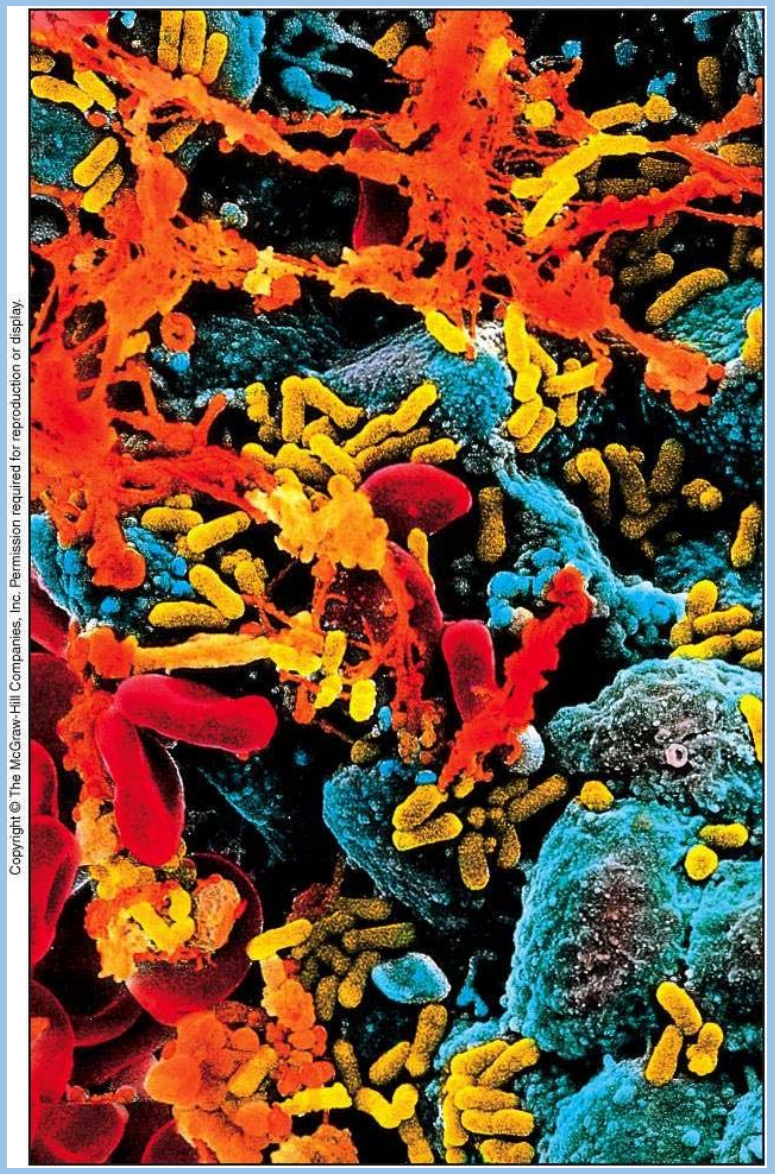

How to “Hijack” the Host Cells

——The manipulation of host-cell pathways by bacterial pathogens

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Microbiology

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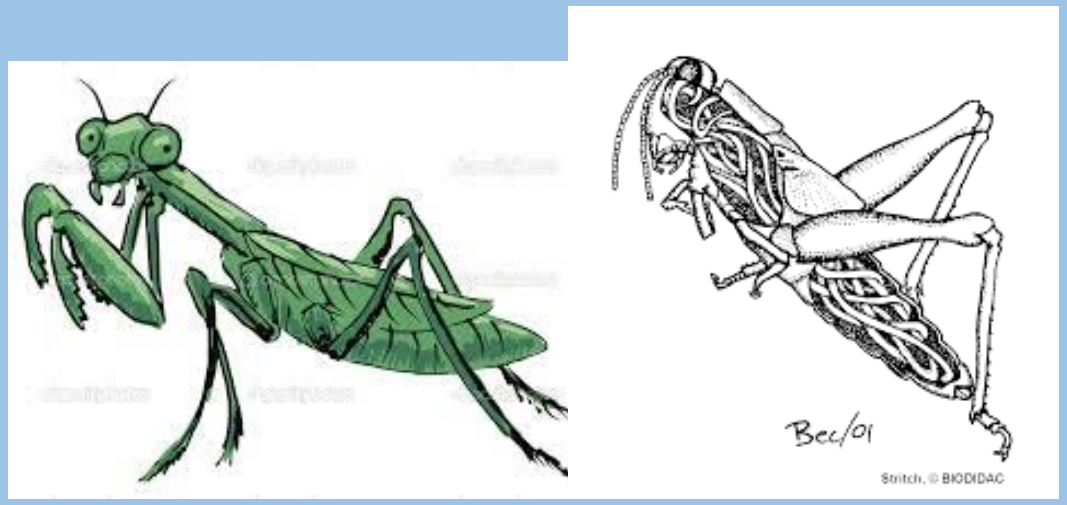
- Virus “Hijack” zombie’s brain



- Gordiacea “Hijack” Mantis

Outline

- Introduction
- Research Objectives
- “Hijack” targets
  - During invading
    - Cytoskeleton(Actin Filaments)
    - Microtubules
    - Phagosomes
    - Signaling Pathway
  - During preservation
    - Inflammation reaction
    - antigen presentation
- A typical “hijacking” pathogen: *Mycobacterium tuberculosis*
- Summary

Relationships between bacteria and host

- **mutualistic relationship**
- both the bacteria and the host benefit
- The host provides the microbiota a niche with a stable nutrient supply
- Intestinal flora

