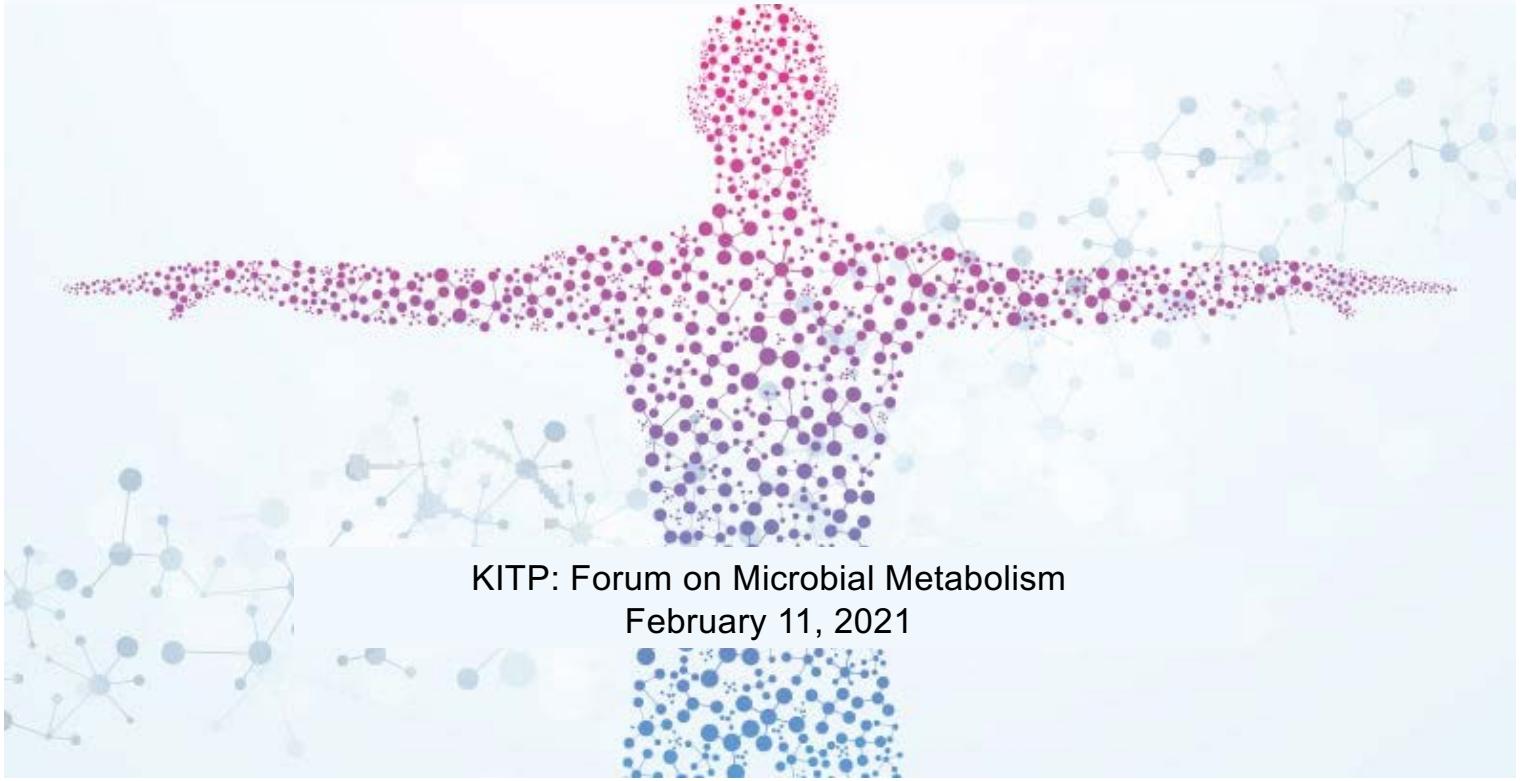
Metabolic strategies of pathogens in the human gut

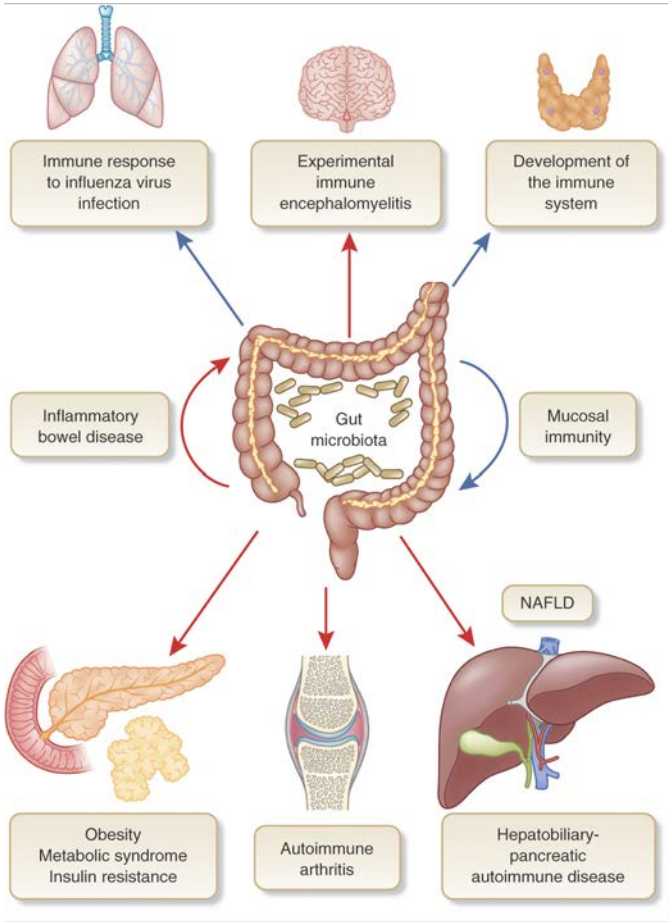


KITP: Forum on Microbial Metabolism
February 11, 2021

Microbiota

Microbiome

The Human Microbiota



The Human Microbiota: Terminology

Microbiota: The microbial communities inhabiting our body

Organ metaphor

Microbiome: A: Collection of genes, gene products and metabolites of the microbiota

"Joshua Lederberg suggested using the term 'microbiome' to describe the collective genome of our indigenous microbes (microflora), the idea being that a comprehensive genetic view of *Homo sapiens* as a life-form should include the genes in our microbiome."

Hooper & Gordon, Science. 2001 May 11;292(5519):1115-8.

The Human Microbiota: Terminology

Microbiota: The microbial communities inhabiting our body

Organ metaphor

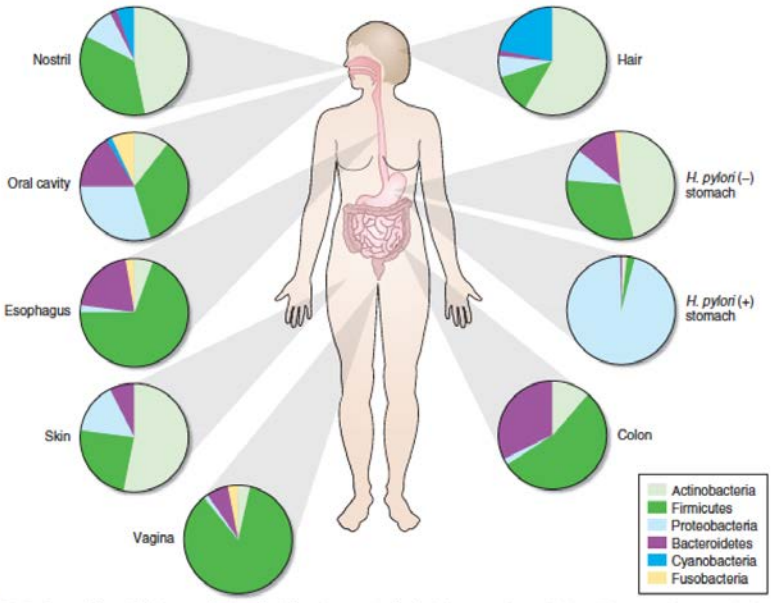
Microbiome: A: Collection of genes, gene products and metabolites of the microbiota
B: The microbiota and its environment

Ecosystem framework

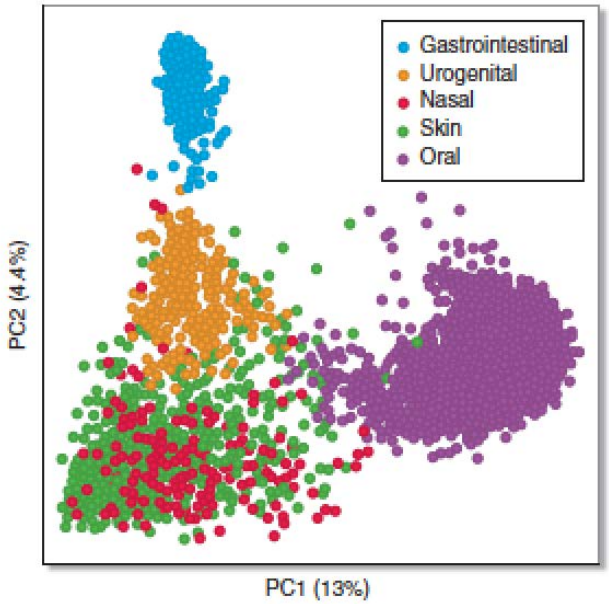
(2019 Frontiers in Microbiology
10 doi:10.3389/fmicb.2019.00292)

The Human Microbiota: Complexity

Different communities
at different body sites

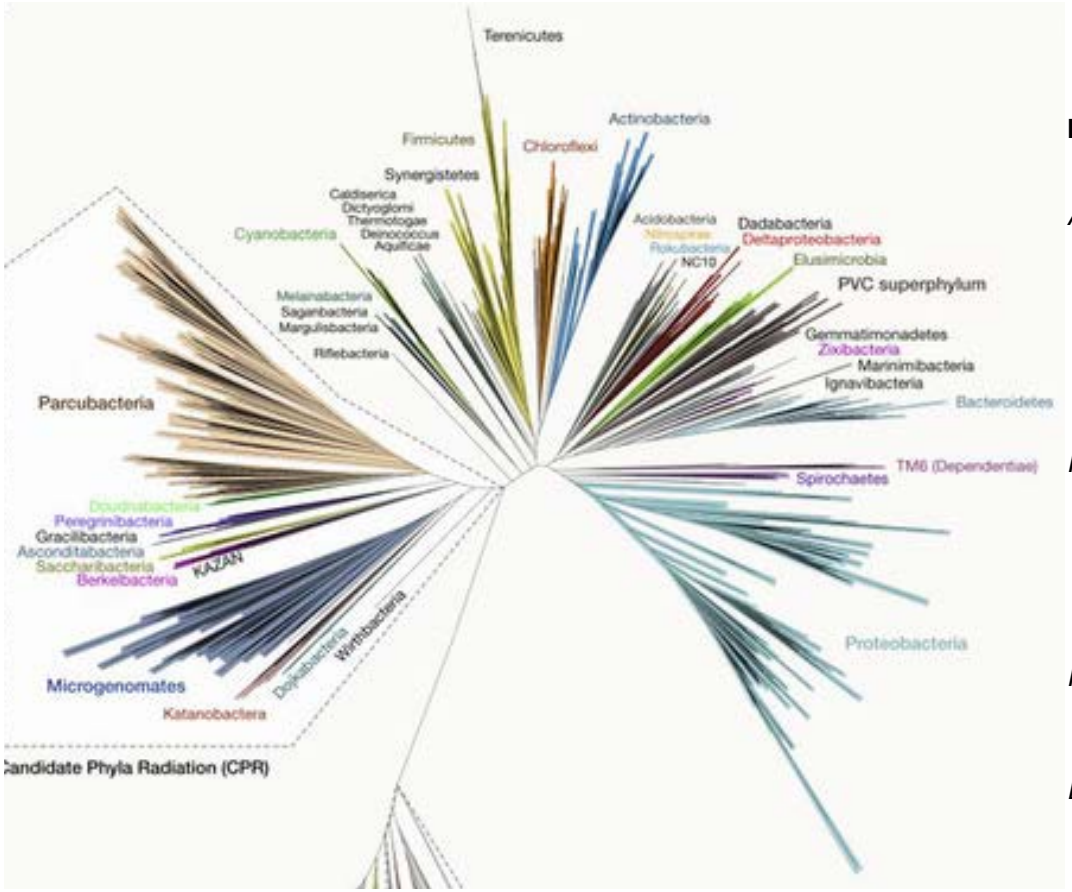


Compositional difference in the microbiota by anatomical site (Nature Review Genetics, 2012, 13:260)



The human microbiota is composed of distinct bacterial populations at different body sites. This principle component analysis (PCA) plot shows different body sites (colors) in healthy adults determined by 16S rRNA gene sequencing (dots). Similar microbiota compositions are grouped more closely together in two-dimensional space. (Nature, 2012, 486:207)

The Human Microbiota: Complexity



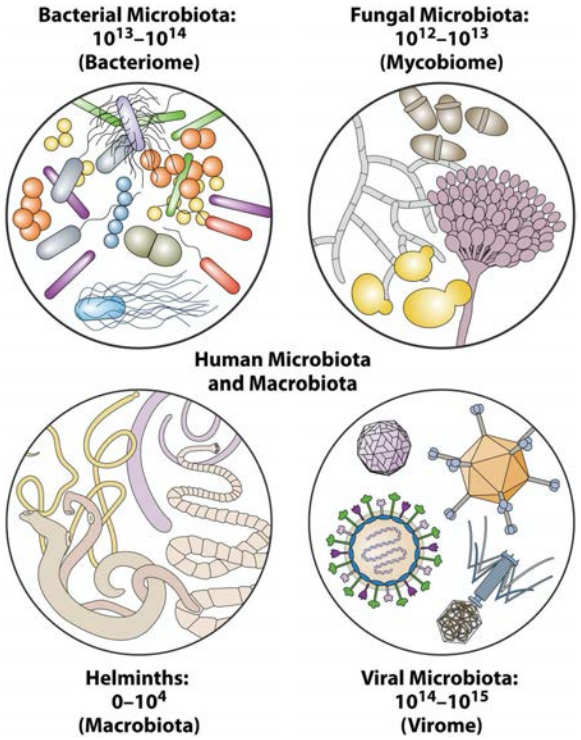
Phylum	Class	Species
Actinobacteria	*Actinobacteria*	*Bifidobacterium infantis*
Firmicutes	*Clostridia*	*Clostridium sp.* *Peptostreptococcus* *Lachnospira sp.* *Ruminococcus sp.* *Eubacterium rectale*
	Bacilli	*Lactobacillus sp.* *Streptococcus sp.* *Bacillus subtilis*
Proteobacteria	*γ-Proteobacteria*	*E. coli, Proteus sp.* *Klebsiella sp.*
Bacteroidetes	*Bacteroidia*	*Bacteroides fragilis* *B. thetaiotaomicron* *Prevotella sp.*

The Human Microbiota: Complexity

Different communities at different body sites

Very diverse ecosystem

- Bacteria, Archaea, Viruses, Fungi, Protozoa
- More than 1000 different species



2019 MMBR 83:00044-18

The Human Microbiota: Complexity

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Very diverse ecosystem

- Bacteria, Archaea, Viruses, Fungi, Protozoa
- More than 1000 different species

- Total number of cells: ~10^{14}
- Total number of human cells: ~10^{13}

Revised estimates for the number of human and bacteria cells in the body

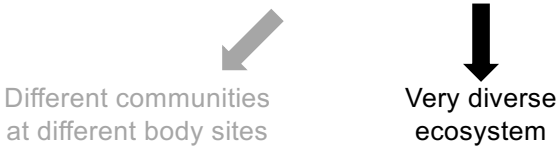
Ron Sender[1], Shai Fuchs[2,3,*] & Ron Milo[1,*]

[1]Department of Plant and Environmental Sciences, Weizmann institute of science, Rehovot, Israel.
[2]Department of Molecular Genetics, Weizmann institute of science, Rehovot, Israel.
[3]Current address: Department of Pediatric Endocrinology and Metabolism, the Hospital for Sick Children, Toronto, Canada

*Corresponding authors: ron.milo@weizmann.ac.il, shai.fuchs@sickkids.ca

We critically revisit the "common knowledge" that bacteria outnumber human cells by a ratio of at least 10:1 in the human body. We found the total number of bacteria in the "reference man" to be $3.9 \cdot 10^{13}$, with an uncertainty (SEM) of 25%, and a variation over the population (CV) of 52%. For human cells we identify the dominant role of the hematopoietic lineage to the total count of body cells (≈90%), and revise past estimates to reach a total of $3.0 \cdot 10^{13}$ human cells in the 70 kg "reference man" with 2% uncertainty and 14% CV. Our analysis updates the widely-cited 10:1 ratio, showing that the number of bacteria in our bodies is actually of the same order as the number of human cells. Indeed, the numbers are similar enough that each defecation event may flip the ratio to favor human cells over bacteria.

