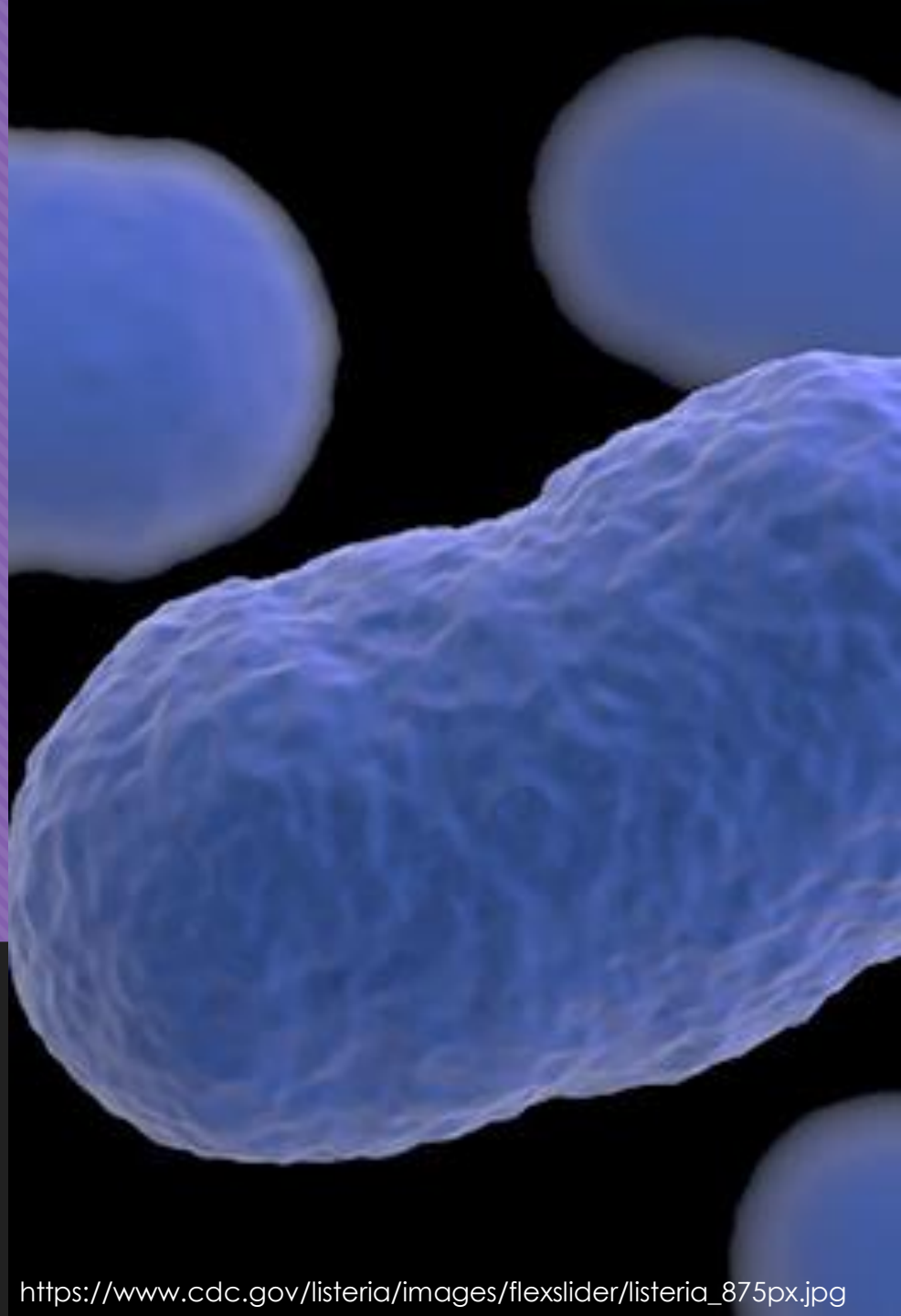
Bacterial pathogenesis : Listeriosis

By Ayoung Hong



https://www.cdc.gov/listeria/images/flexslider/listeria_875px.jpg

CASE 4

Carry, a 29-year-old woman, is 32 weeks pregnant with her first child. As a foodie, she loves trying different gourmet restaurants in Vancouver. A new "farm-to-table" restaurant has opened and she gets a bunch of friends to go out for a nice dinner. Carry orders a toasted pecan, strawberry and mature goat cheese salad to start. She knows that, in pregnancy, she should not eat raw or unpasteurized cheeses but cannot help the temptation - she's heard that this is the best salad in Vancouver. A few days later, she develops mild diarrhea and night sweats that she thinks will eventually pass, but the following day she has a fever so she goes to the emergency department where she has blood and stool cultures collected. The blood cultures turn positive for Listeria monocytogenes. She wonders what effect this will have on her unborn baby.

