Two functionally distinct Type III Secretion Systems for *Salmonella* pathogenesis

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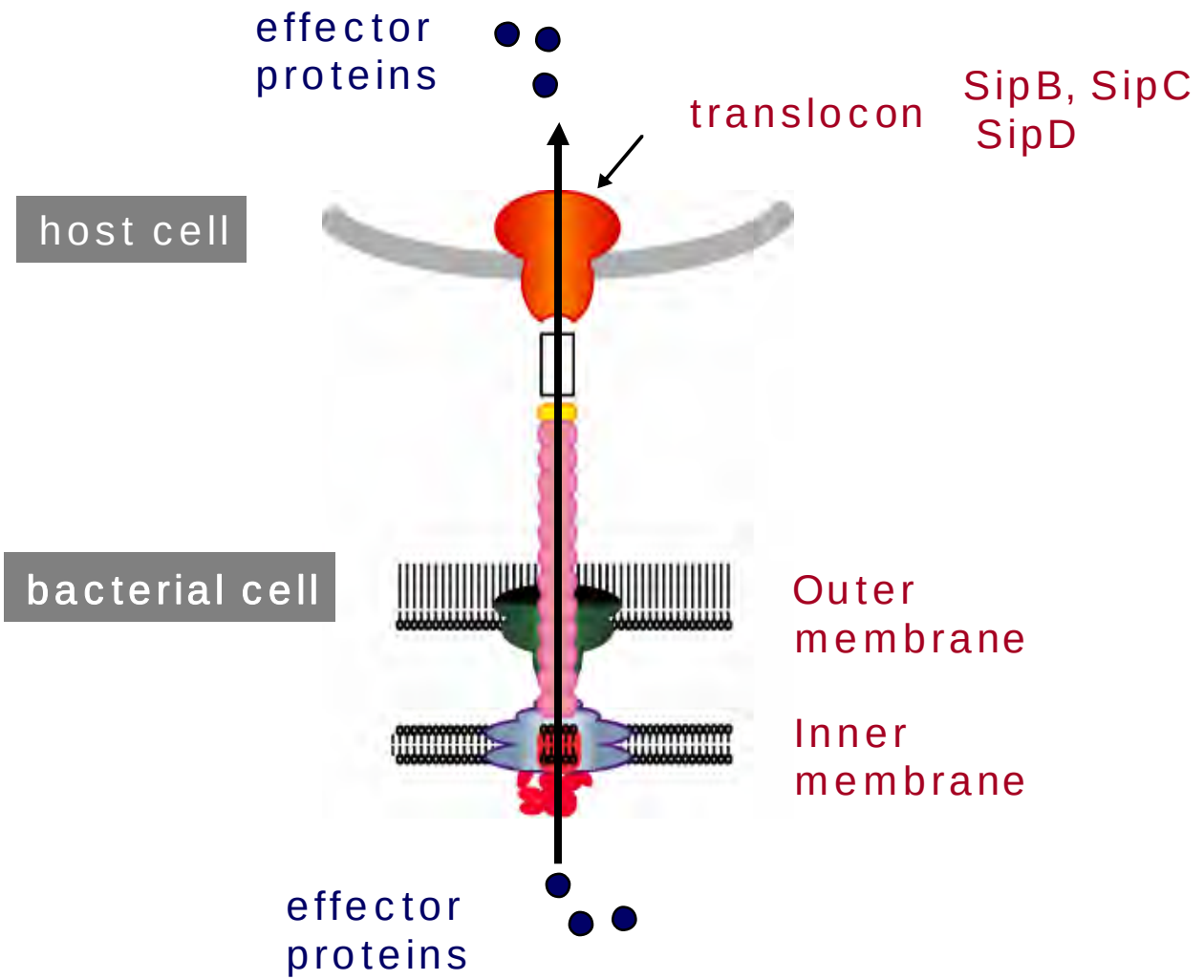
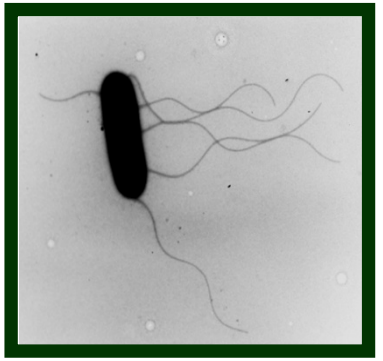
Type III protein secretion system (TTSS)



Salmonella spp

important pathogens of humans and animals

- Cause a wide variety of diseases ranging from mild diarrhoea to severe systemic infections like typhoid fever



- Estimated 16 million cases of typhoid fever per year occur with about 600,000 fatal outcomes

an interesting model organism

- For the study of host-pathogen interaction

  -able to enter into non-phagocytic cells (e.g. epithelial cells) and grow within phagocytic cells (e.g. macrophages)

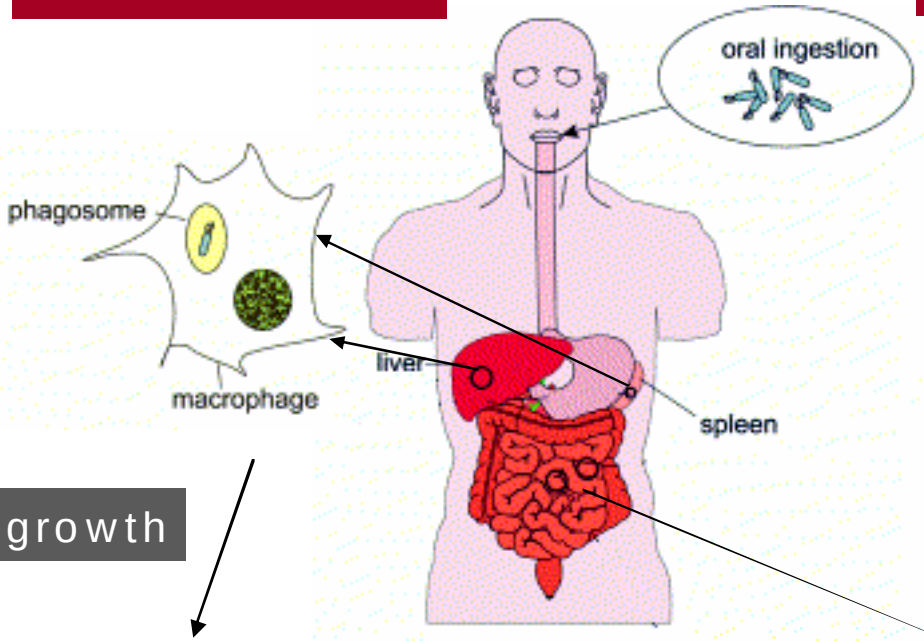
Salmonella Pathogenicity island (SPI): SPI1 and SPI2 encoding Type III protein secretion system

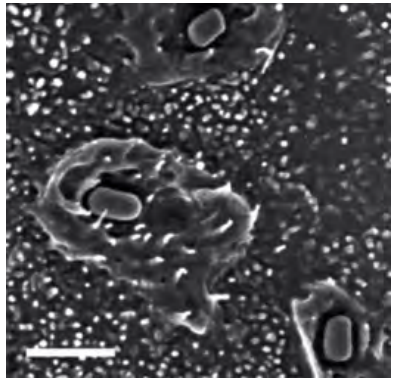
Outline

- Functions of SPI-1 and SPI-2 Type III secretion systems (TTSSs) on *Salmonella* pathogenesis
- Inverse regulation of SPI1-TTSS and SPI2-TTSS within macrophages
- Control of host macrophage cell death, pyroptosis and apoptosis, by SPI-1 effectors