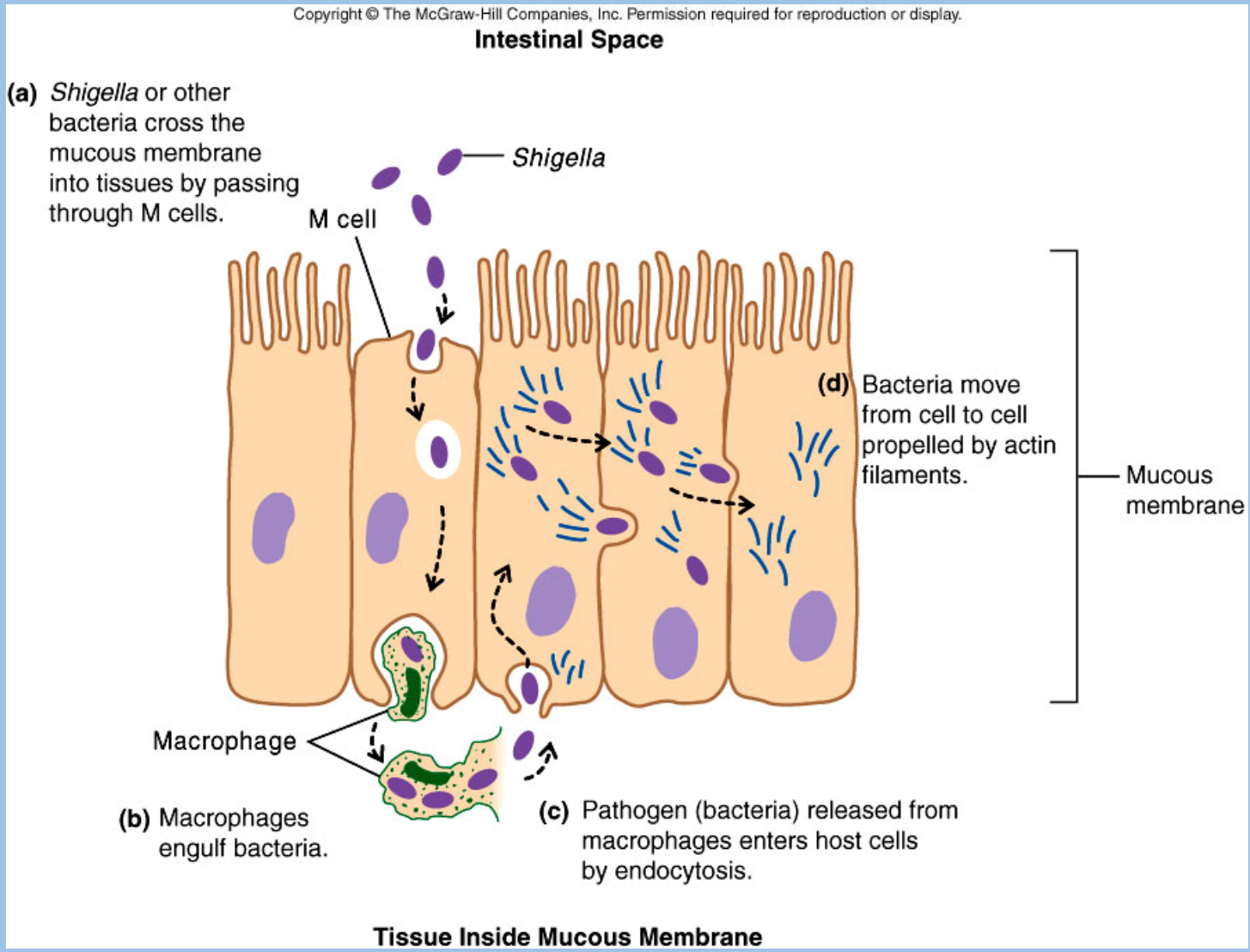
- **parasitic relationship**
- the bacteria benefit while the host is harmed
- The bacteria seize the a niche and nutrient from host
- Pathogens

