Manipulation of host cell biology By bacterial pathogens:

with particular interest on intracellular vesicular trafficking

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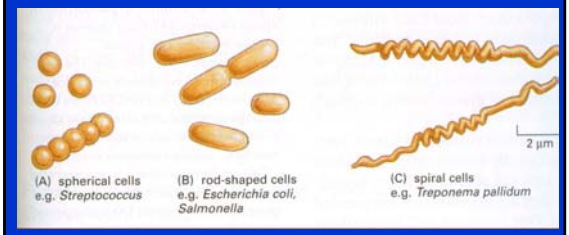
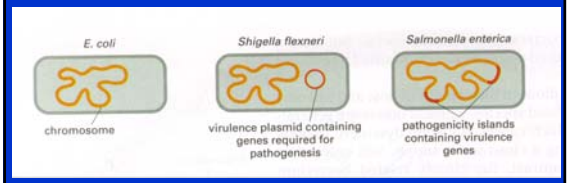
A variety of bacterial pathogens

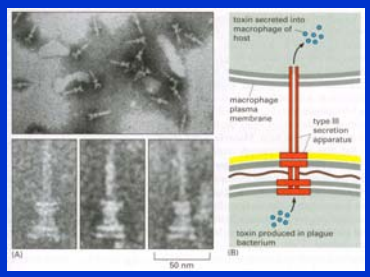


Extracellular
vs
intracelluar

Pathogenic bacteria have virulence genes at different locations



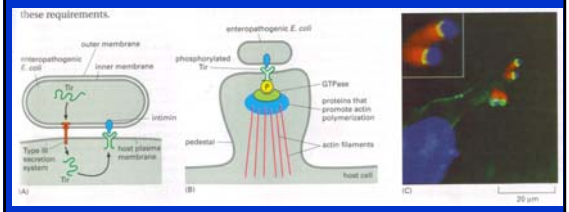
Virulence factors are produced by specialized secretion apparatus



Type III secretion machinery:
Utilized by both extracellular and intracellular bacteria

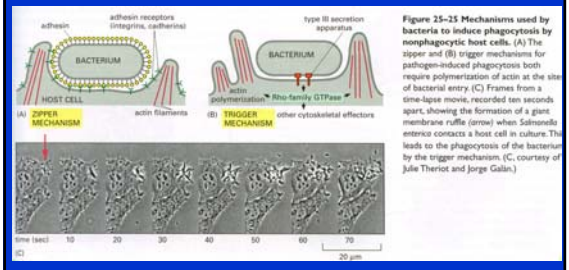
Extracellular bacteria utilize Type III secretion for colonization

Enteropathogenic *E. coli* use Type III secretion to induce pedestal formation



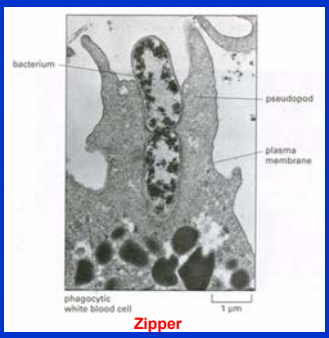
Intracellular bacteria utilize Type III secretion for cell invasion

Salmonella use Type III secretion to induce trigger mechanism of phagocytosis



Yersinia adhesins bind to cell integrins for zipper mechanism of phagocytosis

Intracellular bacteria enter host cell by phagocytosis



Zipper

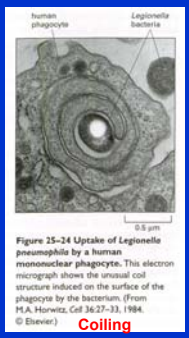


Figure 25–24 Uptake of *Legionella pneumophila* by a human mononuclear phagocyte. This electron micrograph shows the unusual coil structure induced on the surface of the phagocyte by the bacterium. (From M.A. Horwitz, *Cell* 36:27–33, 1984. © Elsevier.)