SPI2 function

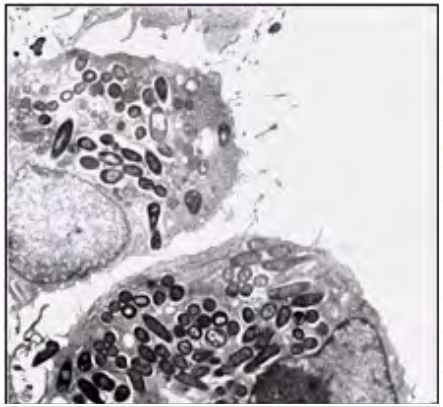
SPI1 function

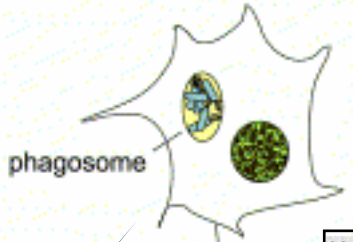


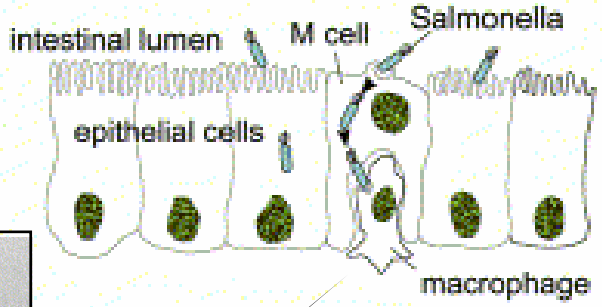


Intracellular growth

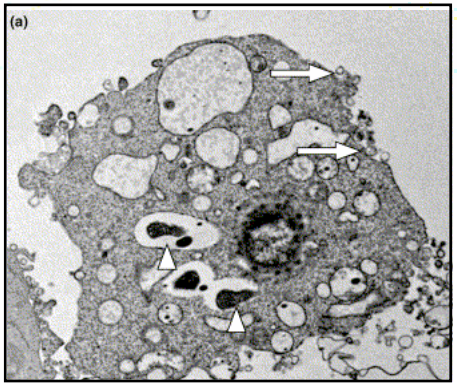
Invasion





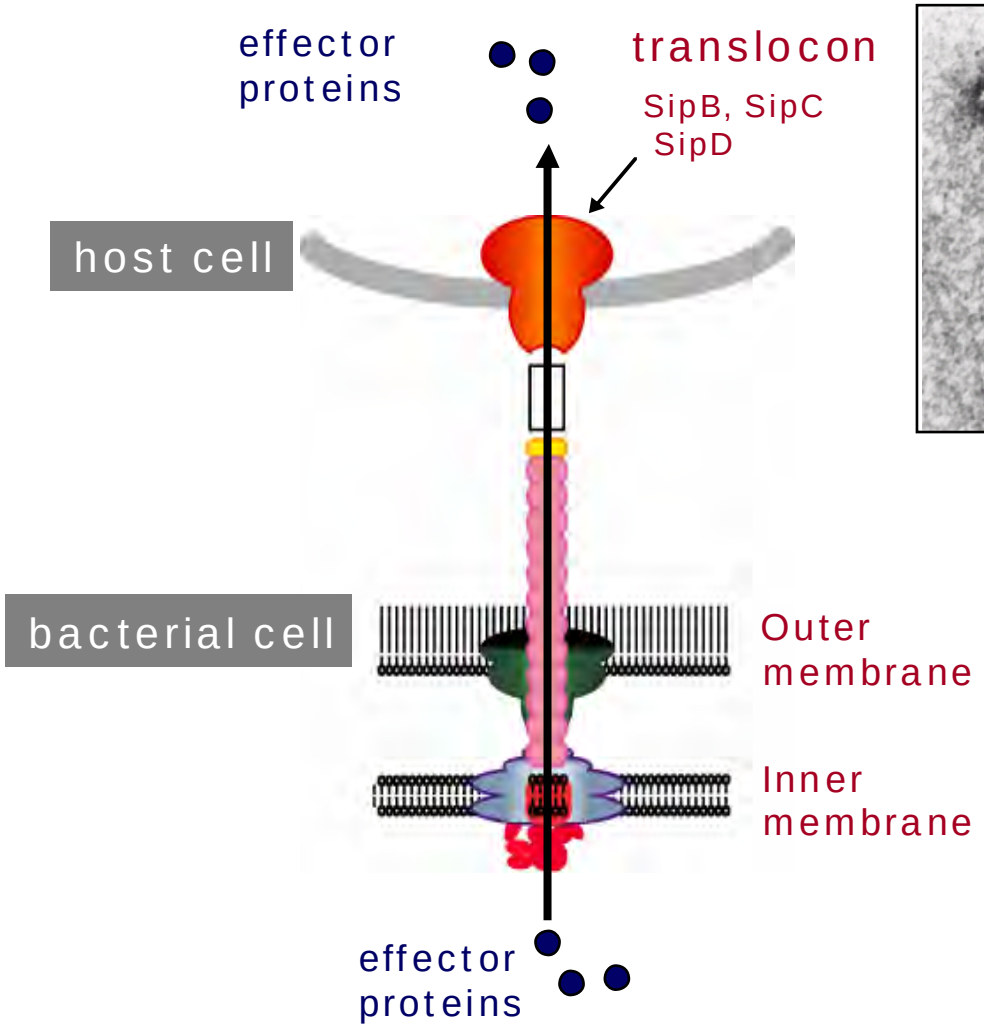


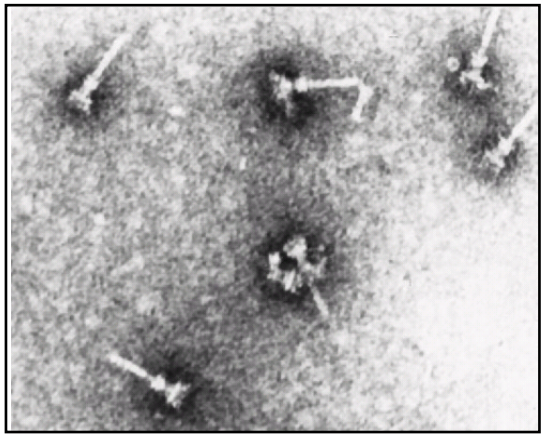
Systemic spreading



