Cell Host & Microbe
Article

CellPress

Salmonella Manipulation of Host Signaling Pathways Provokes Cellular Transformation Associated with Gallbladder Carcinoma

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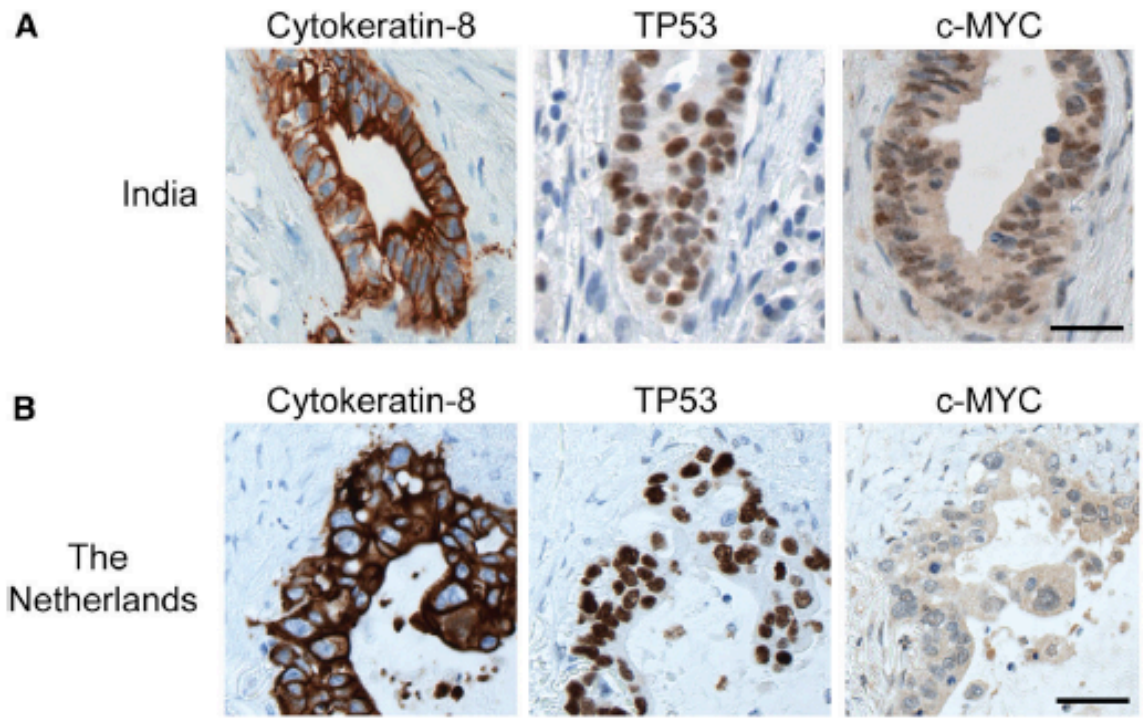
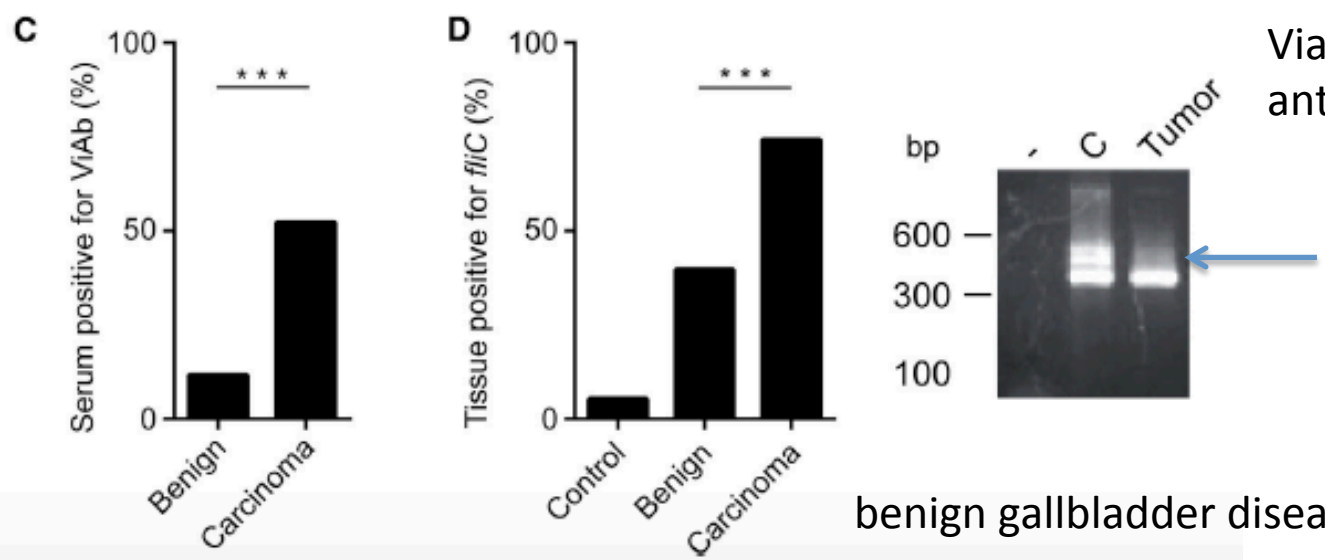
Background

- Gallbladder carcinoma (GBC) mainly occurs in India and Pakistan, and rarely in western world.
- A relationship has been shown between chronic *Salmonella* infection with GBC.
- How bacteria may contribute to cancer is poorly understood， e.g. inflammation, epigenetic modification

Figure 1. Salmonella Typhi Infection and GBC: India versus the Netherlands.



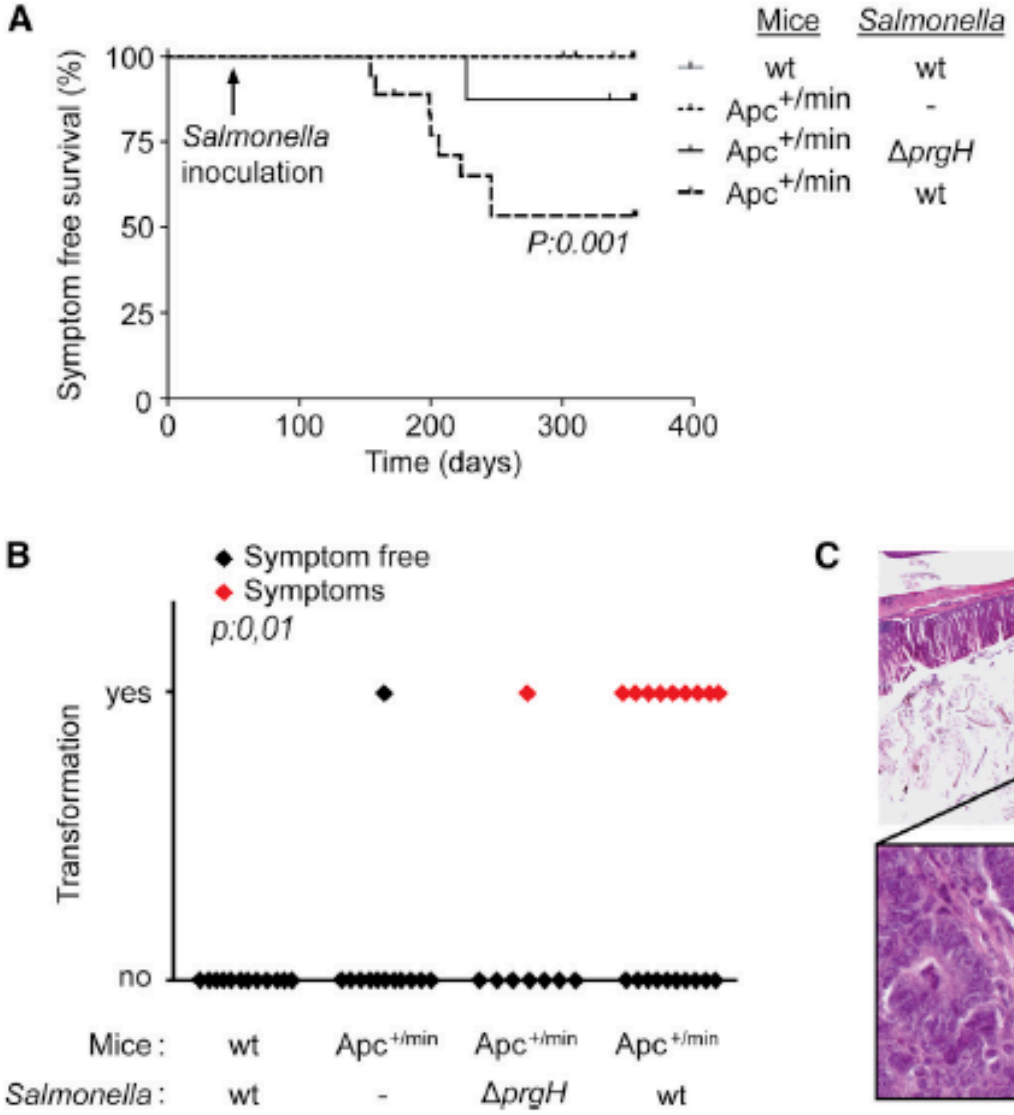
Cytokeratin-8:
a secretory epithelial differentiation marker