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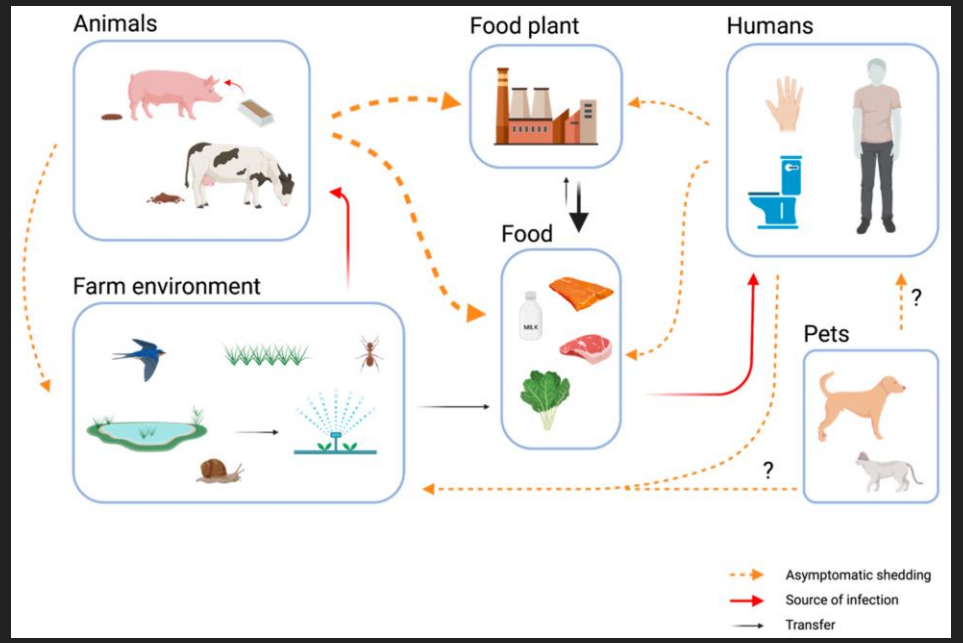

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- *L. monocytogenes* exists in water, soil, and fecal matter (1)
- *L. monocytogenes* can survive (1)
  - Salty
  - Acidic (pH>3.5)
  - low oxygen
  - broad temperature (4-37 °C)
- *Listeria* can be found globally. (1) *Listeria* infection has a higher incidence in industrialized countries because they have more food manufacturers. (1)

Encounter

Habitat of
Listeria monocytogenes in
the environment & the host

- In the environment, these characteristics make *Listeria* survive within (1)
  - the farm environment
    (outside of the host animal)
  - the food processing environment
  - Salty, refrigerated food: unpasteurized diary, uncooked meat, delicatessen meat, vegetables that are usually eaten raw such as salad, cantaloupe, and sprouts, and frozen vegetables
- In the host, these characteristics make *Listeria* survive within (1)
  - GI tract: *Listeria* can survive better in low pH compared to other foodborne pathogens. Moreover, bile salt makes the gallbladder and the duodenum less acidic, hence more suitable for the survival of *Listeria* (1)