The Human Microbiota: Complexity



- Bacteria, Archaea, Viruses, Fungi, Protozoa
- More than 1000 different species

- Total number of cells: ~10^{14}
- Total number of human cells: ~10^{13}

- 100-times more microbial genes than human genes

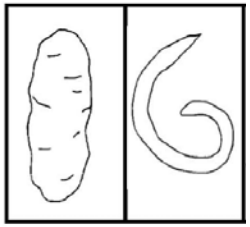
The Human Microbiota: Complexity

Different communities at different body sites

Very diverse ecosystem

Taxa carriage varies between individuals

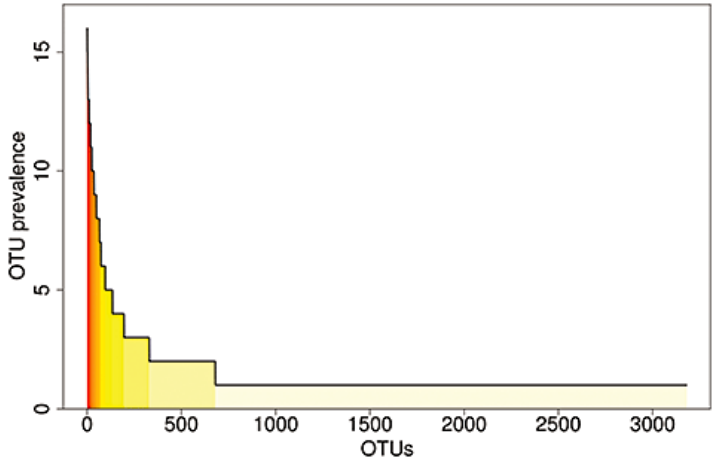
17 individuals



Fecal samples

Sequencing

> 8,000 OTUs



Most prevalent OTUs, present in 8 out of 17 individuals or more, corresponded to 2.1% of all OTUs

(2009 Environmental Microbiology 11: 2574)

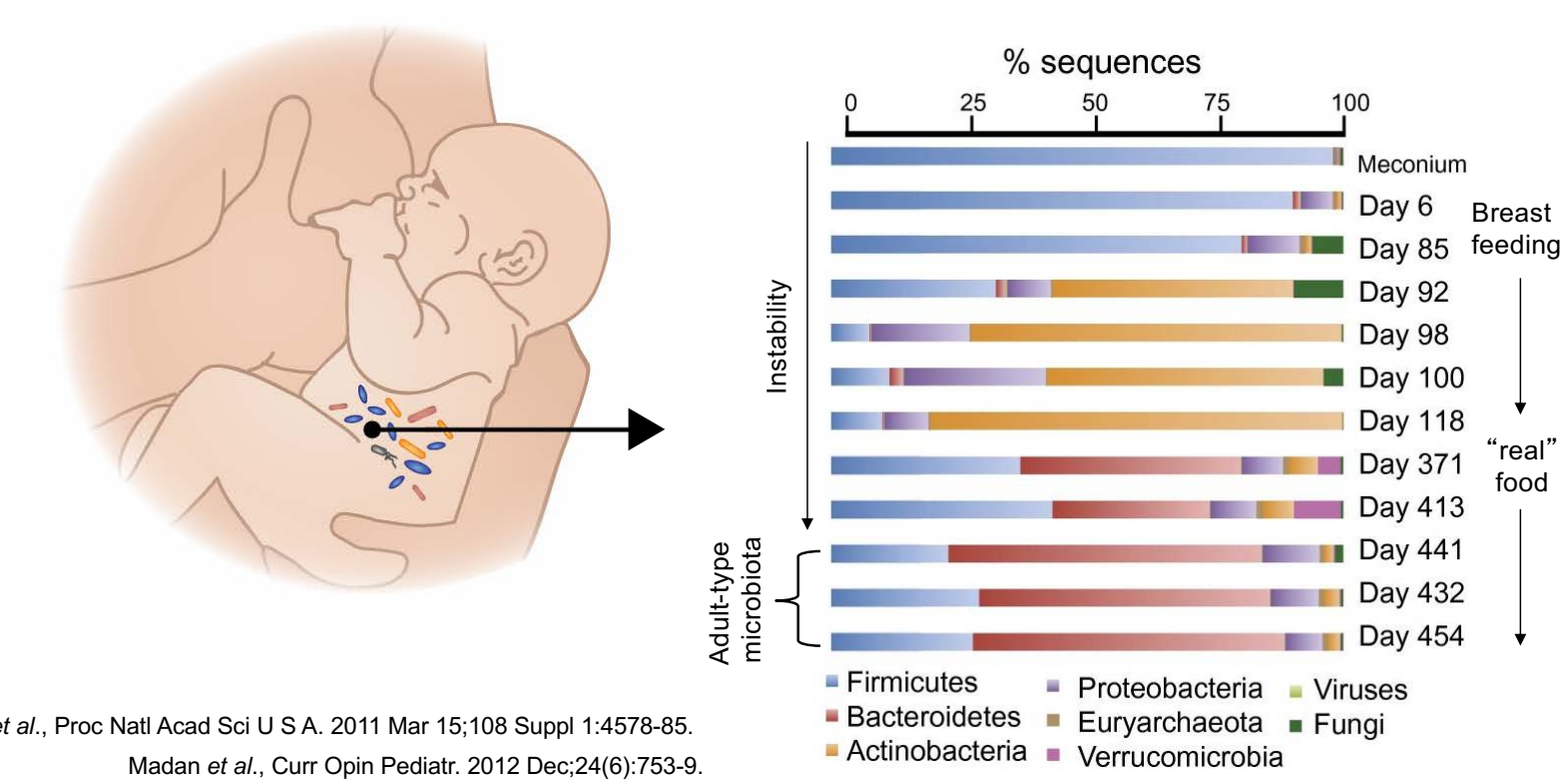
The Human Microbiota: Complexity

Different communities at different body sites

Very diverse ecosystem

Taxa carriage varies between individuals

Microbiota composition fluctuates over time



Koenig *et al*., Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1:4578-85.

Madan *et al*., Curr Opin Pediatr. 2012 Dec;24(6):753-9.

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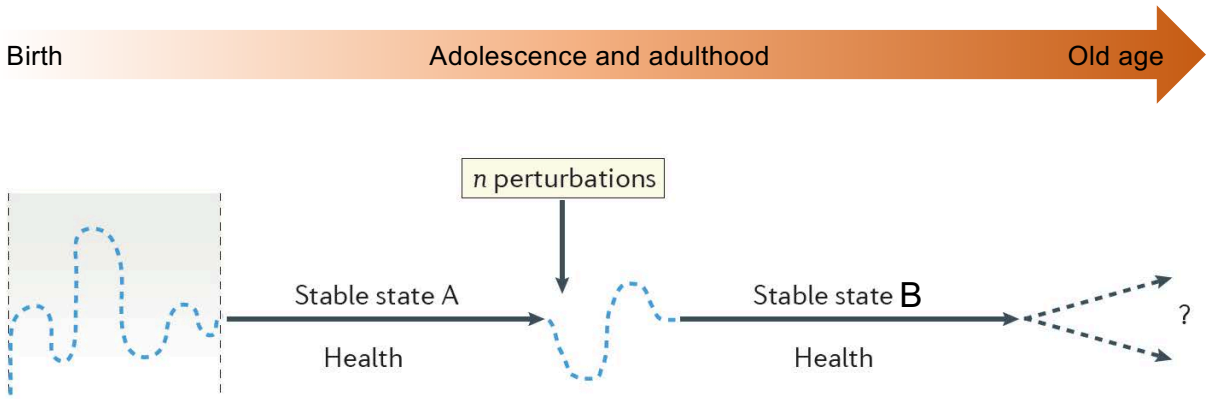

Schematic representation of the resilience phenomena in host-associated microbial communities (2017 Nature Reviews Microbiology 15:631)

The Human Microbiota: Complexity

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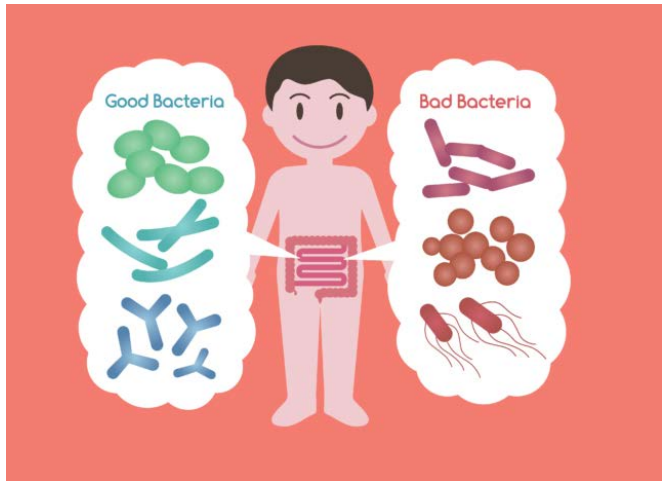
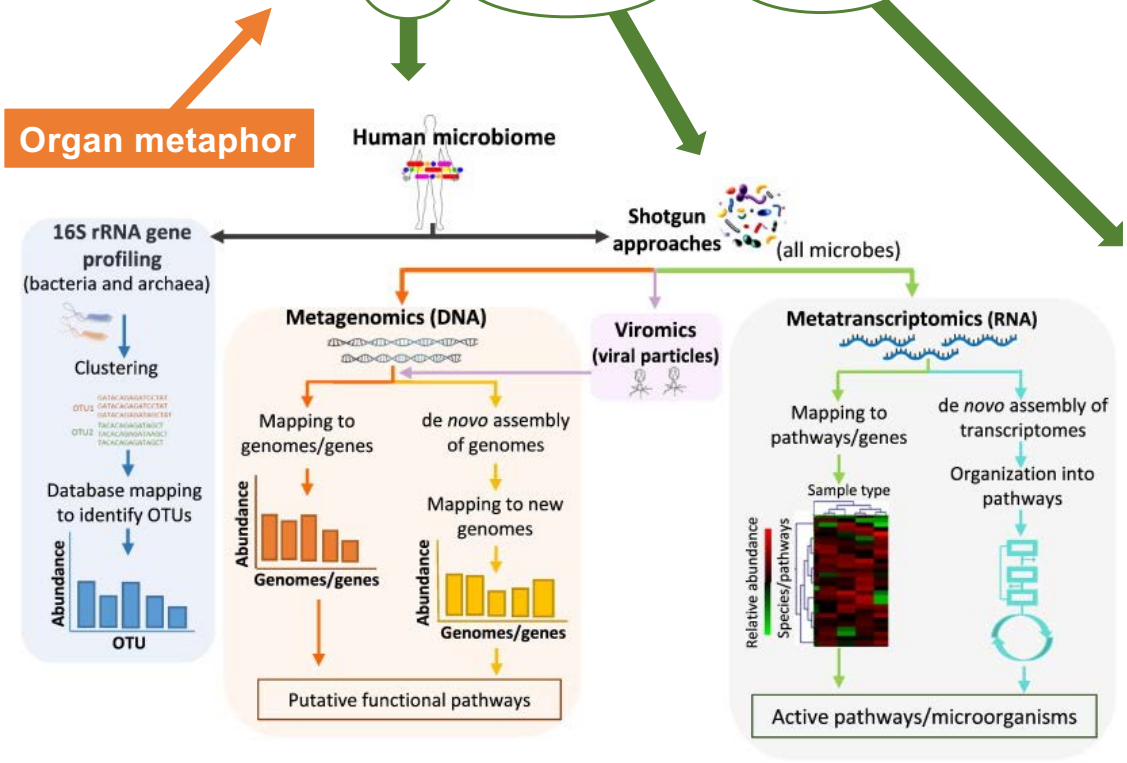
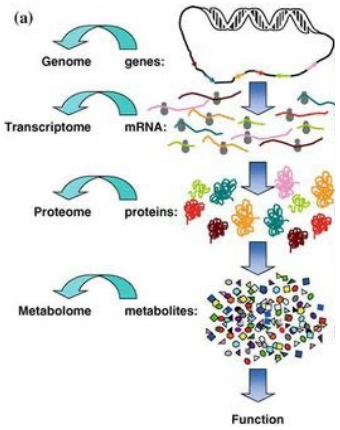


What constitutes a healthy microbiome?
What is dysbiosis?

The Human Microbiota: Homeostasis

Microbiome: Collection of genes, gene products and metabolites of the microbiota





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The Human Microbiota: Homeostasis

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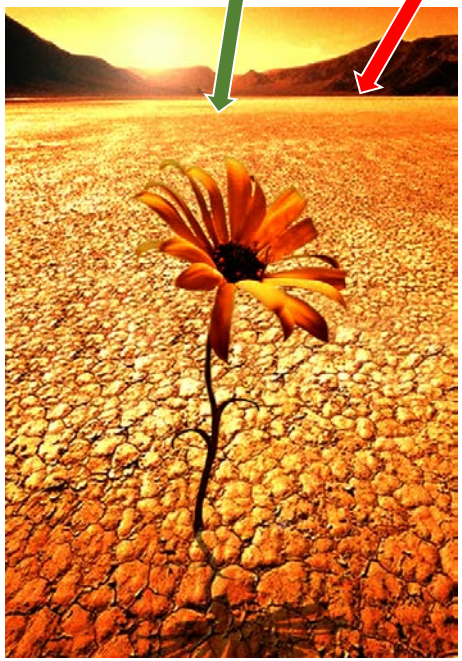
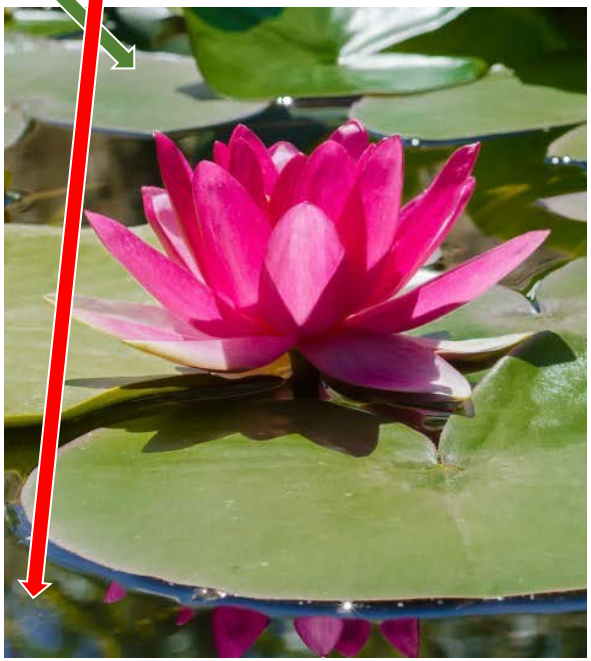
Microbiome: The microbiota and its environment