- Infectious disease

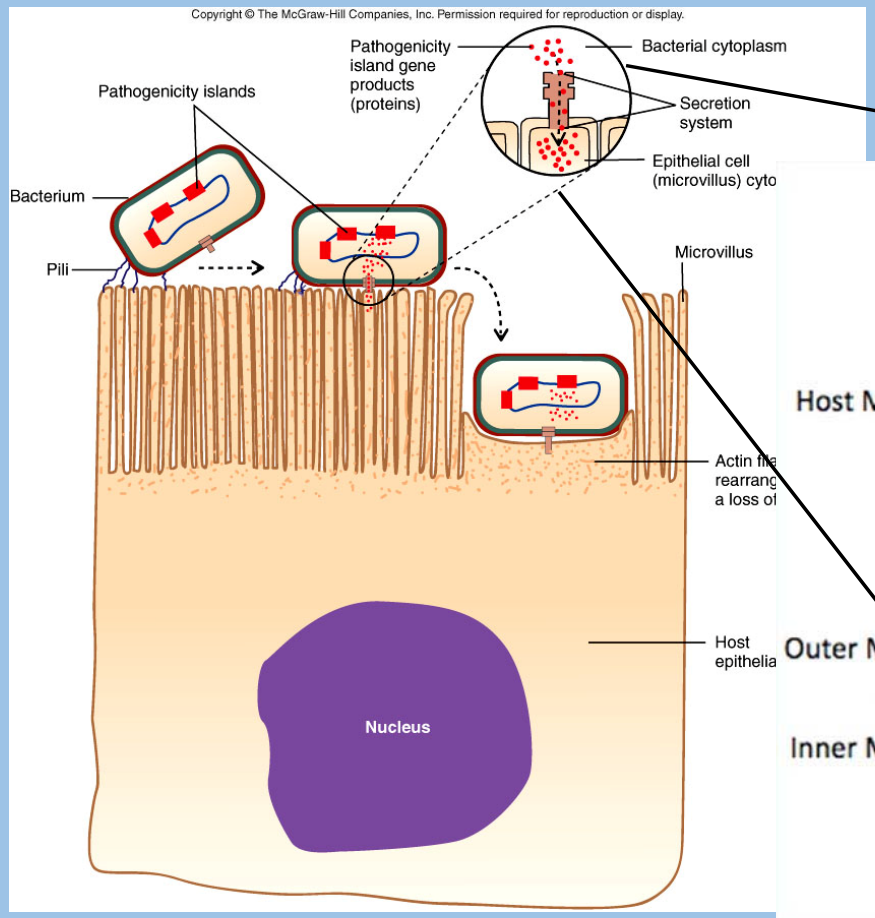
Struggle during infection

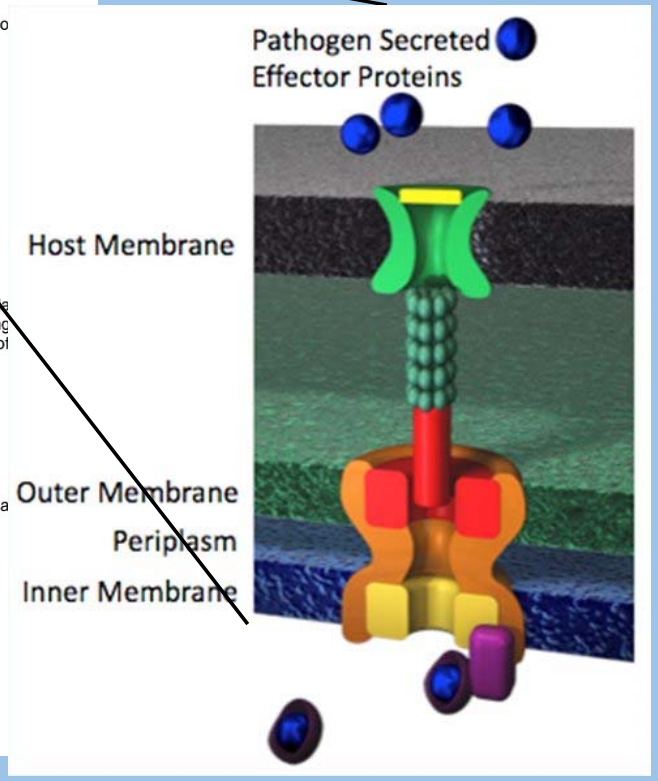
- Establishing an Infection
- Invasion
- Avoiding the Host Defenses
- Survival Strategies within Phagocytes

- The effector proteins may much helped



What is Bacterial Effector?





- **Bacterial effectors** are proteins secreted by pathogenic bacteria into the host cell
- **Effectors** have different activities
- Using T3SS or T4SS
- Some Effectors help to Hijack the host cells

Why bacteria hijacking is worth to study?

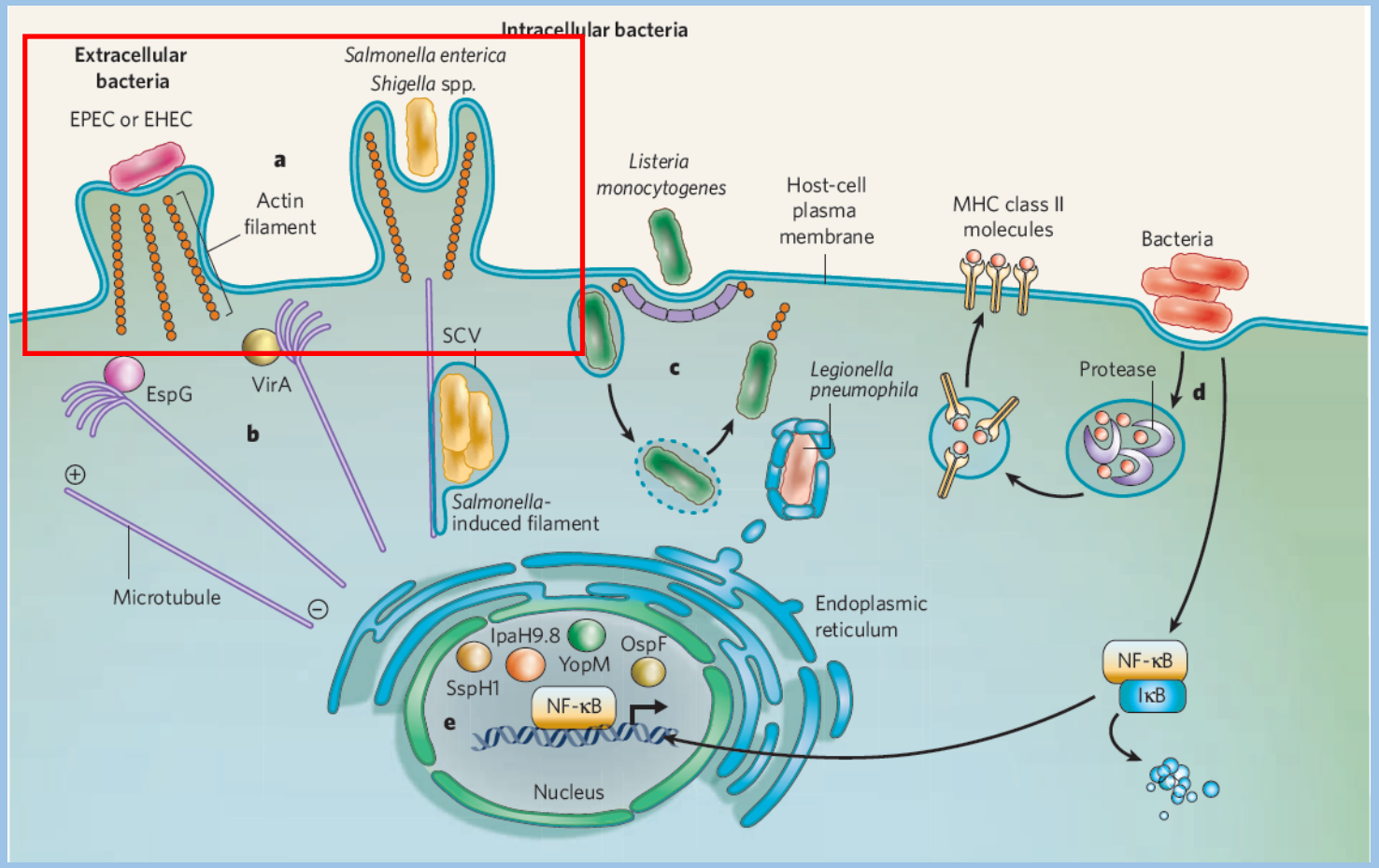
- To demonstrate how pathogens overcome host defenses
- To understand the bacterial virulence at a molecular level
- To find new method to prevent, block or eliminate infectious pathogens