Encounter

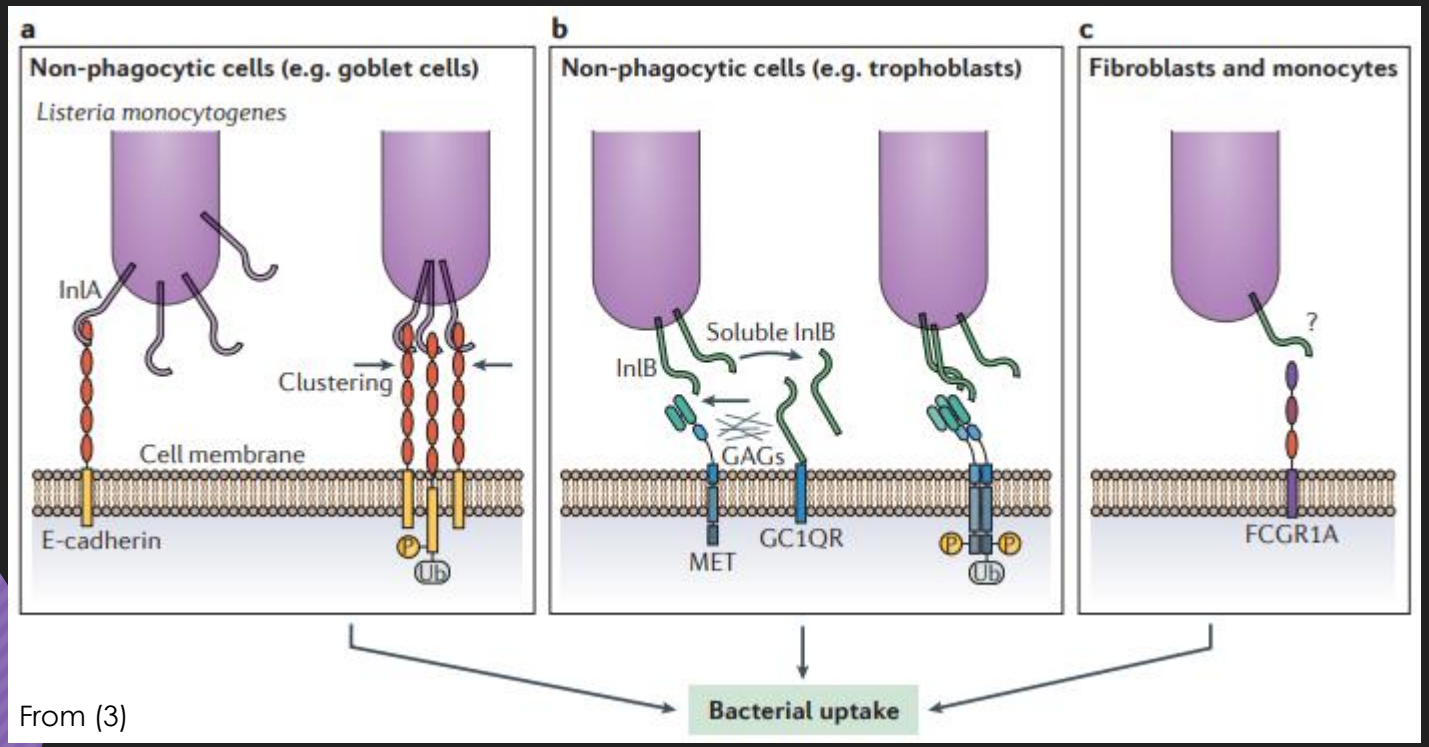
How would have Carry come in contact with *L. monocytogenes*?

Carry would have come in contact with *L. monocytogenes* by

- Consuming goat cheese salad : contaminated salad and cheese made from unpasteurized milk
- Pregnant women are at higher risk of listeriosis due to the susceptible cell-mediated immunity, especially in the third trimester. (1) Carry was in the third trimester, 32 weeks.
- The pathogen can pass the placental barrier. (1) Infection can cause fetal damage

Entry

Facilitating factors of the bacterial entry into the human host



From (3)

- *Listeria* enters the human body via contaminated food (1, 2)
- **Internalin A (InlA)** is a virulence factor employed for entry. (1, 3)
- *Listeria* can pass acidic GI tract by adapting low pH
  - Glutamate decarboxylase (GAD) system: mediates pH homeostasis (2)
  - Arginine deaminase (ADI) pathway and agmantine deaminase (AgDI) system contribute to pH homeostasis
- *Listeria* can survive bile salt in the duodenum by expressing bile salt hydrolase (1, 2)
- The virulence factor Listeriolysin S disrupts the host gut microbiota to create an advantageous environment for entry. (1)

Entry

Factors in
the initial entry/adherence step

At the intestinal wall, *L. monocytogenes* invade phagocytic and non-phagocytic cells.