Viab:
antibodies against S. Typhi

benign gallbladder diseases

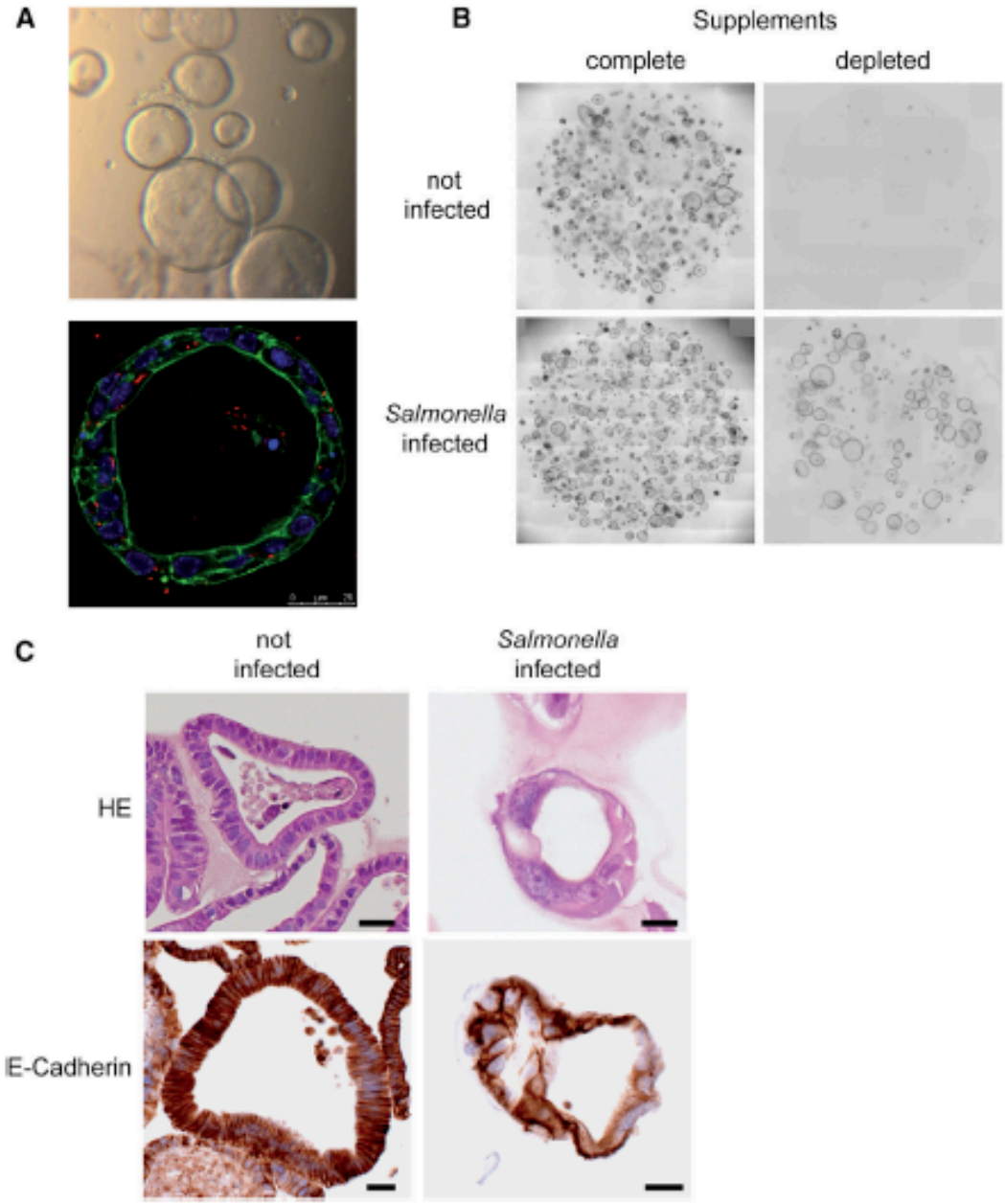
Figure 2. Salmonella Infection Drives Tumor Development in Predisposed Mice



Apc+/-:
Model of c-MYC overexpression

ΔprgH:
Type III secretion System deficient

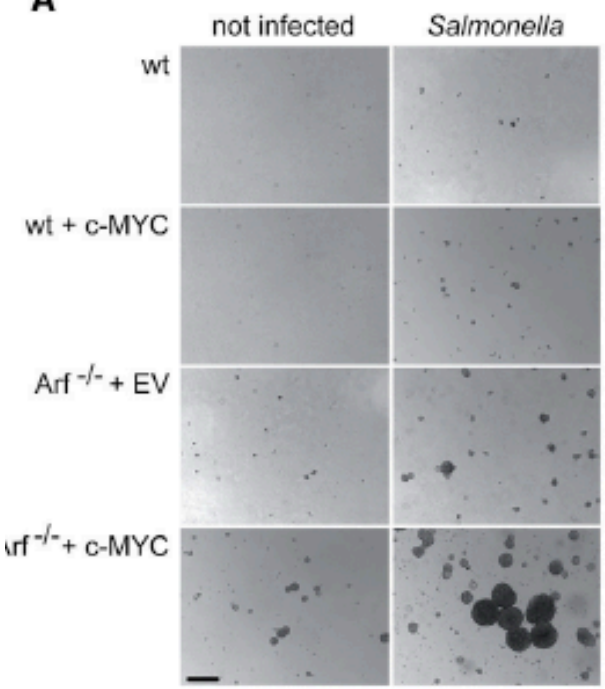
Figure 3. Salmonella Infection of Gallbladder Organoids Induces Cell Transformation



