BACTERIAL PATHOGENESIS QUESTION FOR CASE 3

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L. PNEUMOPHILA HABITATS

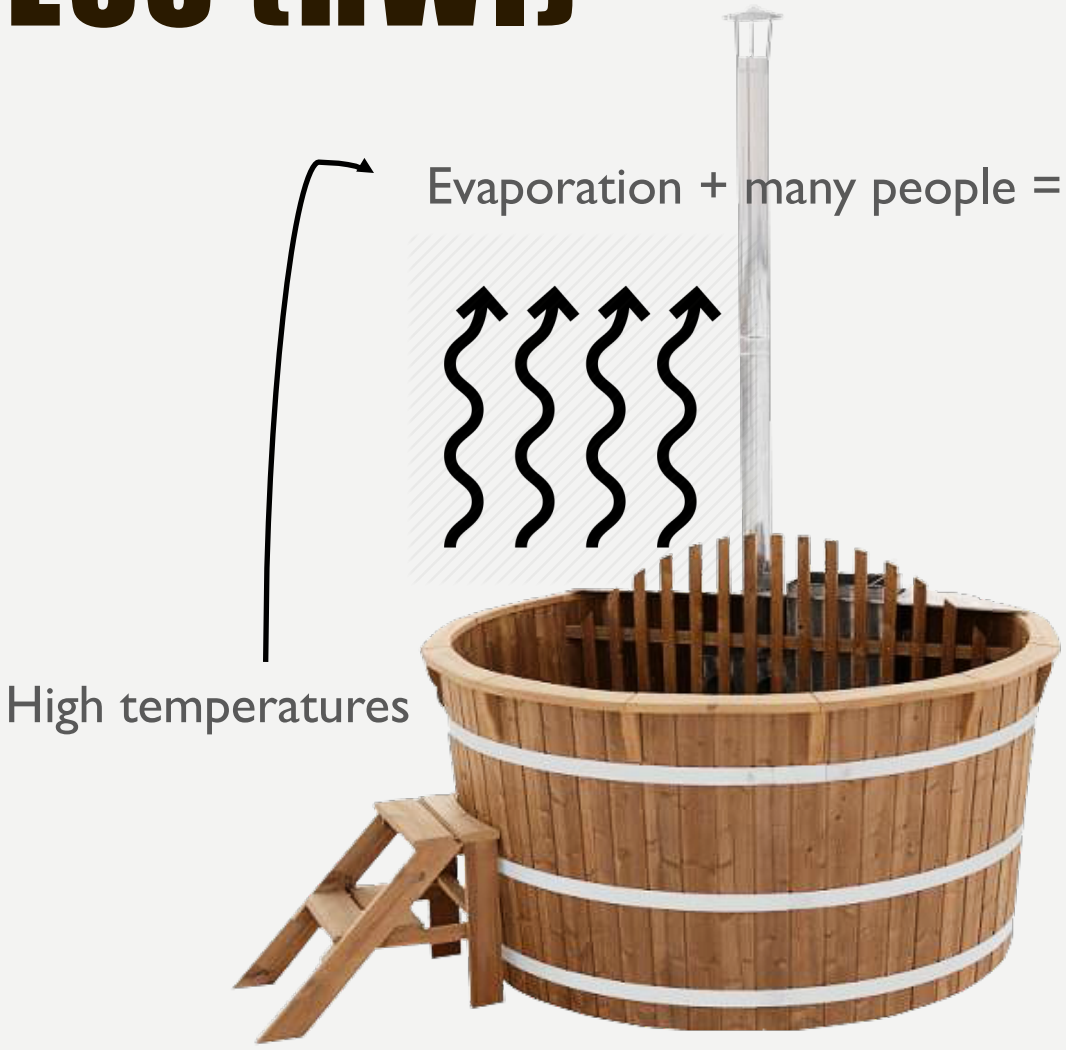
Natural Habitat

- Freshwater – lakes and rivers
- Inside amoeba and protozoa – protection

Conditions in which they thrive

- Optimal temperature – 35C
  - For example – hot tubs*
- Aerosols and droplets from artificial water sources
- Warm moist soil

HOT TUB AND RECREATIONAL WATER ILLNESS (RWI)



RWI causes?