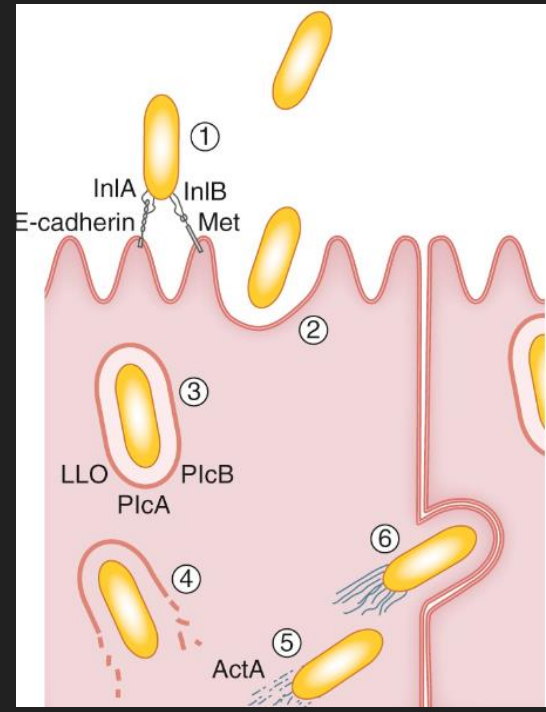
- For phagocytic cells: enters via complement dependent or -independent pathways via vacuole. (4, 5)
- For non-phagocytic cells

  ① **Bacterial InlA and Internalin B (InlB)** bind to E-cadherin and Met of non-phagocytic cells. (1) This "zipper"-like mechanism facilitates entry by receptor-mediated endocytosis. (1) InlB is required for the entry into human placental cells in pregnancy (6)

  ② The binding of these factors signals intracellularly to rearrange the cell cytoskeleton of host. (4) Bacteria can be internalized after the rearrangement. (4)

  ③ After the internalization, **listeriolysin O (LLO)** is activated by the low pH of the phagosome. (1)

  ④LLO, along with **phospholipases A and B (PlcA and PlcB)** form pore in the vacuole and the pathogen can escape into the cytosol. (1)



From (1)

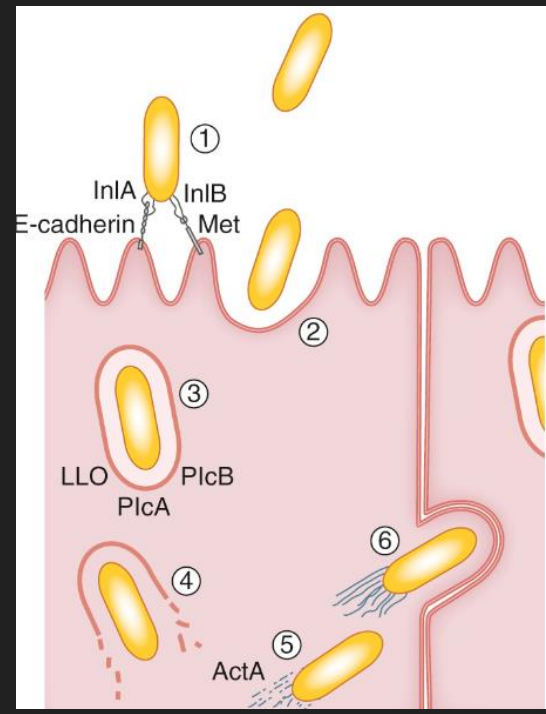
Multiplication & Spread

Entry into cell
&
Molecular/cellular determinants of the entry into cell

- *L. monocytogenes* enter into phagocytic and non-phagocytic cells. Intracellularly, the pathogen is protected from the host immune system and can multiply. (1)

⑤ **Actin-assembly-inducing protein A (ActA)** (1): A bacterial surface protein that recruits actin and forms an actin comet tail. This tail propels through the cytoplasm and allows escaping the host cell and spreading to neighboring cells. (1)