Ecosystem framework





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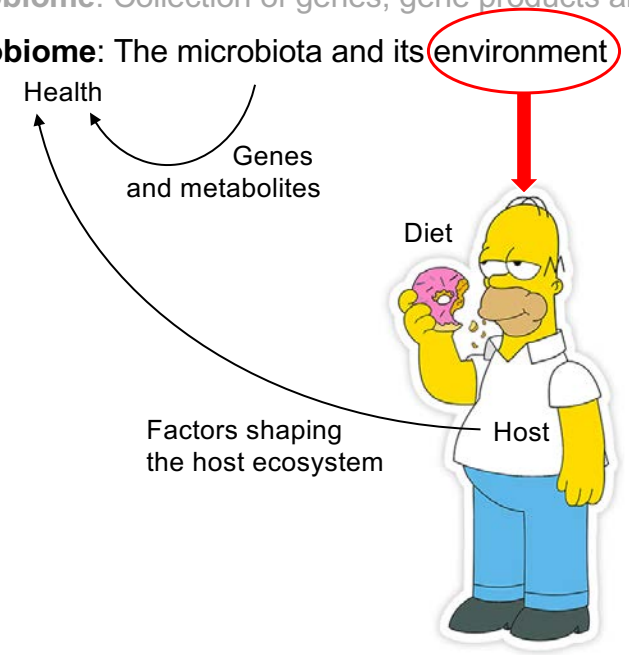
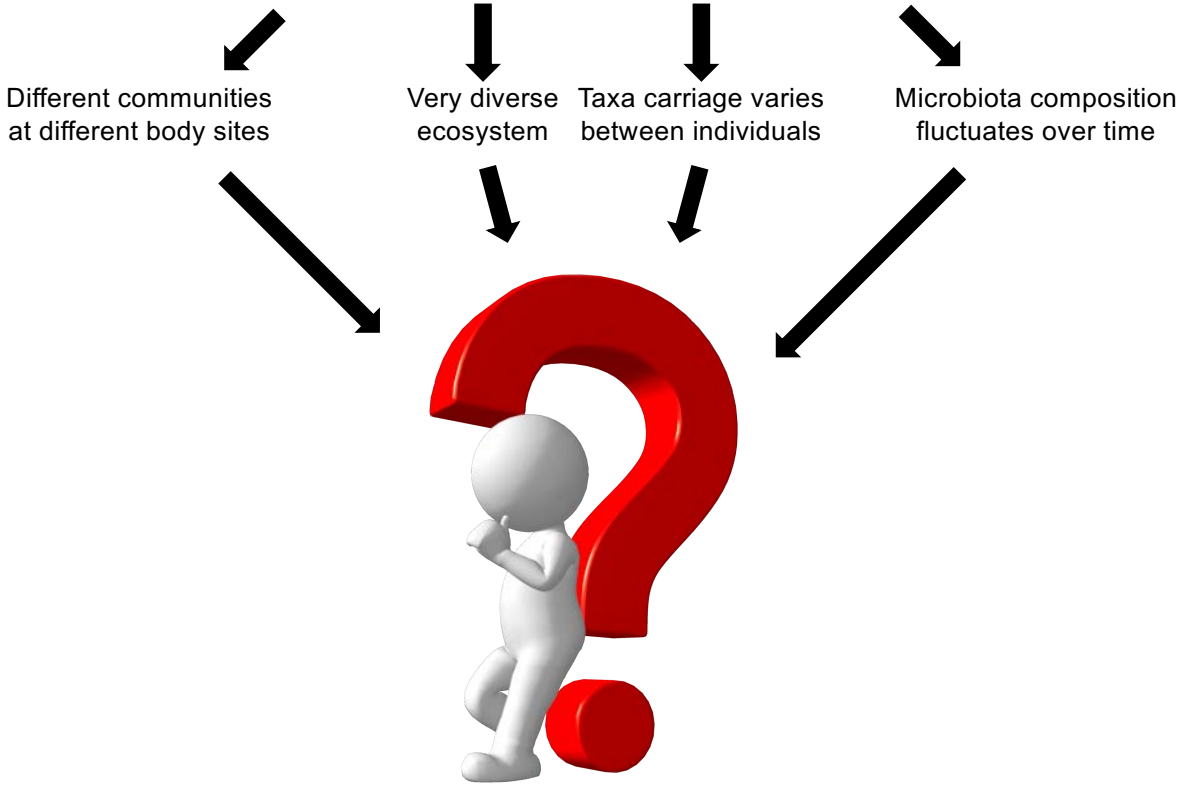


The Human Microbiota: Complexity

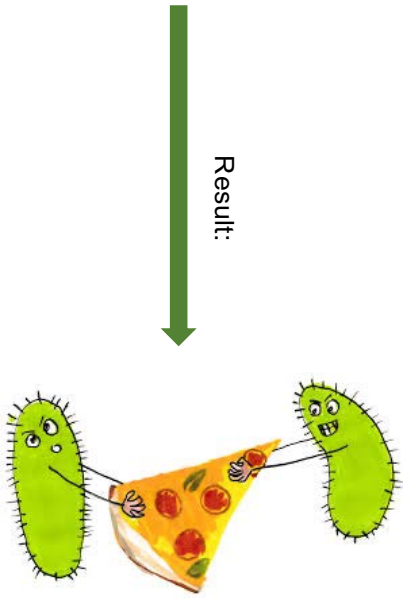


What constitutes a healthy microbiome?

Principles of community assembly

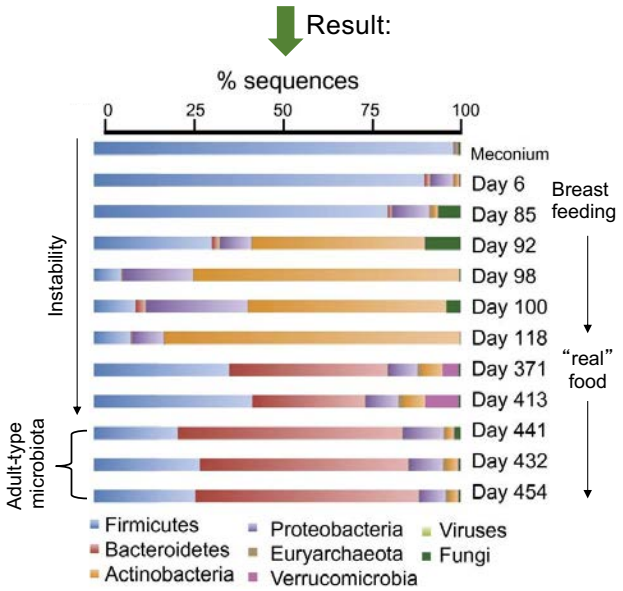
Competition and habitat filtering govern gut microbiota assembly

Competition: Interaction between species



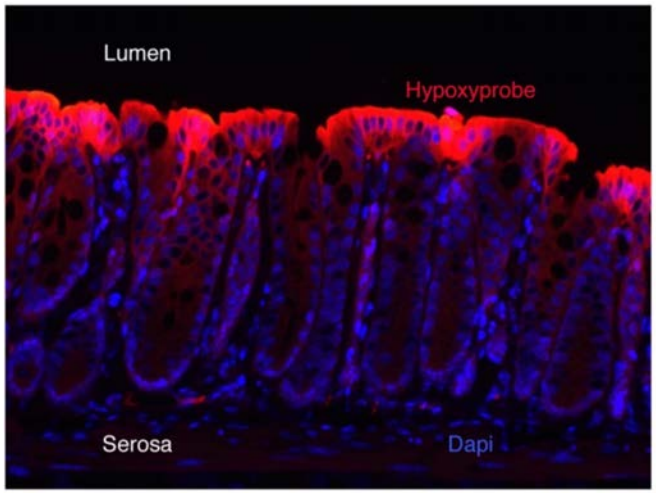
Competition limits the number of similar coexisting species

Habitat filtering: Interaction of species with their environment



Habitat filtering establishes dominant taxa in the colonic microbiota

Principles of community assembly: Habitat filtering



Maintenance of anaerobiosis

Epithelial hypoxia in the colon (<1% O_2)

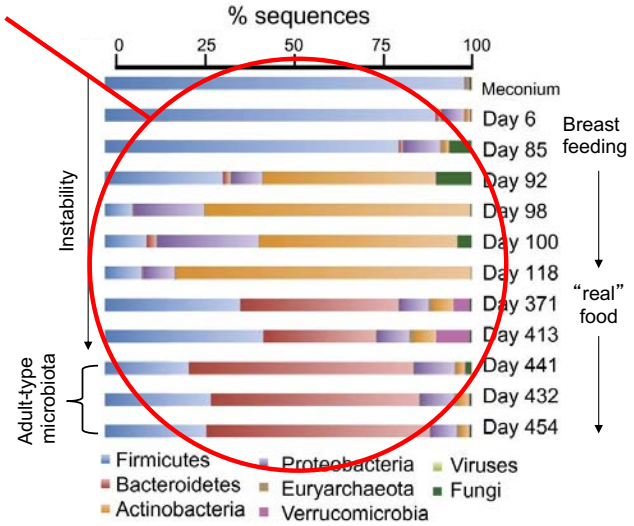
Tissue oxygenation (3-10% O_2)

Host control:

Dominance of obligately anaerobic bacteria

Habitat filtering: Interaction of species with their environment

Result:



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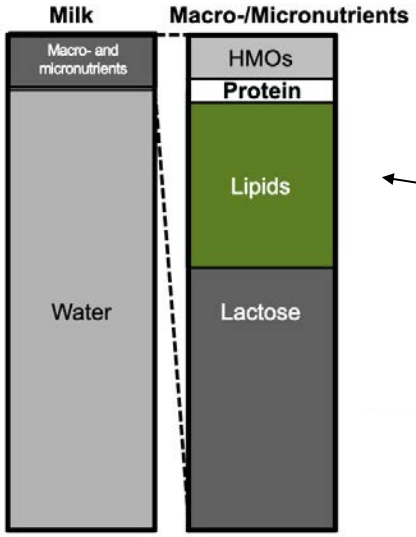
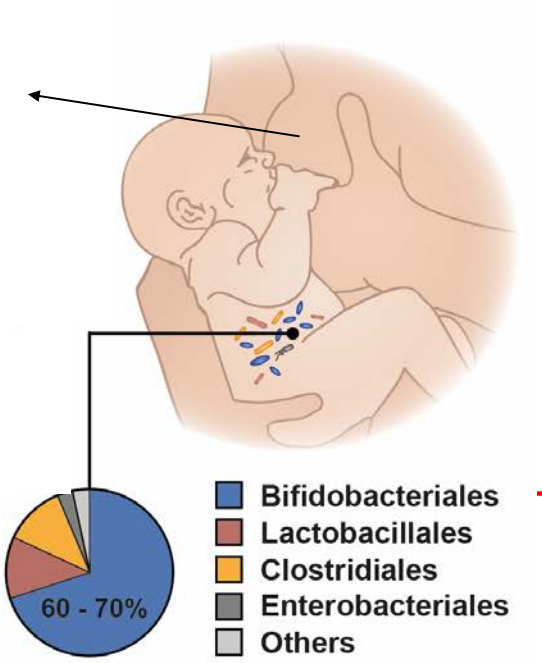




Host control:

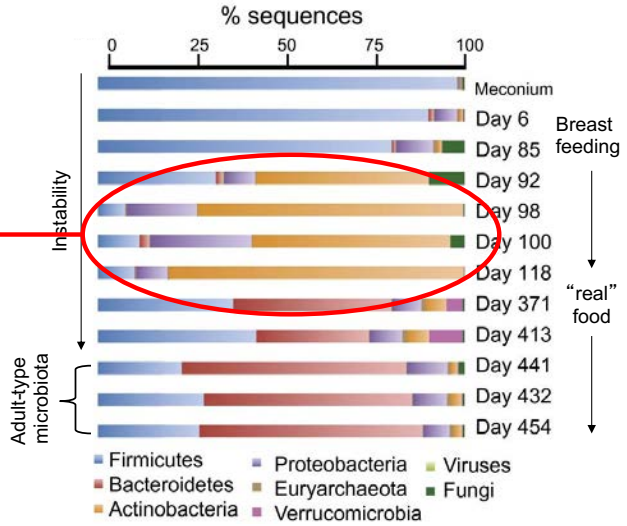
Dominance of obligately anaerobic bacteria

Dominance of milk oligosaccharide consumers

Diet:

Habitat filtering: Interaction of species with their environment

Result:



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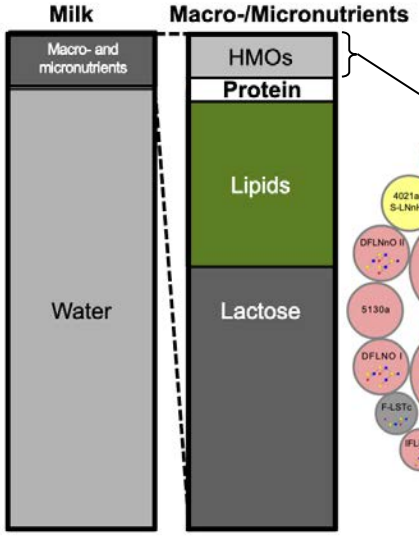
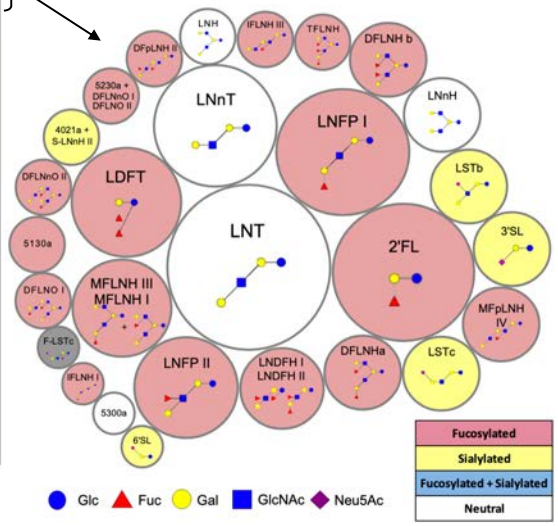
Principles of community assembly : Habitat filtering





Human milk oligosaccharides (HMOs)
>200 species

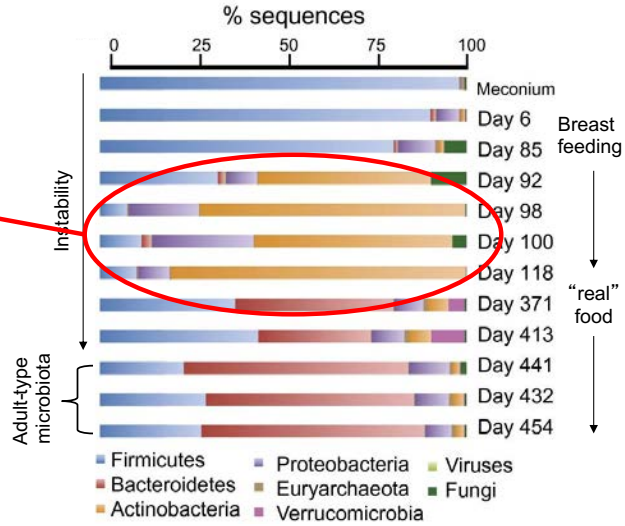
Host control:

Dominance of obligately anaerobic bacteria

Habitat filtering: Interaction of species with their environment

Result:

Dominance of milk oligosaccharide consumers



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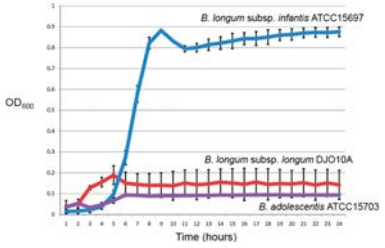
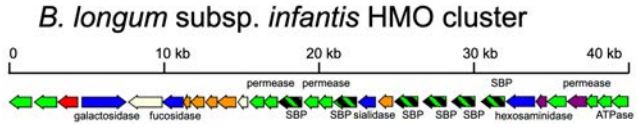
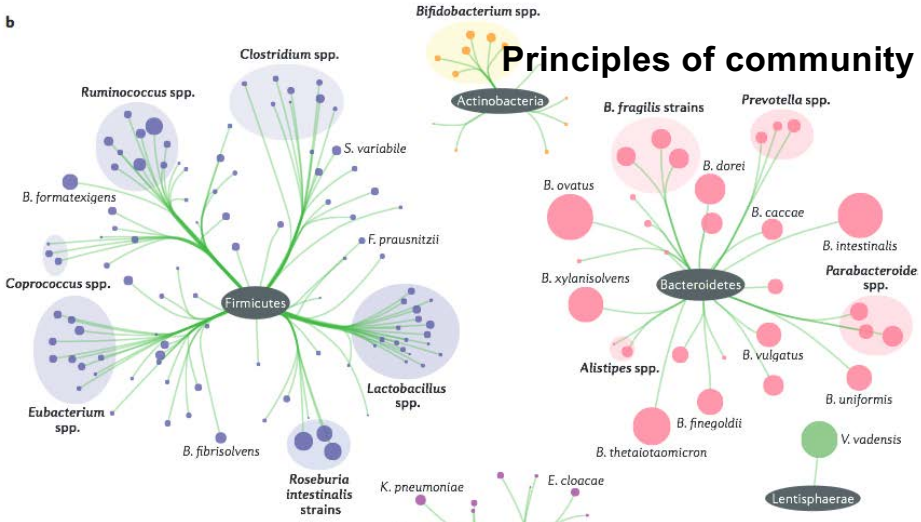




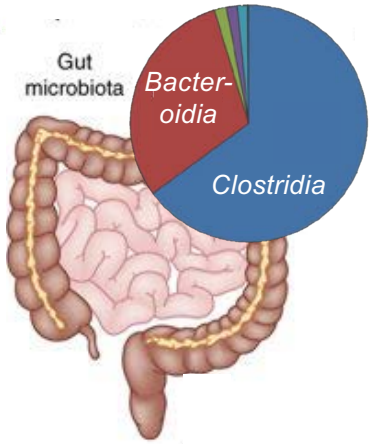
Diet:

Principles of community assembly : Habitat filtering



2013 Nat Rev Microbiol. 11:497

Dietary fiber



Host control:

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Dominance of fiber eaters

Diet:

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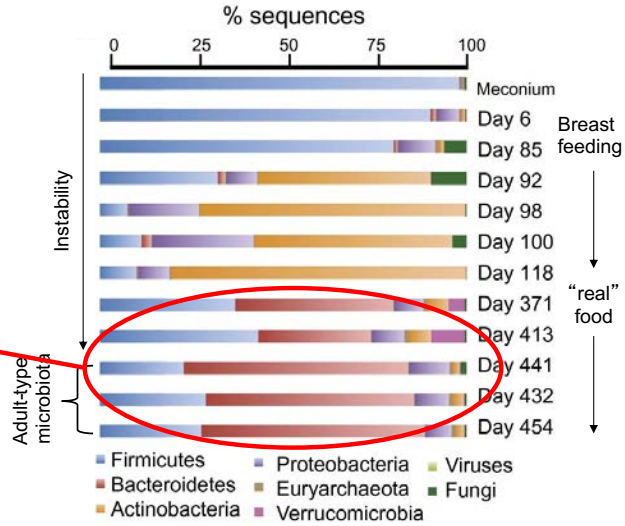
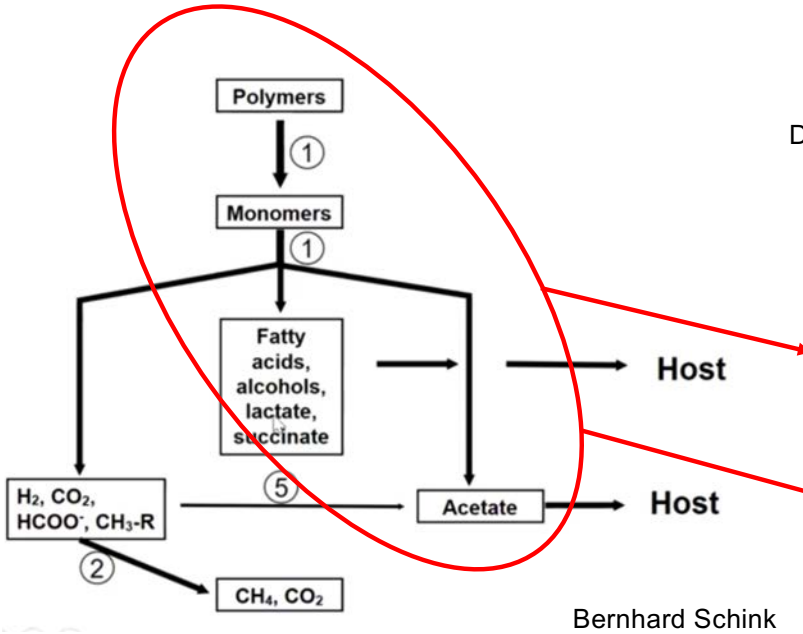
Result:



Habitat filtering establishes dominant taxa in the colonic microbiota

Principles of community assembly : Habitat filtering



Bernhard Schink

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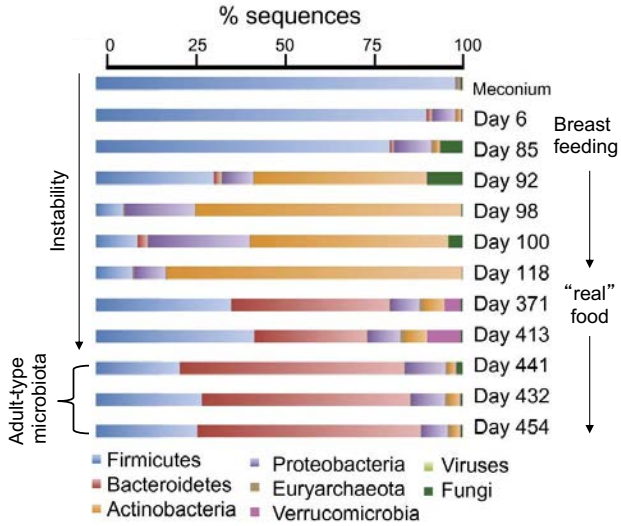

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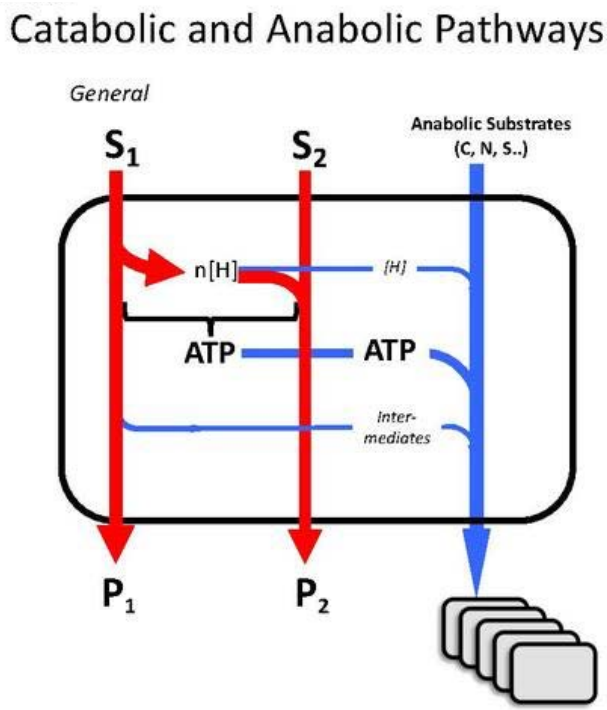

Alfred Spormann

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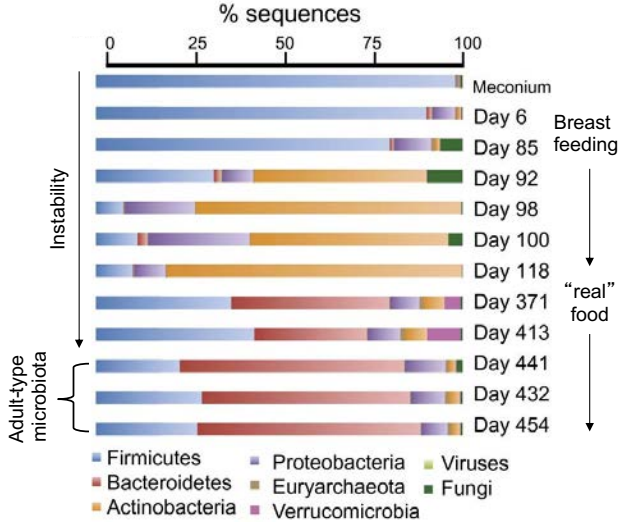
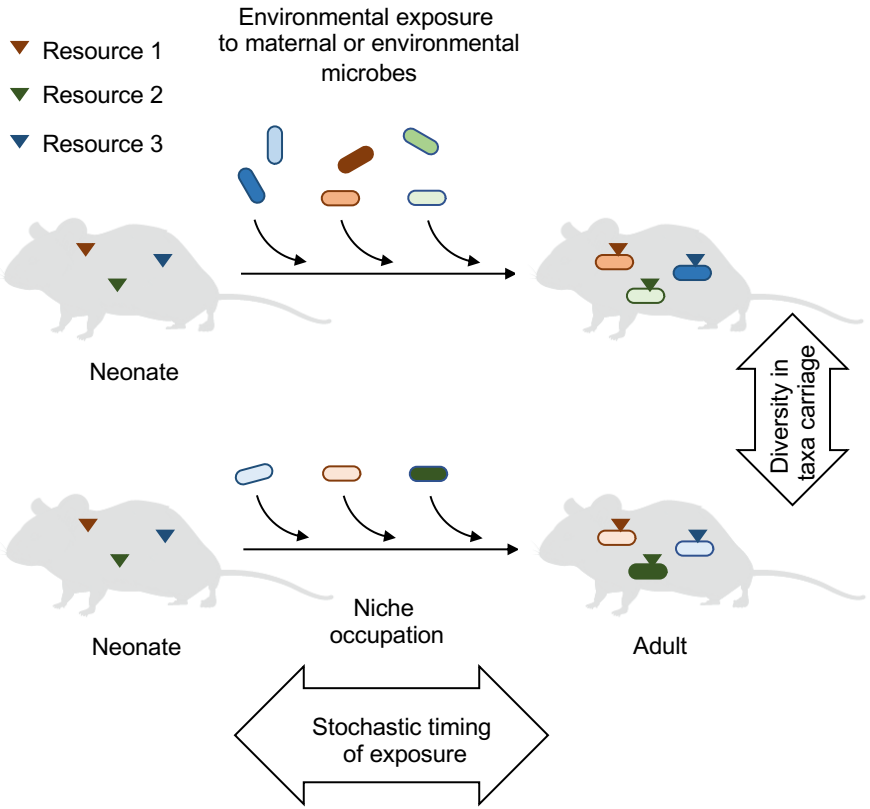


Habitat filtering establishes dominant taxa in the colonic microbiota

Principles of community assembly: Priority effects

Nutrient-niche hypothesis: To coexist, each member of the microbiota must consume some critical resource better than any other member within the community and the abundance of this critical resource determines its abundance (1983 Infect Immun 39:686)



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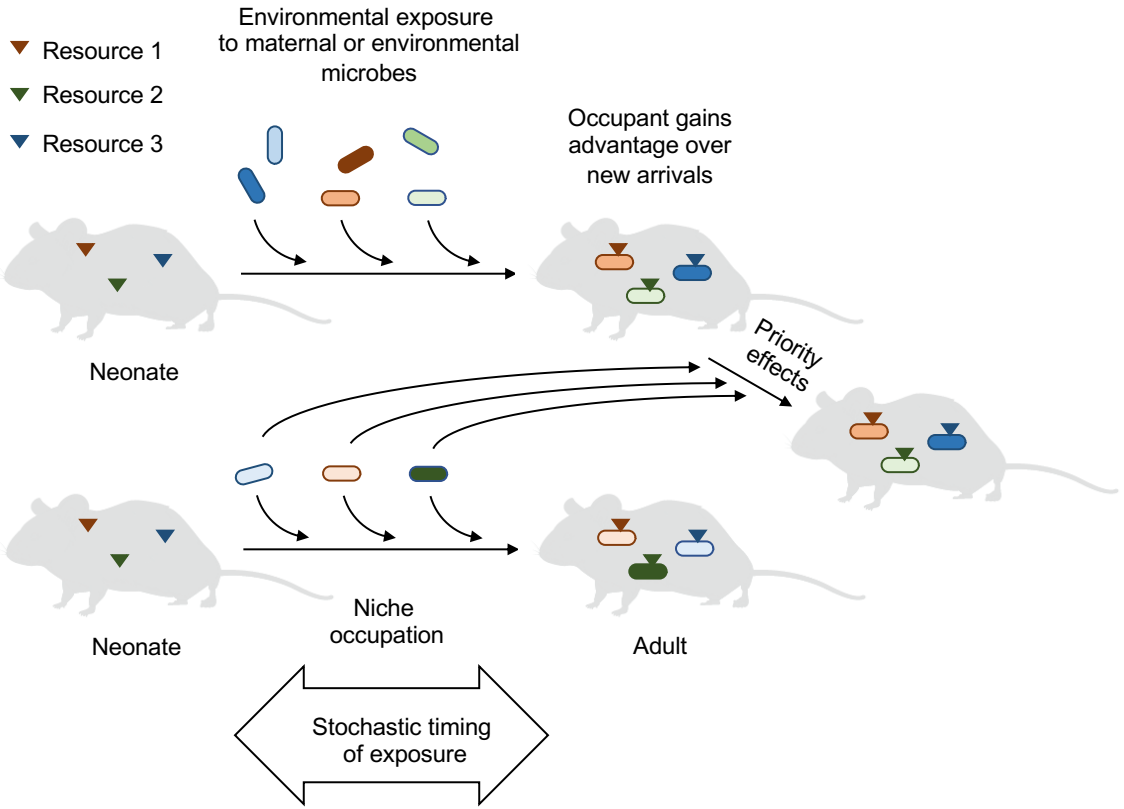


Principles of community assembly: Microbiota resistance

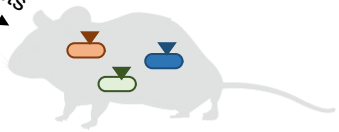
NIH HUMAN MICROBIOME PROJECT

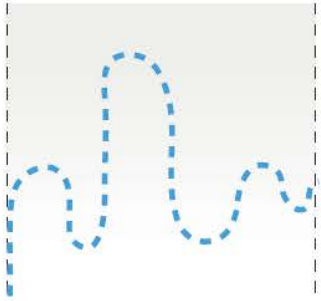
What is a balanced microbial community?