- Uncontrolled water levels
- Insufficient disinfectants
- Lack of cleaning = biolfilms

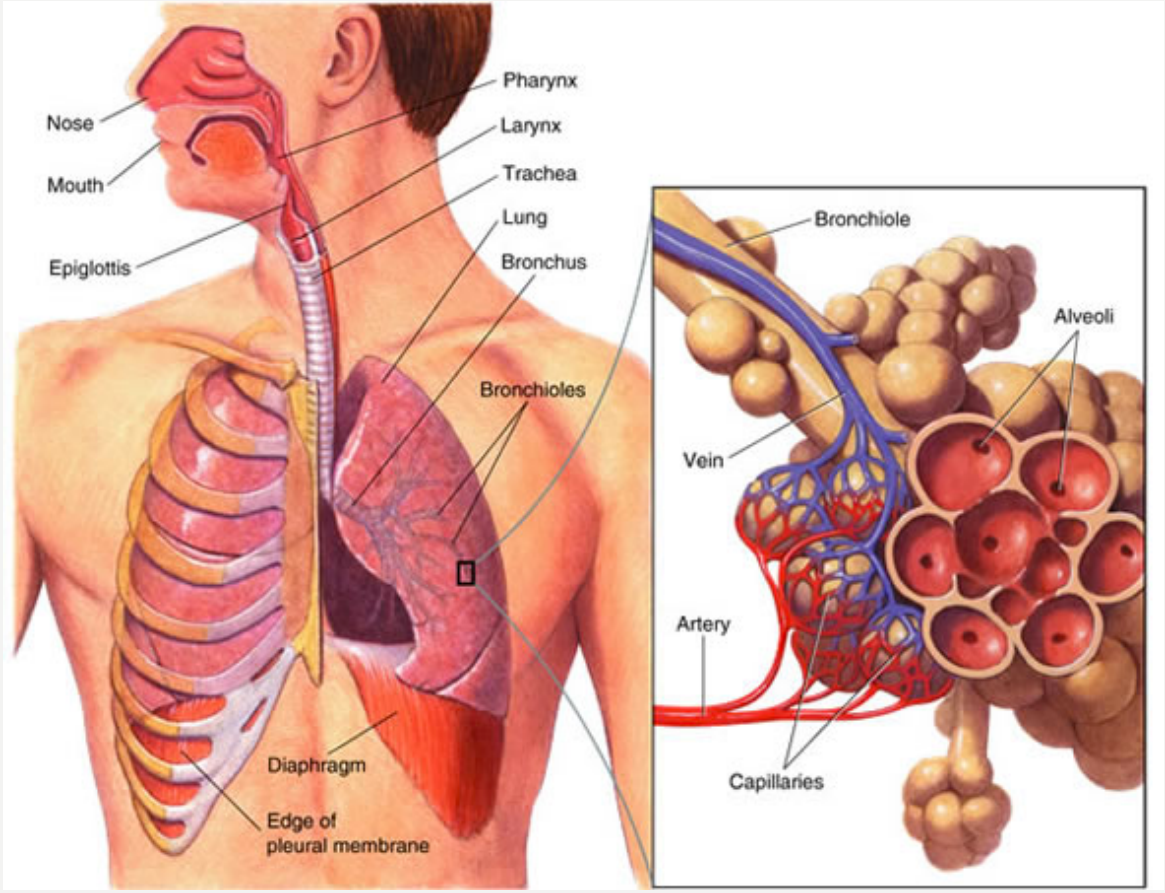
COPING MECHANISMS TO ITS ENVIRONMENT

Uncultivatable state	Biofilm formation	Type II secretion system	Specific genes
• During stressful conditions • Decreased cell division • Regular metabolic activity	• Protection when outside of the host • Nutrient gradients	• Produces effectors to survive stress and to obtain nutrients	• Survival and replication in both amoeba and host macrophage cells

ENTRY

Respiratory pathway
- Inhalation of infected aerosols
- Usually cleared out – unless patient is immunocompromised
    - Travels down lower respiratory tract - infection

