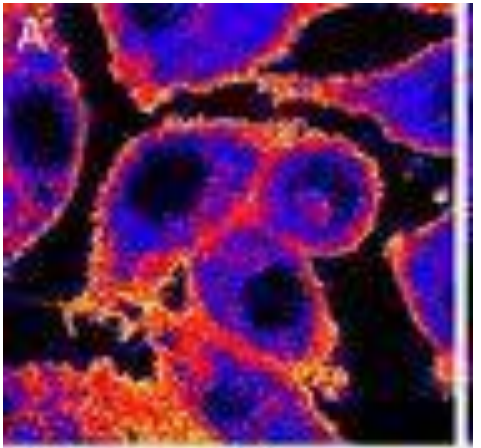
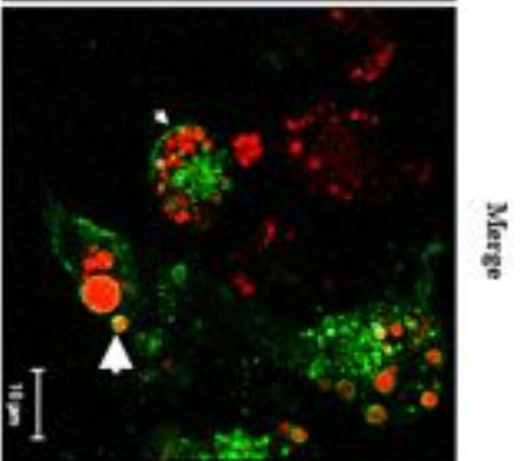
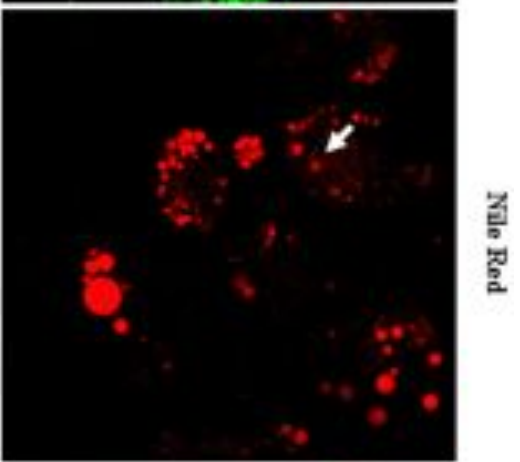
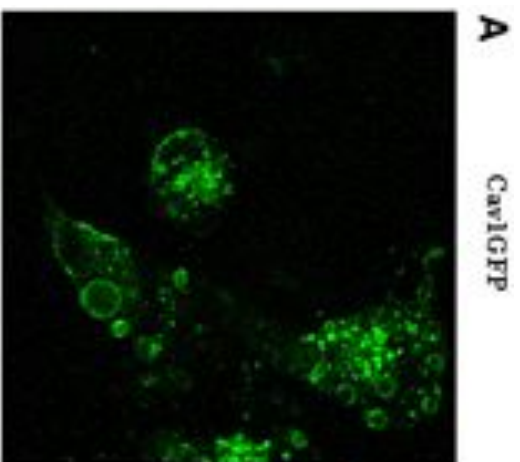
A. Planar non-caveolar raft

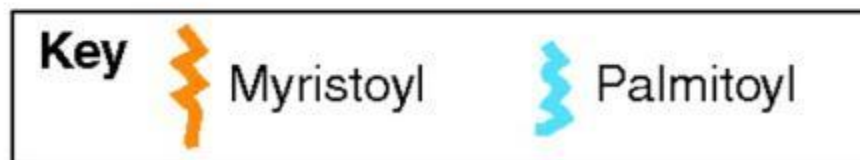
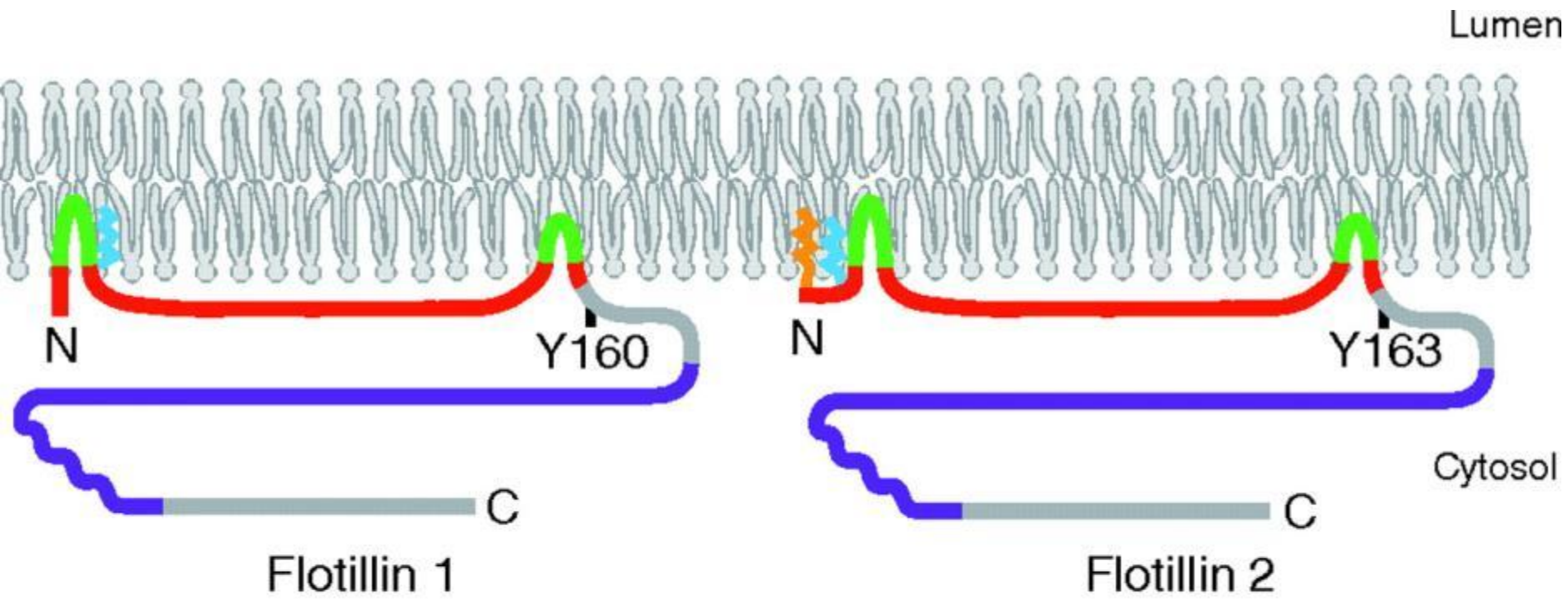