Historical contingency

Occupant gains advantage over new arrivals

Priority effects





Stable state A

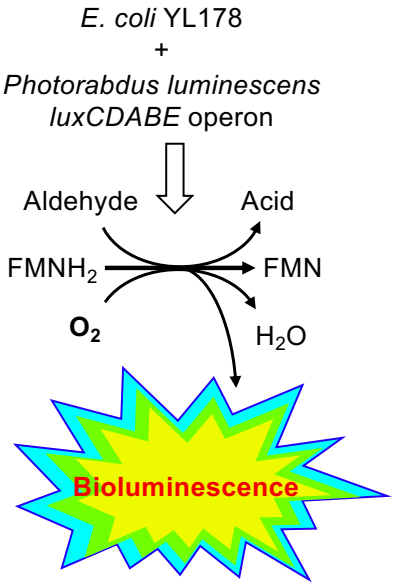
Health

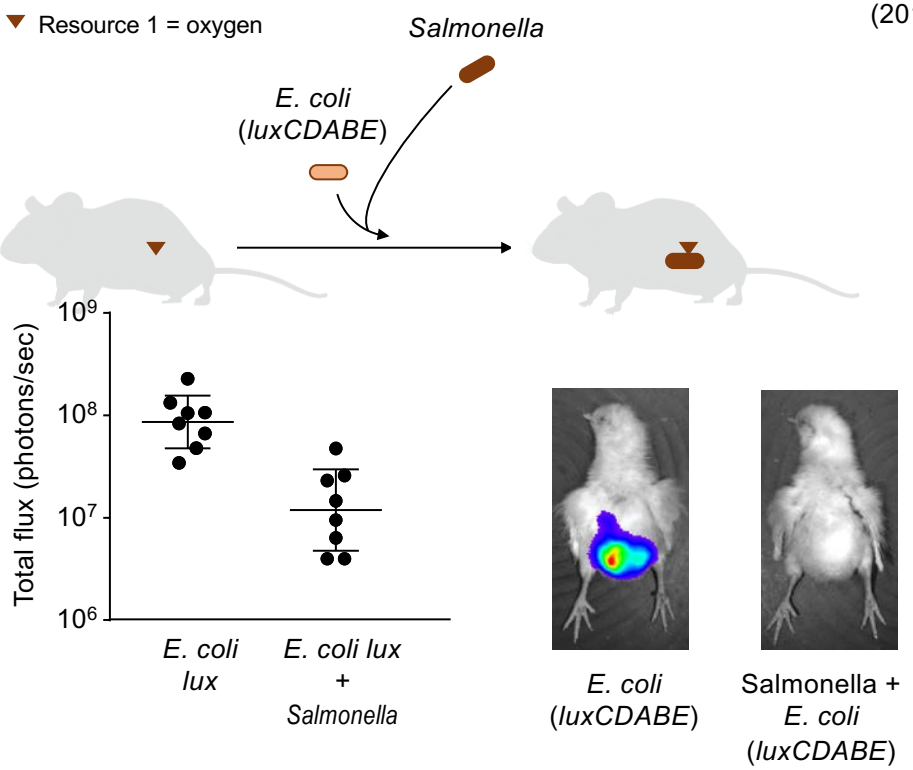
Microbiota resistance: The phenomenon that the adult microbiota is resistant to change

Principles of community assembly: Priority effects

Yael Litvak

(2019 CHM 25:128)

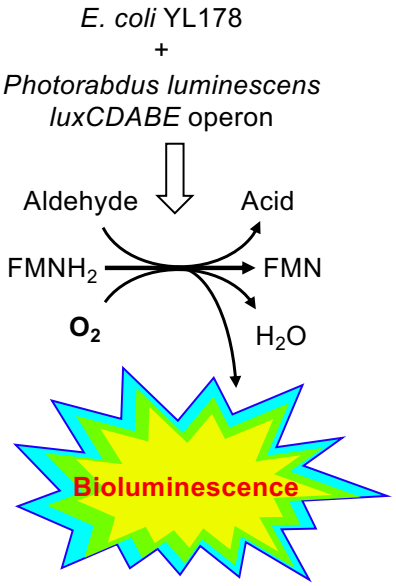


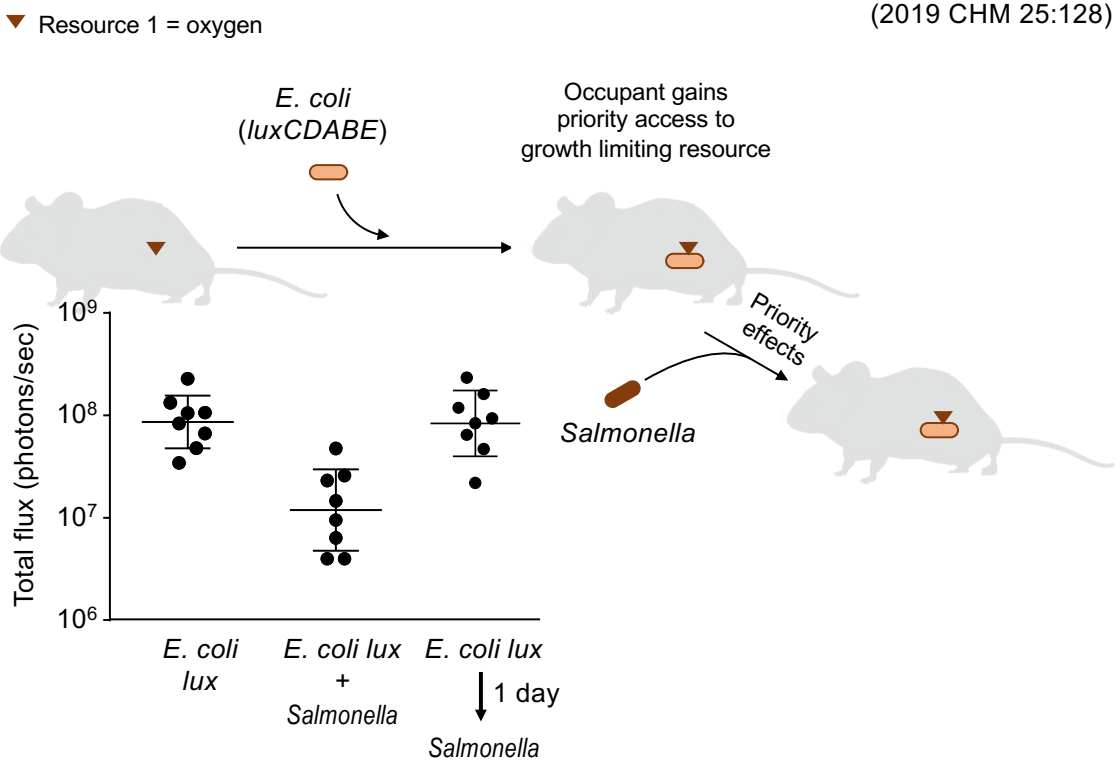


Principles of community assembly: Priority effects

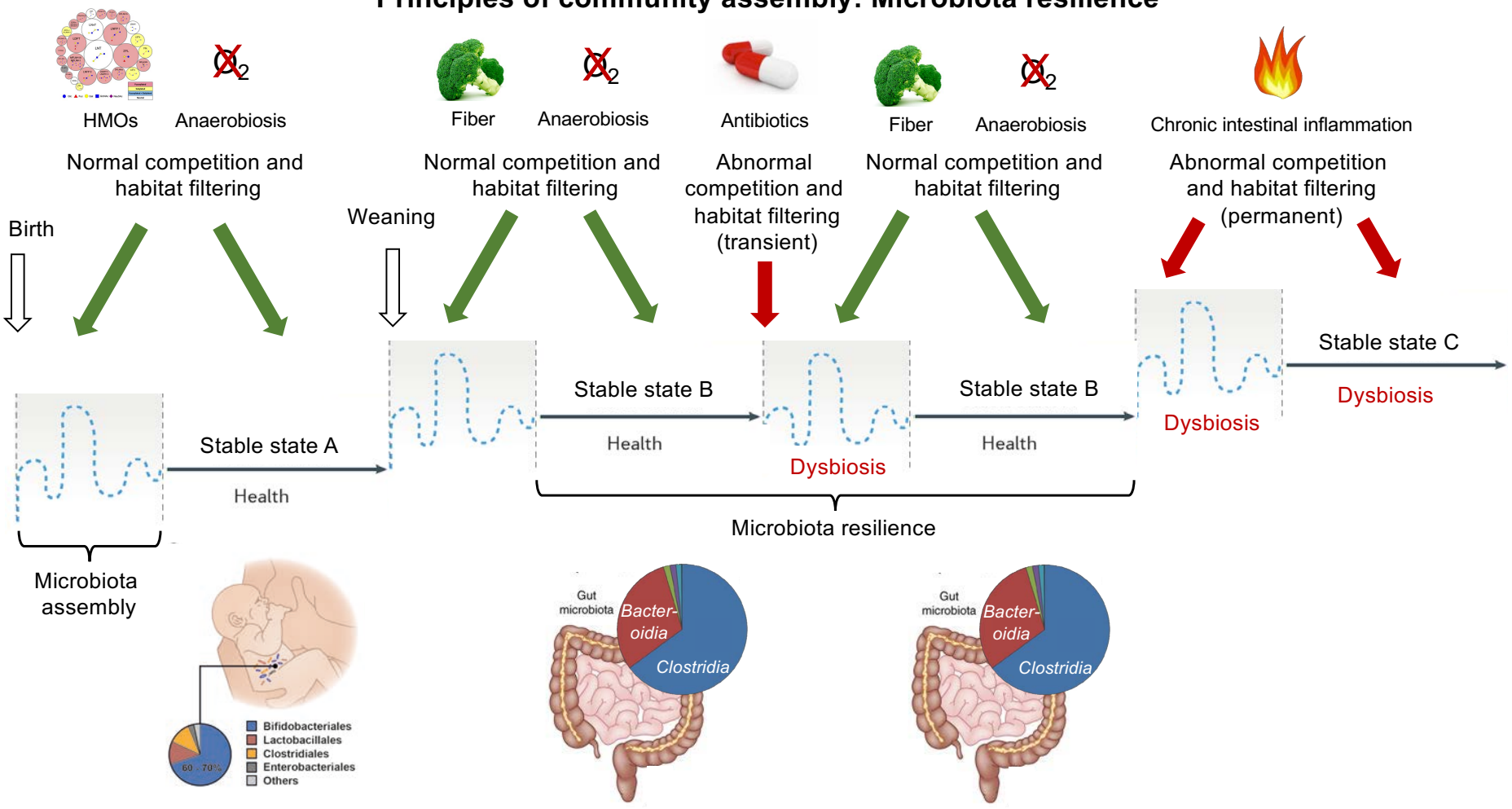
Yael Litvak

(2019 CHM 25:128)

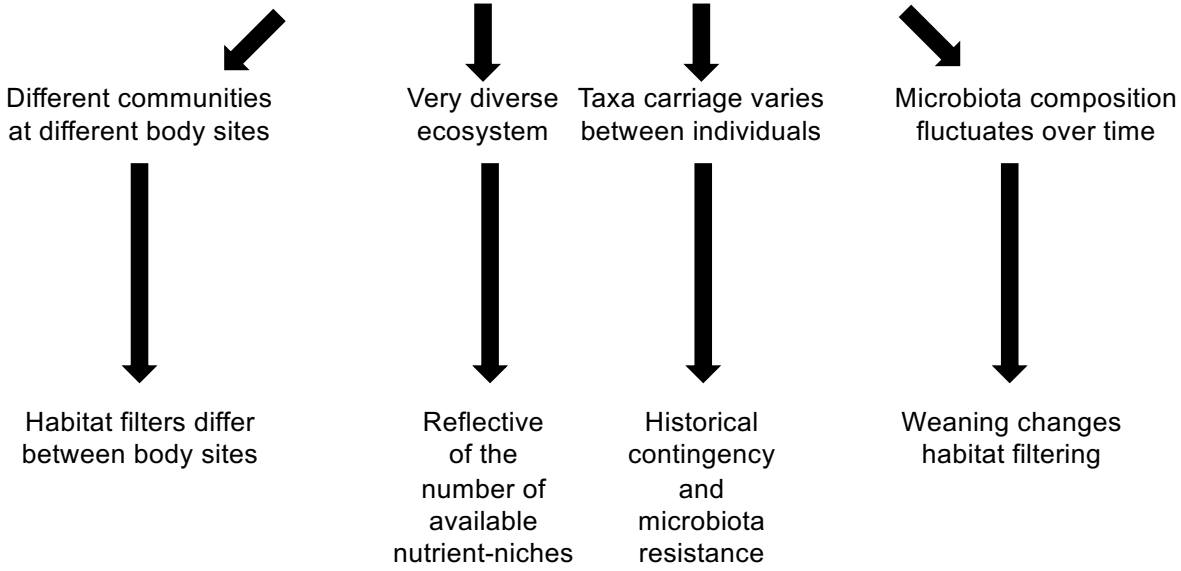




Principles of community assembly: Microbiota resilience



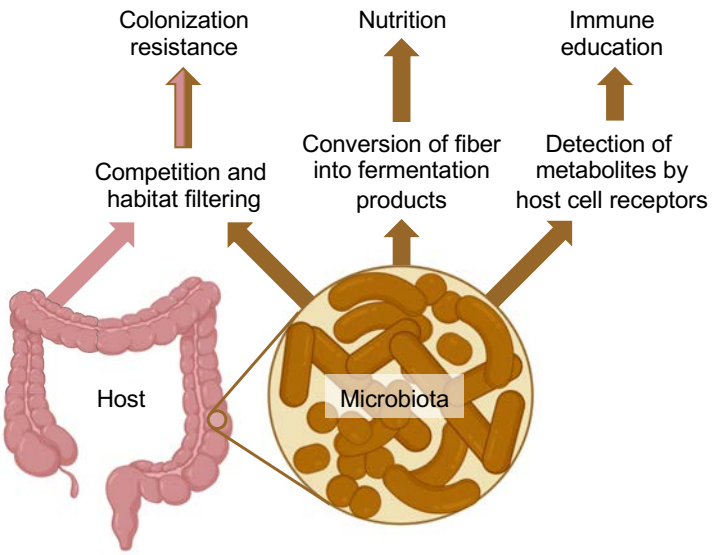
The Human Microbiota: Complexity



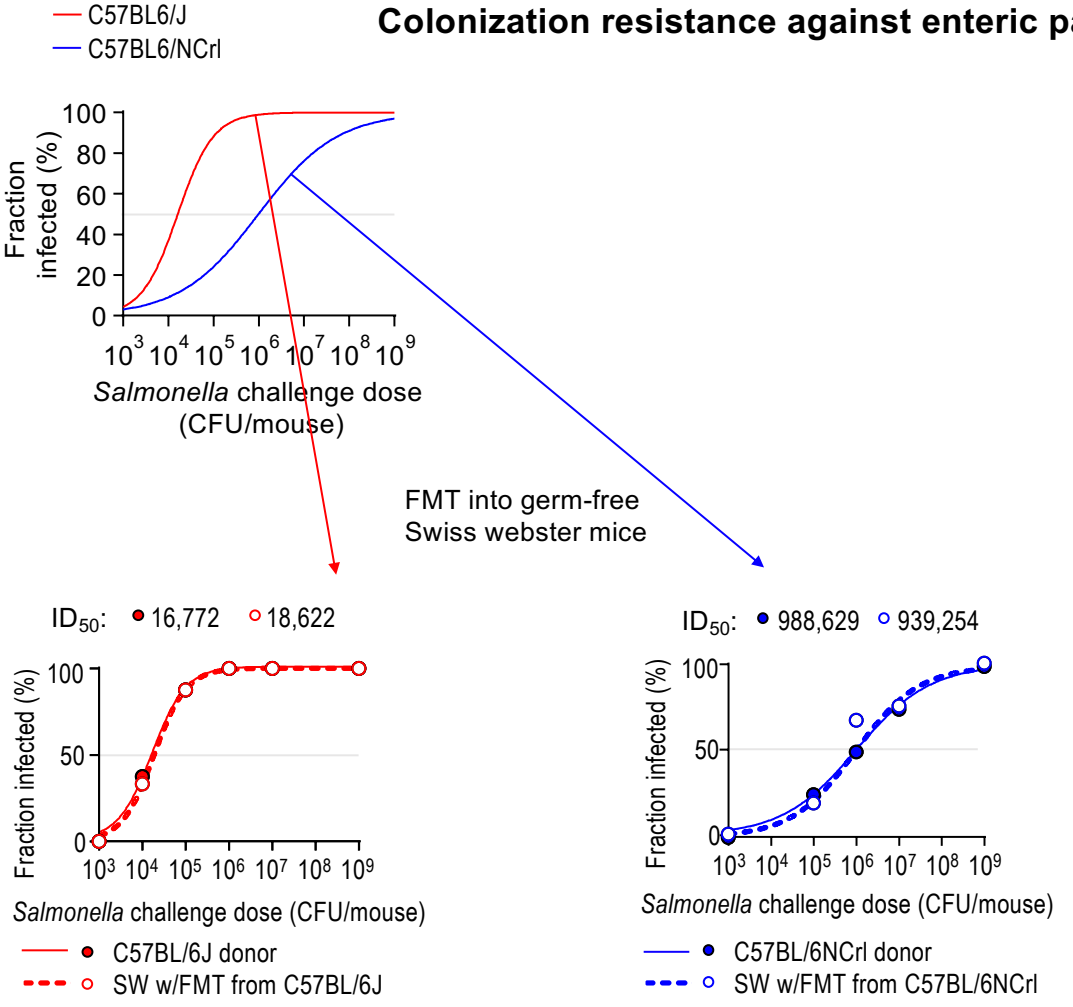
Dysbiosis is the result of abnormal competition and habitat filtering