Coiling

Intracellular bacteria alter vesicular traffic in the cell

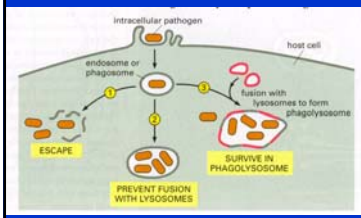
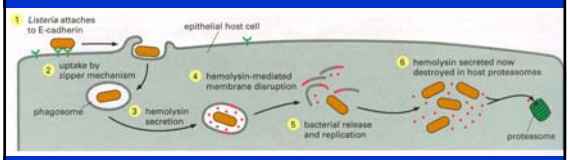


Figure 25–28 The choices faced by an intracellular pathogen. After entry, generally through endocytosis or phagocytosis into a membrane-enclosed compartment, intracellular pathogens may use one of three strategies to survive and replicate. Pathogens that follow strategy (1) include all viruses, *Trypanosoma cruzi*, *Listeria monocytogenes*, and *Shigella flexneri*. Those that follow strategy (2) include *Plasmodium falciparum*, *Mycobacterium tuberculosis*, *Salmonella enterica*, *Legionella pneumophila*, and *Chlamydia trachomatis*. Those that follow strategy (3) include *Coxiella burnetii* and *Leishmania*.

Listeria escape from phagocytic vacuole into cytosol



Other intracellular bacteria survive in the vacuole

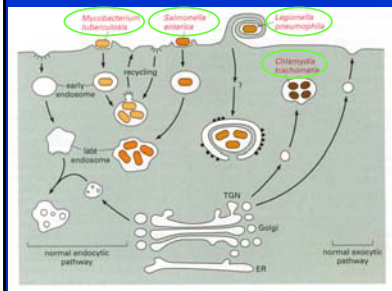


Figure 25–30 Modifications of intracellular membrane trafficking by bacterial pathogens. Four intracellular bacterial pathogens, *Mycobacterium tuberculosis*, *Salmonella enterica*, *Legionella pneumophila*, and *Chlamydia trachomatis*, all replicate in membrane-enclosed compartments, but the four compartments differ. *M. tuberculosis* remains in a compartment that has early endosomal markers and continues to communicate with the plasma membrane. *S. enterica* replicates in a compartment that has late endosomal markers and does not communicate with the surface. *L. pneumophila* replicates in an unusual compartment that is wrapped in several layers of rough endoplasmic reticulum membrane. *C. trachomatis* replicates in an exocytic compartment that fuses with vesicles coming from the Golgi apparatus.

Listeria in the cytosol polymerize actin for spreading

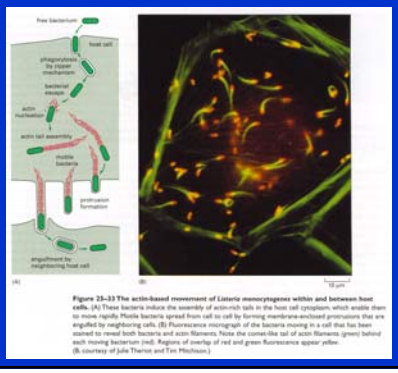
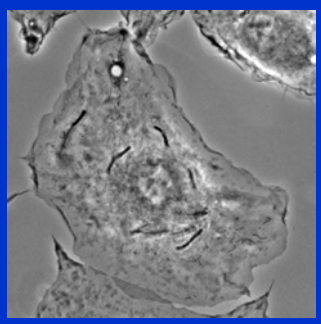
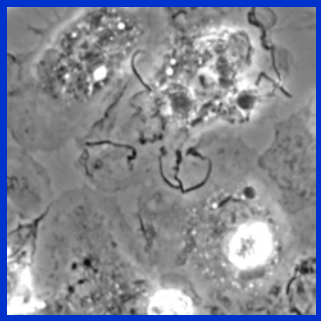


Figure 25–33 The actin-based movement of *Listeria monocytogenes* within and between host cells. (A) These bacteria induce the assembly of actin-rich tails in the host cell cytoplasm, which enable them to move rapidly. Motile bacteria spread from cell to cell by forming membrane-enclosed protrusions that are engulfed by neighboring cells. (B) Fluorescence micrograph of the bacteria moving in a cell that has been stained to reveal both bacteria and actin filaments. Note the comet-like tail of actin filaments (green) behind each moving bacterium (red). Regions of overlap of red and green fluorescence appear yellow. (B, courtesy of Julie Theriot and Tim Mitchison.)