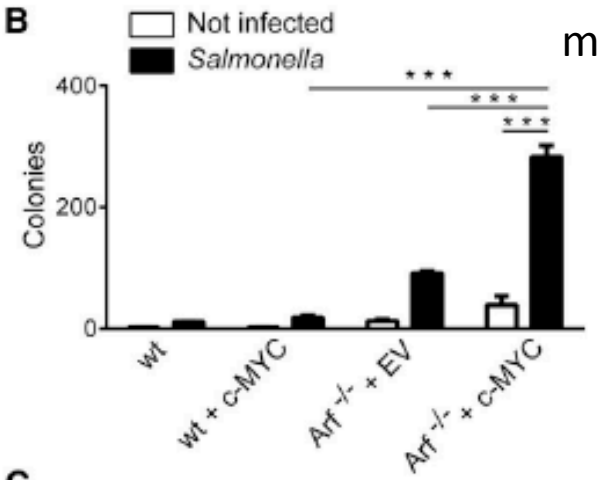
Gallbladder organoids:
Ink4b-Arf-Ink4a KO backgorund:
TP53 inactivated mice

Figure 4. Salmonella Infection of Primary Pre-transformed Fibroblasts Induces Cell Transformation

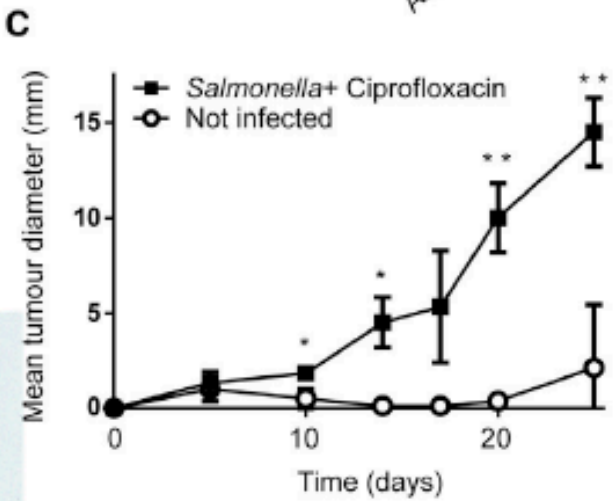
Soft agar assay

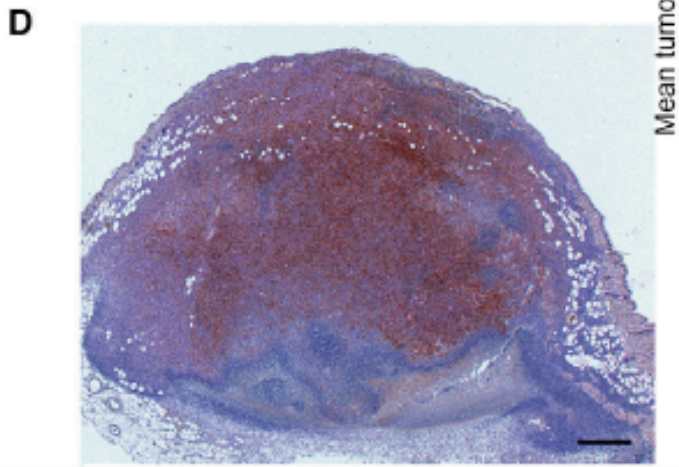


MEFs:
mouse embryonal fibroblasts



Arf-deficient:
TP53 inactivation



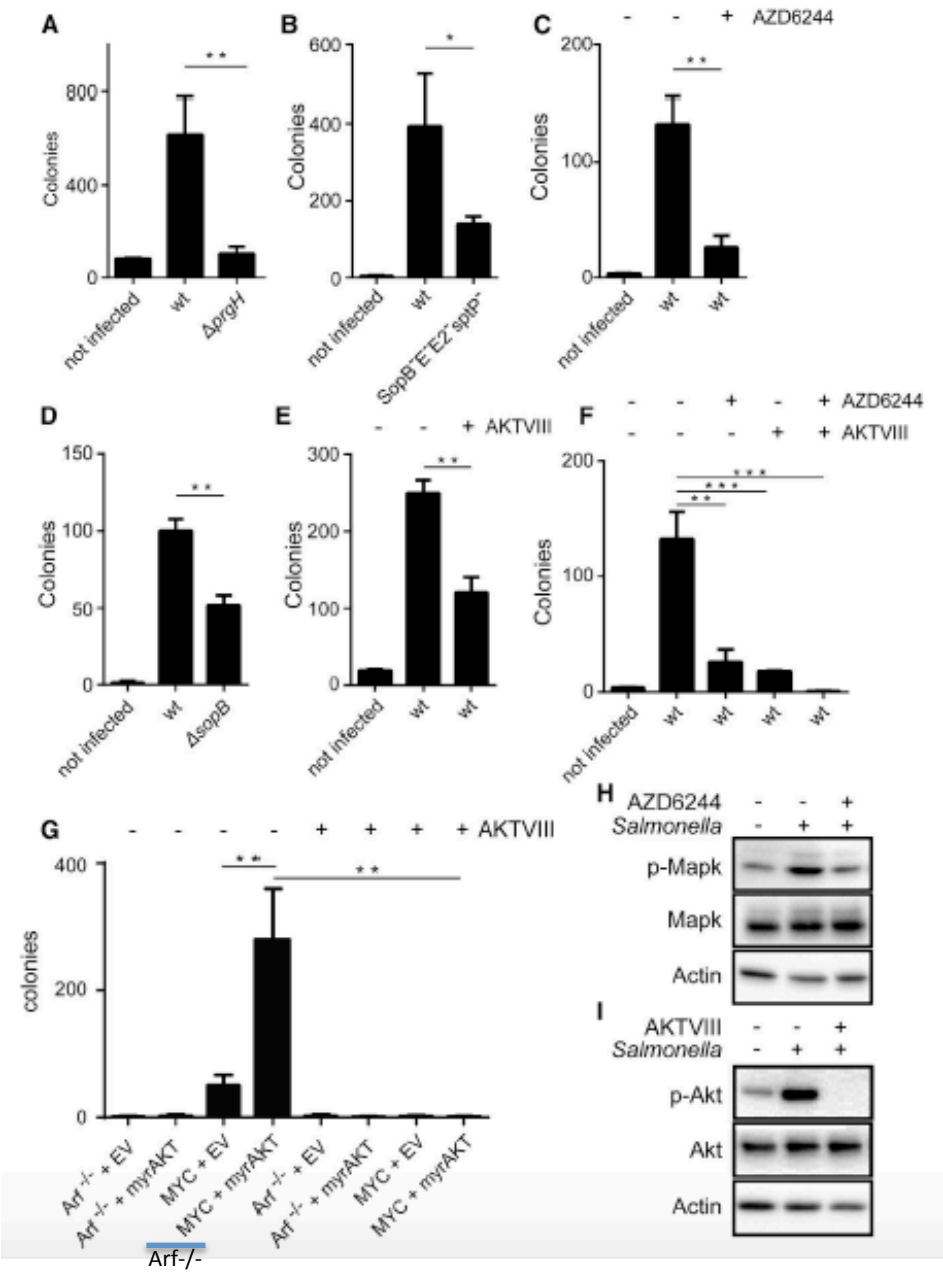


*Rag1-/-γc-/-*mice

Subcutaneously injected

Suppl.4B

Figure 5. Salmonella-Mediated Activation of Akt and Map Kinase Pathways Drives Transformation in Pre-transformed Cells