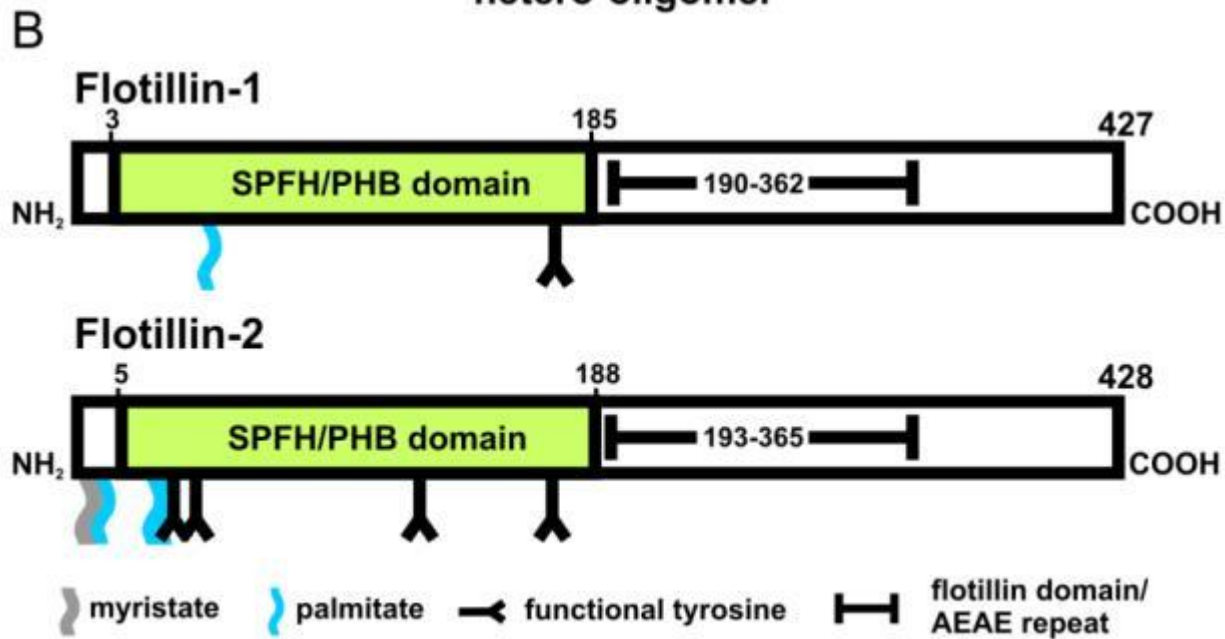
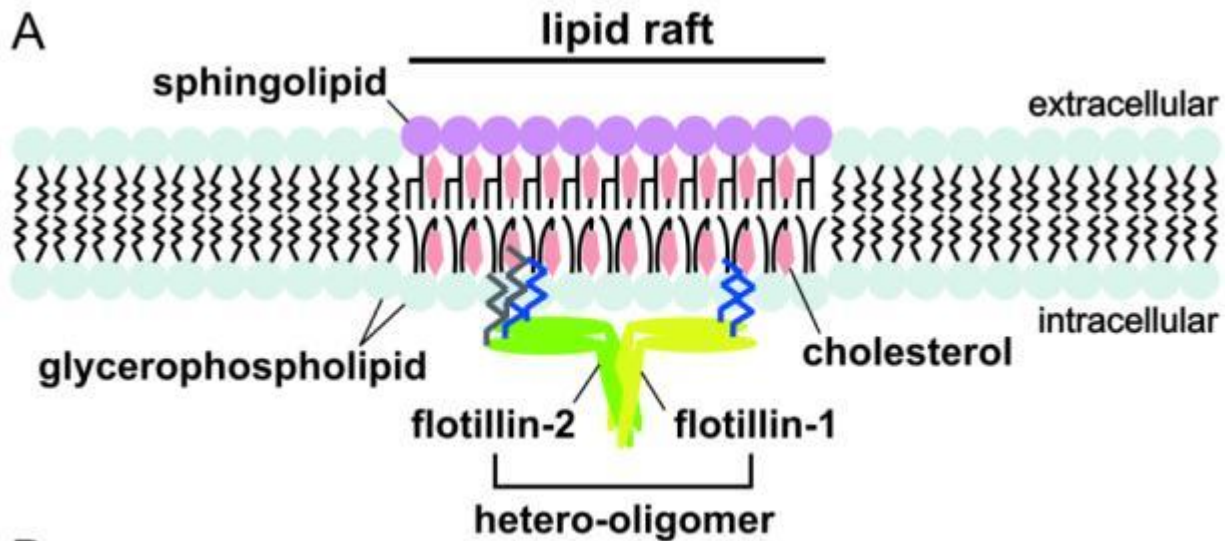
B. Caveolae