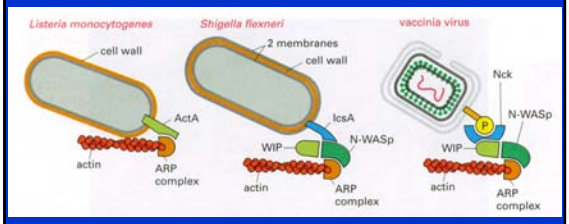
Mycobacterium marinum escape into cytosol and polymerize actin



Mycobacterium marinum spread from cell to cell via actin-based motility

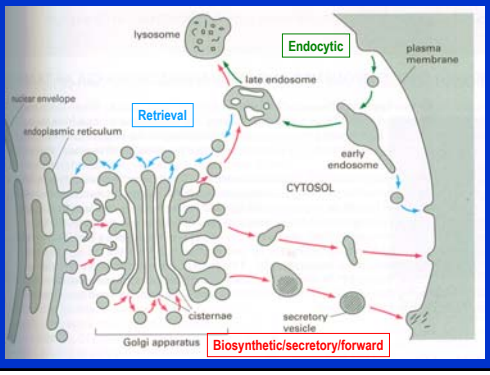


Pathogens intercept different cellular components for the same function

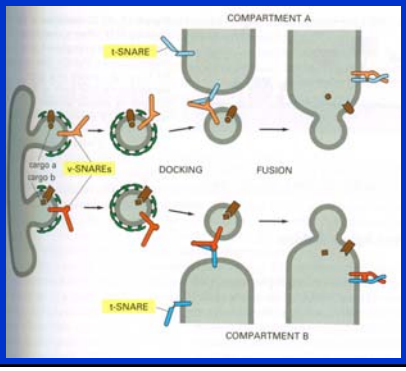


Mycobacteria: utilize mechanism similar to *Shigella*

Intracellular vesicular trafficking network

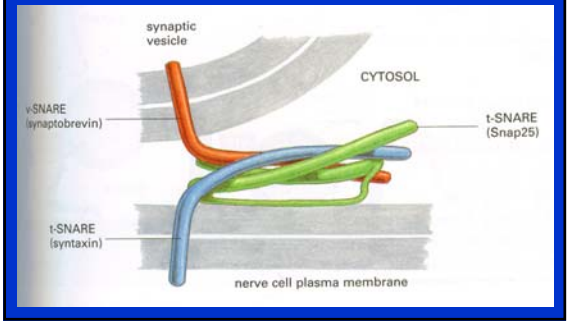


Intracellular vesicular fusion requires SNAREs



v-SNAREs pair with particular t-SNAREs for fusion

Syntaxins are t-SNAREs that bind to other t-SNARE and v-SNARE



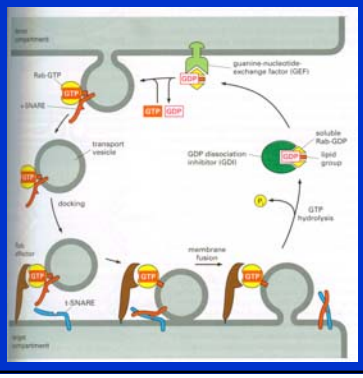
Rab GTPases guide vesicular membrane transport

Rabs work together with Rab effectors to regulate the initial docking and tethering of the vesicle to the target membrane

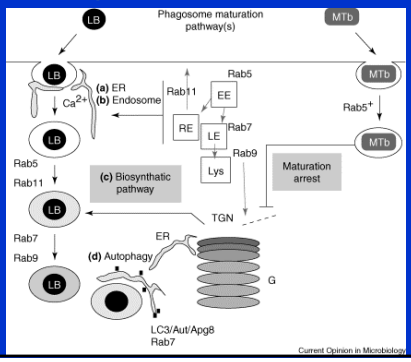
TABLE 13–1 Subcellular Locations of Some Rab Proteins