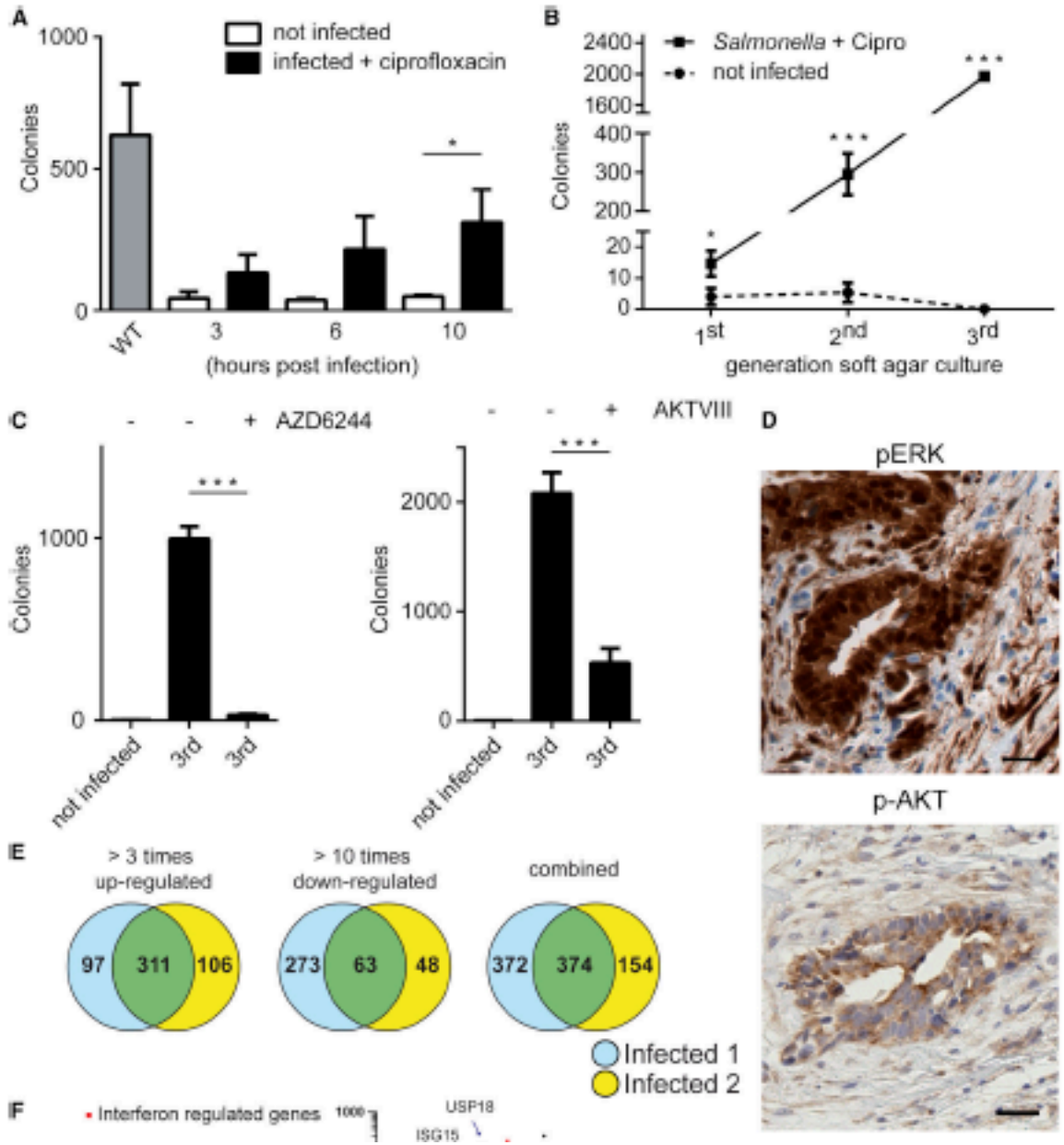


Samonella injected proteins: SopB, SopE, SopE2, and SptP

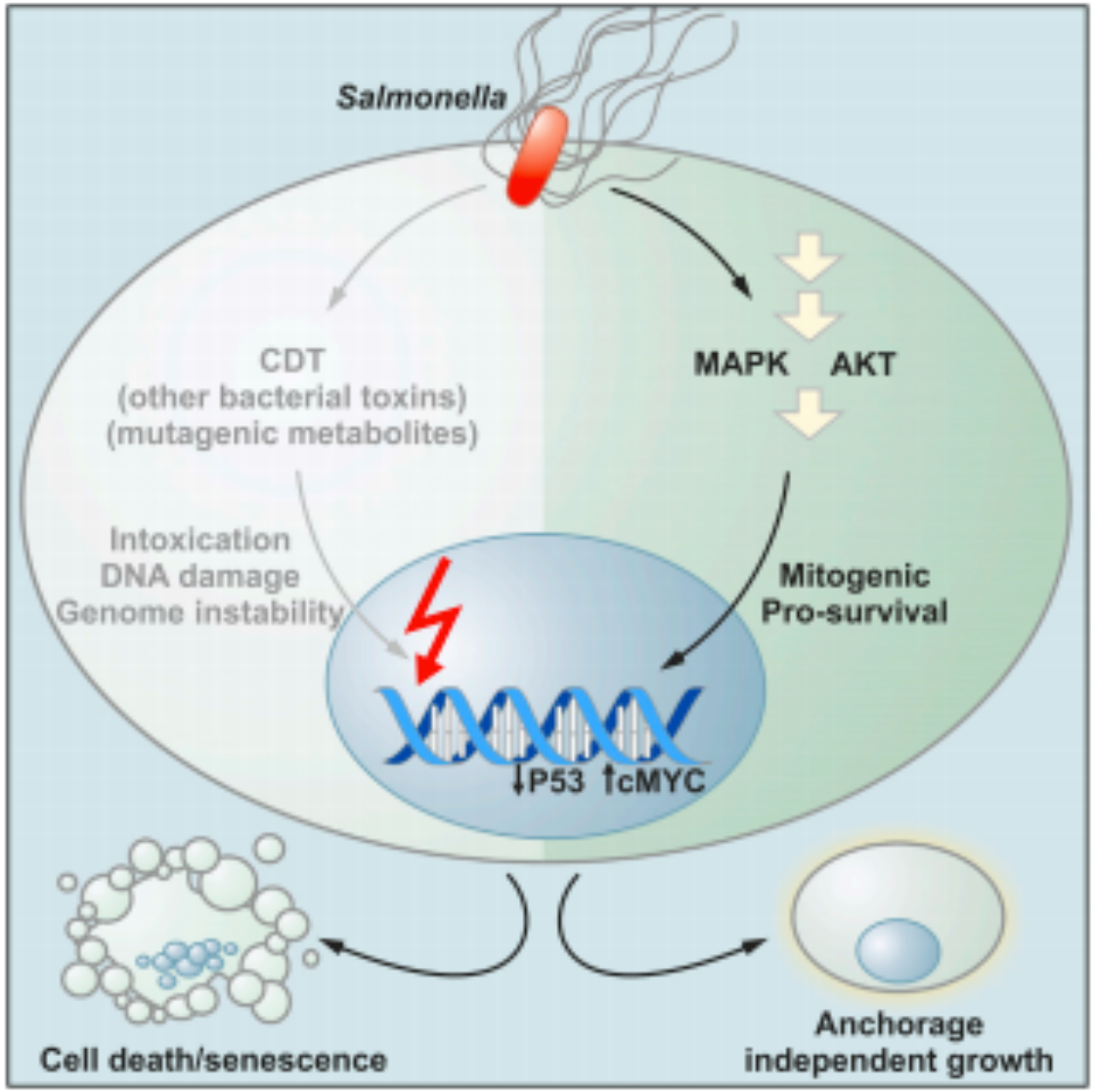
AZD6244: MAPK inhibitor

AKTVIII: AKT inhibitor

Figure 6. The Transformed State Induced by Salmonella Persists after Bacterial Eradication