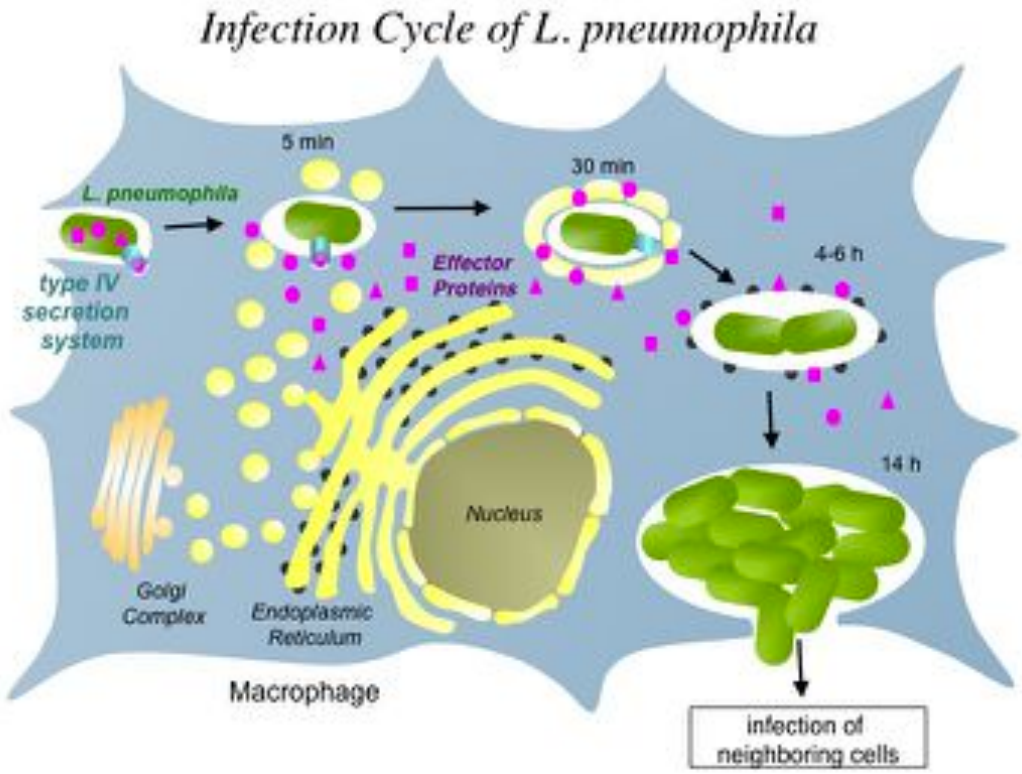
Superficial wound
- Very rare



INTRACELLULAR COMPONENTS

Mechanism?

- Exact process is not well understood
- Components that play a role in attachment and entry of bacteria
  - EnhC
  - Hsp60
  - MOMP
  - type IV pili
  - LpnE
  - RtxA



BACTERIAL FACTORS

EnhC – periplasmic protein
- Efficient replication in host
- Reduce NOD I in host – reduced innate immunity