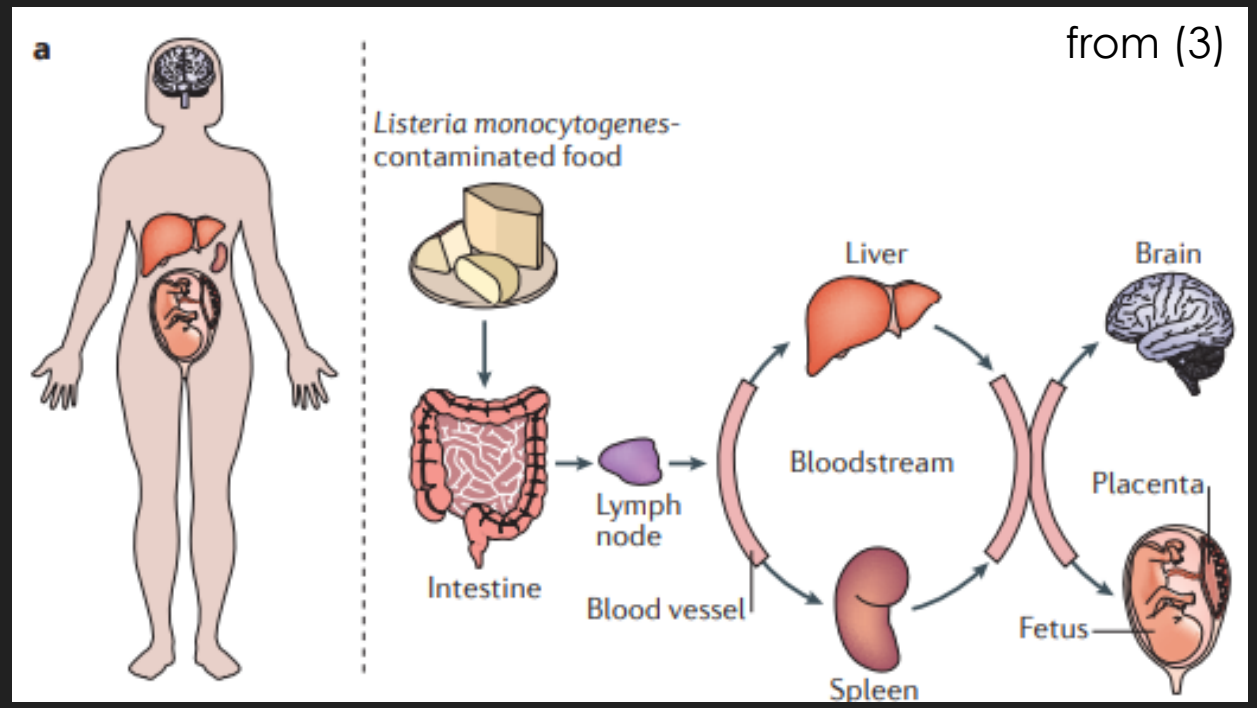
⑥ A bacterium finds host plasma membrane and be enveloped in it. (1) This extrudes from the infected cell and is phagocytosed by a neighboring cell. (1)



From (1)

Multiplication & Spread

Bacterial spread
(secondary site of infection)



from (3)

After initial infection in the GI tract, bacteria can spread to multiple body sites. (1)

- *Listeria* crosses the intestinal barrier and enters the bloodstream and lymph. (1) It spreads to the spleen, liver, brain, and more. (7)
- Spleen and liver infections are important to cause further systemic infection. (8)
- *Listeria* can infect the central and peripheral nervous systems. (8)
- *Listeria* can also pass placenta via the fetal bloodstream in pregnant women. (6) The infection increases the risk of chorioamnionitis, stillbirth, preterm labor, and neonatal infection. (1)

Bacterial Damage

Damage attributable to the host immune response

- Triggering a proinflammatory immune response causes hyperinflammation and tissue damage. (3)
  - Activates interferon-a, which leads to the activation of type I interferon response. (3) This releases cytokine. (3)
  - TNF-a initiates proinflammatory Th1 immune response. (9)
- Host cell necrosis:
  - LLO mediates necroptosis of macrophage. (3, 9) This necroptosis of macrophage releases IL-1, a pro-inflammatory cytokine. (3, 9, 10)
  - Neutrophils release reactive oxygen species (ROS) against the pathogen. (9) This also induces host cell necrosis.
- Abscess in CNS, liver, and spleen. (11)