Discussion


Salmonella
CDT
(other bacterial toxins)
(mutagenic metabolites)
MAPK
AKT
Intoxication
DNA damage
Genome instability
Mitogenic
Pro-survival
↓P53 ↑cMYC
Cell death/senescence
Anchorage
independent growth

LETTERS

nature medicine

Activation of HIF-1α and LL-37 by commensal bacteria inhibits *Candida albicans* colonization

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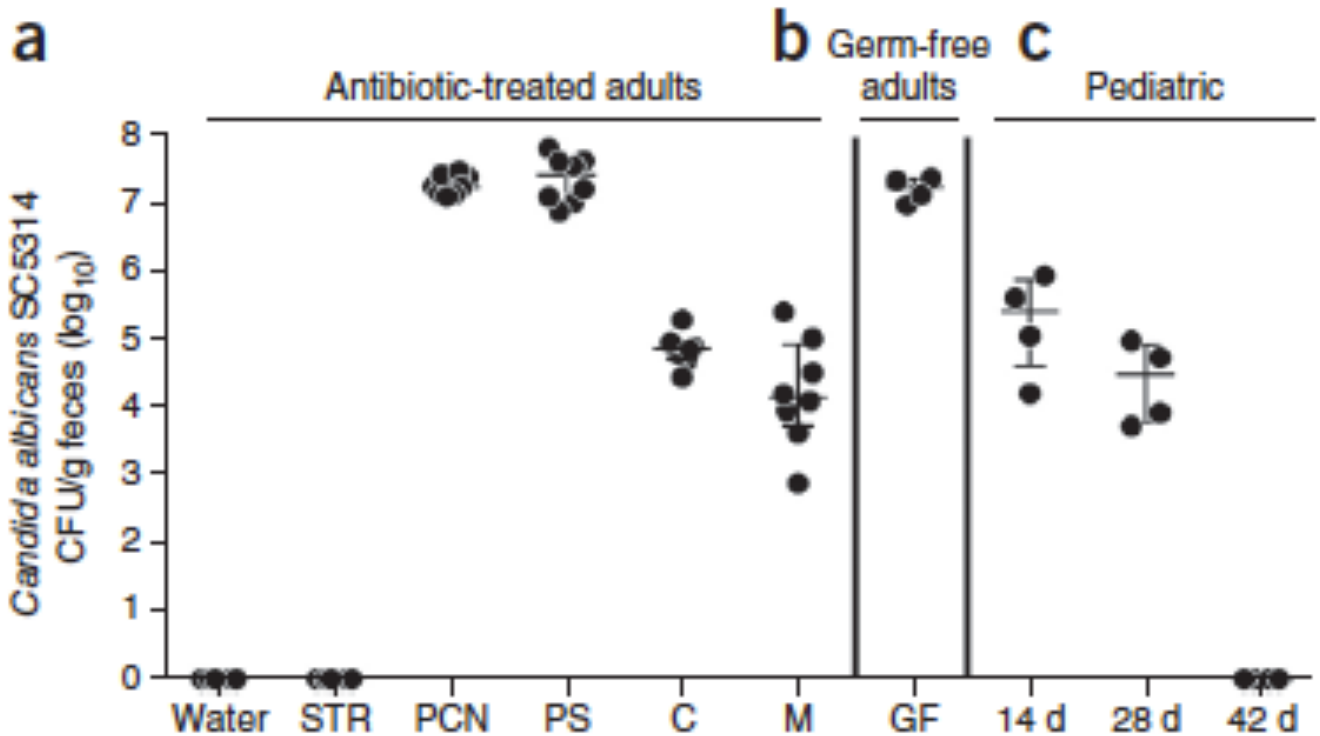
Background

- Commensal fungi, mostly *Candida* spp. are detected in human guts but adult mice are resistant to its colonisation.

- Candida spp. colonization is a prerequisite for CA invasive disease, as fungemia.

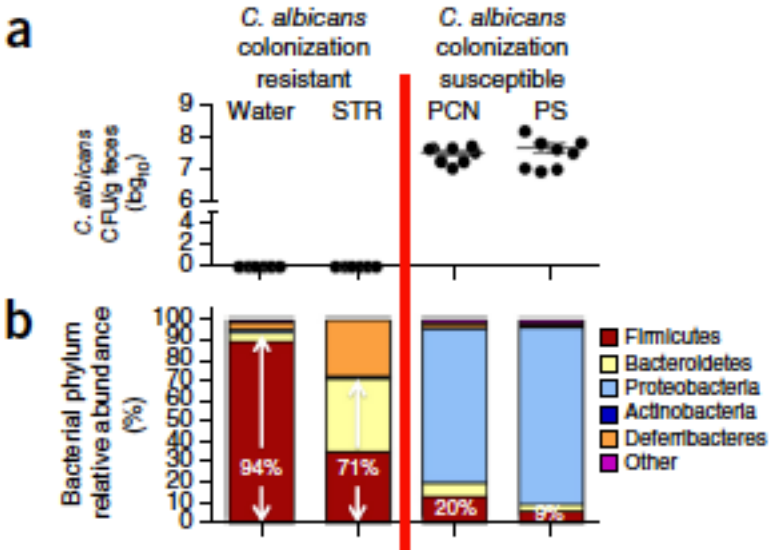
- The function of commensal bacteria in fungi colonisation resistance is unknown.

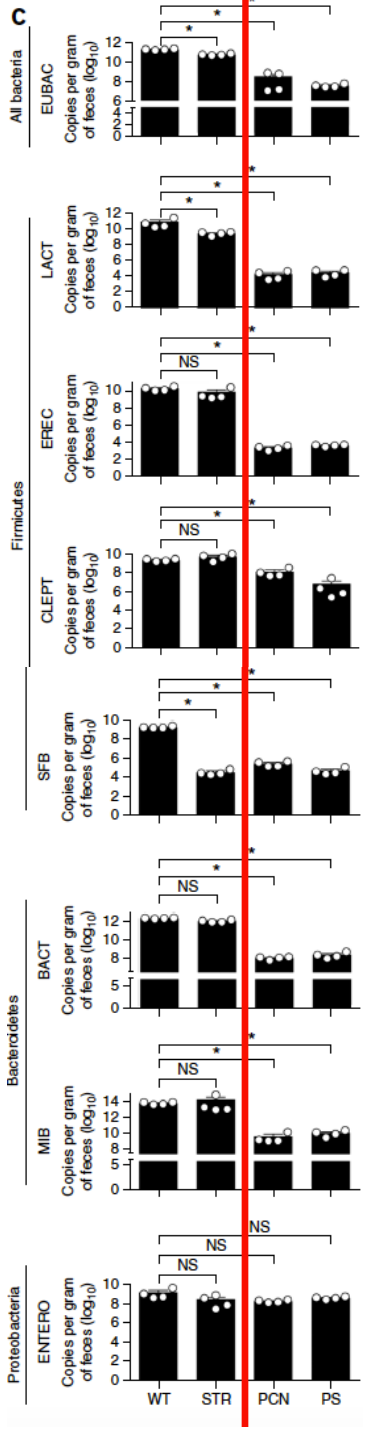
Figure 1 Gastrointestinal colonization levels of *Candida* spp. in antibiotic-treated adult, germ-free adult mice and in infant to adolescent mice.