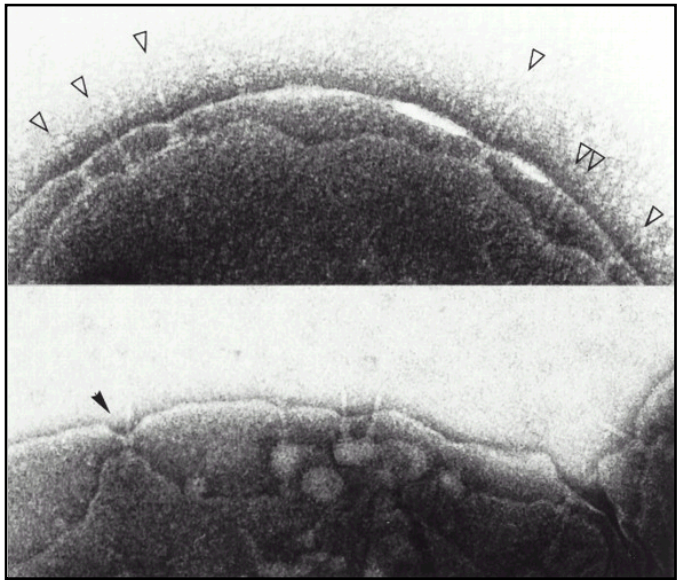
Macrophage cell death

SPI1-Type III secretion system



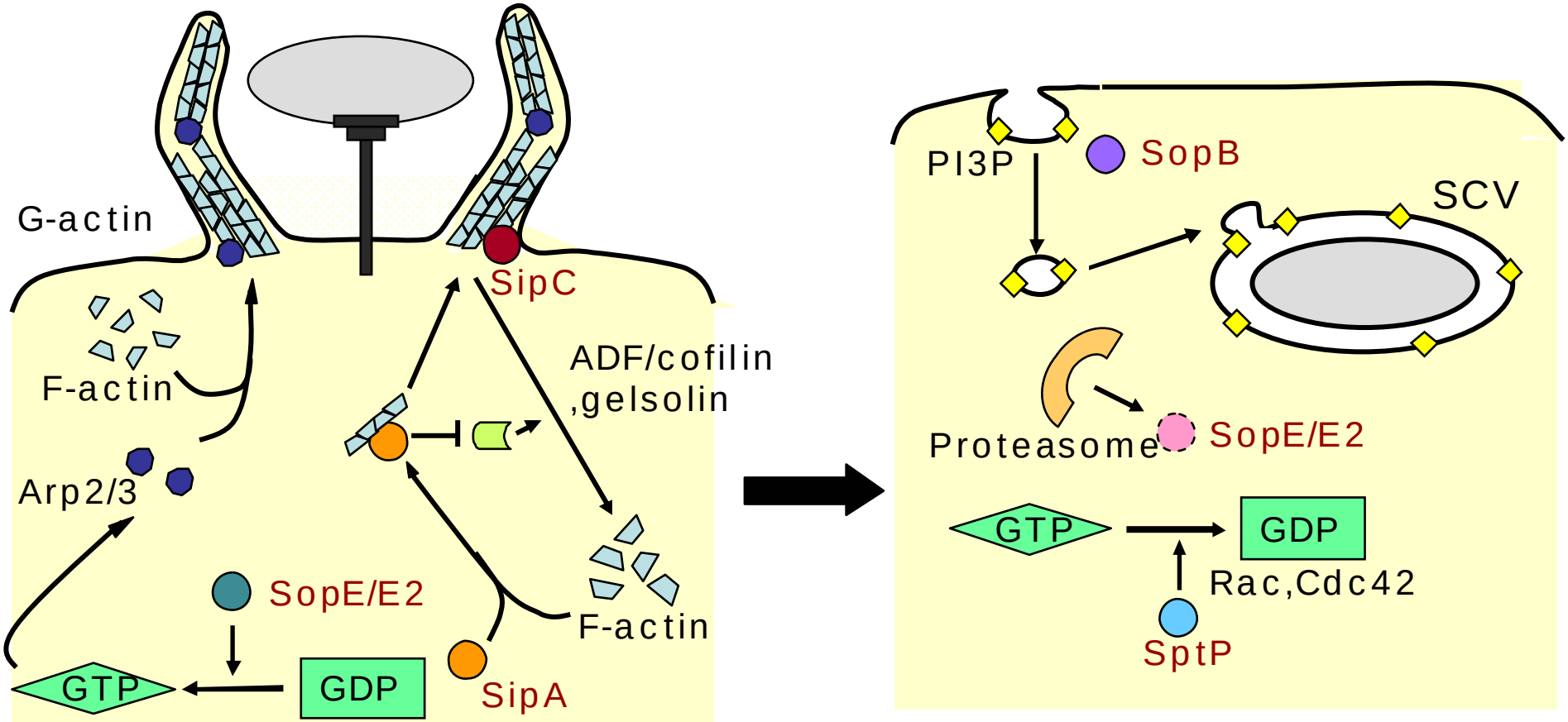


Kubori et al.
Science
280:602-605
(1998)



SPI1-TTSS promotes invasion

Effectors induce actin rearrangements and alter vacuole trafficking to trigger invasion, without causing cellular damage