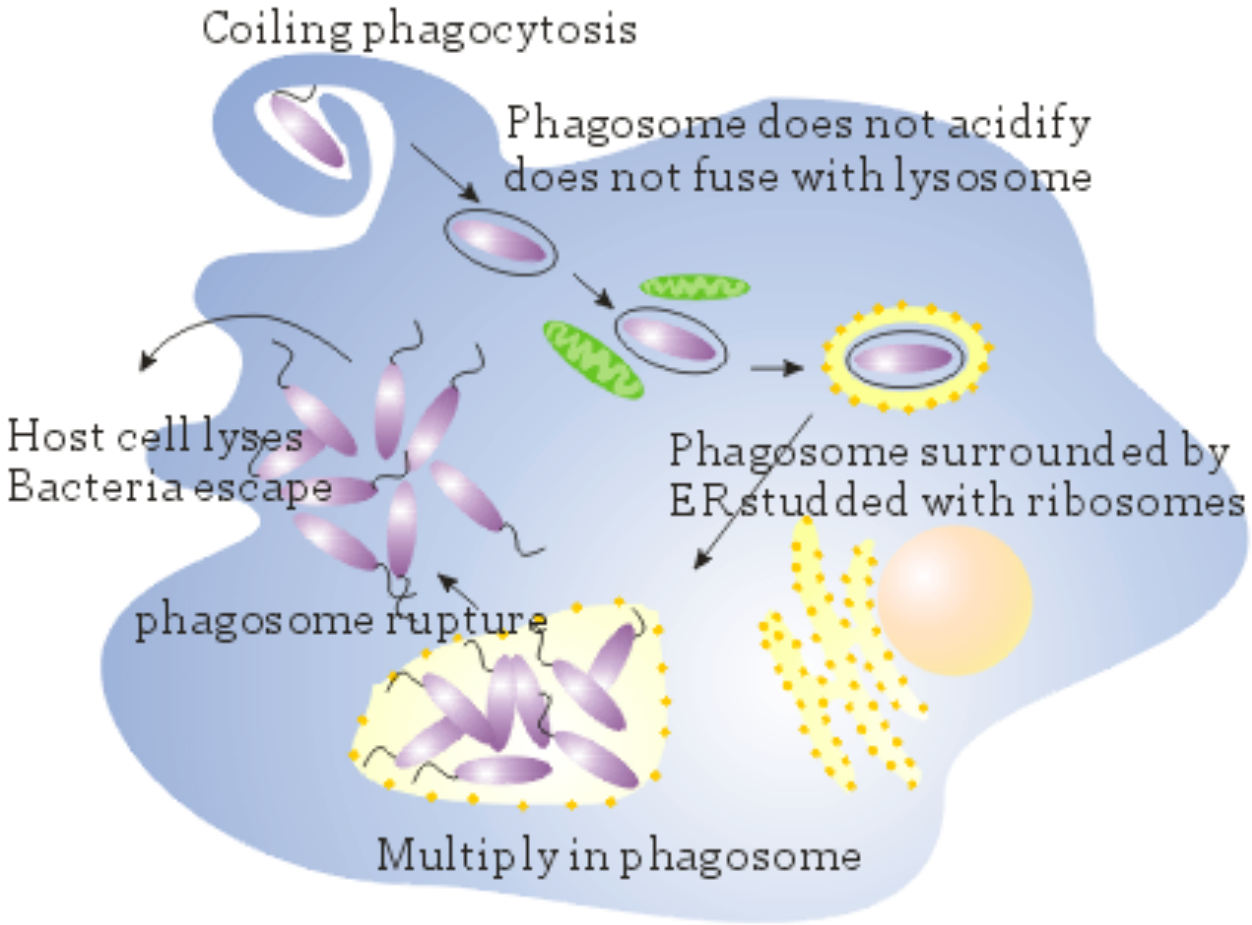
Hsp60 – bacterial protein
- Mediate phagocytosis – modulates macrophage function

MOMP
- Attaches to host C3 from alternative pathway to bacteria
  - More convenient entry into the cell

Type IV pili
- Attachment and entry
- Also play role in biofilm formation - adherence

LpnE
- Mediates bacterial attachment
- Trafficking of the L. pneumophilia vacuole

RtxA
- Attachment and entry
- Unknown mechanism



ENGULFMENT

Macrophage – permissive environment

- Bacteria is phagocytosed
  - Decreases acidification
  - Modification of organelle tracking – nutrient supply

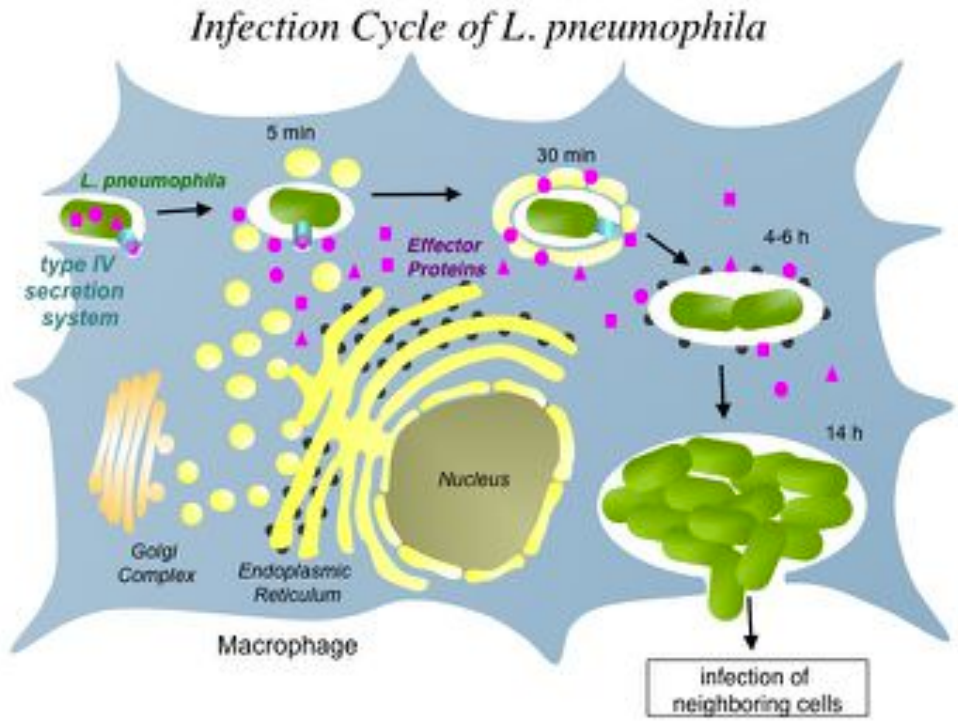
Cronins may also be required to assist with the phagosome formation

