



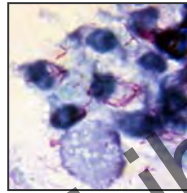

Rickettsial pathogenesis

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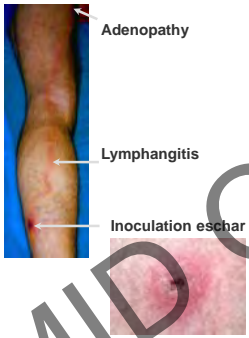


Rickettsia spp.

- small bacilli
- Gimenez positive, Gram negative
- Strict intracellular bacteria
- ➔ difficult to grow and to purify

Spotted fever





Adenopathy

Lymphangitis

Inoculation eschar

Fever
 Headache
 Inoculation eschar
 Skin rash

Spotted fever

Fever
 Headache
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 Skin rash





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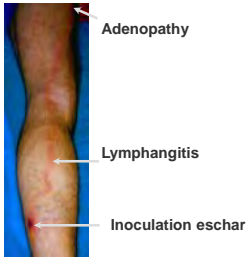

PATHOGENESIS

- Route of spread
- Target cells
- Injury
- Host cell interactions
- Immunity



Routes of spread in the body

Spread from the site of inoculation to the regional lymph node via lymphatic vessels




Adenopathy

Lymphangitis


Inoculation eschar

Rickettsia africana (ATBF)



Rickettsia slovaca (TIBOLA)

Lakos et al. Lancet 1997




Routes of spread in the body

Spread from the site of inoculation to the regional lymph node via lymphatic vessels

followed by

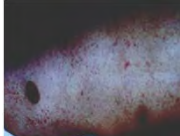
dissemination throughout the body via the bloodstream

Rickettsia rickettsii
(RMSF)



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Rickettsia prowazekii
(Epidemic typhus)



Raouf et al. Lancet 1998

Target cells / target organs

Possible dermal target cells

- Fibroblasts
- Macrophages
- Dermal dendritic cells
- Lymphatic endothelium

Main target cell

Endothelial cell

- no specific receptor / adhesion
- hematogenous spread
- **brain / lungs** are key target organs
- invasion of smooth muscle cells in arterioles only by *R. rickettsii*

Injury associated with rickettsial infection

Multifocal lesions

Silent multifocal seeding

↓

Vasodilatation

↓

Perivascular edema

↓

Disruption of vascular integrity

The skin, the tip of the iceberg

↓


Macular rash

↓

Maculopapular rash

↓

Petechial rash



Injury associated with rickettsial infection

Typhus: burst of highly infected cells

- Allows infection of new endothelial cells
- Hemorrhage due to disrupted endothelium
- Thrombosis due to basal membrane exposure to platelets & clotting factors

Spotted fever:

- Spread from cell to cell (actin-based motility)
- Damage to cell membrane (lipid peroxidation) by reactive oxygen species produced by infected endothelial cells
- Damaged cells die / detached → hemorrhage
- Increased permeability

Host-cell interactions

1- ENTRY

OmpA, B β-peptide } bacterial ligands

Interaction with **Ku70** (host cell protein)

Ubiquitination

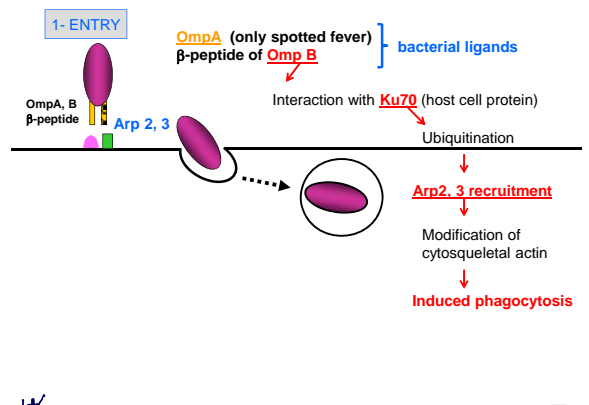
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Arp2, 3 recruitment