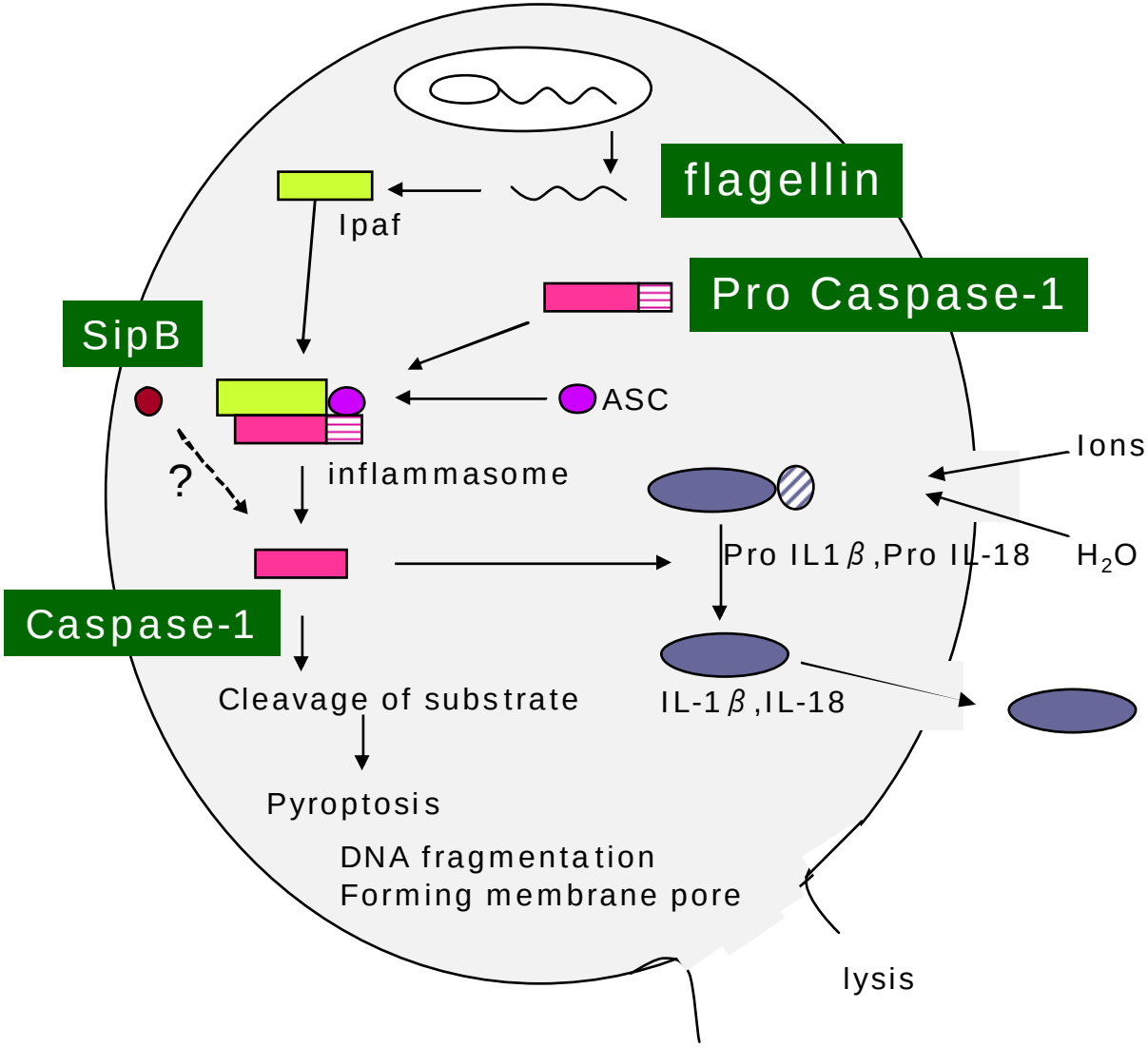


Arp2/3: actin-related protein complex

PI3P: phosphatidylinositol (3,4,5)-3phosphate

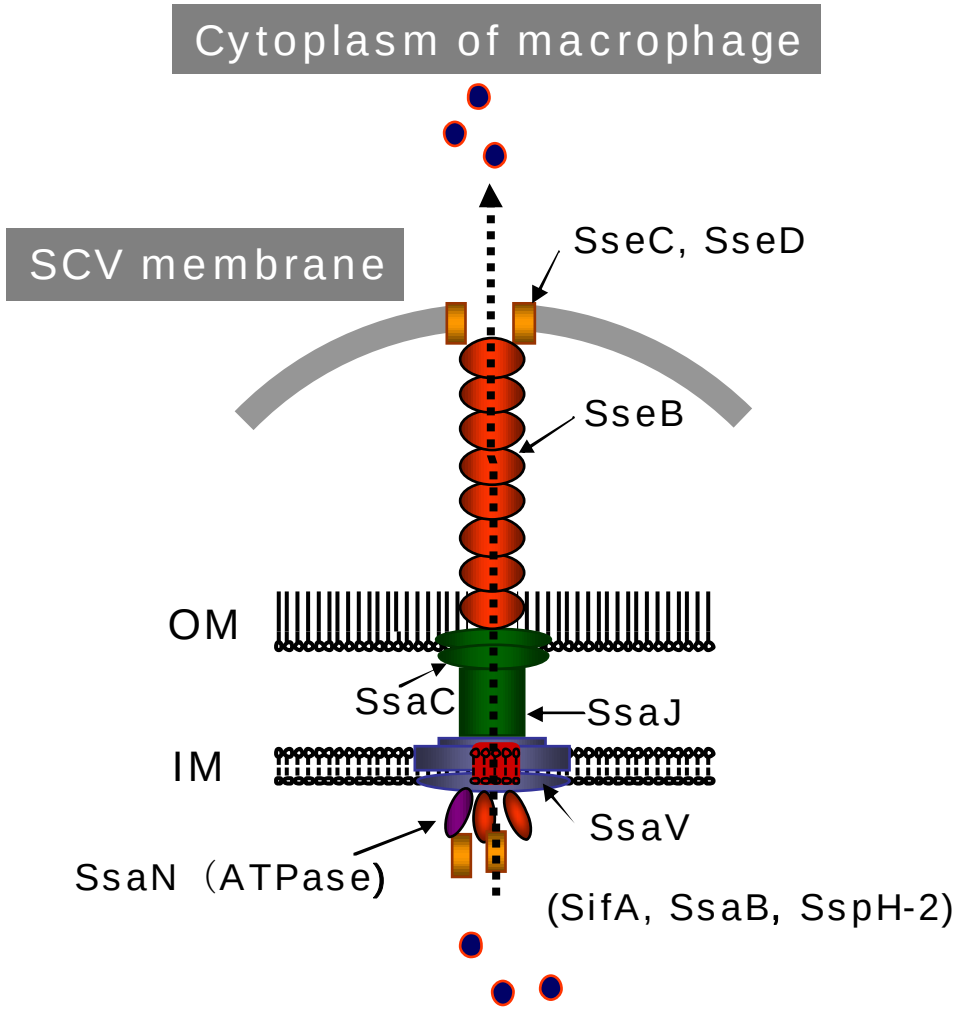
SCV: *Salmonella* containing vacuole

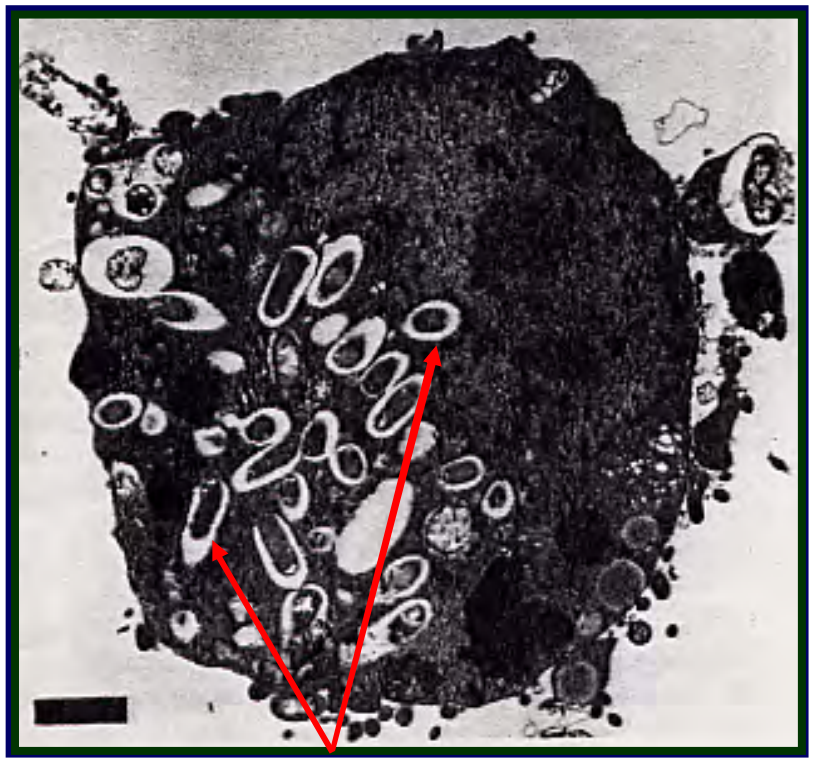
SPI1-TTSS-dependent activation of caspase-1, leading to macrophage cell death, pyroptosis