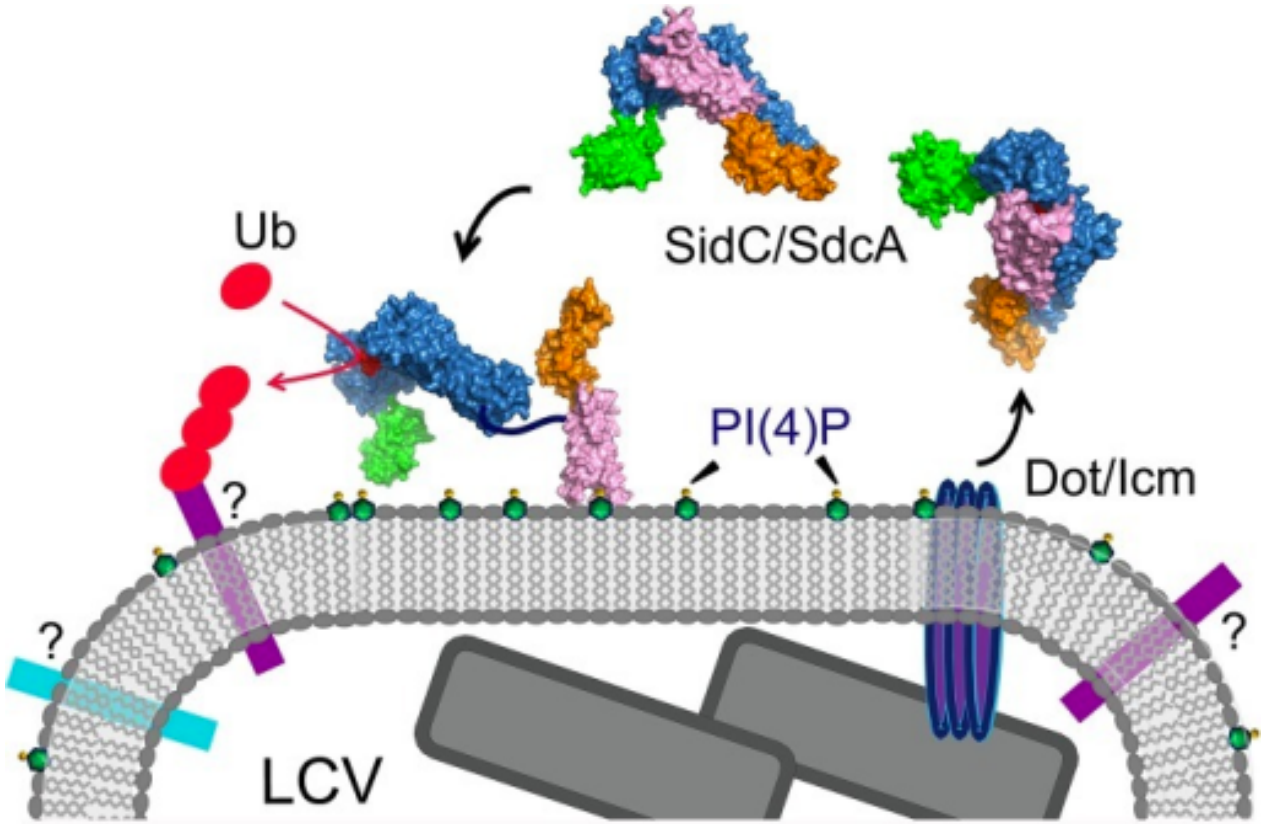
AVOIDING THE ENDOCYTIC PATHWAY

Early stages (6hrs)
Regulation of v-ATPase of the macrophage – may be important of avoidance of acidification

Later stages (18hrs)
LCV (legionella containing vesicles) acidified and take on lysosomal characteristics

Outer membrane vesicles OMV
May block lysosome and phagosome binding
May deliver packages of molecules