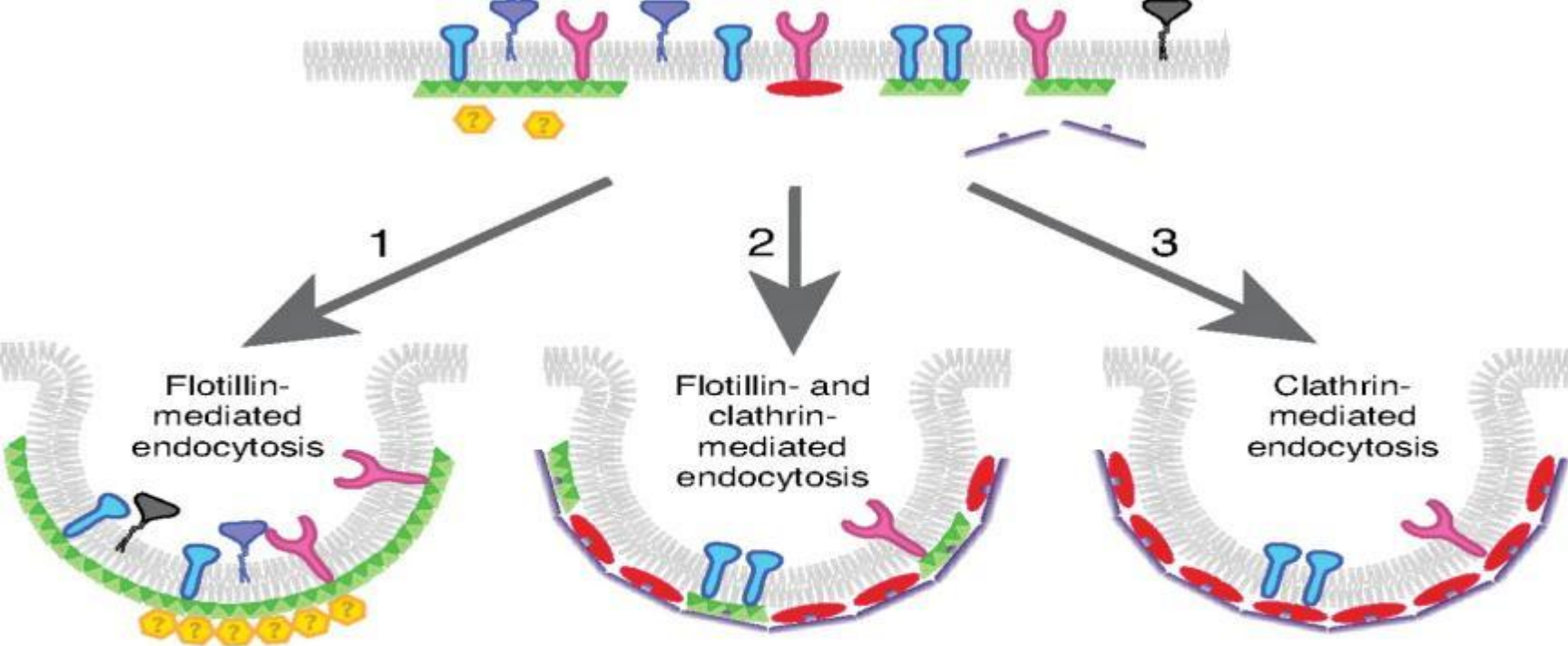






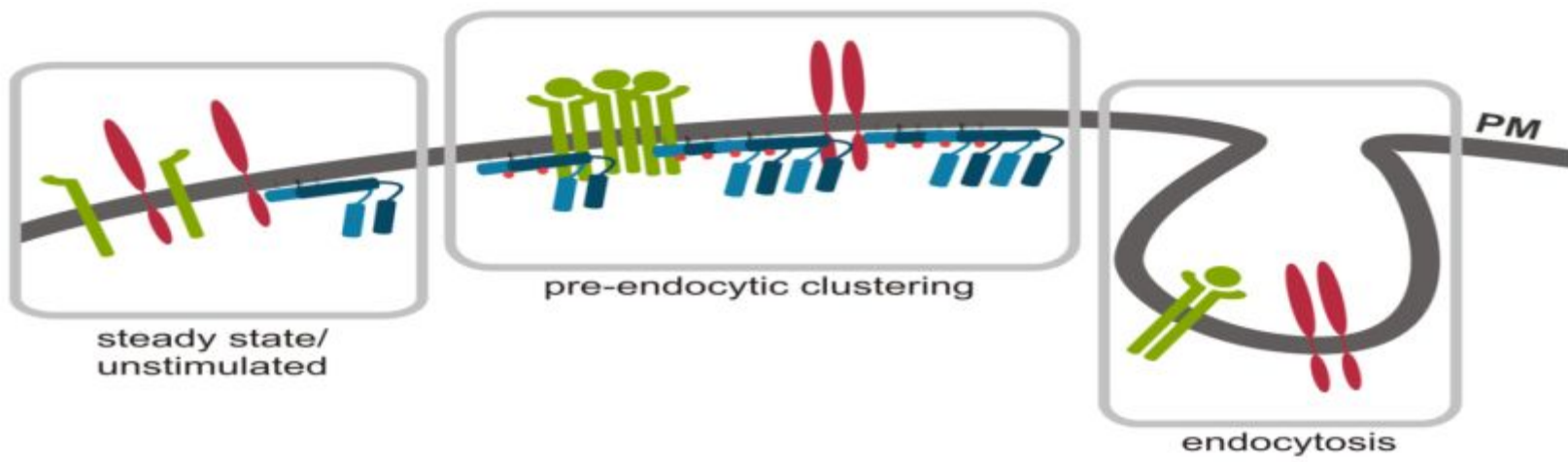


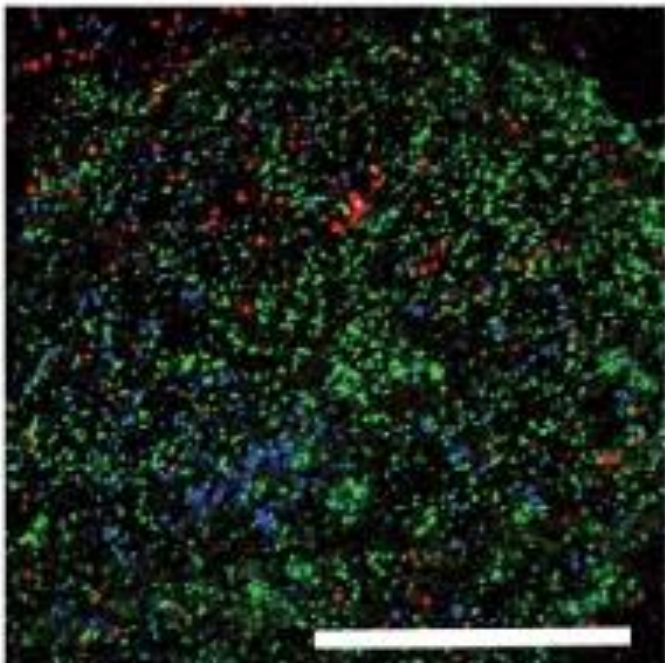
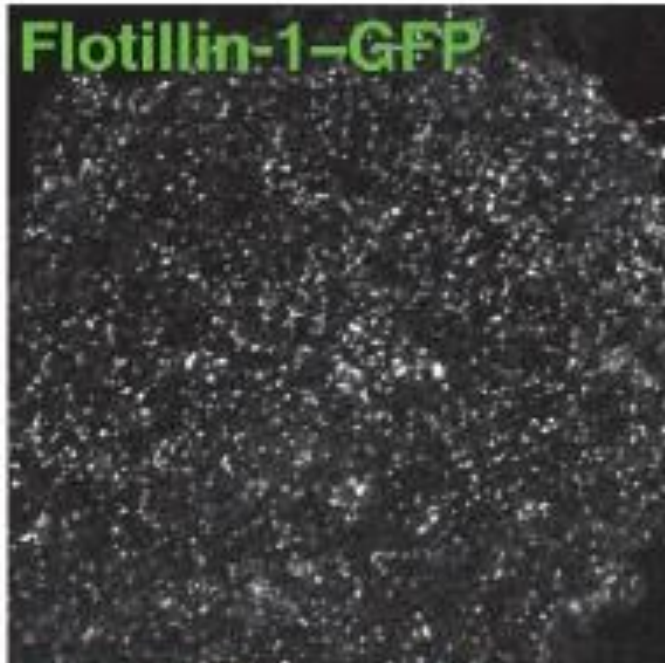
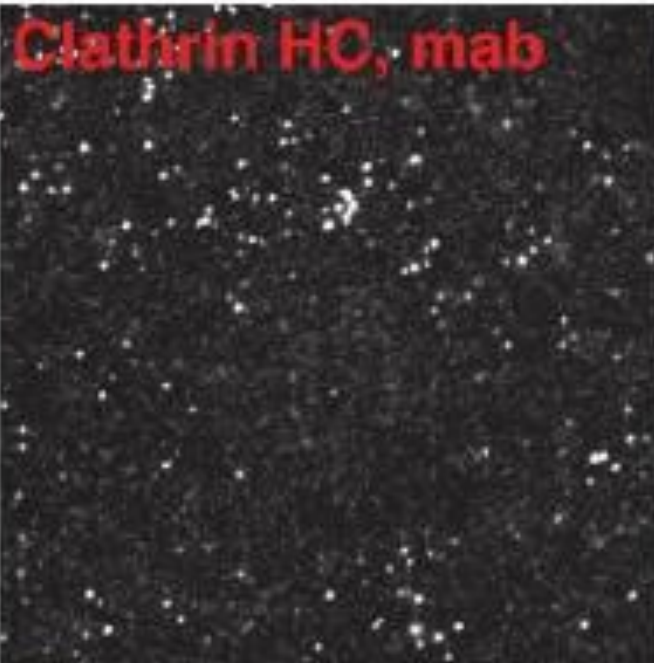