Periods for pathogen to Hijack host cells

- During invading and replicating
  - Targets: cytoskeleton, membranous structures and key signalling pathways
- During preservation
  - Target: immune response

Cytoskeleton

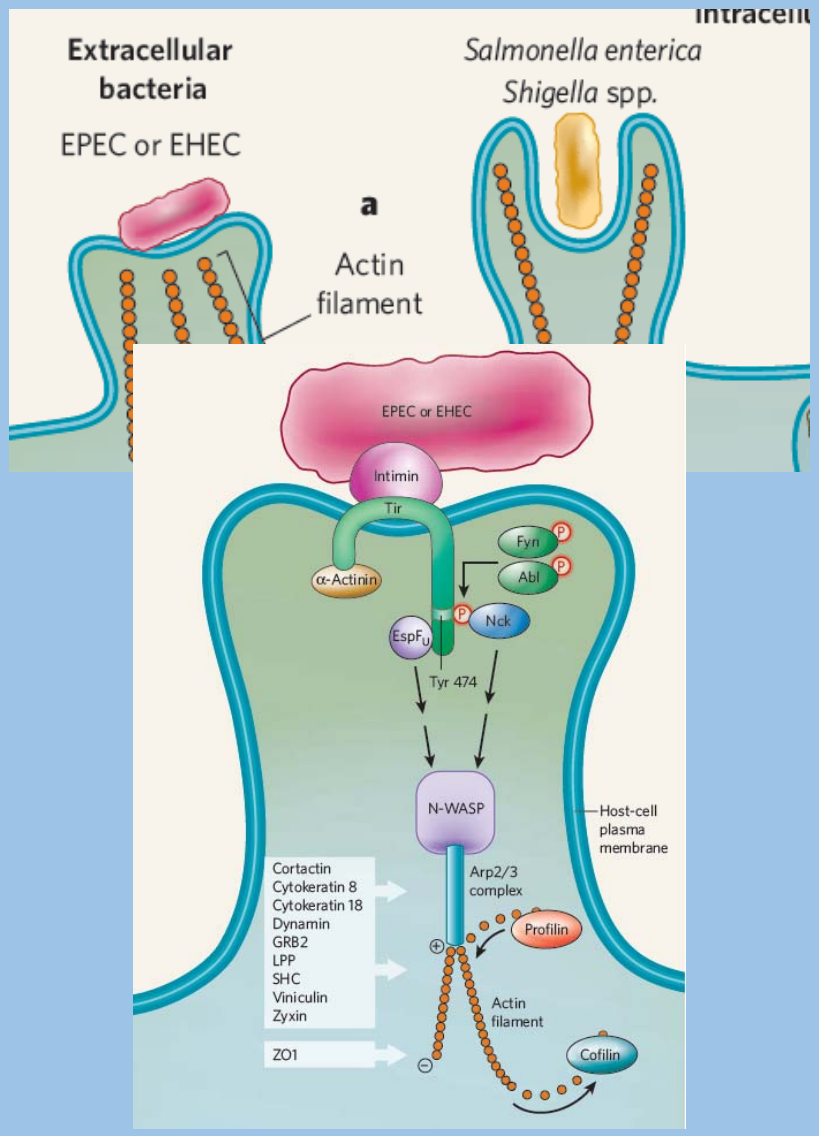
- Bacterial pathogens manipulate the cytoskeleton to help invade a host cell and/or to gain motility in the cell
- They often interact with actin filaments in particular, by modulating G proteins.