FORMATION OF LCV

Legionella changes phagosome into LCV – no binding to lysosome

- Changes LCV membrane similar to that of an ER
    - Hijacks secretory vesicles leaving ER/ adopts luminal contents of vesicles cycling golgi and ER

Dot/icm IVB secretion system

- Manipulates vesicle trafficking at this stage

Phosphoinositide lipids (PIs)

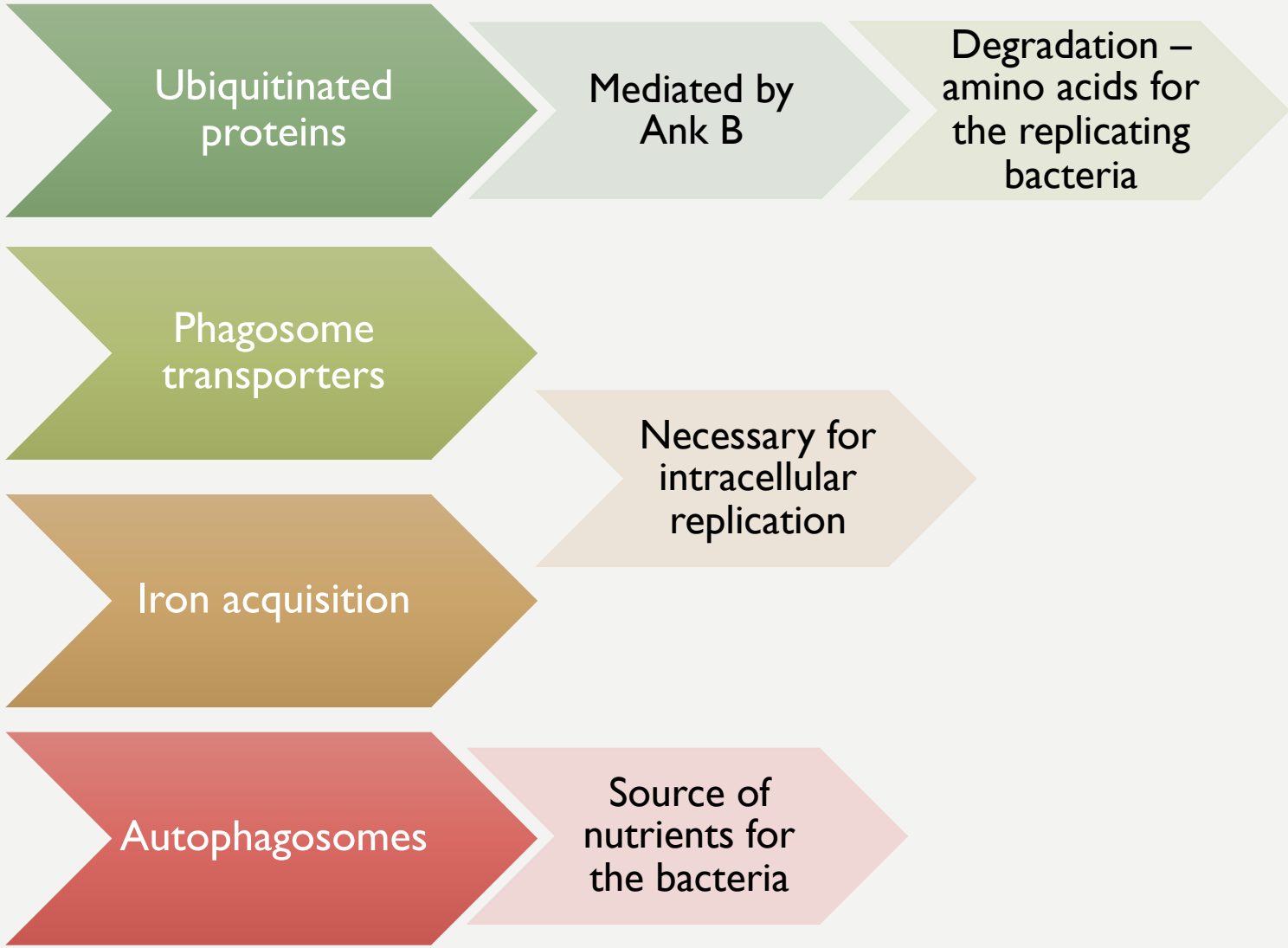
- Bacteria manipulates PI – membrane transport
- Attachment site for effector cells
- Level of PI(4)P on LCV will enhance due to sid family effectors
    - Enhancing attachment of LCV to ER like vesicles