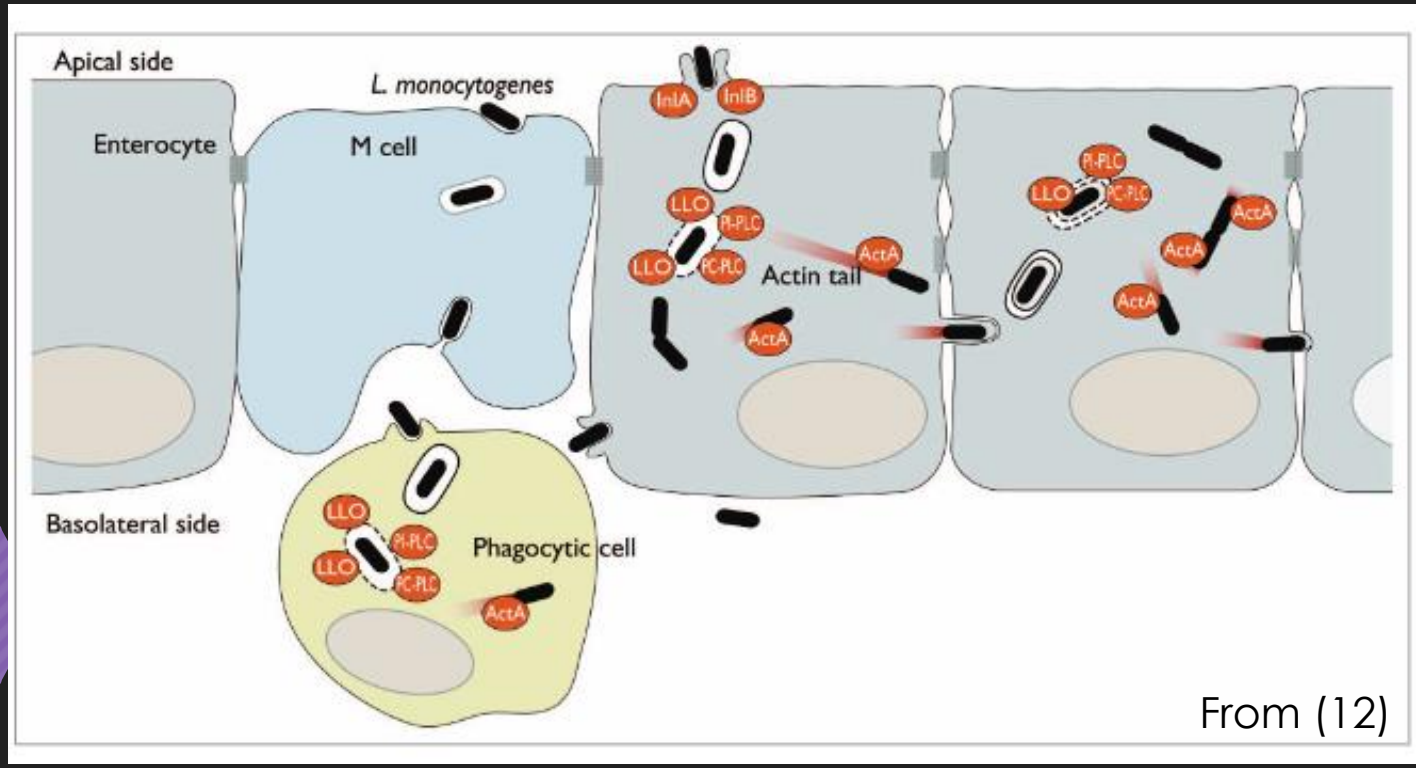
Bacterial Damage

Damage attributable to the pathogen

- LLO
  - attributes to alteration in mitochondrial morphology. (3)
  - LLO is activated by low pH in the phagosome. (1) LLO allows the pathogen to escape the vacuole and prevent lysosome fusion. (1)
  - LLO also damages host DNA by degrading the DNA damage sensor meiotic recombination 11 homologue 1 (DMRE11). (3) This DNA damage activates DNA damage checkpoints, extends the cell cycle, and makes a favorable environment for the pathogen. (3) This dysfunction leads to tissue or organ damage.
  - LLO triggers apoptosis in lymphocytes, dendritic cells, and hepatocytes (10)

Bacterial Damage

Damage attributable to the pathogen



From (12)

- LLO, bacterial phospholipase PI-PLC and PC-PLC, and hemolysin allow *Listeria* to rupture the double membrane and enter neighboring cells. (12)

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