Cytoskeleton

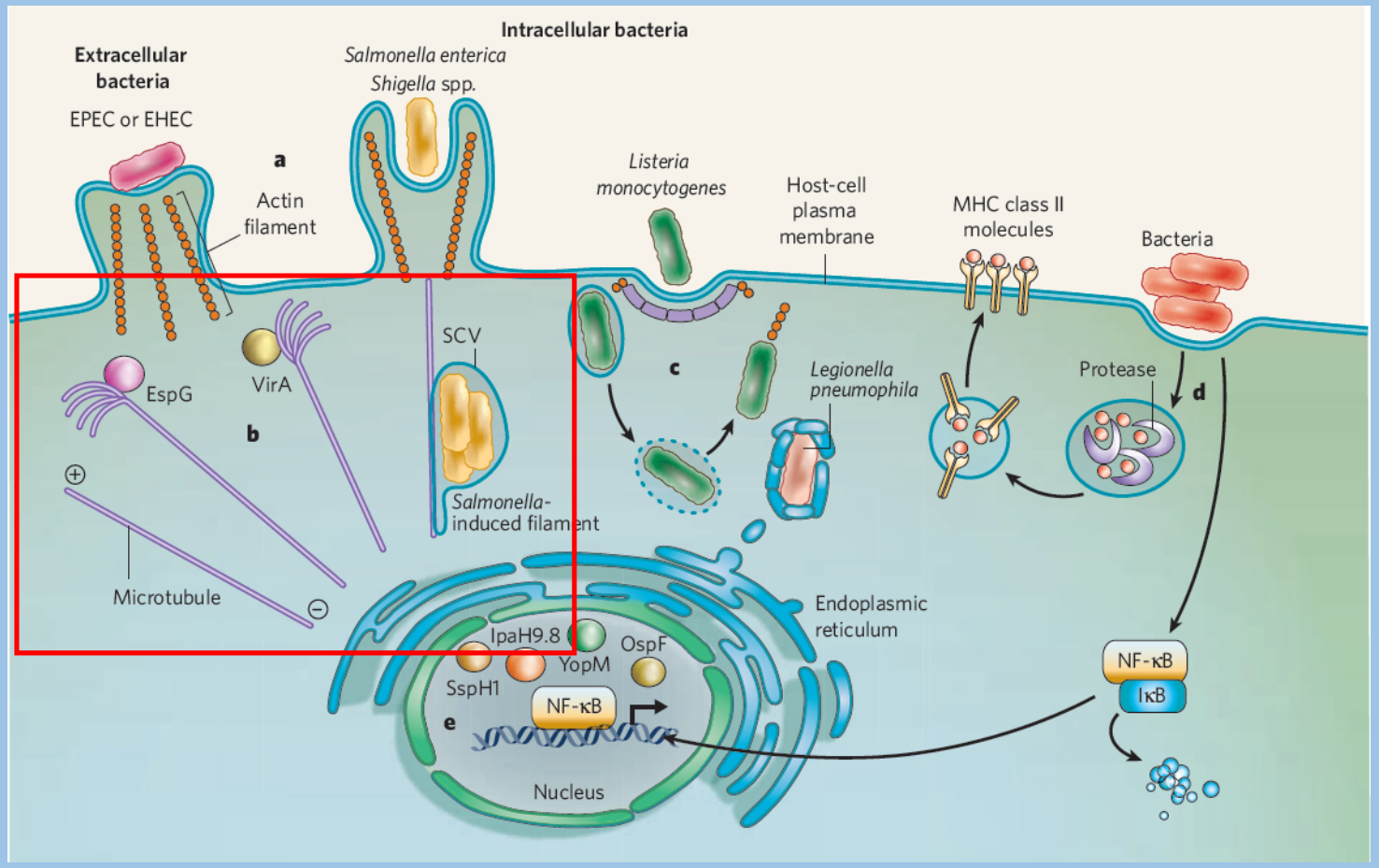
- *Salmonella enterica*

- Enterohaemorrhagic *Escherichia coli* (EHEC)
  - Having an elaborate actin recruiting process as an extracellular pathogen



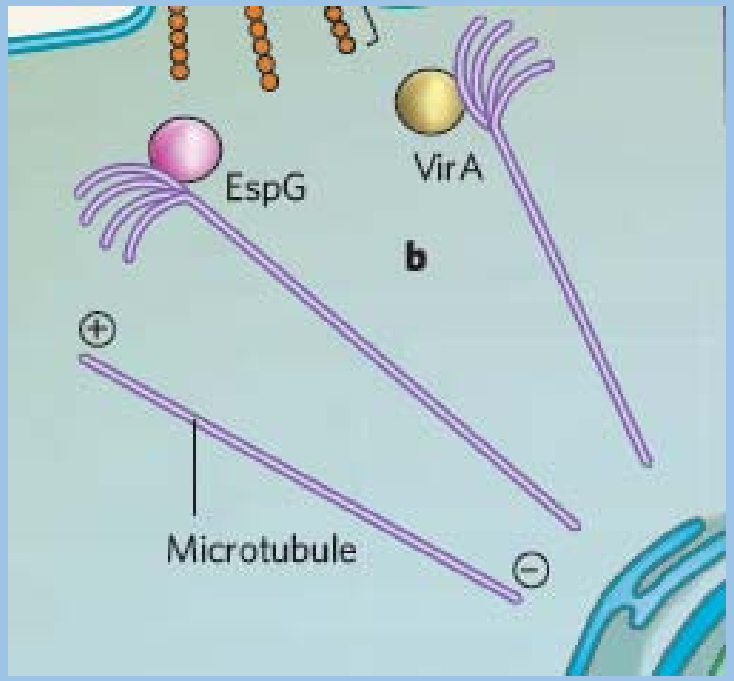
Microtubules

- Guide and transport intracellular cargo
- Transport and the microtubule assembly and/or disassembly dynamics can be modified and controlled by the pathogen