Homeostasis is the result of normal competition and habitat filtering

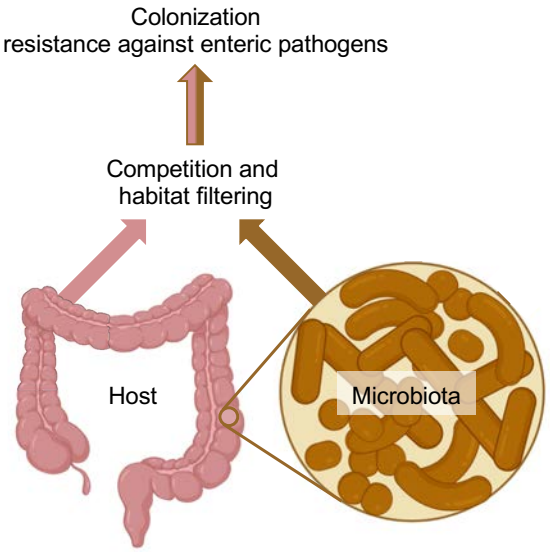
The Human Microbiota: Function



Colonization resistance against enteric pathogens: Competition



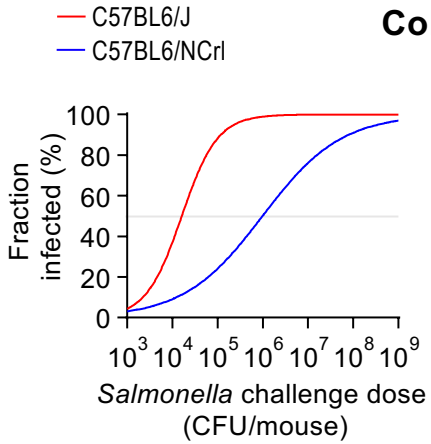
Eric Velazquez

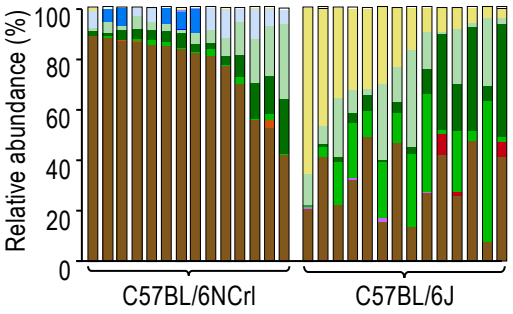


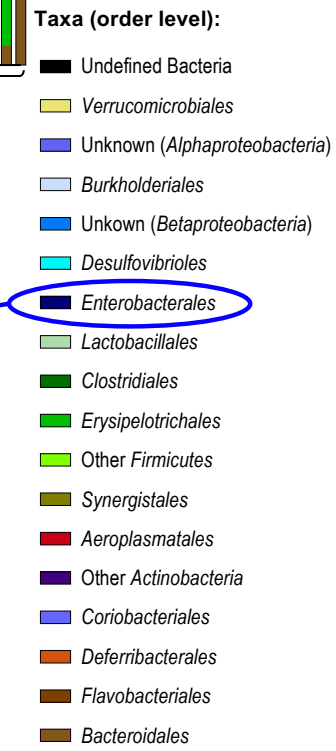
2019 Nature Microbiology 4:1057

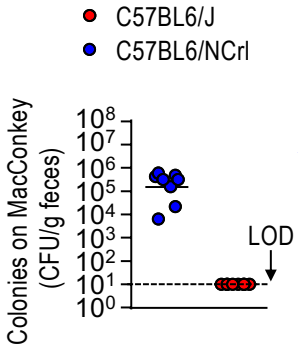
Colonization resistance against enteric pathogens: Competition

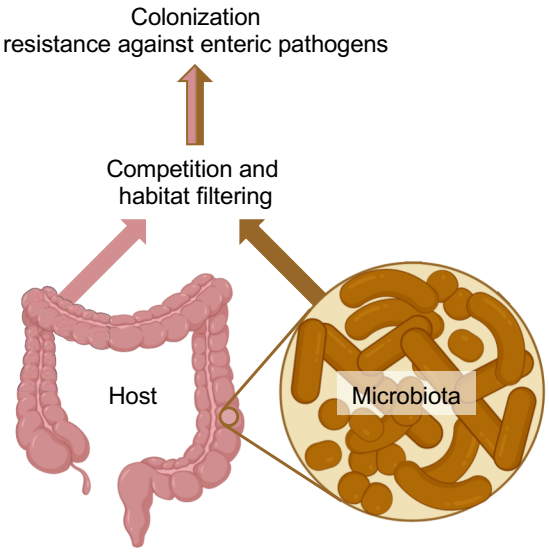
Eric Velazquez











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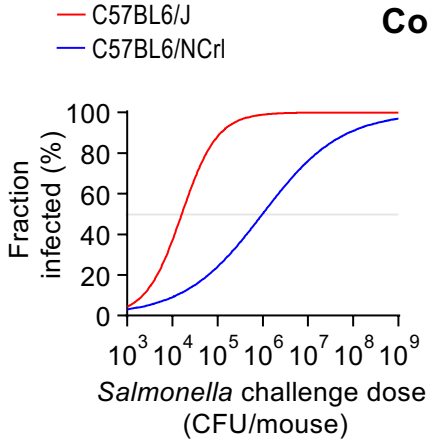
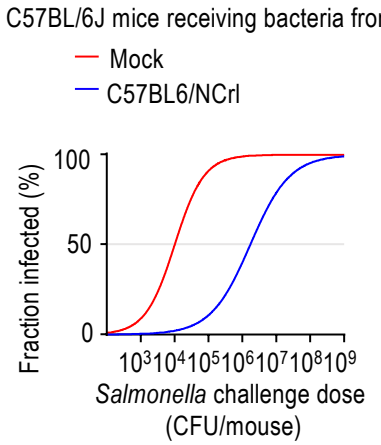
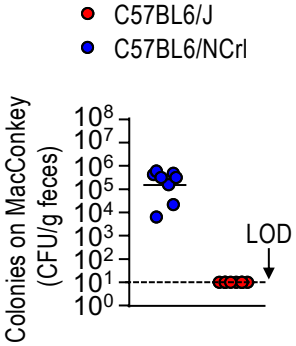
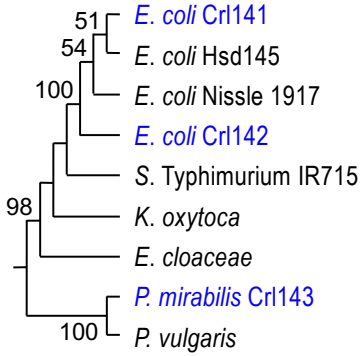
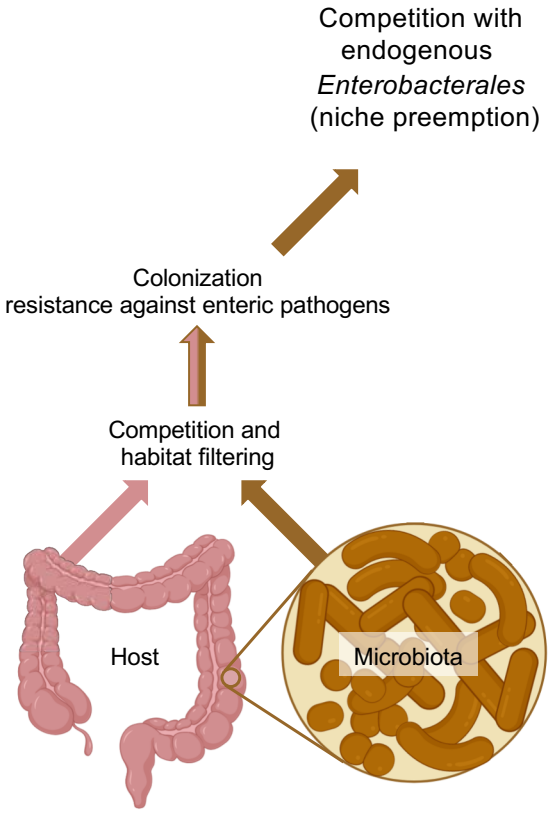
Colonization resistance against enteric pathogens: Competition











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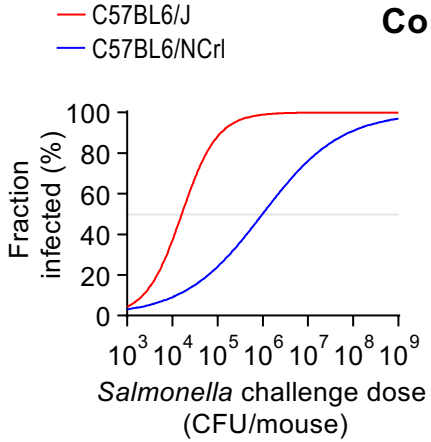
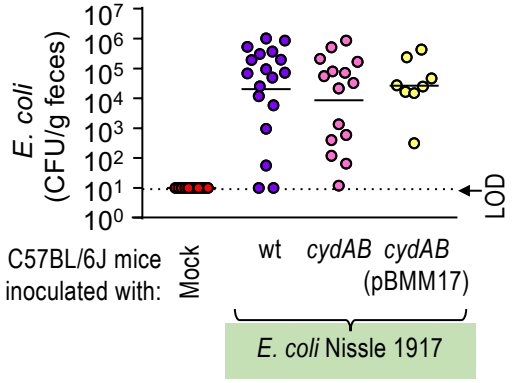
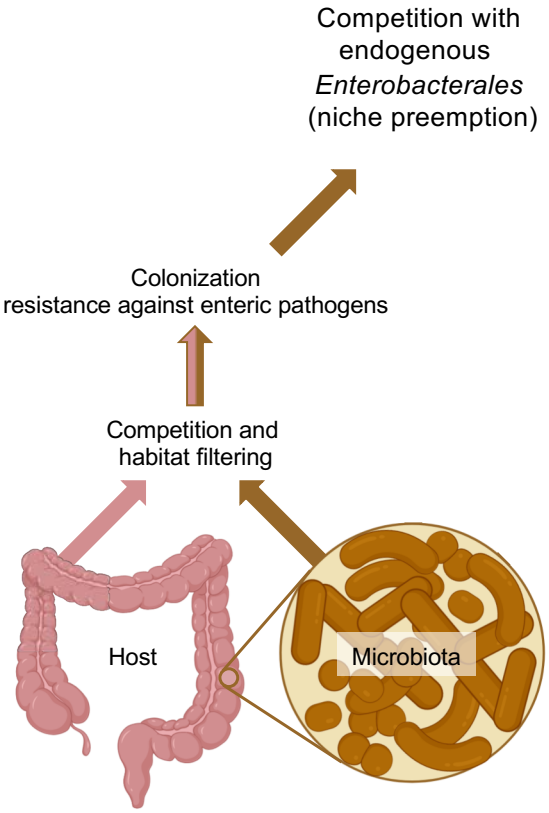
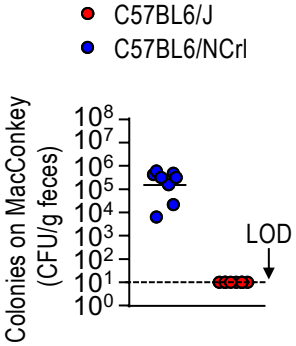
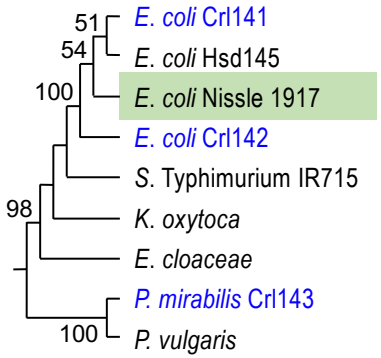
Colonization resistance against enteric pathogens: Competition











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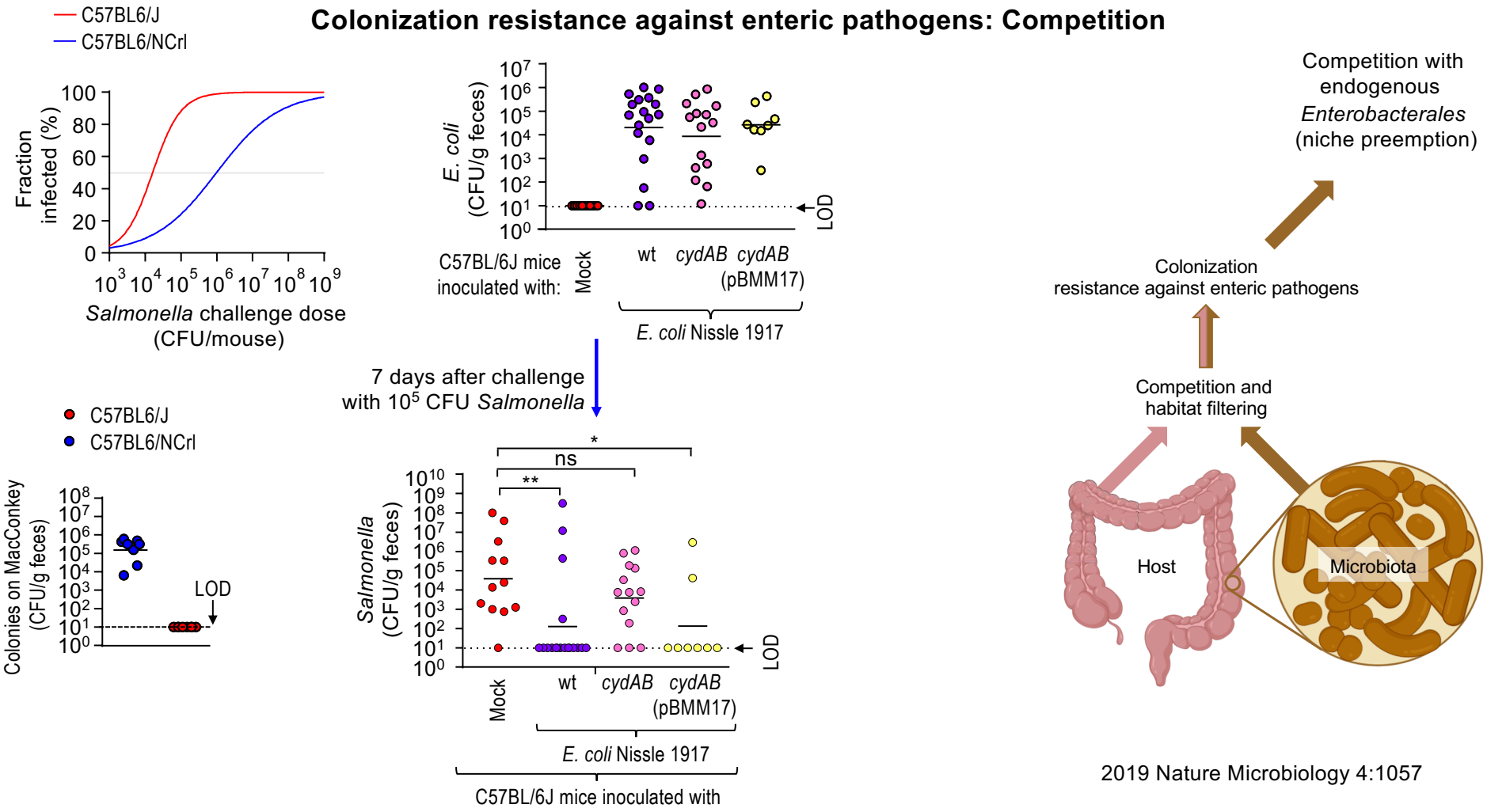
Colonization resistance against enteric pathogens: Competition