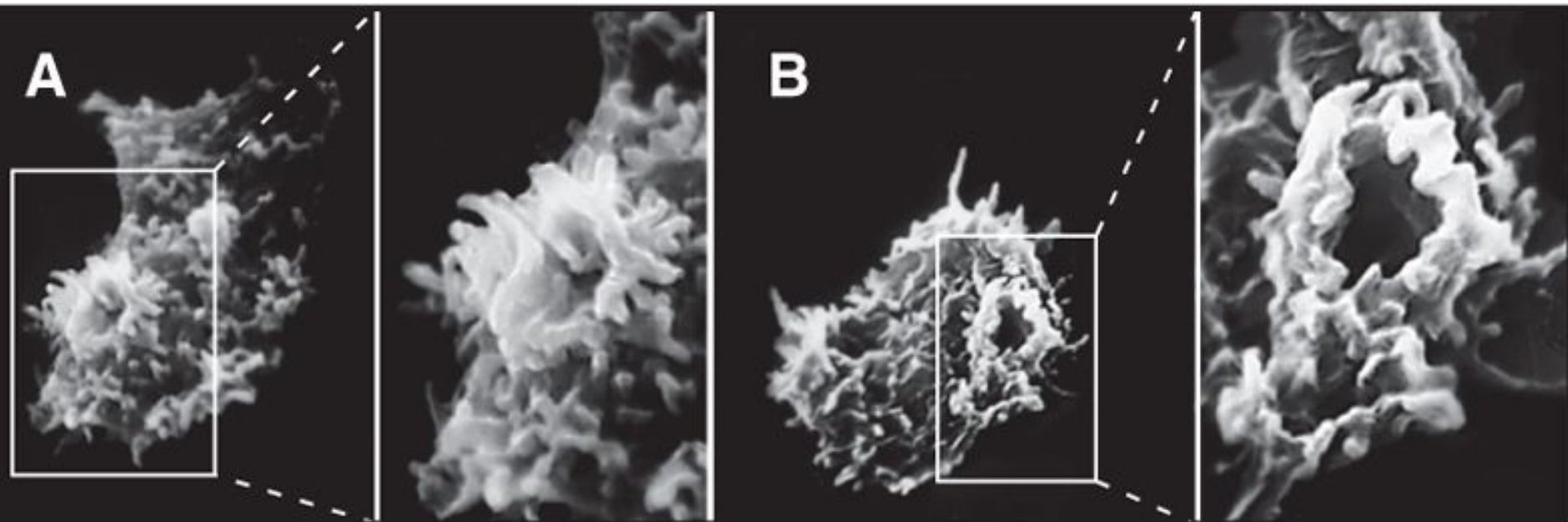


Key

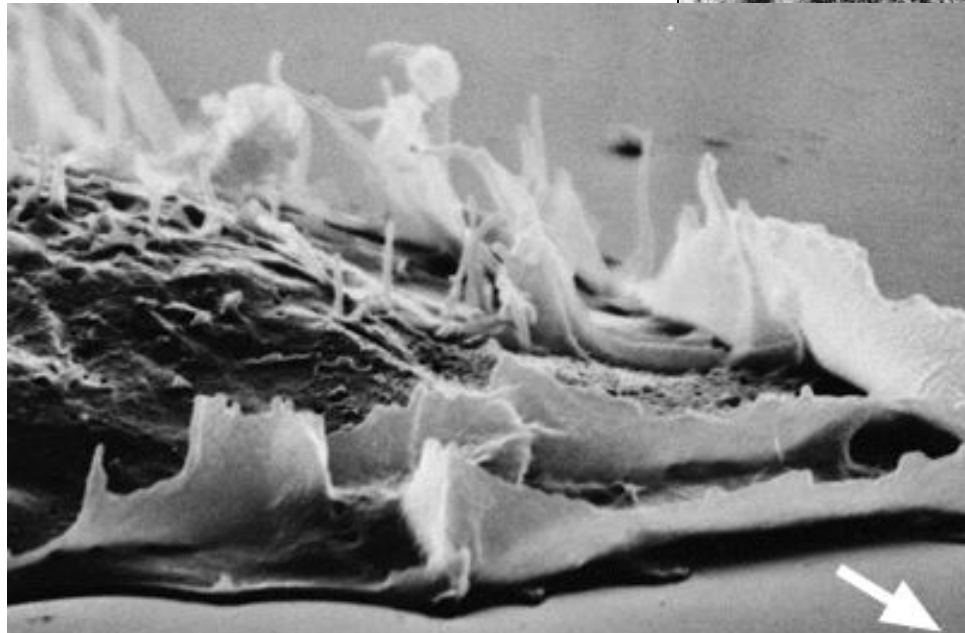
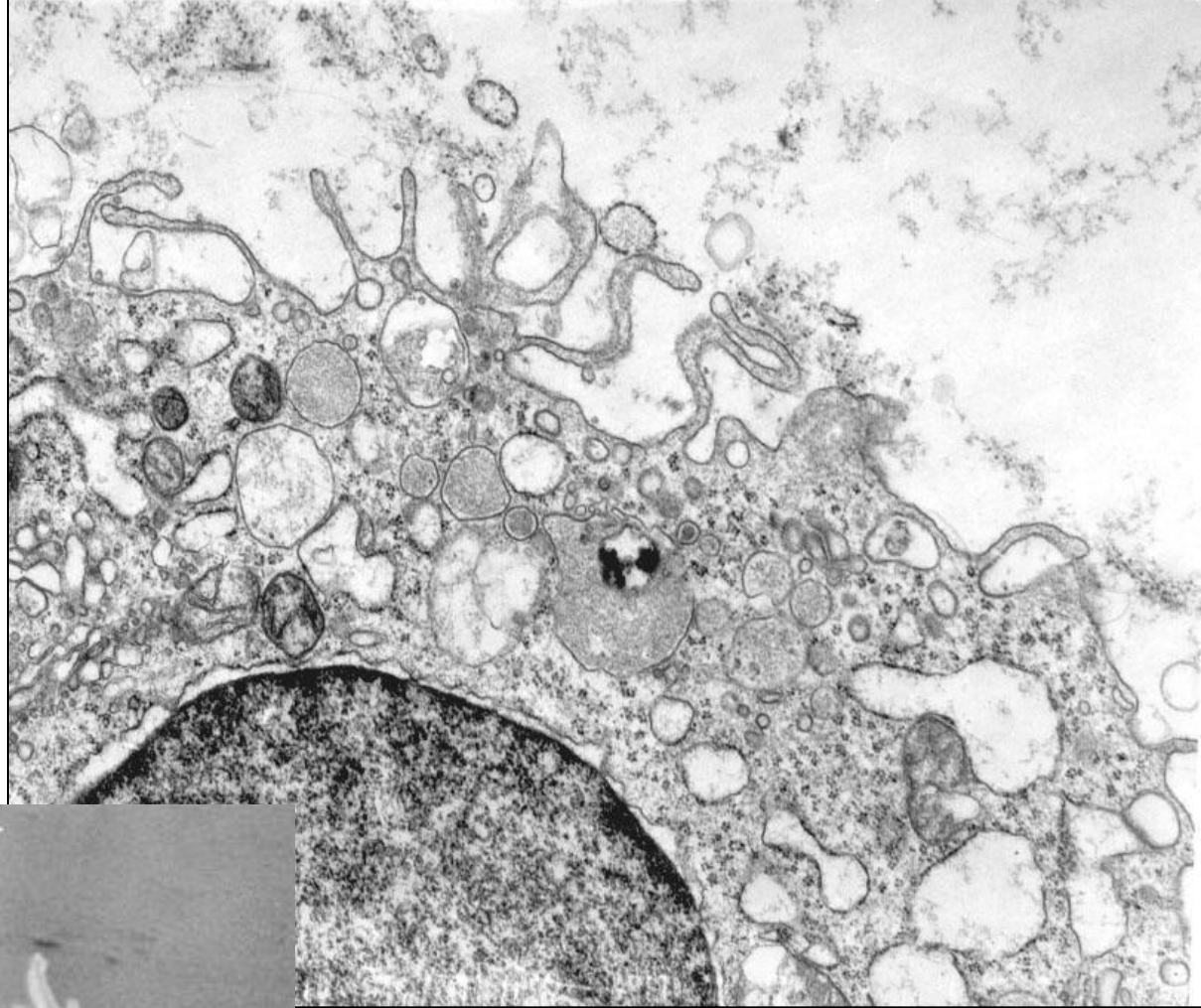
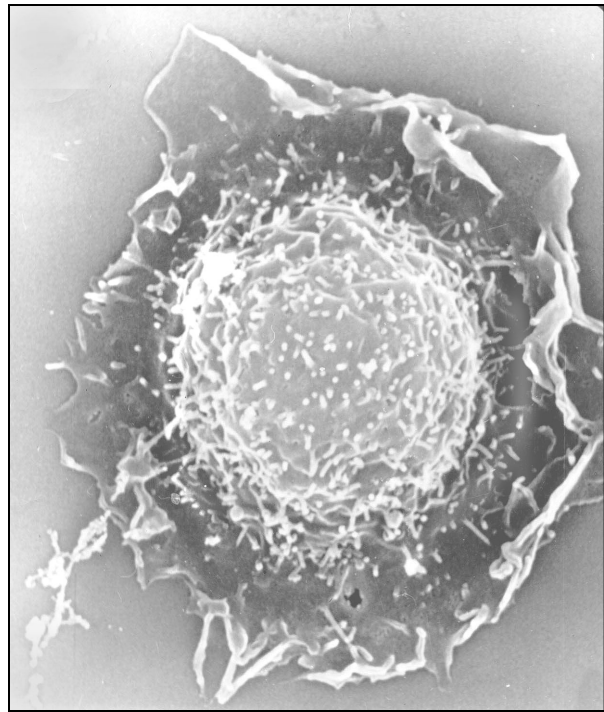
							Flotillins		Flotillin cofactors
							Clathrin		Clathrin adaptor
Cargo									

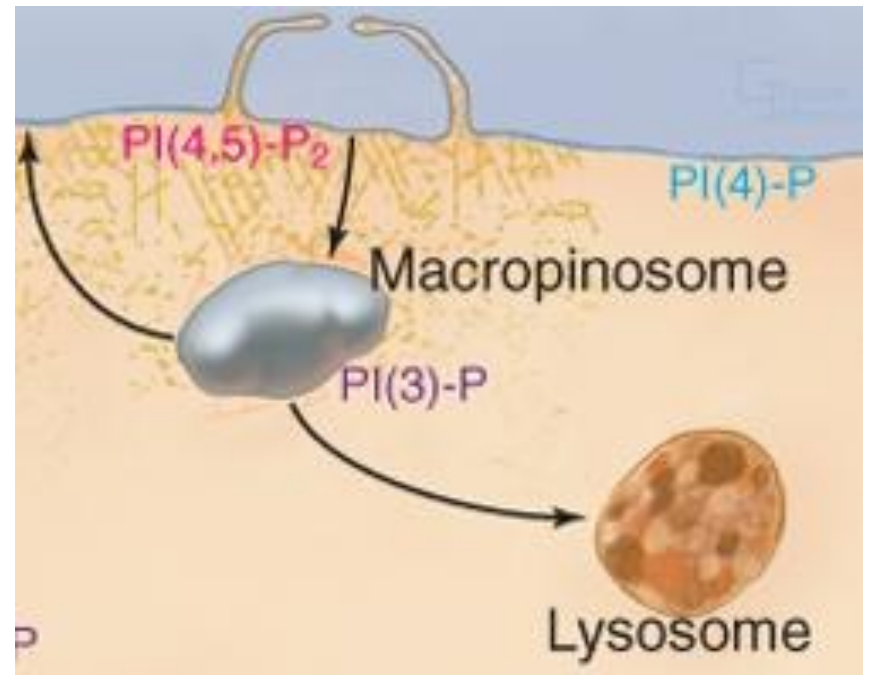
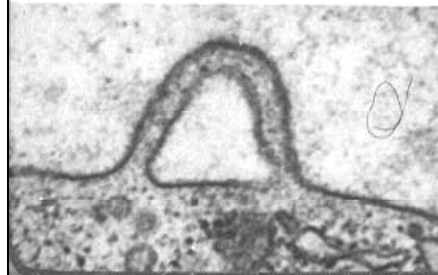
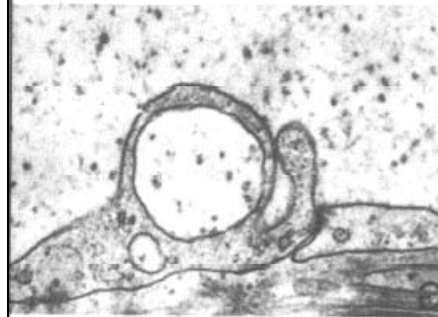
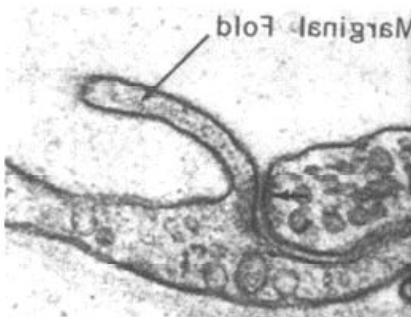
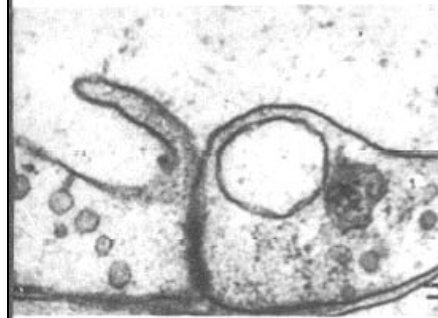
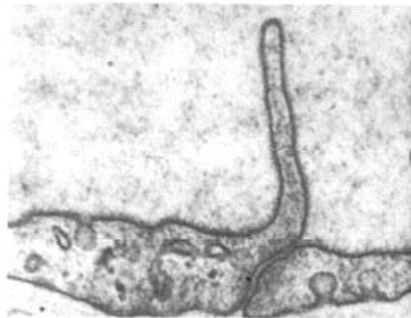
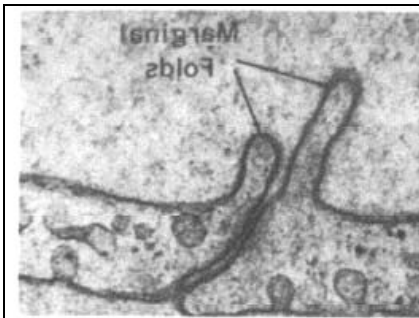