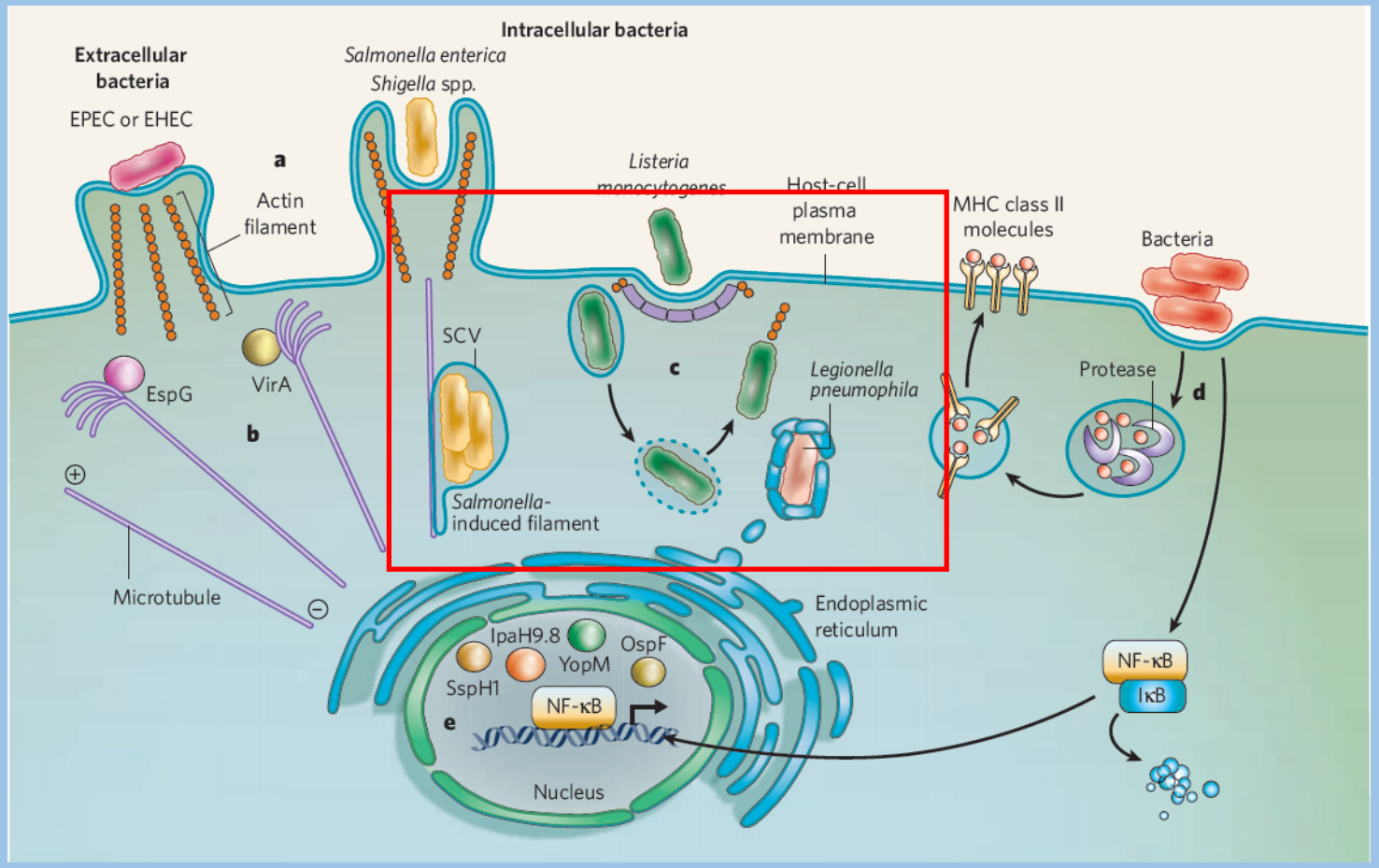
Microtubules

- *Shigella* spp
- Effector: VirA protein
- This results in invasion by *Shigella* spp.



Vacuoles and modified phagosomes

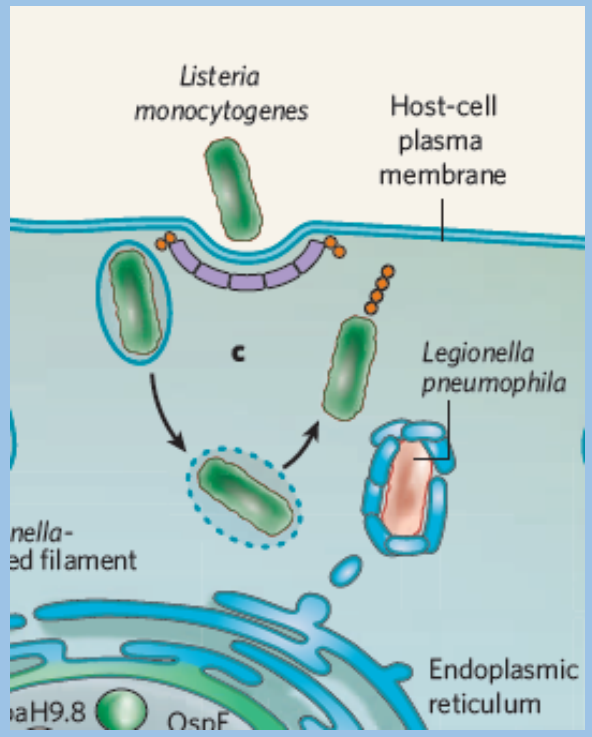
- Pathogens have adopted various strategies to multiply in, or escape from, these structures before surviving in the cytosol
- They will able to live in vacuoles and modified phagosomes



Phagosomes

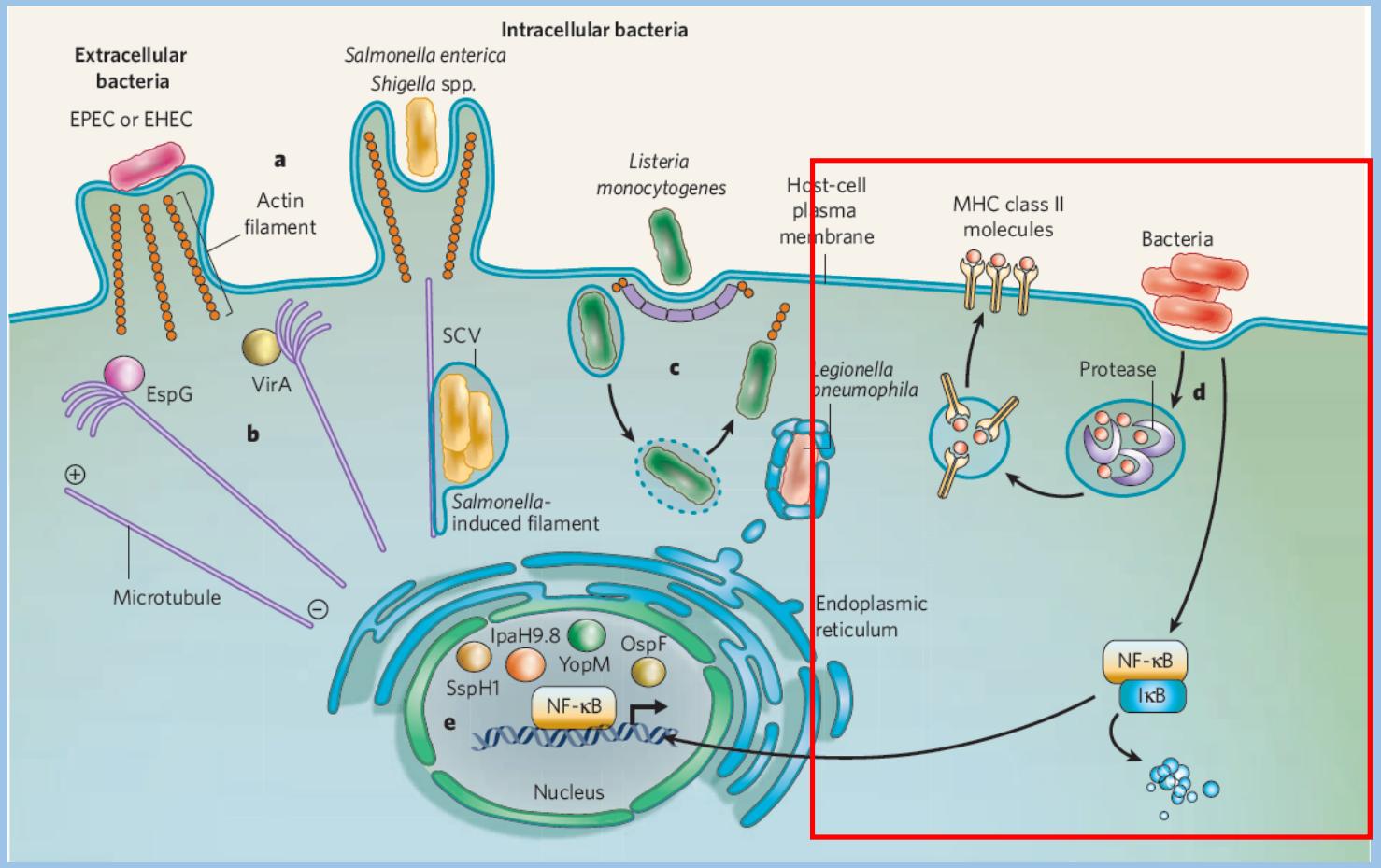
- *Legionella* spp.