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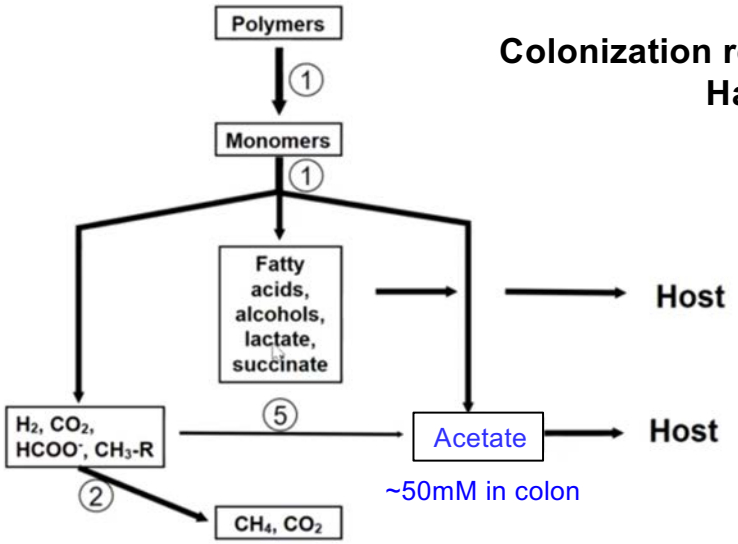
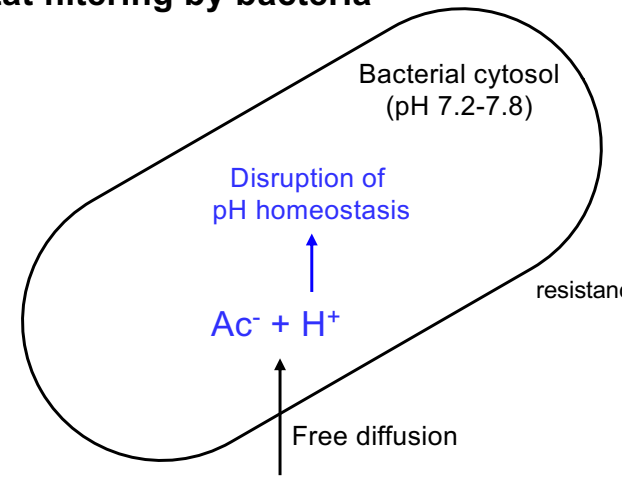
Colonization resistance against enteric pathogens: Habitat filtering by bacteria



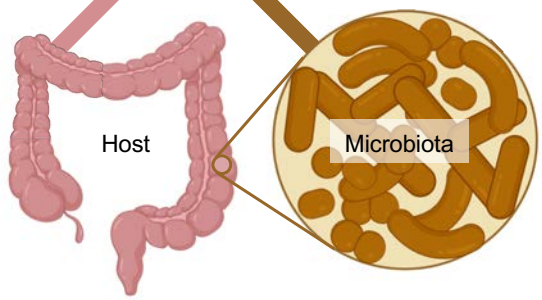
Bernhard Schink



Competition with endogenous *Enterobacterales* (niche preemption)

Colonization resistance against enteric pathogens

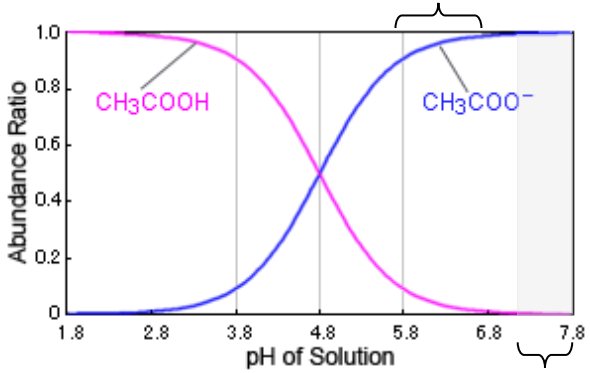
Competition and habitat filtering



pH range in colon

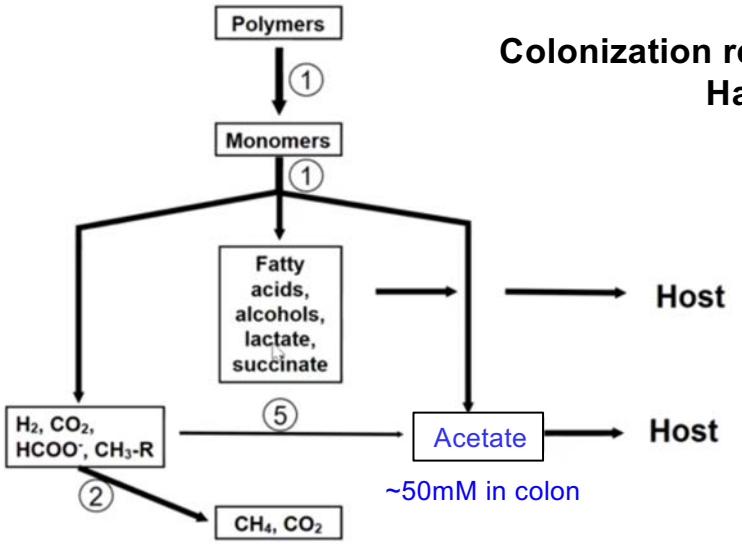
$Ac^- + H^+ \rightleftharpoons HAc$

(90-99 %) (1-10 %)



pH range in bacterial cytosol

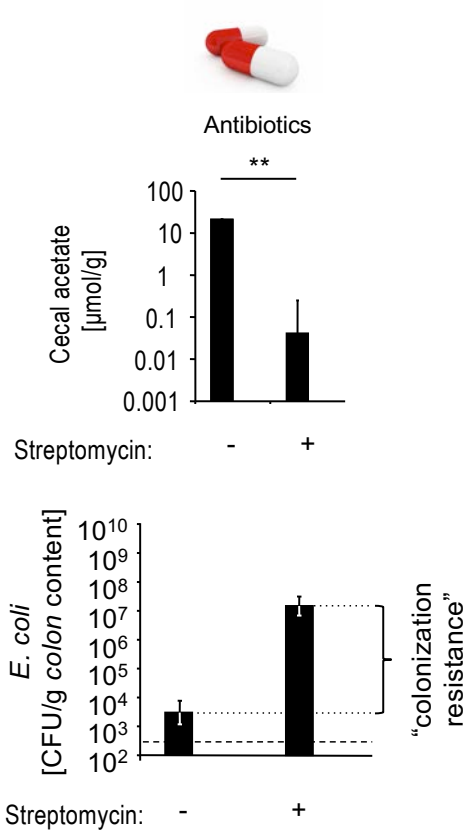
Colonization resistance against enteric pathogens: Habitat filtering by bacteria

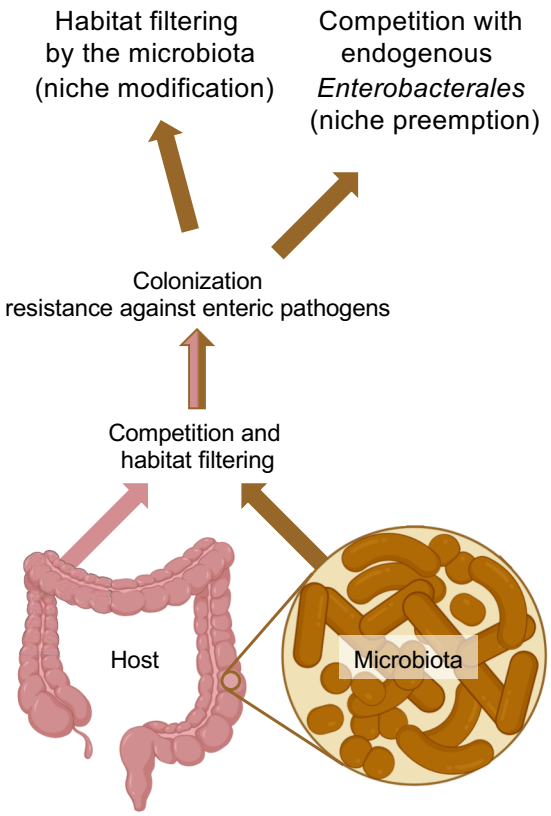


Bernhard Schink

Habitat filtering by the gut microbiota (niche modification)

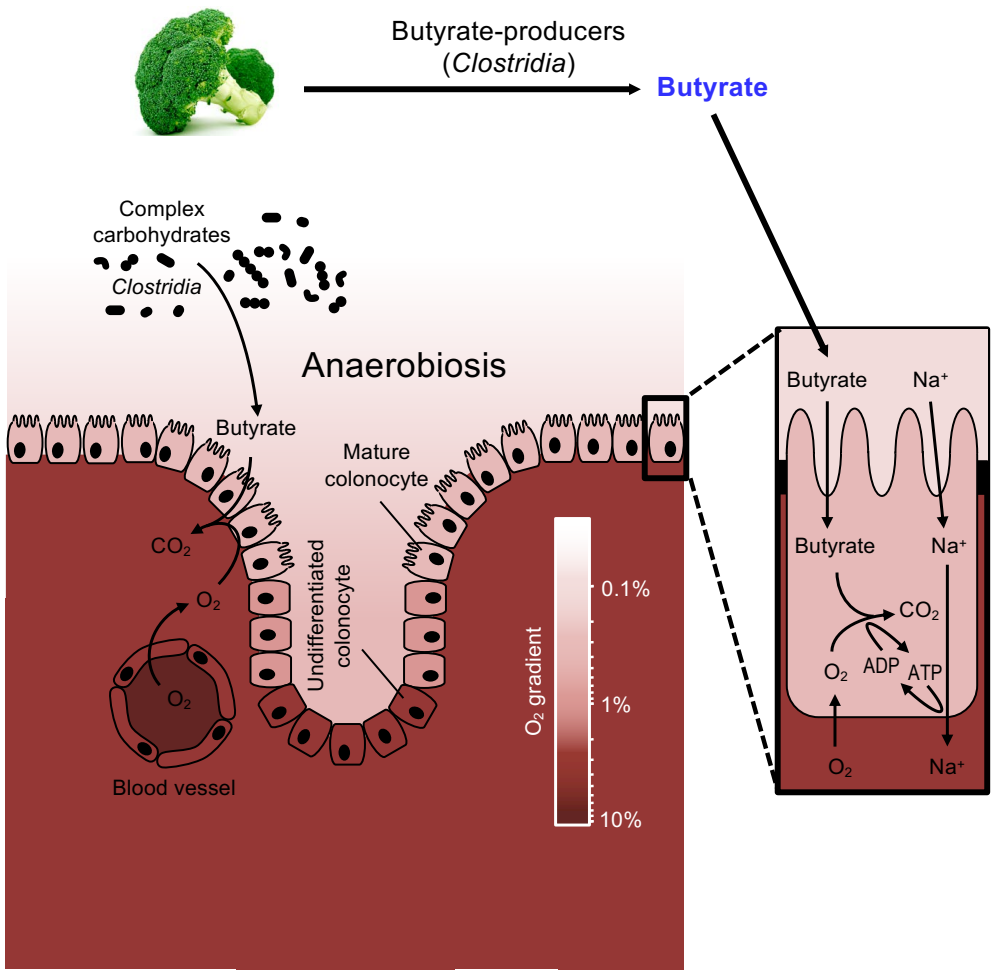
Growth is limited by the availability of resources needed to maintain pH homeostasis

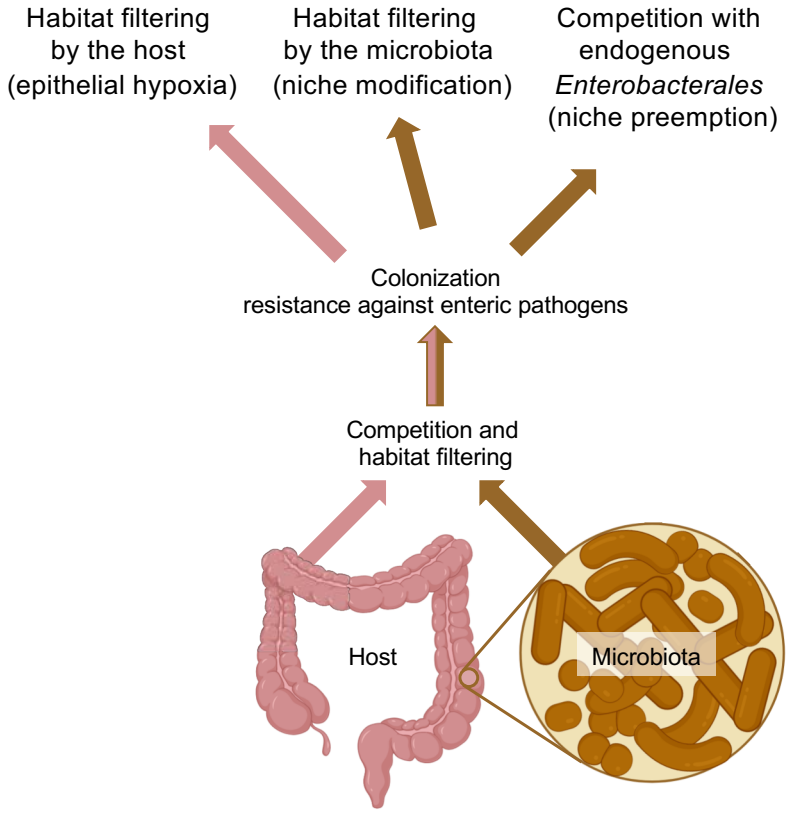




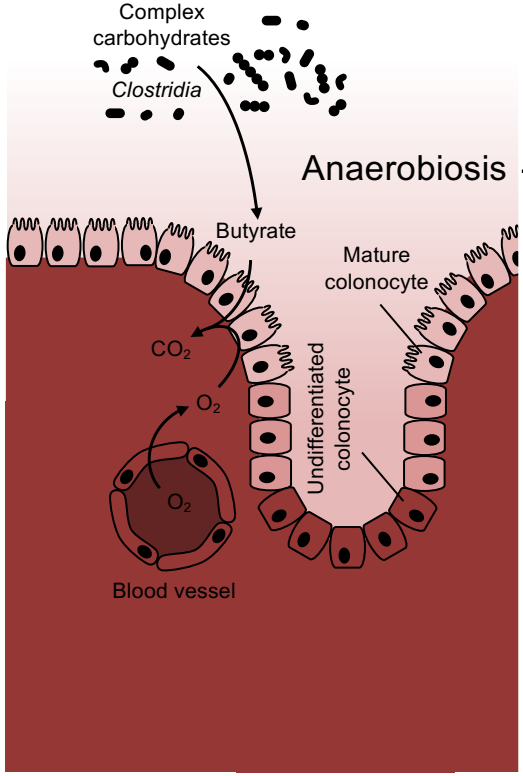
2017 Science 357:570

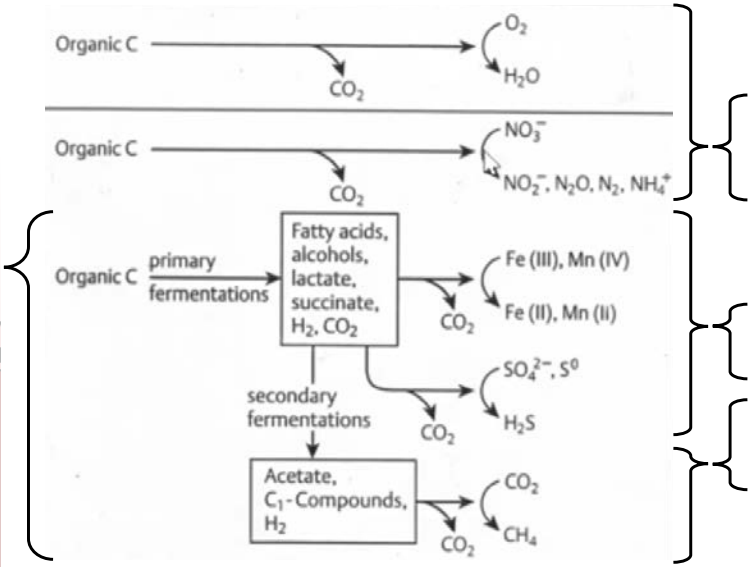
Colonization resistance against enteric pathogens: Habitat filtering by the host