SPI2-Type III secretion system

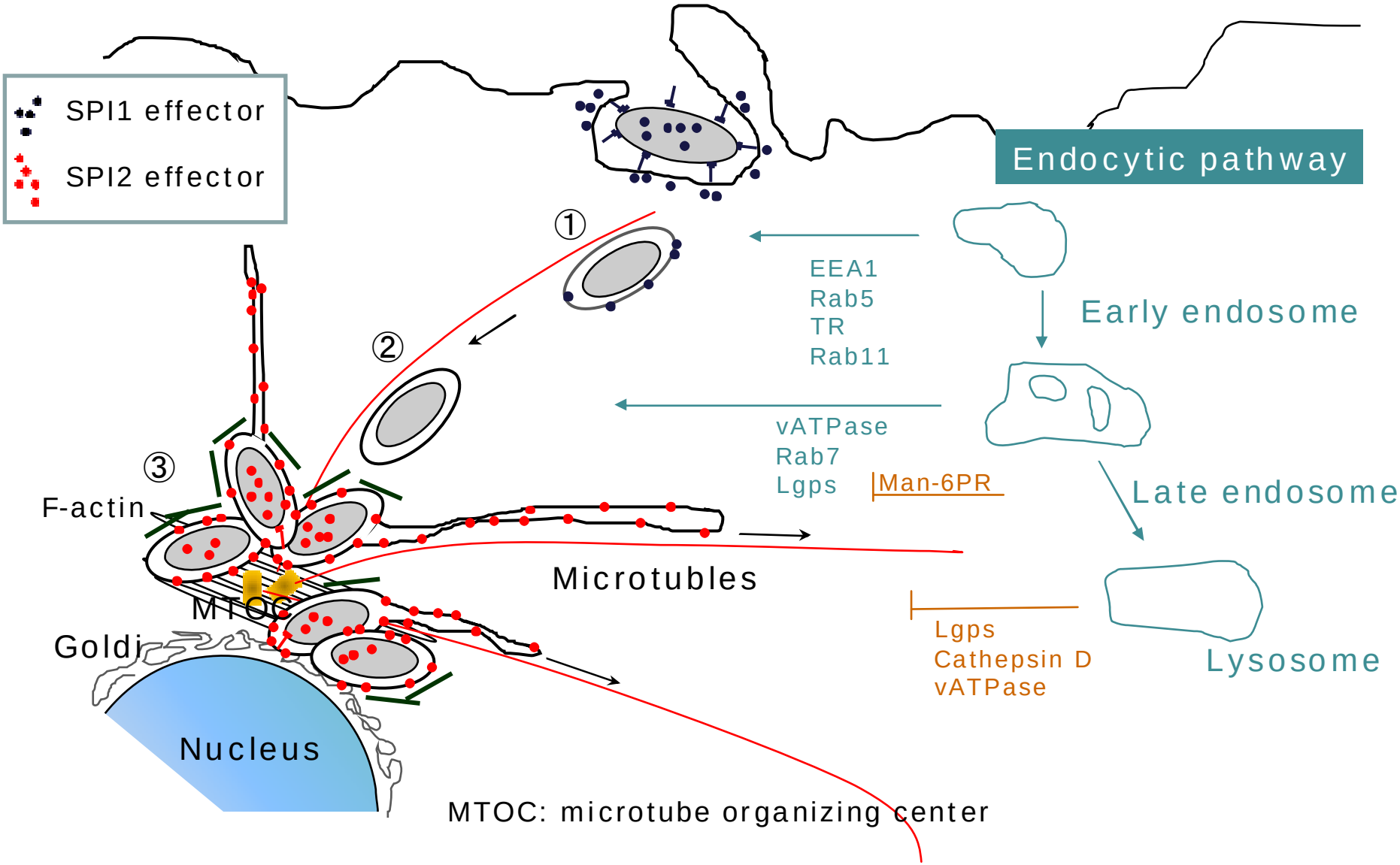
*SPI2:*Salmonella* pathogenicity Island at cs31