- Providing a nutrient-rich resource for the bacteria



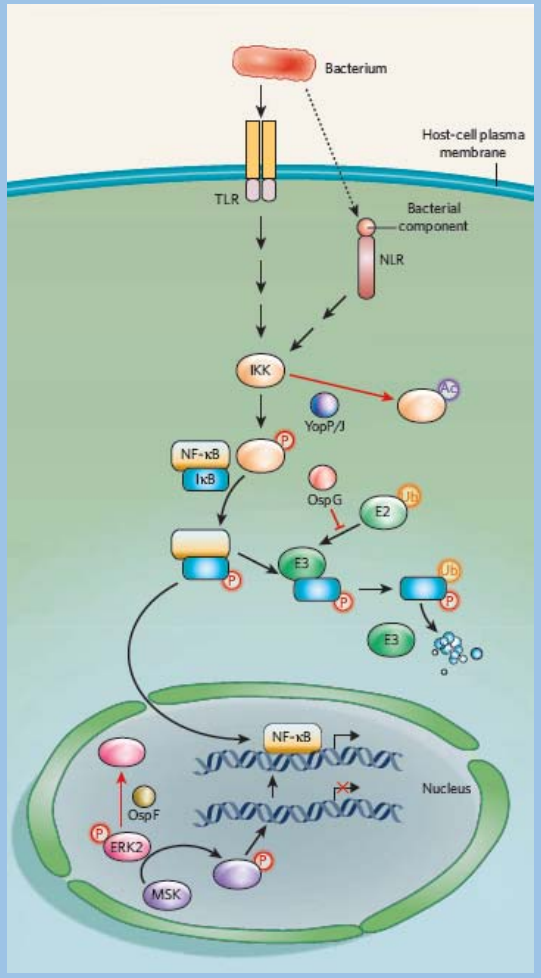
Signaling pathways

- Many pathogens interfere with the phosphorylation cascades of the host cell.
- bacterial effector proteins mimicked host kinases and phosphatases



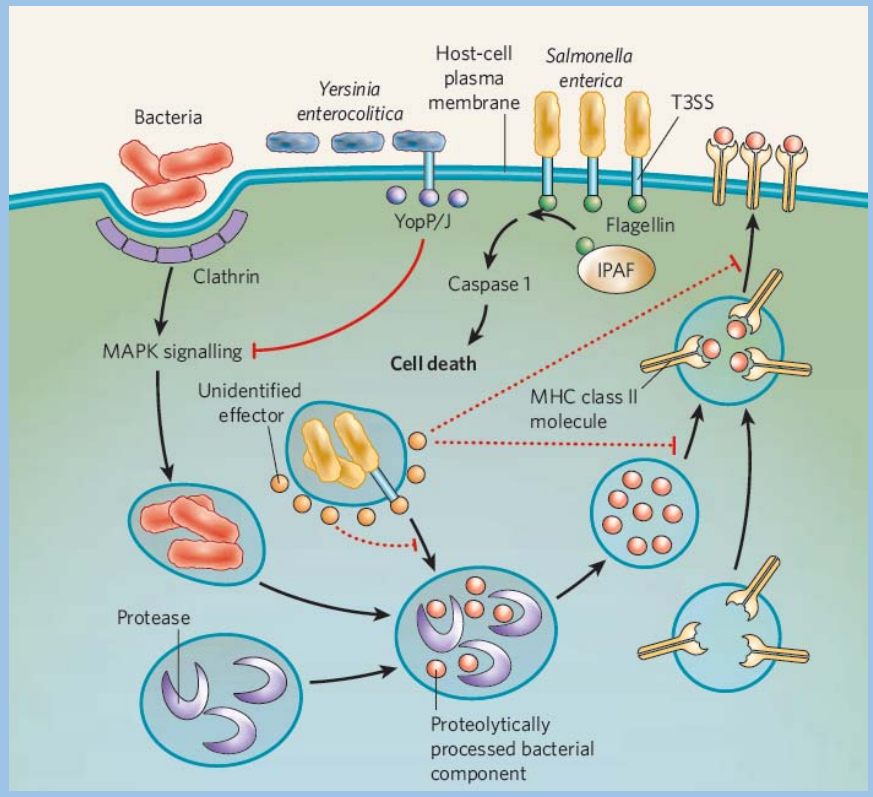
Inflammation and nuclear factor-κB

- Factor nuclear factor-κB (NF-κB) plays a role in inflammation reactivation
- *S. flexneri* have come to 'understand' the NF-κBactivation pathway
- *S*prevent IκB from being ubiquitylated and remain inactive
- This bacteria effect this through the T3SS effector proteins OspG