1) 2 mg/ml streptomycin (STR), 2) 1500 U/ml penicillin G (PCN), 3) PCN/STR (PS), 4) 0.5 mg/ml clindamycin (C) or 5) 1 mg/ml metronidazole (M) for 5 d

Figure 2 Clostridial Firmicutes and Bacteroidetes promote *C. albicans* GI colonization resistance.





LACT: *Lactobacillus*
EREC: clostridial cluster XIVa
CLEPT: clostridial cluster IV
MIB: mouse intestinal Bacteroides

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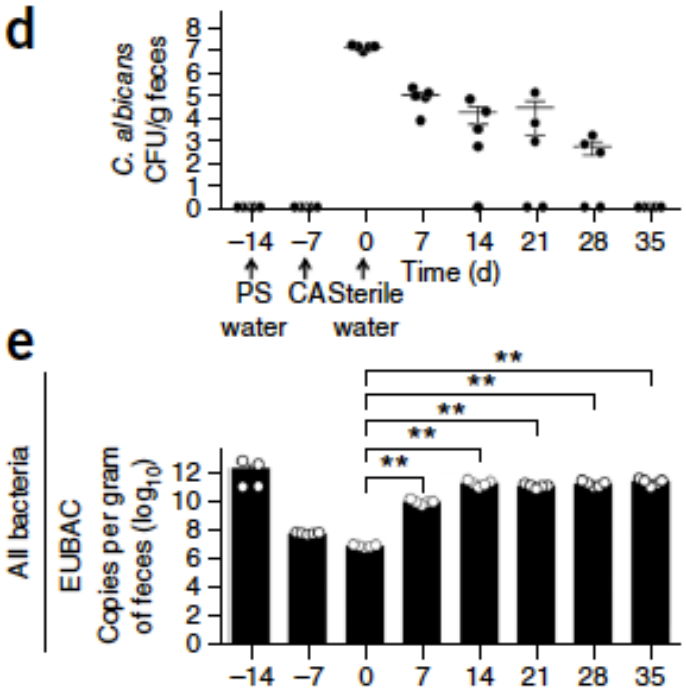

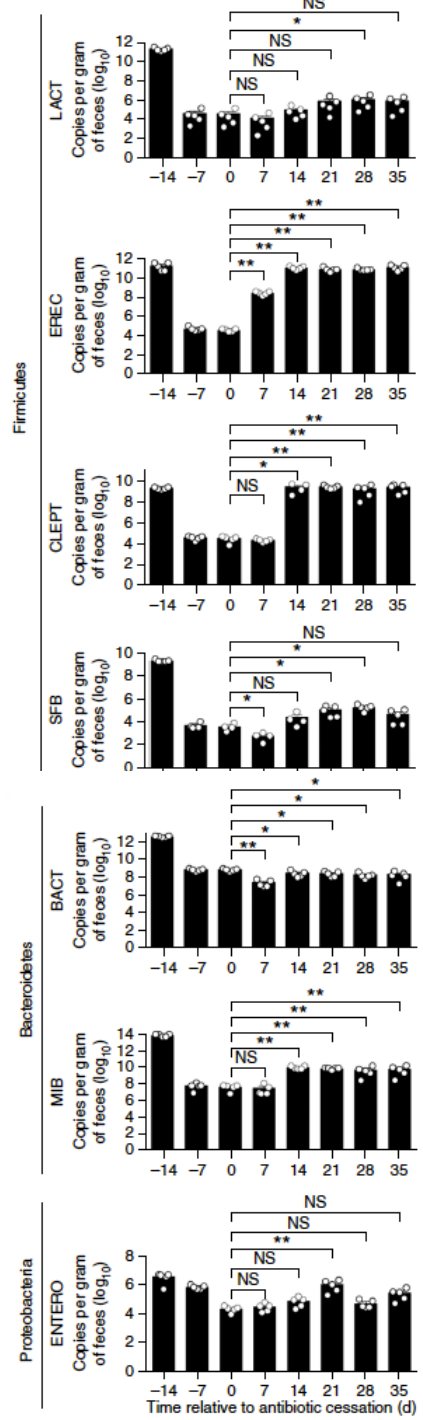

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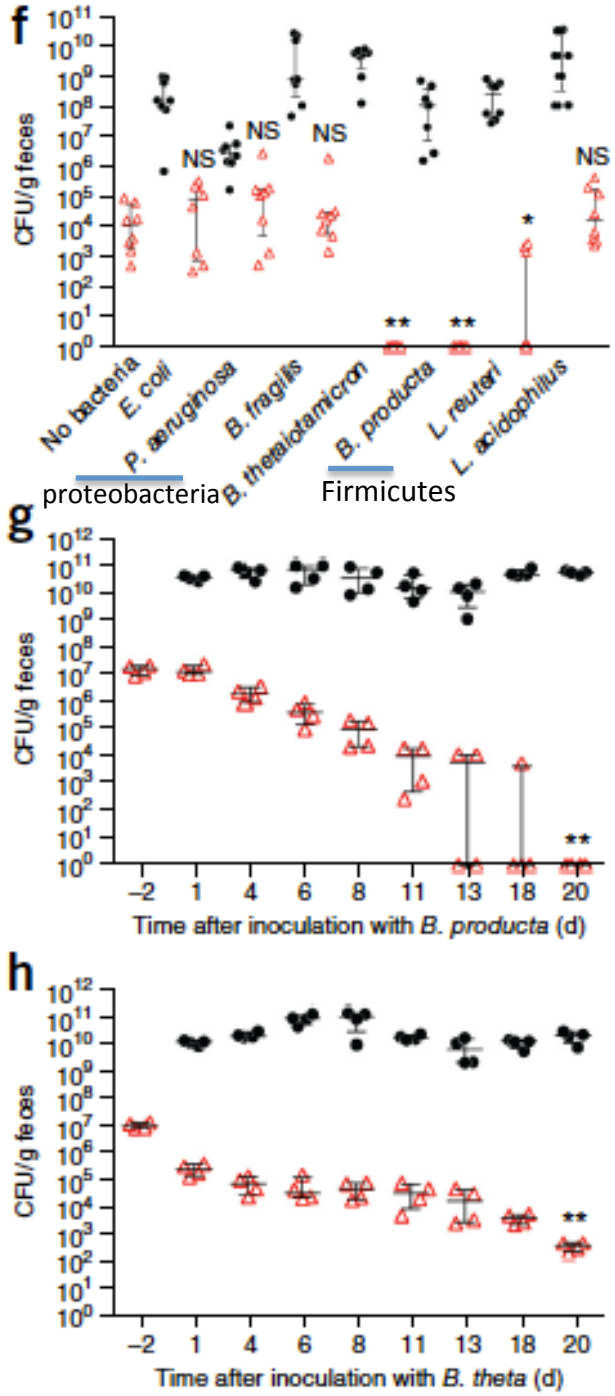
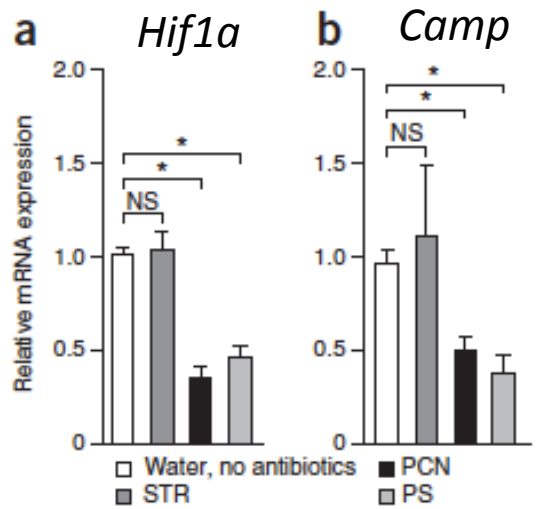