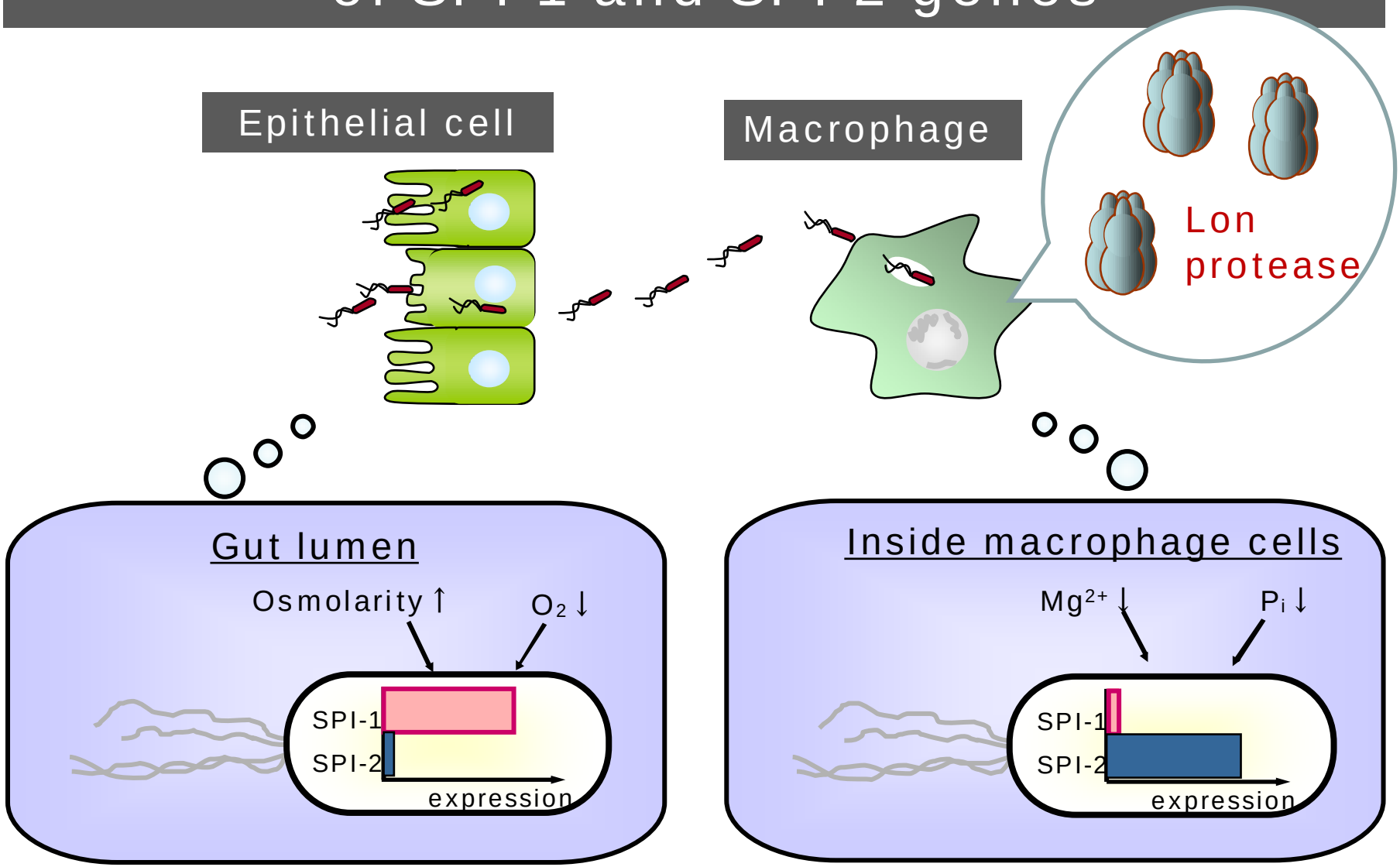


SCV
:*Salmonella*
containing vacuole

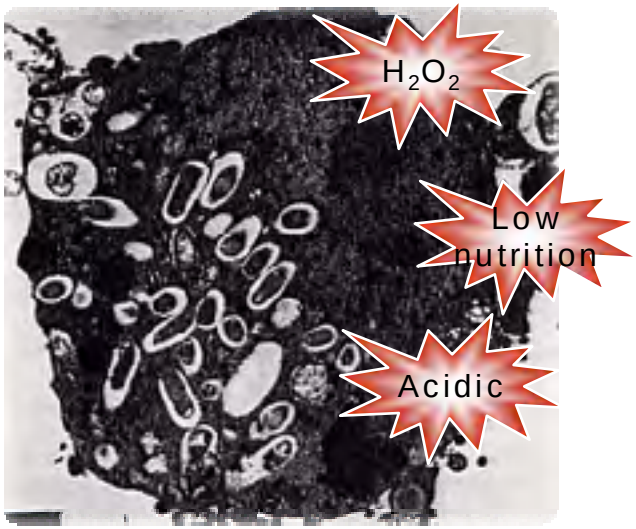
SPI2-mediated SCV membrane dynamics, leading to *Salmonella* multiplication within host cells



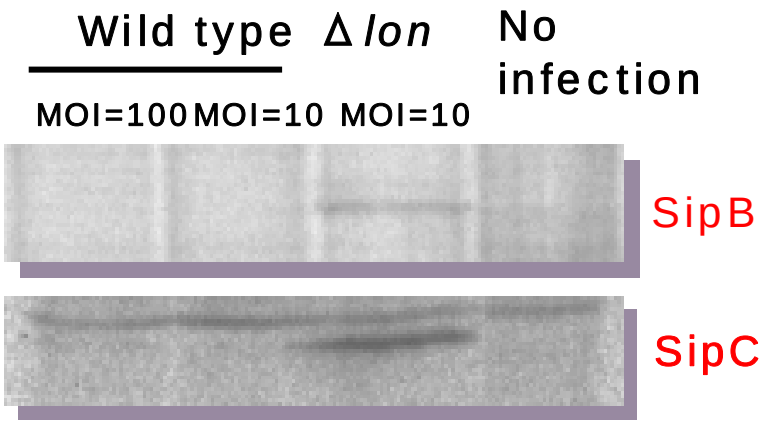
Inverse regulation of expression of SPI-1 and SPI-2 genes



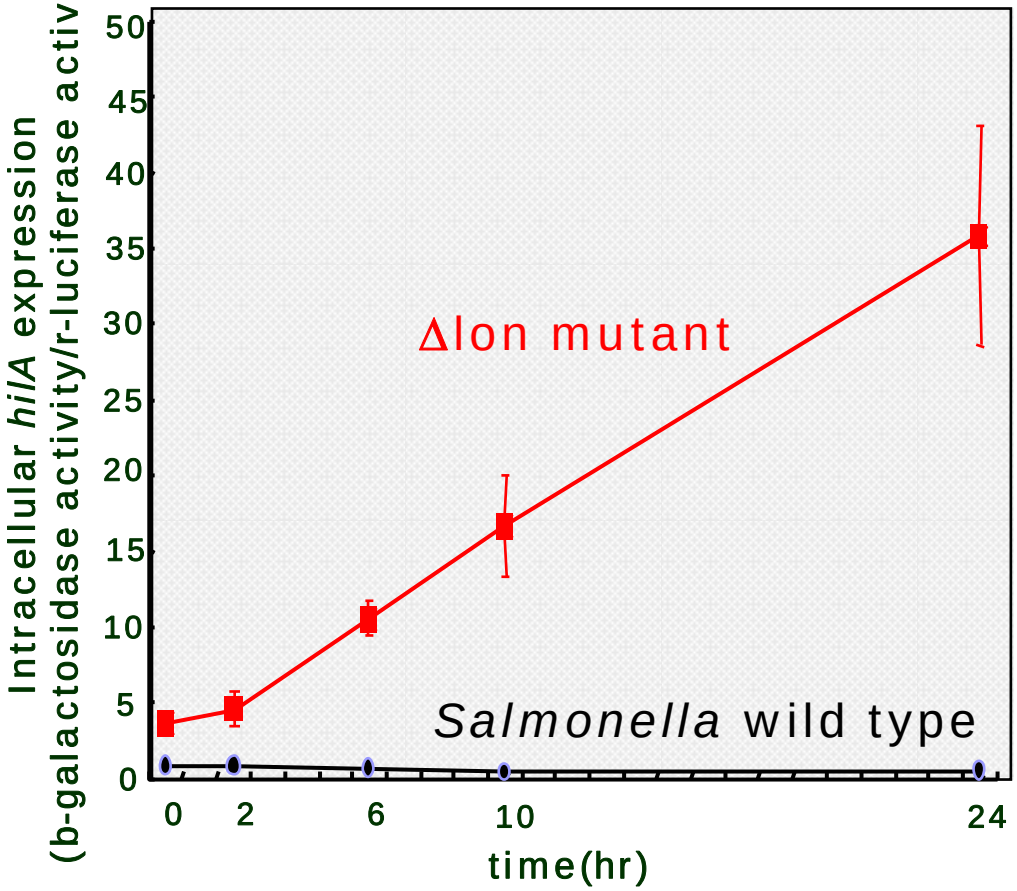
Lon is induced as a stress response by *Salmonella* to hostile environment in macrophages



Levels of SPI1 proteins in macrophage cells



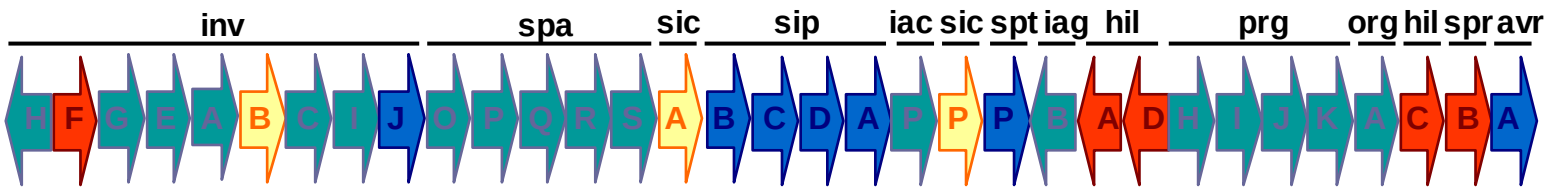
Transcription of SPI1 gene, *hilA* in macrophage cells