PROTEIN	ORGANELLE
Rab1	ER and Golgi complex
Rab2	*cis* Golgi network
Rab3A	synaptic vesicles, secretory granules
Rab4	early endosomes
Rab5A	plasma membrane, clathrin-coated vesicles
Rab5C	early endosomes
Rab6	*medial* and *trans* Golgi cisternae
Rab7	late endosomes
Rab8	secretory vesicles (basolateral)
Rab9	late endosomes, *trans* Golgi network

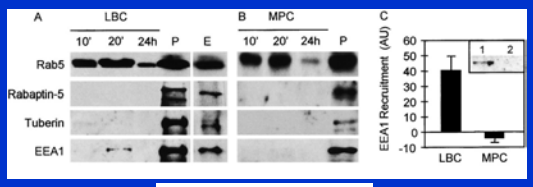
Rab GTPases cycling and Rab effector tethering

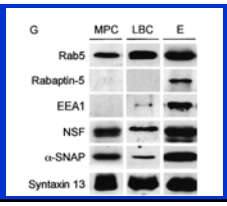


Mycobacteria phagosome maturation is arrested at steps between Rab5 and Rab7

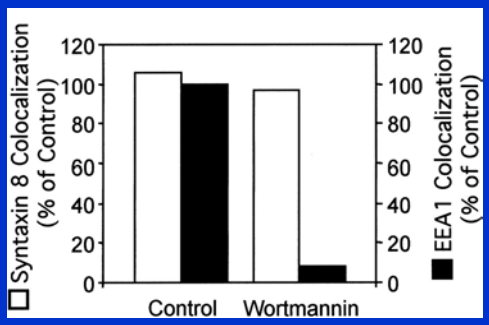


Mycobacteria phagosome retains Rab5 but excludes EEA1

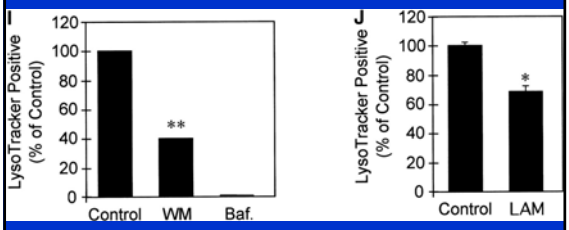




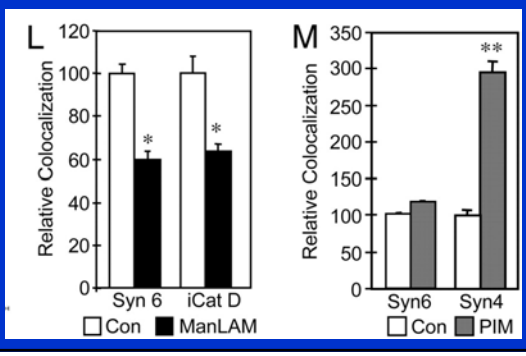
Recruitment of EEA1 on phagosome of latex beads is dependent on PI3-kinase



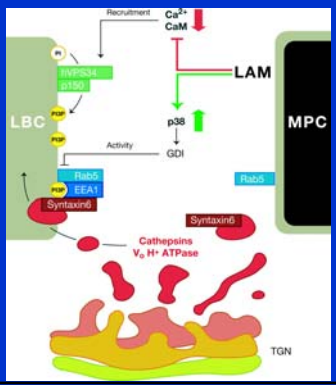
Mycobacteria ManLAM or inhibition of PI-3K activity abrogates phagosomal acidification