2×10^8 CFU

14 d after bacterial gavage

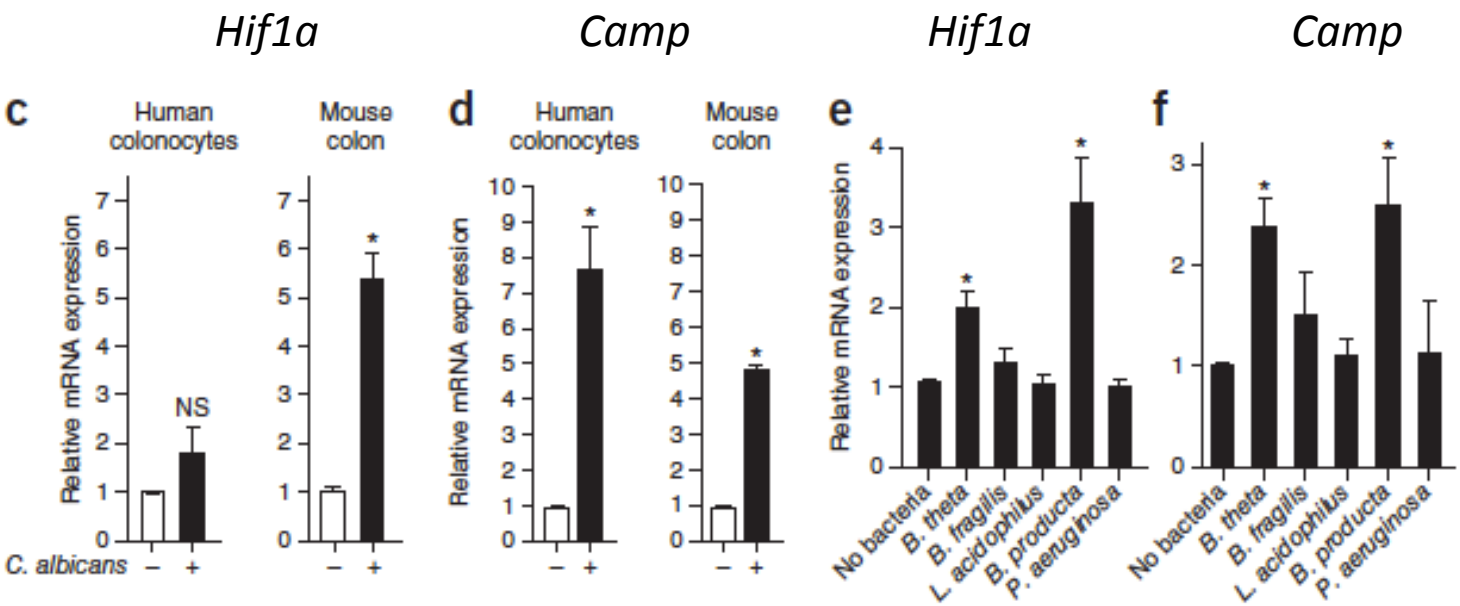
Germ-free mice

Figure 3 *B. theta* induces *Hif1a* and *Camp* in mouse colons.



Antimicrobial peptide LL-37 (*Camp-gene or* CRAMP-protein)
Cathelicidin-related antimicrobial peptide

HIF-1α is an essential regulator of mammalian innate defense
Hypoxia-inducible factor 1, a subunit



Mice treated with antibiotics and gavage with commensals

Figure 3 *B. theta* induces *Hif1a* and *Camp* in mouse colons.

Antibiotics treated mice

Germ-free mice

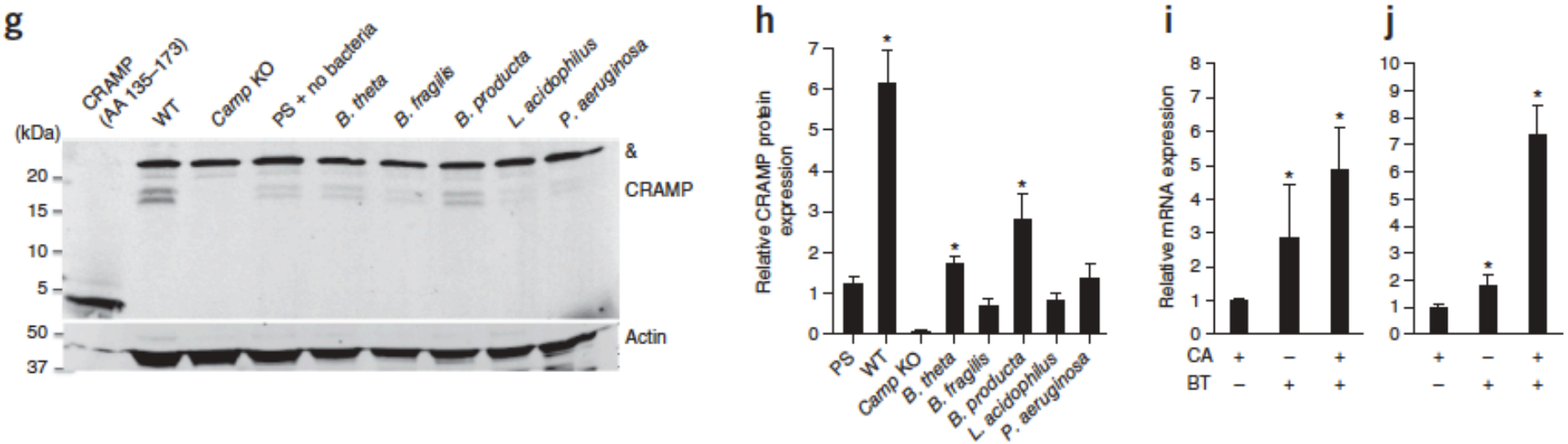
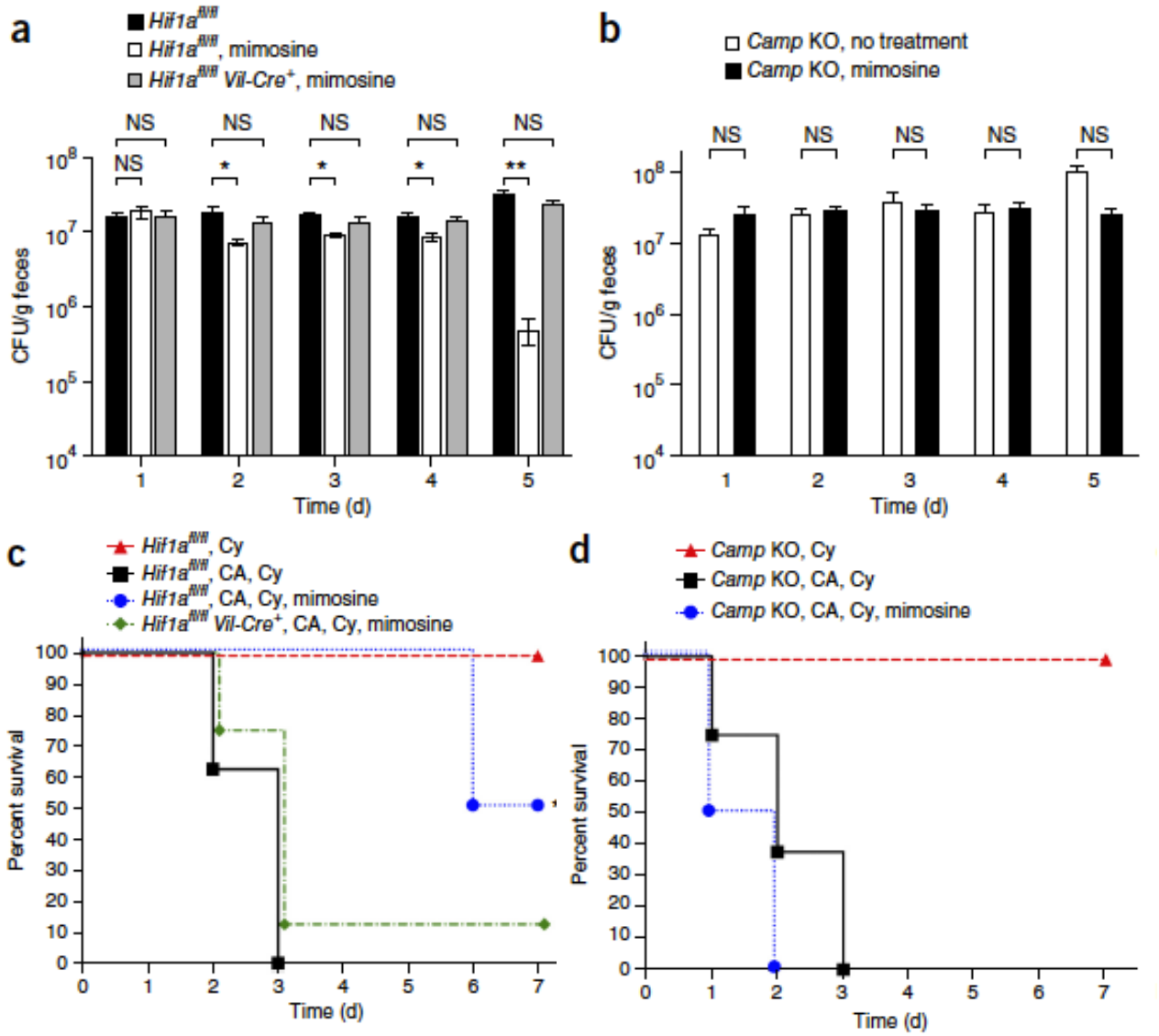