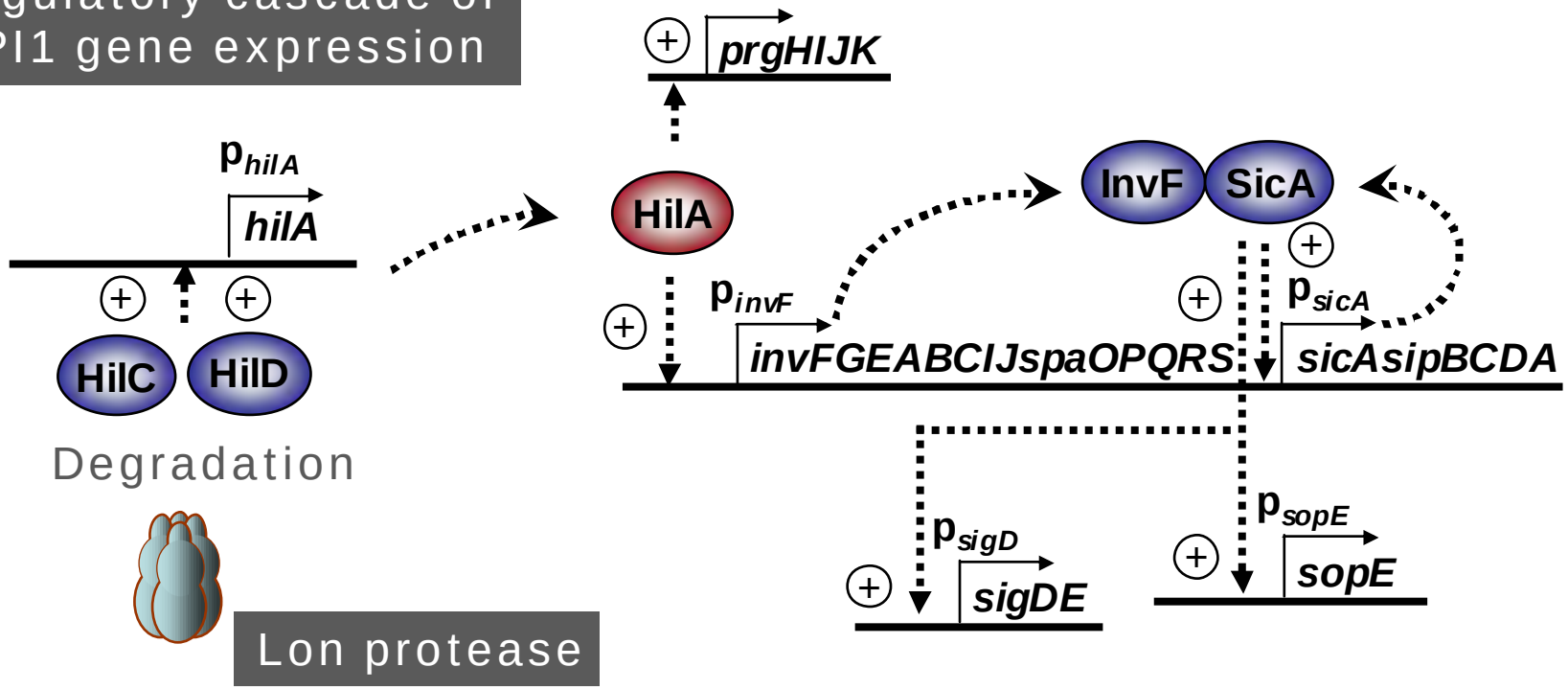
Lon is essential for down-regulation of SPI1-expression in macrophage cells after phagocytosis