Modification of cytoskeletal actin

↓

Induced phagocytosis



Host-cell interactions

1- ENTRY

OmpA, B β-peptide } bacterial ligands

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Ubiquitination

↓

Arp2, 3 recruitment

Modification of cytoskeletal actin

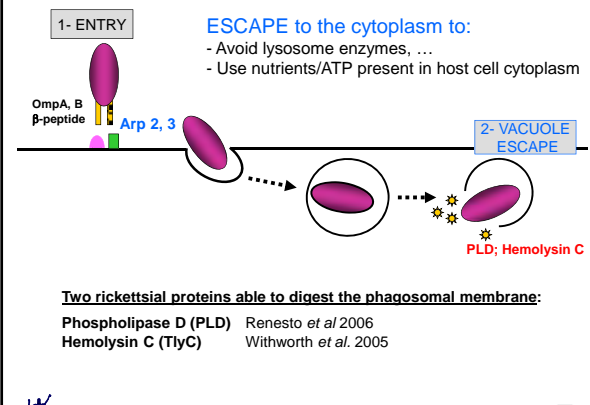
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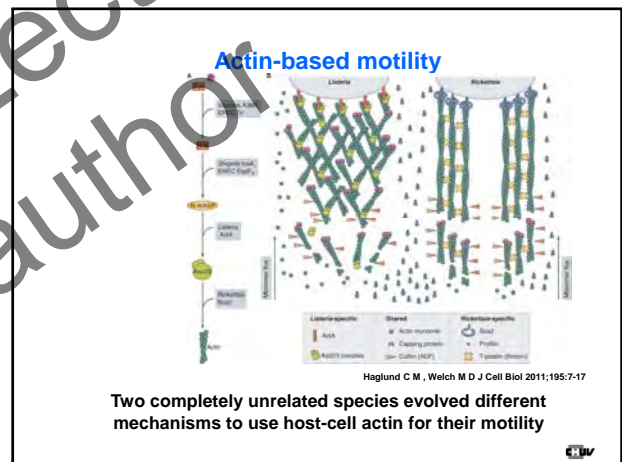
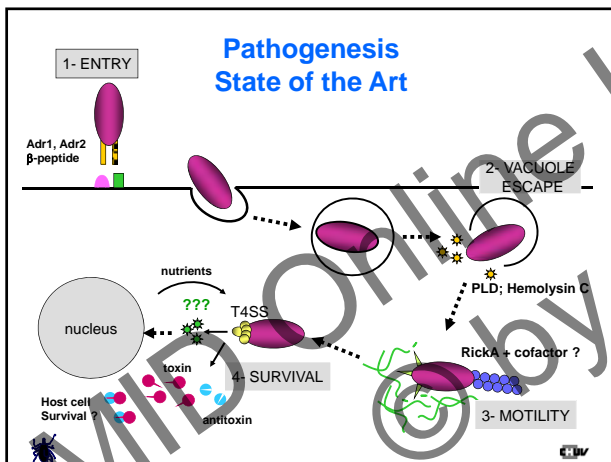
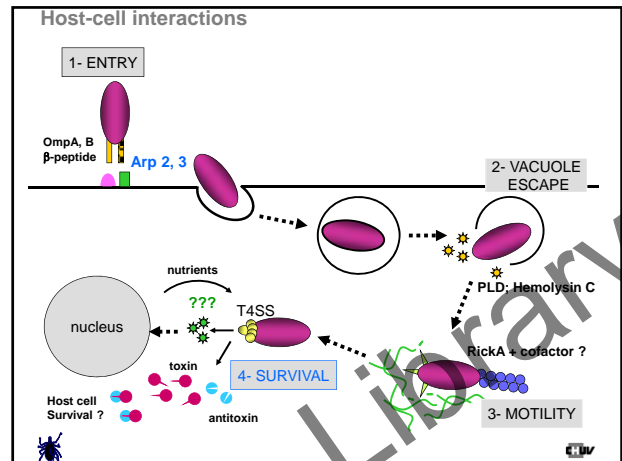
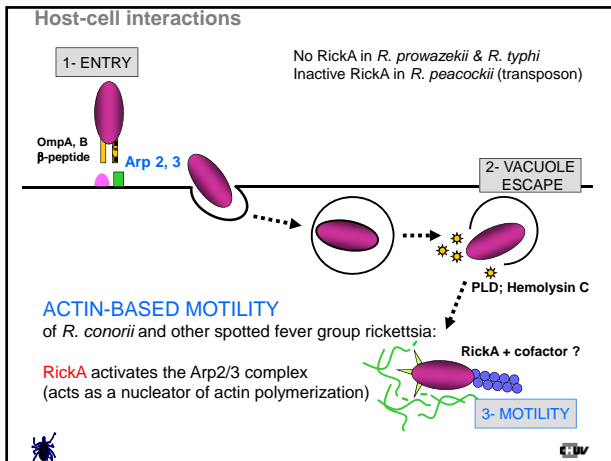
2- VACUOLE ESCAPE

PLD; Hemolysin C

Two rickettsial proteins able to digest the phagosomal membrane:

- Phospholipase D (PLD) Renesto et al 2006
- Hemolysin C (TlyC) Withworth et al. 2005





Immunity

Rickettsial infection

i. induces secretion:

- by NK cells IFN-gamma \rightarrow Nitric oxide
- by Endothelial cells IL-6, IL-8, MCP-1
- by Macrophages TNF-alpha

- In vivo: IL-6, IL-1
 = **proinflammatory cytokines**

ii. activates NF-kappa B (transcription factor):
Mediates the production of proinflammatory cytokines
Inhibition of apoptosis (inhibition of caspases activation)
 \rightarrow Increased number of target endothelial cells

iii. IL-10 production on day 10
 \rightarrow transient immunosuppression

Conclusions

Direct link between biology (tropism, ...) and clinical presentation

Cell corruption by intracellular bacteria

Immunomodulation by intracellular bacteria

- inhibition of apoptosis
- IL-10