Antigen presentation

- Bacteria are recognized and internalized by specialized cells known as antigen-presenting cells
- Several pathogens able to subvert the immune responses.
- *S. enterica* can block antigen presentation, resulting in the lower activation of fewer T cells



Other targets

- Apoptosis pathways

Bacterial pathogens modulate an apoptosis differentiation program in human neutrophils

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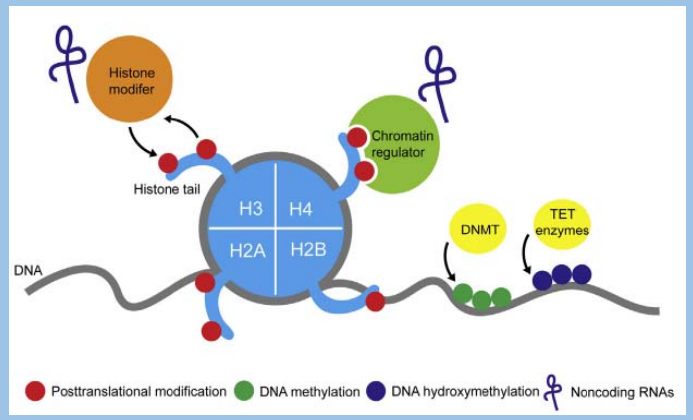
Edited by Richard M. Krause, National Institutes of Health, Bethesda, MD, and approved July 15, 2003 (received for review June 3, 2003)

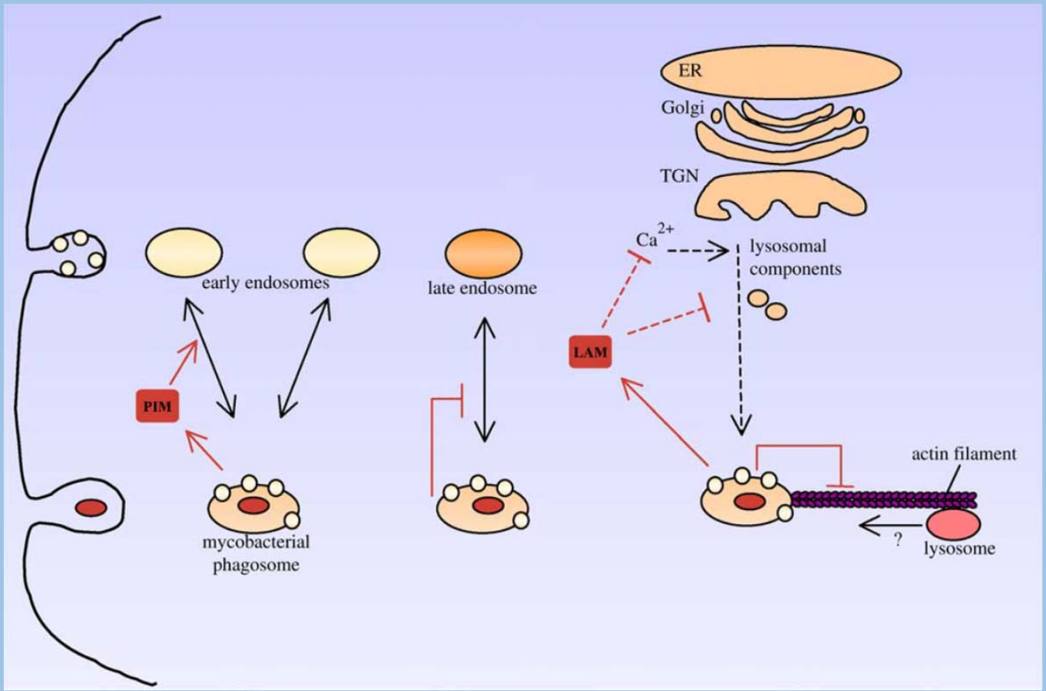
- Epigenome



A typical “hijacking” pathogen: *Mycobacterium tuberculosis*

- A most **“successful”** pathogen in our planet
- The macrophage represents a highly specialized cell of the immune system, yet fails to eliminate the *M. tuberculosis* bacillus
- *M. tuberculosis* has managed to establish itself within the macrophage, avoiding the host killing mechanisms.
- Forming granuloma and living in extreme hypoxia and high lipid environment for decades as latent infection

Mtb hijacks the macrophages



- *M.tb* interference with macrophage trafficking events
- *M.tb* suppress MHC class II expression in macrophages
- *M.tb* reside within phagosomes that retain early endosomal properties and resist fusion with later stages of the endosomal/lysosomal pathway.

New mechanisms?

- The nucleic acid secretion from *M.tb* has been found in macrophage during the infection.

Review article

Molecular requirements for sensing of intracellular microbial nucleic acids by the innate immune system

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ABSTRACT

Nucleic acids sensors of the innate immune system recognize various RNA and DNA structures during infection to induce transcription of interferon and pro-inflammatory cytokines and activation of inflammasomes. Cytosolic RNA is recognized by RIG-I and MDA5, while intracellular DNA is sensed among others by cGAS, AIM2, IFI16 and RNA polymerase III. The diversity of nucleic acid species produced during infection in the cytosol and nucleus and the limited chemical differences between self and non-self nucleic acids challenge the host's innate pattern recognition system to ensure reliable sensing while avoiding immune activation by self nucleic acids. We review the molecular characteristics of intracellular nucleic acid sensor ligands, the structural basis of the binding preferences of the sensors, the identity and origin of immunostimulatory nucleic acid species during infection, the influence of intracellular localization of the sensor on immune activation, and the ability of viruses to use the ligand specificity of the sensors to evade recognition.

Summary

- The manipulation of host-cell pathways by bacterial pathogens is extensively existing in infections, might be much more than we can imagine.
- Knowledge of how pathogens target distinct cytoskeletal components and immune-cell signalling pathways is rapidly advancing, together with the understanding of bacterial virulence at a molecular level.
- Studying how these bacterial pathogens subvert host-cell pathways is central to understanding infectious disease.

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THANK YOU!