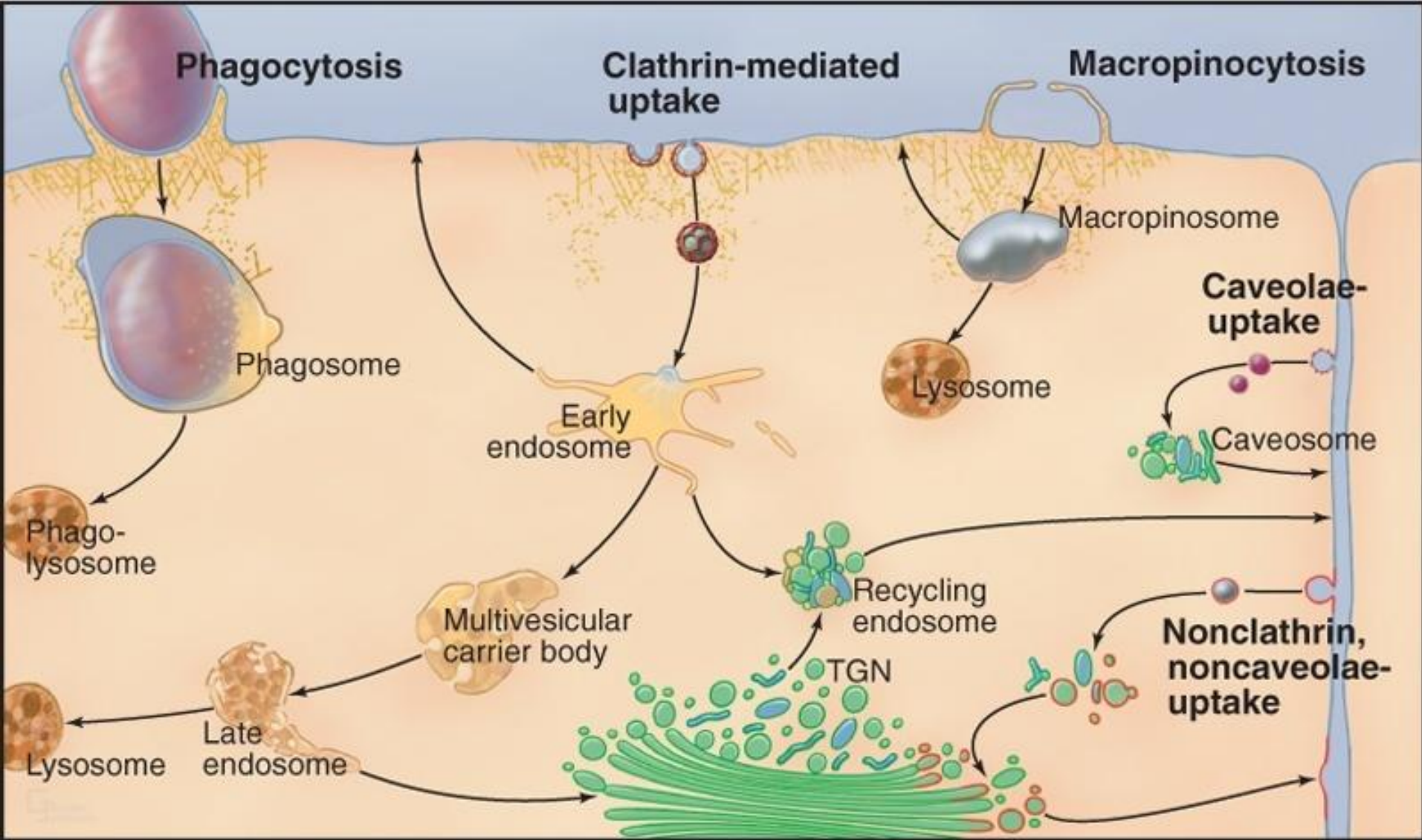


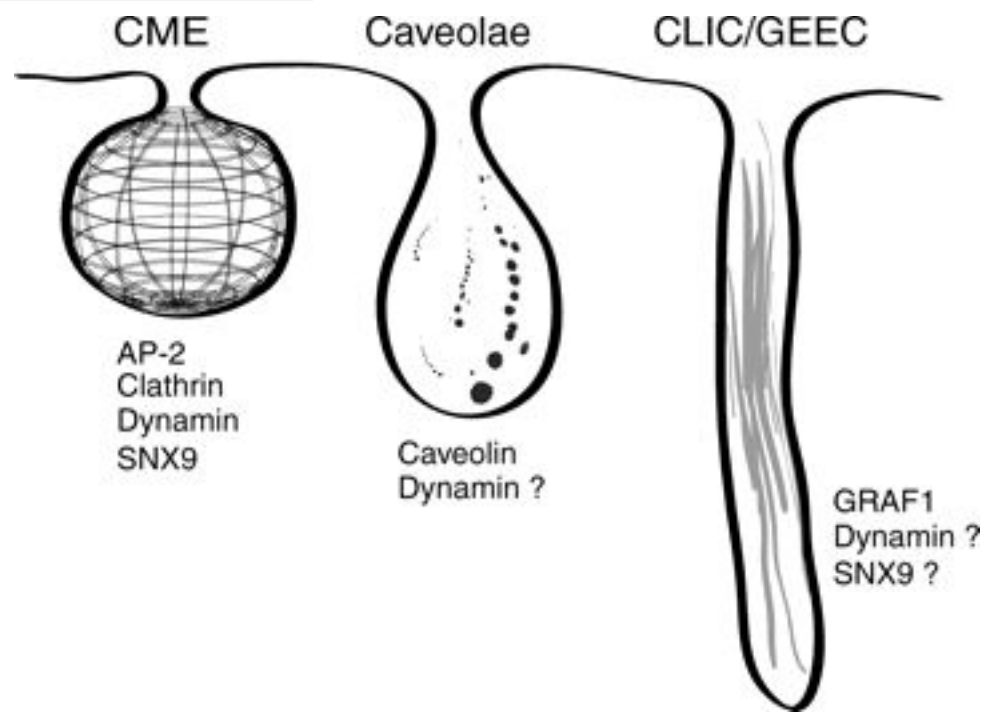
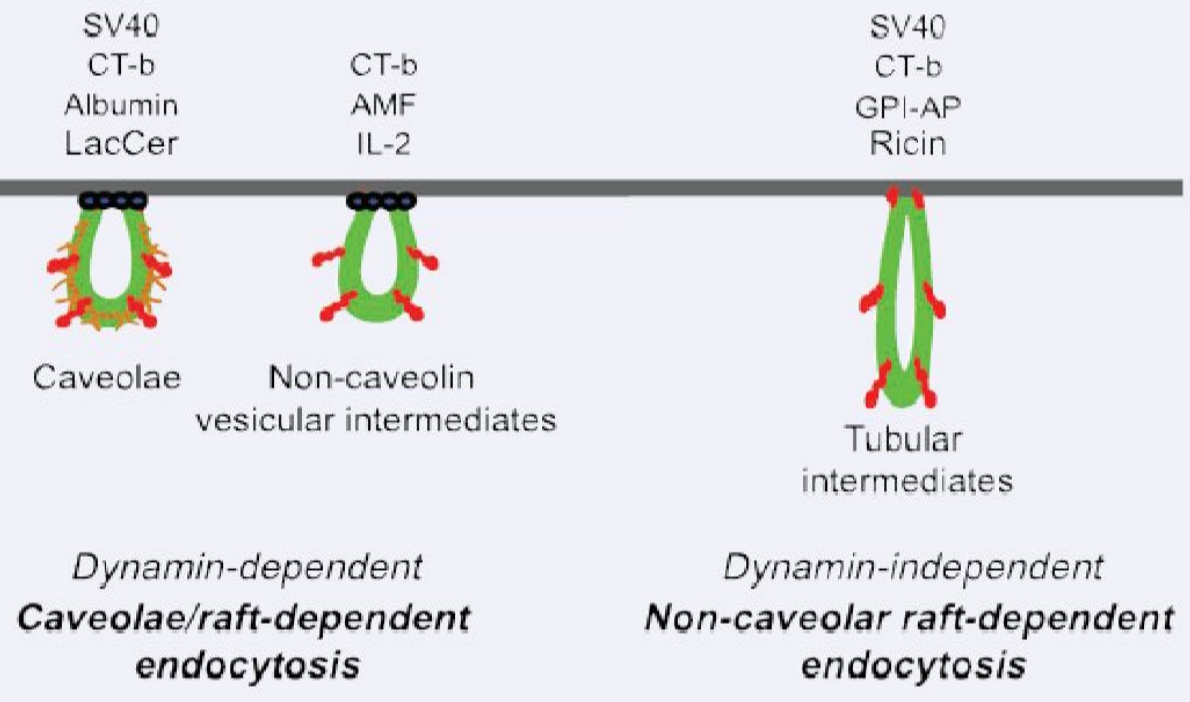


