Salmonella typhi and typhoid fever: new insights into an old disease
Two fundamental questions about *Salmonella* Typhi:

- Why it causes typhoid fever?
- Why it only causes disease in humans?
Typhoid toxin: a unique *Salmonella* Typhi toxin with two active subunits that causes cell cycle arrest in target cells.

Haghjo & Galan, PNASc (2004); Spano et al., Cell Host & Microbe (2009); Song et al., Nature (2013)
Typhoid toxin: when two toxins became one

Pertussis toxin

Cytolethal distending toxin

Song et al, Nature (2013)
Systemic administration of Typhoid toxin can reproduce many of the symptoms of typhoid fever in an animal model.
Two fundamental questions about Salmonella Typhi:

• Why it causes typhoid fever?

because S. Typhi (and S. Paratyphi) encodes “typhoid toxin”, which is responsible for the pathognomonic symptoms of typhoid fever and is absent from non-typhoidal Salmonellae.

• Why it only causes disease in humans?
Typhoid toxin: a novel toxin and a novel pathway for exotoxin delivery by an intracellular pathogen

Two fundamental questions about *Salmonella* Typhi:

- **Why it causes typhoid fever?**

  *because S. Typhi encodes “typhoid toxin”, which is responsible for the pathognomonic symptoms of typhoid fever and is absent from non-typhoidal *Salmonellae*.*

- **Why it only causes disease in humans?**
Host restriction is manifested at the cellular level: *Salmonella typhi* does not survive within mouse macrophages.
Expression of single *Salmonella Typhimurium* gene, *gtgE*, allows *Salmonella Typhi* to overcome host restriction in mouse macrophages (*in vitro*) and mouse tissues (*in vivo*).

Spano & Galan, PNASc (2012); Science (2013)
Salmonella type III secretion system: a molecular machine for protein delivery into host cells
GtgE extends host range by proteolytically removing Rab29, Rab32, and Rab38 from the Salmonella-containing vacuole.

=GtgE

Typhi

=Rab29/32/38

GtgE
Rab29, Rab32, and Rab38 localize to the human-adapted *S. typhi* and *S. paratyphi*-containing vacuoles but not to vacuoles harboring *S. typhimurium*
Rab32/Rab38 delivers antimicrobial factors to the *Salmonella*-containing vacuole in macrophages.
Removal of Rab32 allows *Salmonella typhi* survival in mouse macrophages and tissues.
Two fundamental questions about *Salmonella* Typhi:

- **Why it causes typhoid fever?**

  *because S. Typhi (and S. Paratyphi) encodes “typhoid toxin”, which is responsible for the pathology and symptoms of typhoid fever*

- **Why it only causes disease in humans?**

  *because in non-permissive animals S. typhi replication is restricted by macrophages through a Rab32-dependent pathway, which broad host Salmonellae neutralize by targeting Rab32 with the effector protein GtgE (absent from S. typhi and S. paratyphi)*
STUDIES ON INFECTION AND IMMUNITY IN EXPERIMENTAL
TYPHOID FEVER

I. Typhoid Fever in Chimpanzees Orally Infected with
Salmonella typhosa

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Plates 6 and 7
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The principal apparent differences between typhoid fever as seen in our
chimpanzees and in man were the incubation period, which was relatively short
in the chimpanzees, and the clinical course of the disease, which in the chim-
panzees was relatively mild and brief. Only a few animals in the whole series
appeared seriously ill during the course of the infectious process. The hyper-
toxicity, typhoid facies, stupor, extreme lethargy, etc., which are so generally
associated with the disease in man were not discernible in our infected chim-
panzees. Finally, the pathological changes, although wholly typical of mild
Typhoid toxin recognizes terminally sialylated glycans on specific surface glycoproteins (Podocalixin 1 and CD45) on target cells.
Two major sialic acids in mammalian cells:

**Humans**

**Other mammals**

CMAH (cytidine monophospho-N-acetylgalactosaminic acid hydroxylase) (pseudogene in humans)
Typhoid toxin binds Neu5Ac- but not Neu5Gc-terminated glycans.

Deng et al, Cell (in press)
Typhoid toxin does not bind to chimpanzee cells

Deng et al, Cell (in press)
Typhoid toxin binds to human but not to chimpanzee tissues

Deng et al, Cell (in press)
Constitutive expression of \textit{cmah} renders mice completely resistant to typhoid toxin

Deng et al, Cell (in press)
Two fundamental questions about *Salmonella* Typhi:

- Why it causes typhoid fever?
  
  because *S. Typhi* (and *S. Paratyphi*) encodes “typhoid toxin”, which is responsible for the pathology and symptoms of typhoid fever

- Why it only causes disease in humans?
  
  because in non-permissive animals *S. typhi* replication is restricted by macrophages through a Rab32-dependent pathway, which broad host *Salmonellae* neutralize by targeting Rab32 with the effector protein GtgE (absent from *S. typhi* and *S. Paratyphi*)

  Furthermore, disease can only occur in humans because they are the only species that uniquely express Neu5Ac-terminated glycans, which are the receptors for typhoid toxin, while other mammals predominantly express Neu5Gc-terminated glycans, which are not permissive for typhoid toxin binding
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