Lon degrades HilC and HilD to down-regulate the expression of SPI1 genes

SPI1 at cs63 of *Salmonella* genome

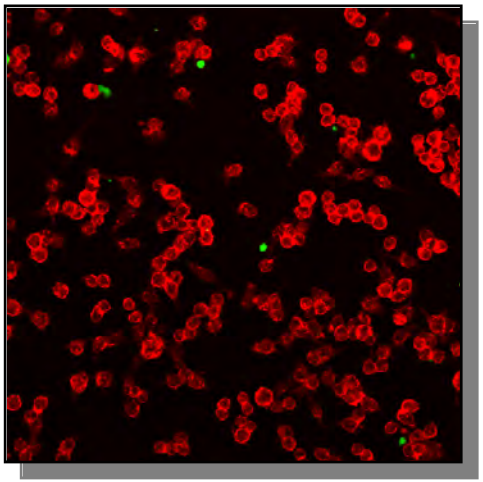


Regulatory cascade of SPI1 gene expression

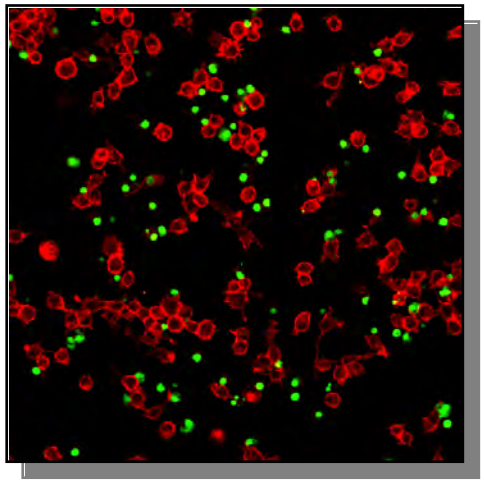


Salmonella Δ*lon* mutant induces massive apoptosis in macrophages

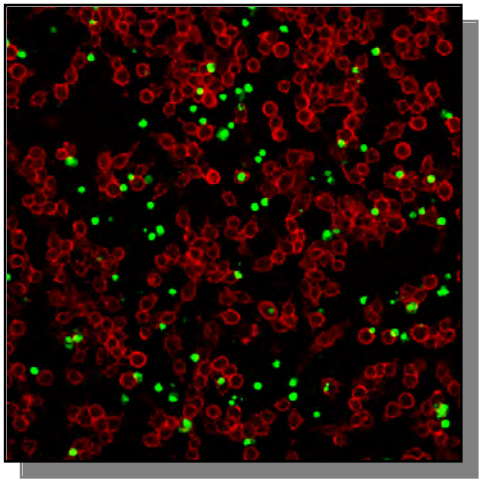
wild type
MOI=10



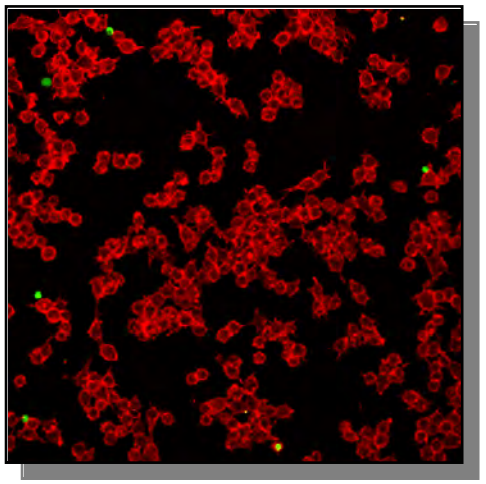
Δ*lon*
MOI=10



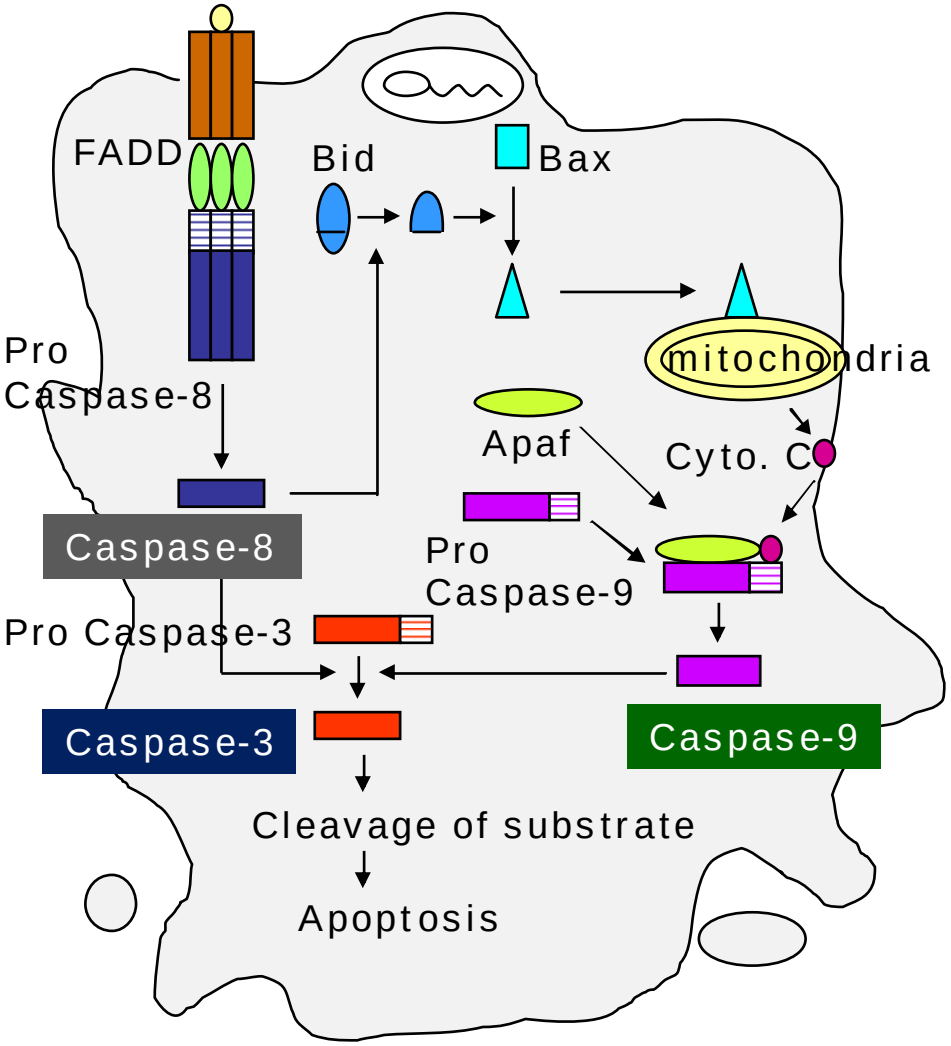
Δ*lon*
MOI=1

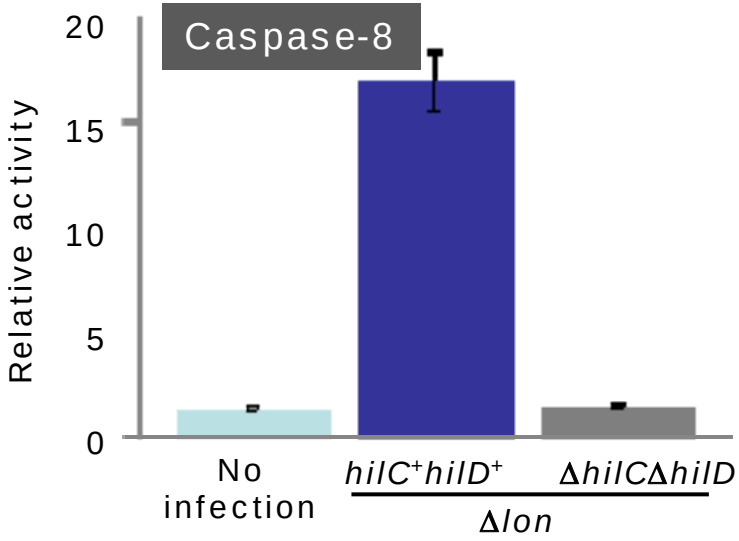


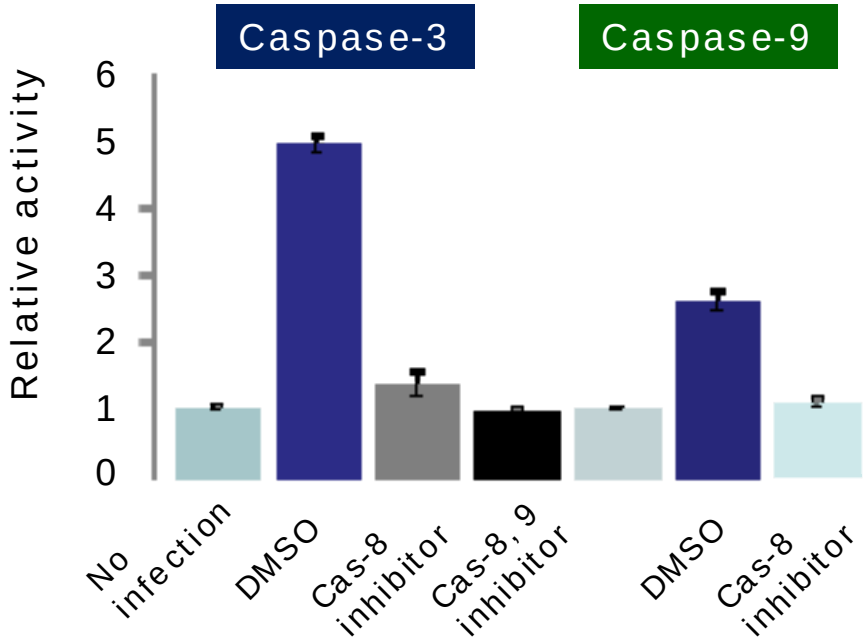
Δ*lon*
ΔSPI1
MOI=10



Over-expression of SPI1 activates caspase-8-dependent procaspase-3 activation pathway







Physiological significance of control of cell death via negative regulation of SPI1 expression

At the initial stage of infection (intestinal phase of infection), *Salmonella* escape the macrophage killing mechanism by induction of flagellin-dependent and SPI1-dependent cell death, pyroptosis.

- Once *Salmonella* has established a systemic infection, excess cell death like apoptosis would be detrimental to the pathogen because *Salmonella* resides in macrophage cells.

- It would be required to suppress apoptosis to allow time for the bacterium to replicate, escape and invade new macrophages for systemic infection.

- Therefore, negative regulation of SPI1-TTSS expression by Lon which is induced in response to the hostile environment in macrophage cells would be essential for the suppression of apoptosis through the control of caspase-8 activity in the macrophage cells after *Salmonella* infection.

Summary

➢Two functionally distinct TTSS

SPI1 • invasion of epithelial cells
• release of inflammatory cytokines
• induction of cell death, pyroptosis
• induction of caspase-8, leading to apoptosis

SPI-2 • SCV membrane dynamics leading to replication and spatial distribution

➢Inverse regulation of Two TTSSs

Lon which is induced in *Salmonella* growing in macrophage cells after phagocytosis controls negatively SPI1 expression and positively SPI2 expression

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