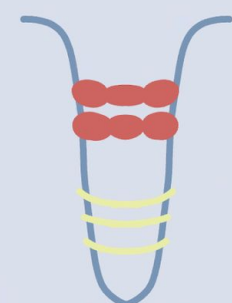
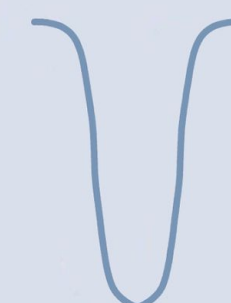
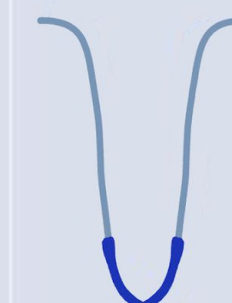
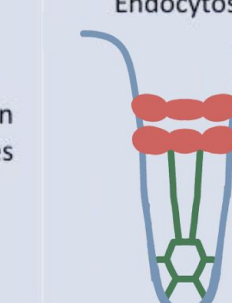
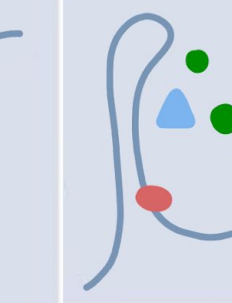
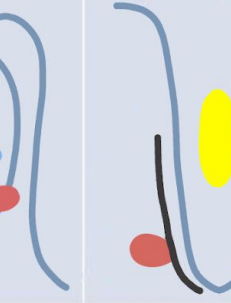
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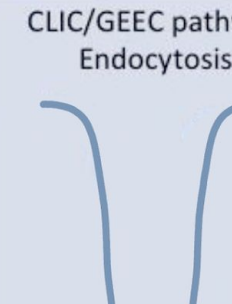
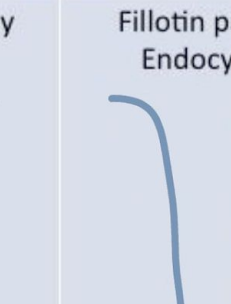
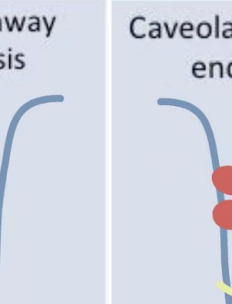
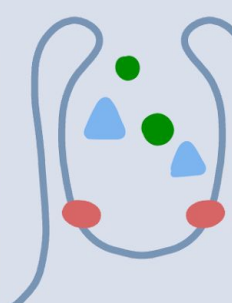
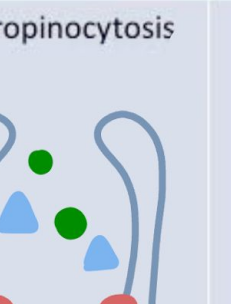
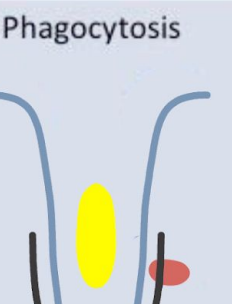








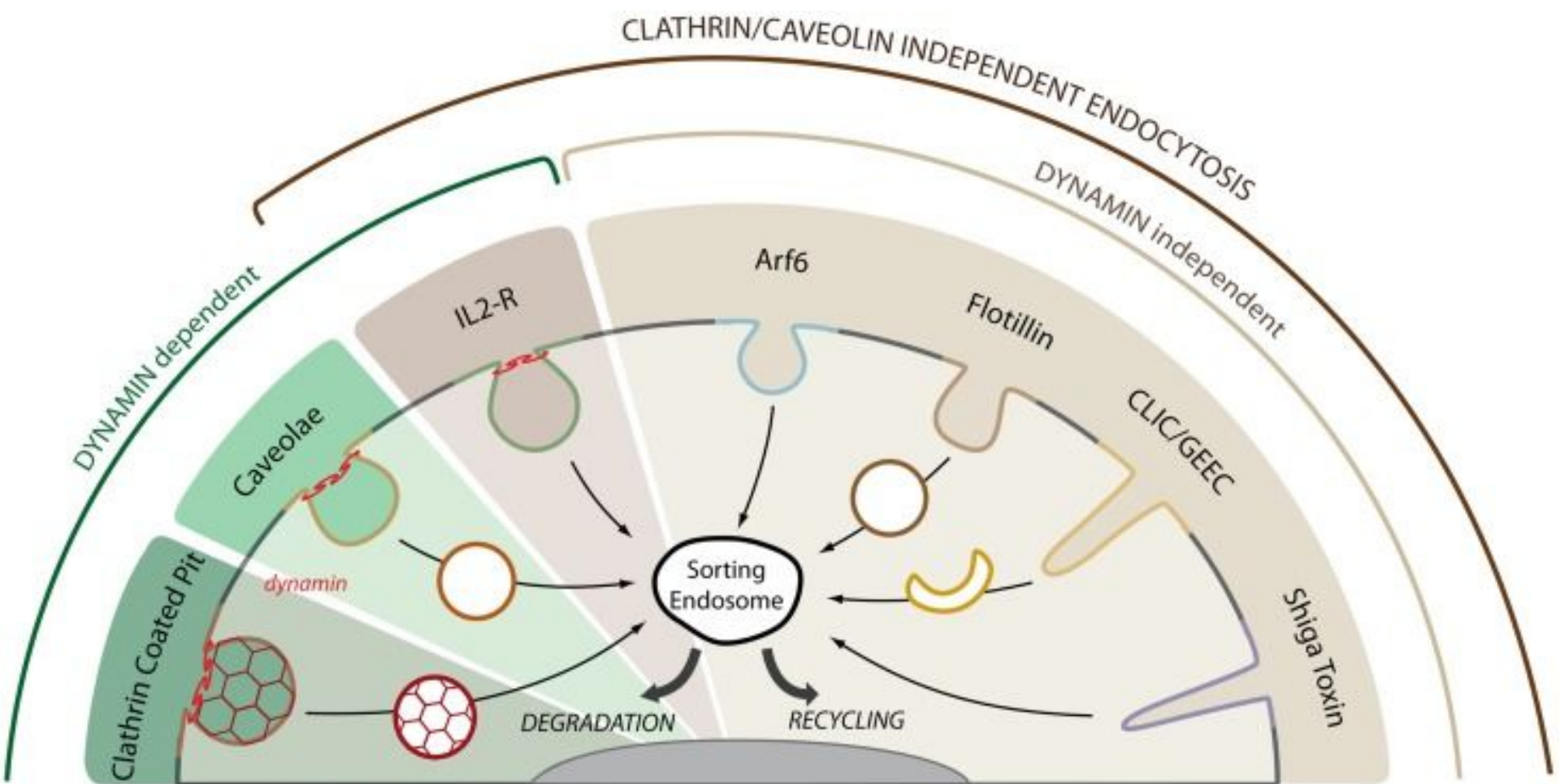
In lipid-rafts membrane domain				Non-lipid rafts membrane domain	Mixed membrane domains	
Caveolae-dependent Endocytosis 	CLIC/GEEC pathway Endocytosis 	Flilotin pathway Endocytosis 	Other Endocytosis pathways Pathways dependent on small GTPases	Clathrin-mediated Endocytosis 	Micropinocytosis 	Phagocytosis 
Main regulators: Caveolin Dynamin Cavins Actin	Main regulators: Cdc42 Actin	Main regulators: Flotillin Actin	Main regulators: Cdc42 Arf1 Arf6 RhoA	Main regulators: Clathrin Dynamin AP2 Eps15 Epsin	Main regulators: Dyn-2 Actin BARs Kinases	Main regulators: Dyn-2 Actin

Clathrin and dynamin independent		Clathrin-independent and dynamin -dependent			Clathrin and dynamin dependent
CLIC/GEEC pathway Endocytosis 	Flilotin pathway Endocytosis 	Caveolae-dependent endocytosis 	Micropinocytosis 	Phagocytosis 	Clathrin-mediated endocytosis 
Main regulators: Cdc42 Actin	Main regulators: Flotillin Actin	Main regulators: Caveolin Dynamin Cavins Actin	Main regulators: Dyn-2 Actin BARs Kinases	Main regulators: Dyn-2 Actin	Main regulators: Clathrin Dynamin AP2 Eps15 Epsin