LCV FORMATION

Later stage LCV – a lot like the ER
- More ribosomes on LCV membrane
- Spontaneous ribosome attachment due to remodeling done earlier

Replication of L. pneumophila
- Normally 4 – 10 hours later, after phagocytosis and LCV formation

NUTRIENT ENVIRONMENT



LATE PHASE

Later stages

- The LCV changes more phagosome-like – so not really escaping lysosomes
  - The bacteria is more resistant to acidity – acquisition of lysosomal proteins aid
- Recruitment of proteins in the endocytic pathway occurs later than usual
- **A possibility:** Vacuole will merge with lysosome where acidity is high but there is a benefit of gaining nutrients

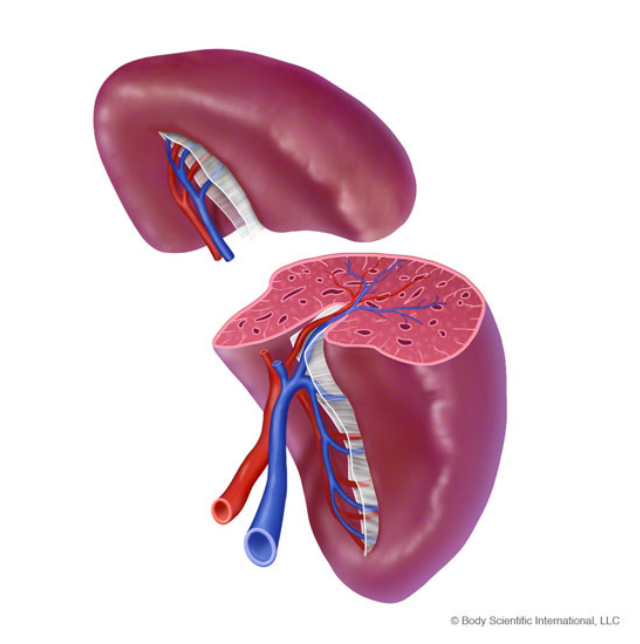
- Depletion of amino acids → accumulation of ppGpp → initiation of transmission process
  - Final evasion from lysosome
  - Bacteria changes to motile phase
  - Cytotoxicity leads to apoptosis of the host cell

SECONDARY INFECTION

Secondary infections
Via wounds – very very rare

Other examples
- Splenomegaly and spleen rupture, pericarditis, wounds, joint infection, and CNS.

Infections normally by blood

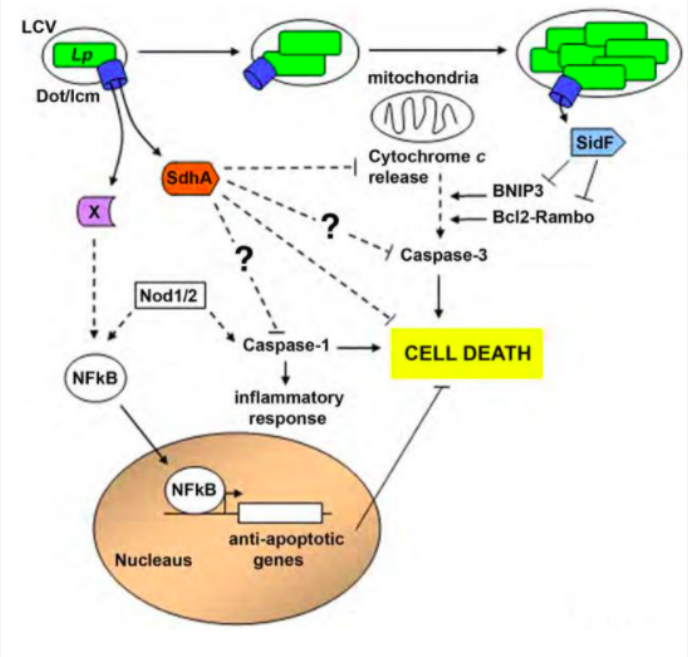


BACTERIAL DAMAGE

Direct

- Host cell killing and uncontrolled lysis
  - May also cause tissue damage
  - Factors relating to cell death not known

- Site of damage – pulmonary tissues



Indirect

- Oxygen dependent killing by neutrophils
  - Accumulates fluid that fills alveolar space

- Inflammation
  - Monocytes – release cell factors – fever
  - Increase in body temperature etc