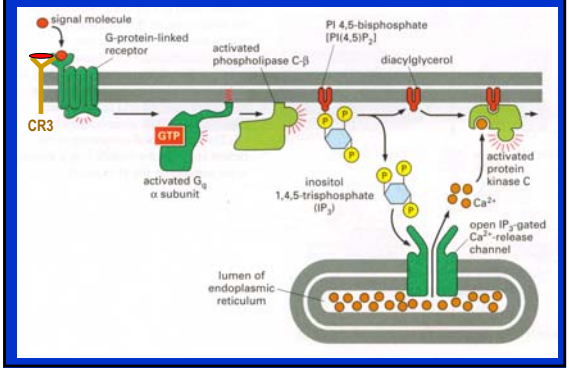
Mycobacteria ManLAM inhibits delivery of syntaxin6 and lysosome hydrolase to the latex bead phagosome



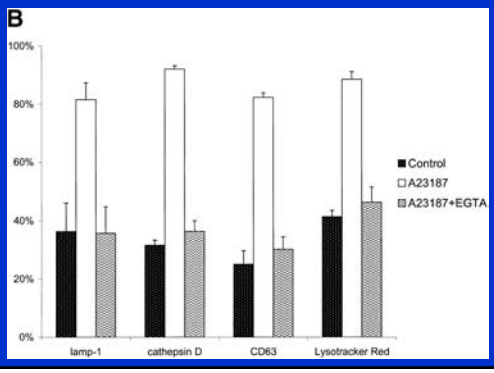
Mycobacteria inhibition of phagosome maturation



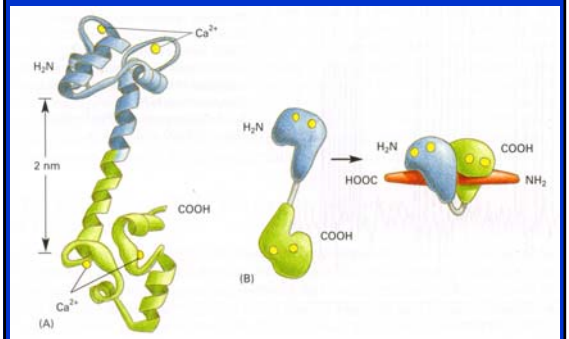
Intracellular Ca^{++} signaling and phago-lysosomal fusion



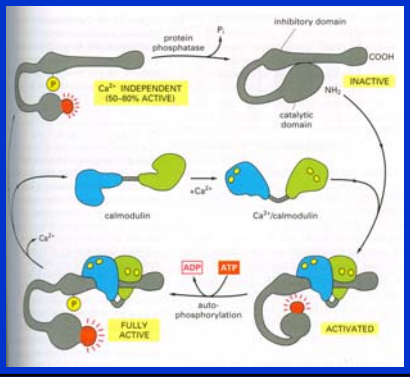
Ca^{++} signaling enhances phagosome-lysosome fusion



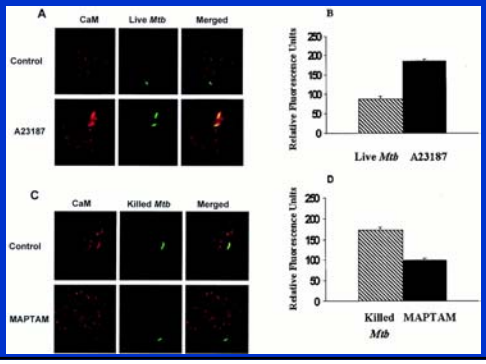
Ca^{++}/Calmodulin complex regulates signaling molecules



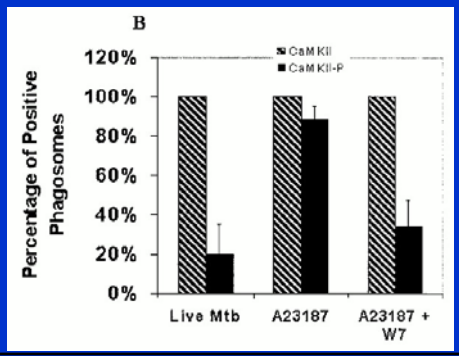
Activation of Ca^{++}/Calmodulin kinase II