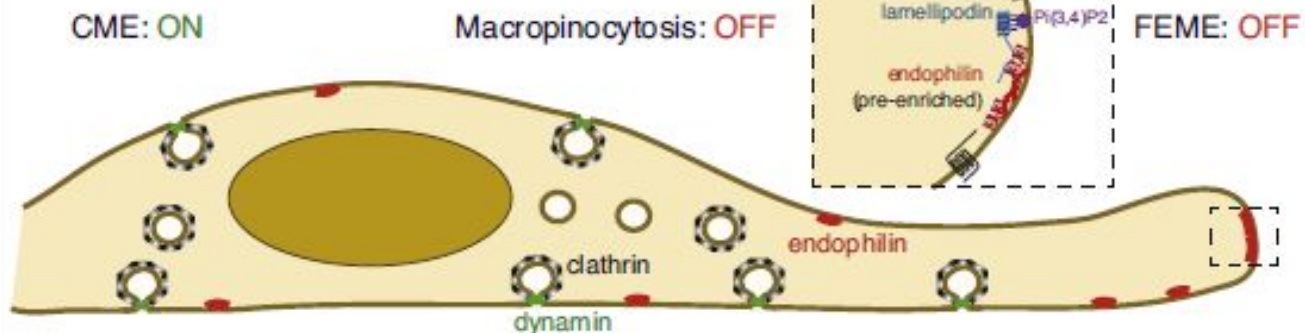
Morphology	Structural components		Cargo	Additional associated proteins
	Involvement of dynamin	Involvement of small GTPases		
Vesicular, flasked-shaped	Yes	Unclear	SV40	Actin, caveolins, PTRF/cavin-1, Src
Vesicular	Both dynamin-dependence and dynamin-independence reported	Unclear	Cholera toxin B, CD59, proteoglycans	Actin, flotillin-1/2
Tubular	No	Cdc42, Arf1	Fluid uptake, cholera toxin B, GPI-APs, VacA toxin	Actin, GRAF1, ARHGAP10
Vesicular	Yes	RhoA, Rac1	IL-2R β , γ c-cytokine receptor, HIV-1, C2 toxin	Pak 1/2
Tubular	Both dynamin-dependence and dynamin-independence reported	Arf6	MHC I, coxsackievirus A9, carboxypeptidase E, GPI-APs	Unclear
Ruffles and large vesicles	No	Rac1, Cdc42, Arf6	Fluid uptake, pathogens	Actin, Abi1, CtBP1/BARS, PI3K, Pak 1, Ras, Src, SNX-PX-BAR proteins

Defining features of CIE pathways

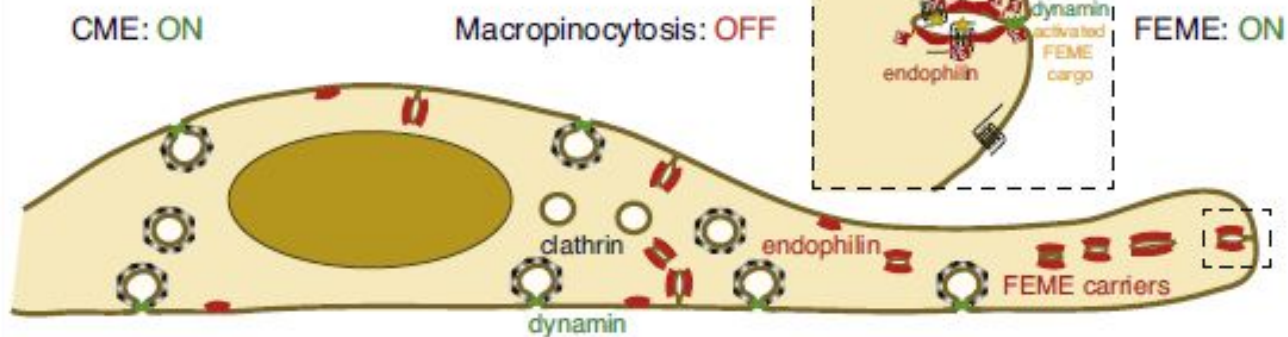
Feature	Caveolae [34]	Arf6 regulated	CLIC/GEEC	RhoA regulated
Major regulator	Cav1/Cav3	Arf6 [6,23]	Cdc42/Arf1 [7,43]	RhoA [5]
Carrier	50–80 nm smooth, flask-shaped (chemically fixed)	Large, tubular [49]	100–200 nm ring-shaped Clathrin-independent carrier (CLIC) [12]	50–60 nm smooth, vesicular [5]
Dynamin	Dependent	Independent [6]	Independent [7,12]	Dependent [5,25]
Cargo	Lipid-rafts	MHCI, Tac [6]	GPI-AP [7]	IL2R [5]



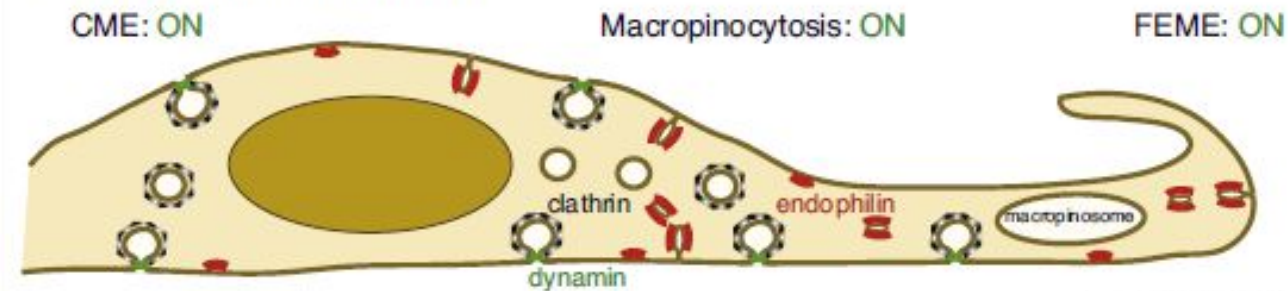
(a) Resting - 'housekeeping' endocytosis



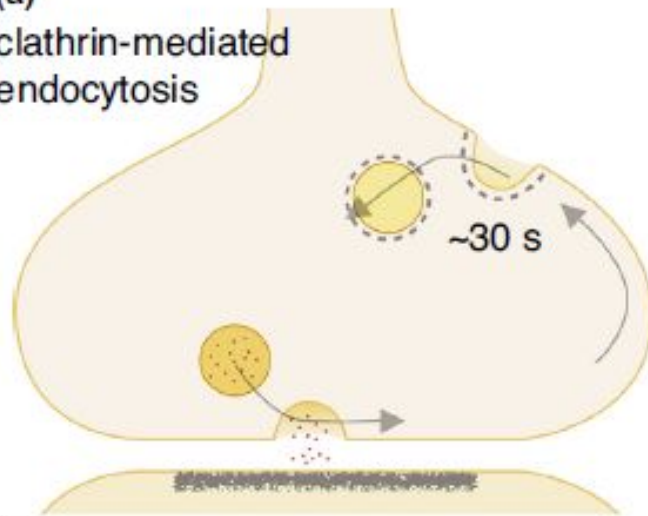
(b) Stimulation with FEME-activating ligands