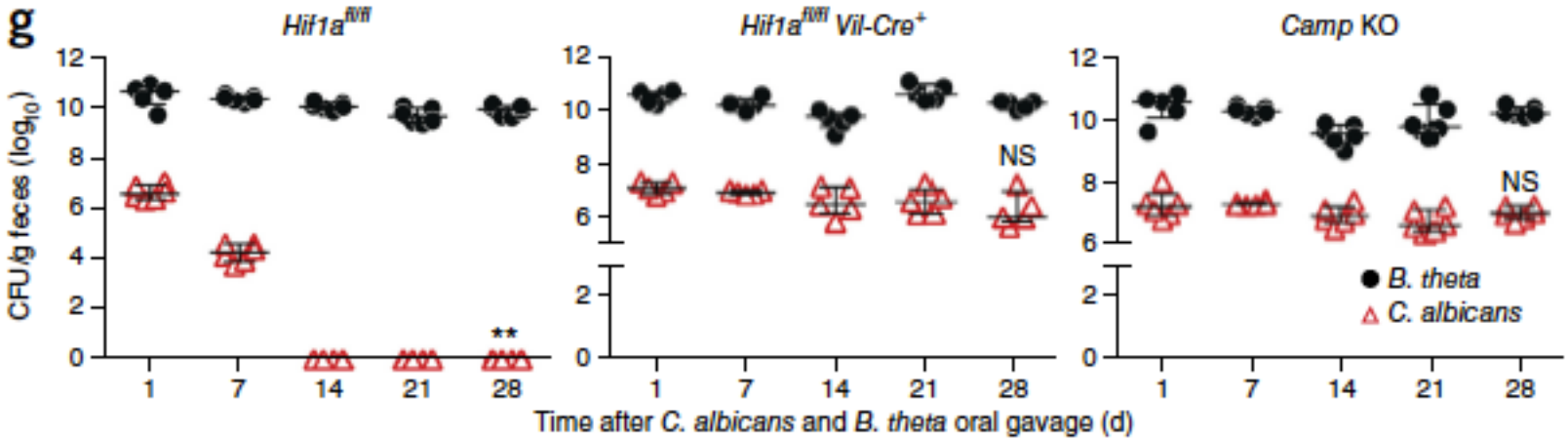
Figure 4 L-mimosine–dependent activation of *Hlf1a* and *Camp in vivo* decreases *C. albicans* GI colonization and dissemination.



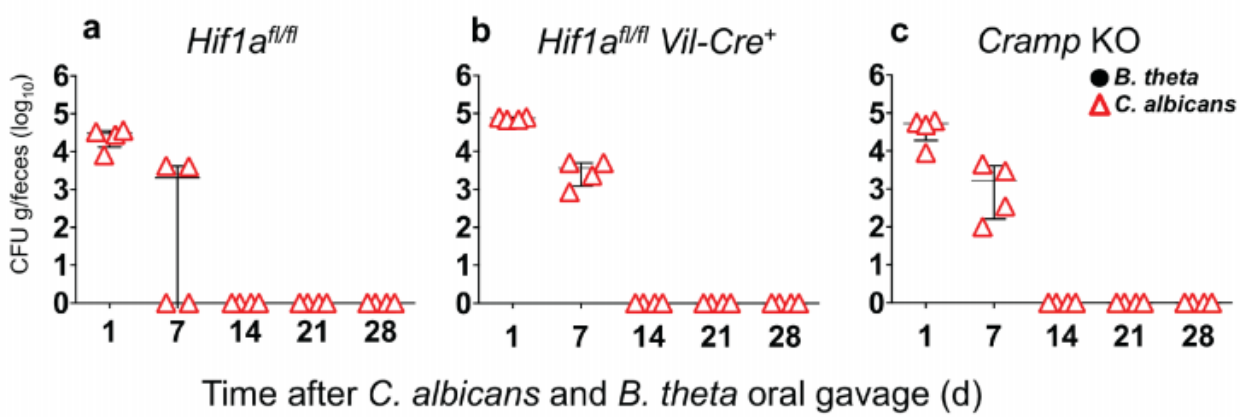
L-mimosine: agonist of HiF1a

Cy: cyclophosphamide

Figure 4 L-mimosine–dependent activation of *Hlf1a* and *Camp in vivo* decreases *C. albicans* GI colonization and dissemination.



HIF-1α and CRAMP were required for *B. theta*–induced protection against CA colonization of the gut



Conclusion

Clostridia Firmicutes and Bacteroides are able to induce Hif1a and CRAMP expression, thereby establishing colonisation resistance to Fungus.

The emergence of invasive fungal disease in humans correlates with advances in medical therapy, particularly antibiotic use and invasive surgical procedures.