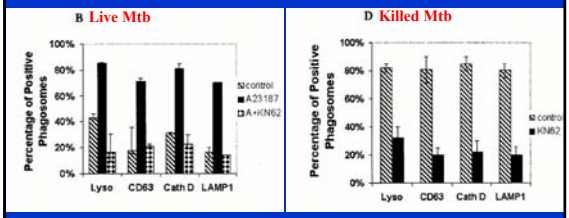
Phagosomes containing live *M. tuberculosis* exhibit decreased levels of CaM compared with phagosomes of killed mycobacteria



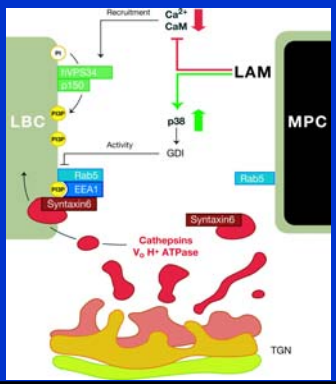
Phosphorylation of CaMKII on *M. tuberculosis* phagosomes is dependent on cytosolic Ca^{2+} and CaM



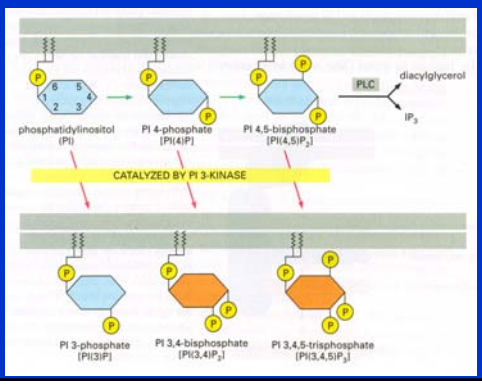
Inhibition of CaMKII blocks the Ca^{2+}-dependent maturation of *M. tuberculosis* phagosomes to phagolysosomes



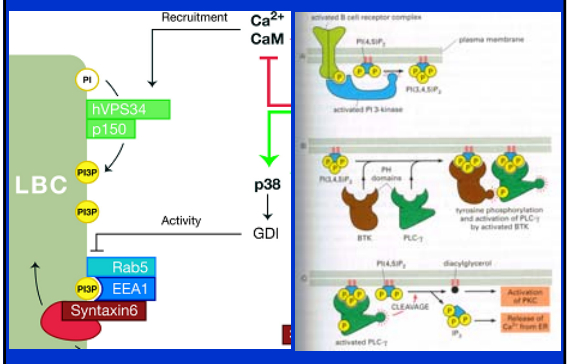
Mycobacteria inhibition of phagosome maturation



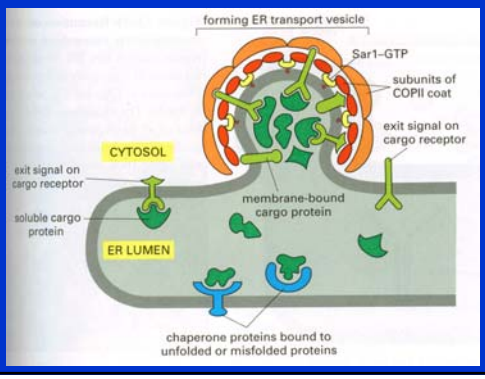
PI3-kinase activity and phosphorylation of inositols



Recruitment of PH-domain molecules to the membrane by PIP3



Vesicular transport from ER to Golgi



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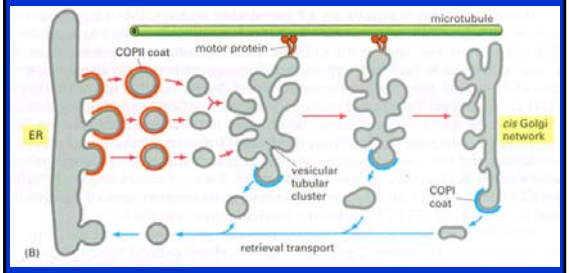

Transport of a phagosome-containing *Legionella* to the ER