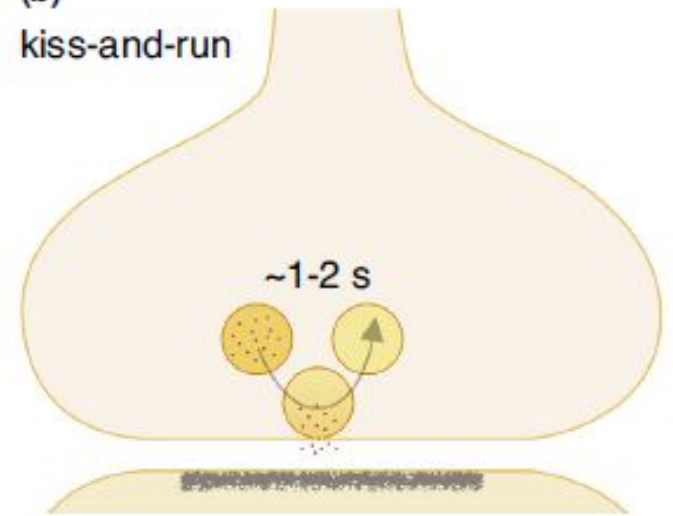
(c) Receptor hyper-stimulation



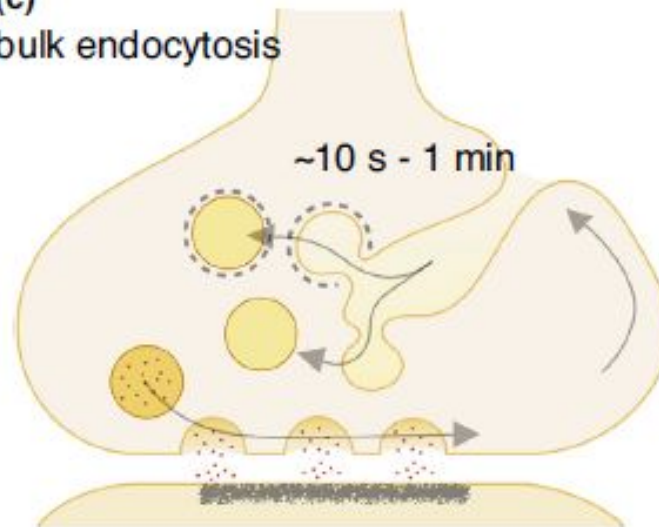
(a)
clathrin-mediated
endocytosis



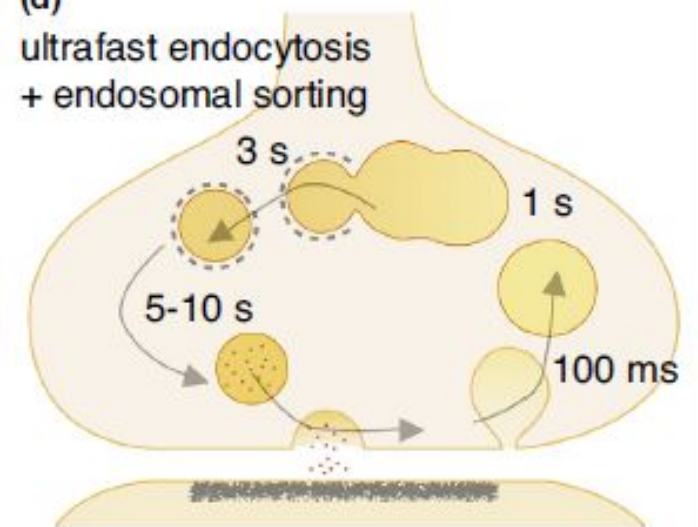
(b)
kiss-and-run

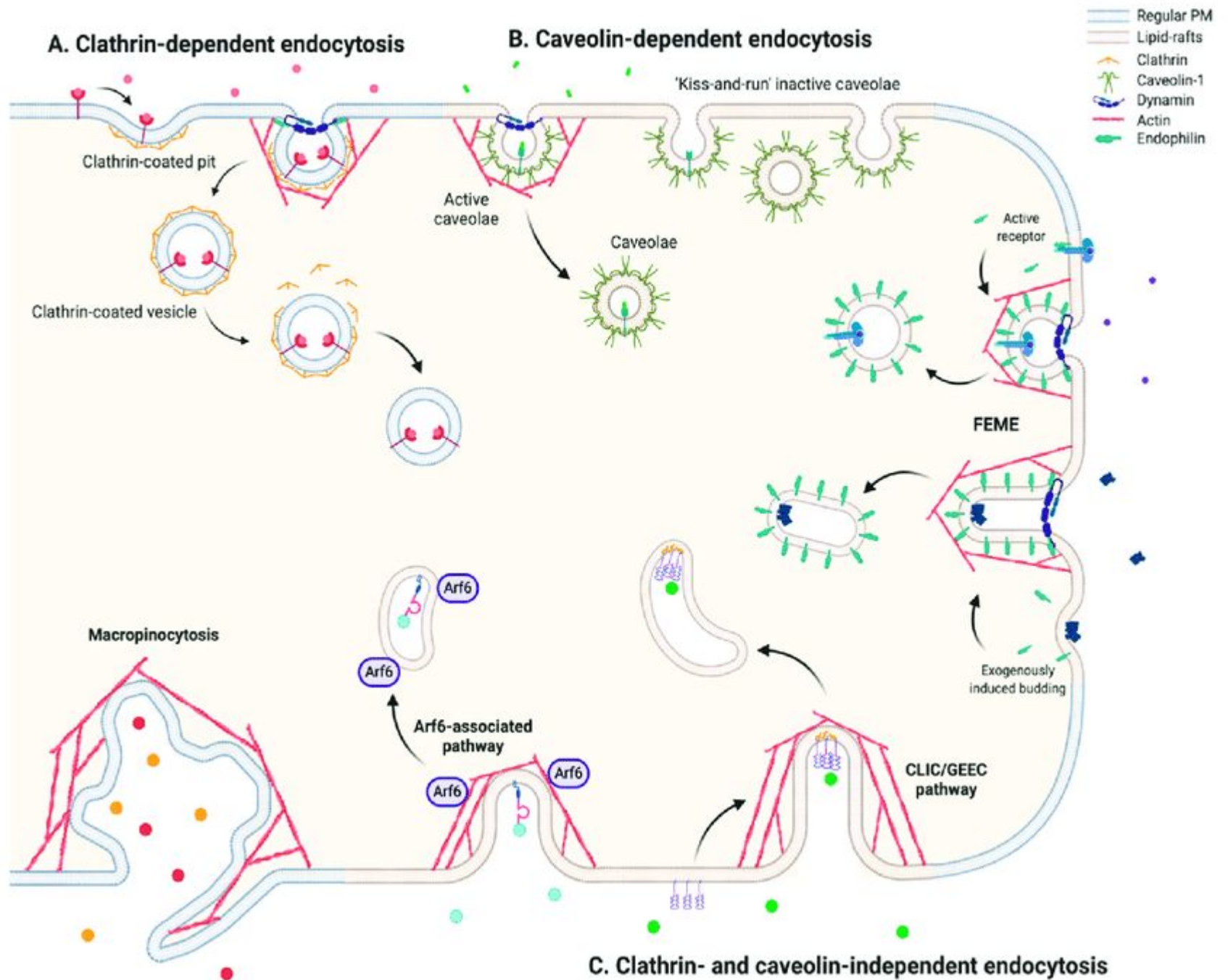


(c)
bulk endocytosis

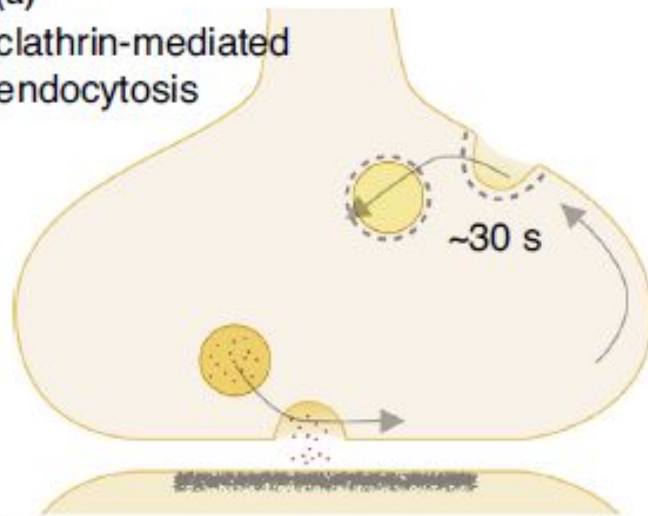


(d)
ultrafast endocytosis
+ endosomal sorting

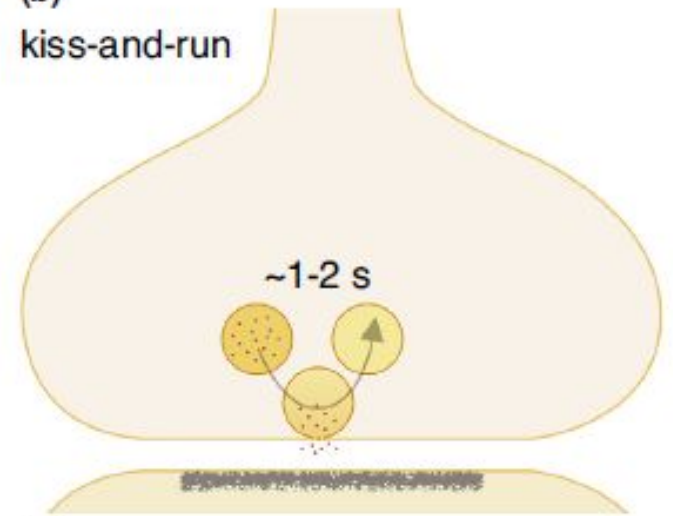




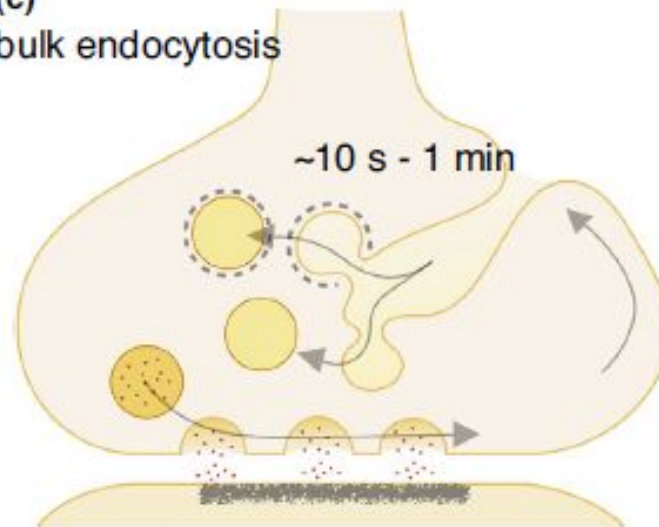
(a)
clathrin-mediated
endocytosis



(b)
kiss-and-run



(c)
bulk endocytosis



(d)
ultrafast endocytosis
+ endosomal sorting