Colonization resistance against enteric pathogens: Habitat filtering by the host



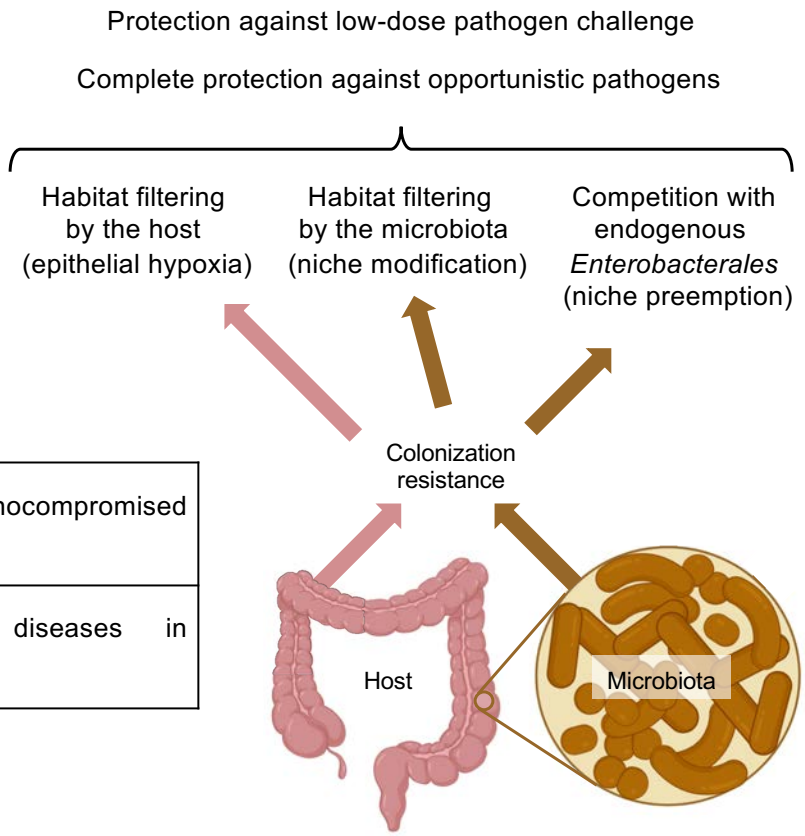


Lake sediment

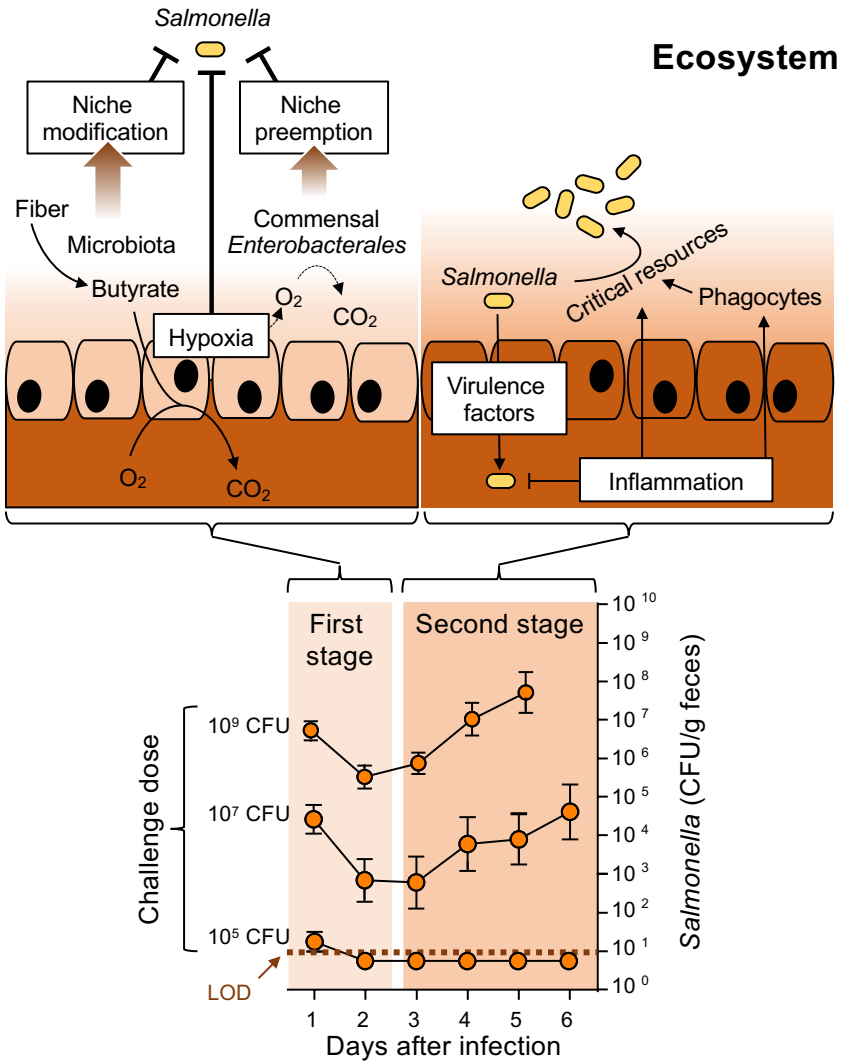
Bernhard Schink

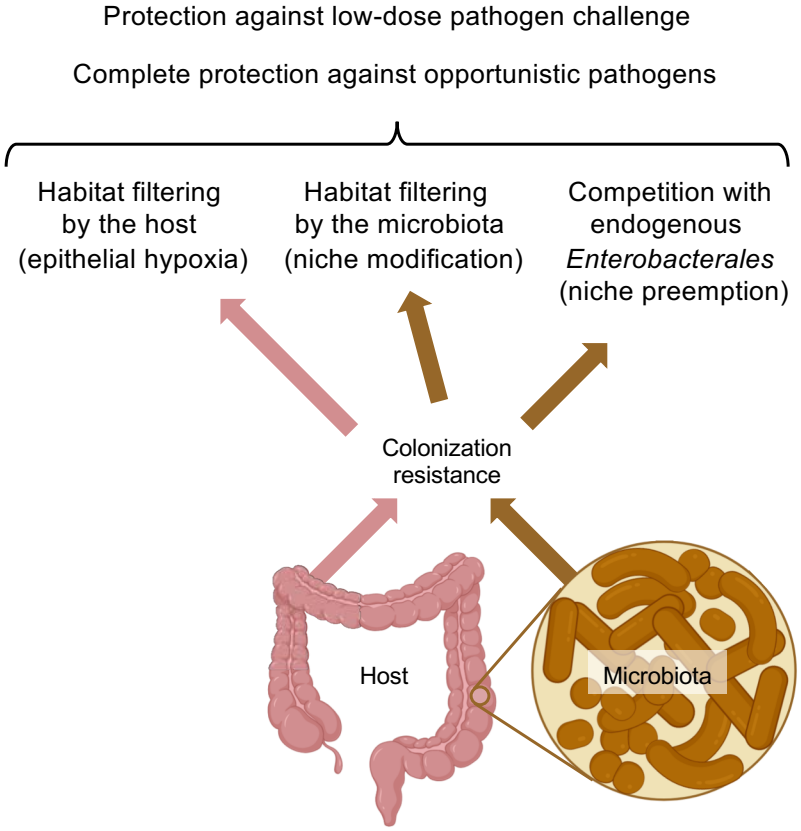
Ecosystem invasion by *Salmonella*

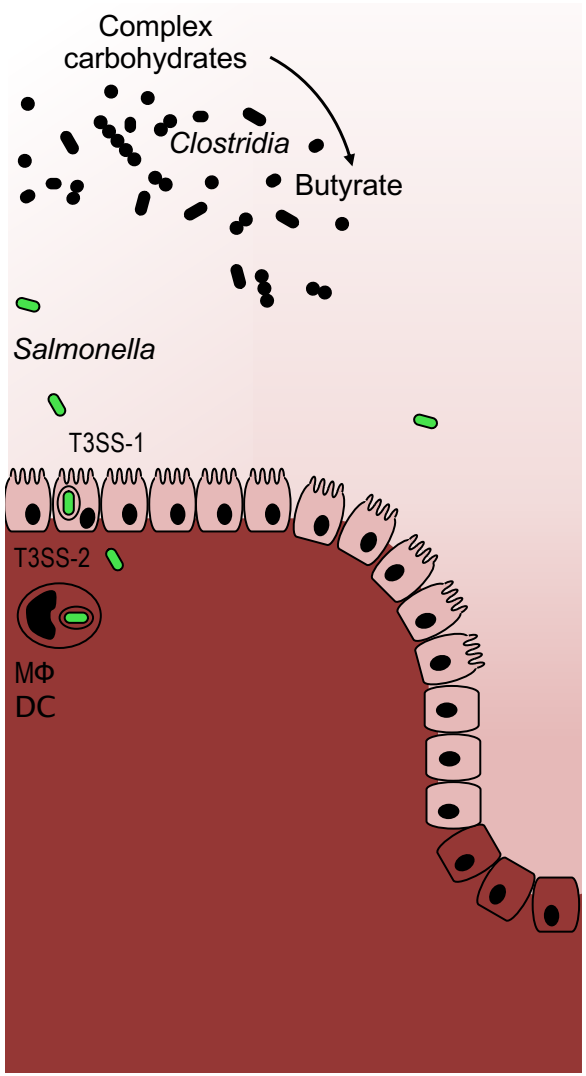
Opportunistic pathogens	Microbes associated with disease in immunocompromised members of a host species
Pathogens (or frank pathogens)	Microbes associated with communicable diseases in immunocompetent members of a host species



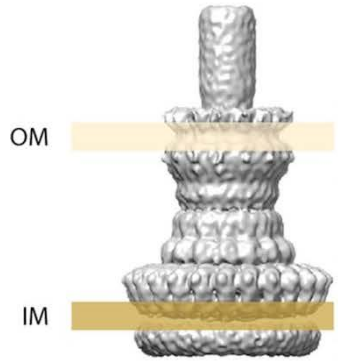
Ecosystem invasion by *Salmonella*



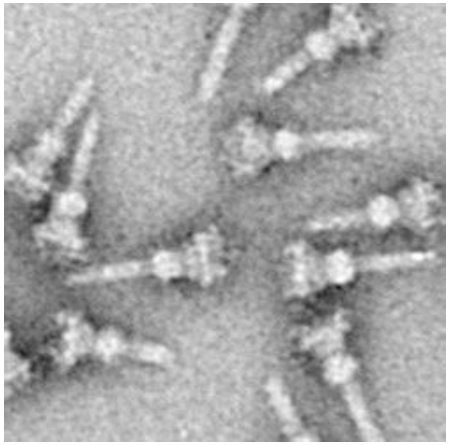




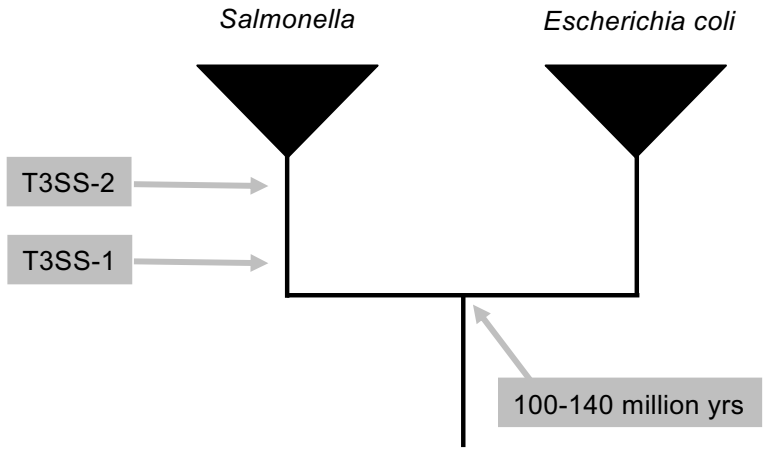
Salmonella virulence factors trigger inflammation

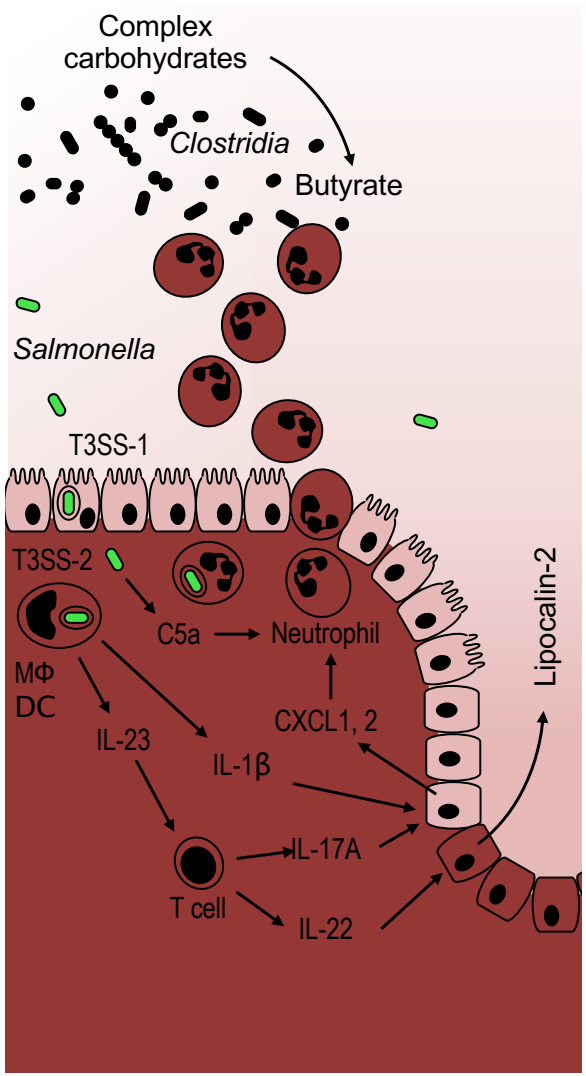


2014 *FEMS Microbiology Reviews*

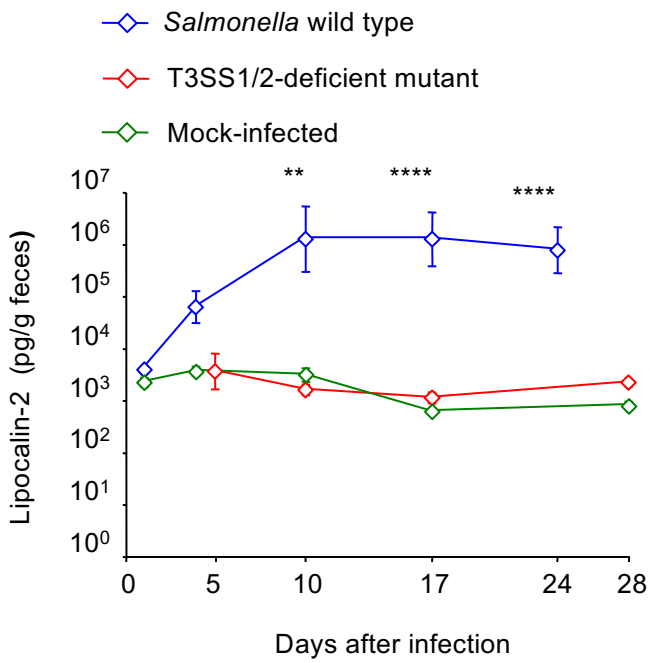


2010 *PLOS Pathogens* 6:e1000824



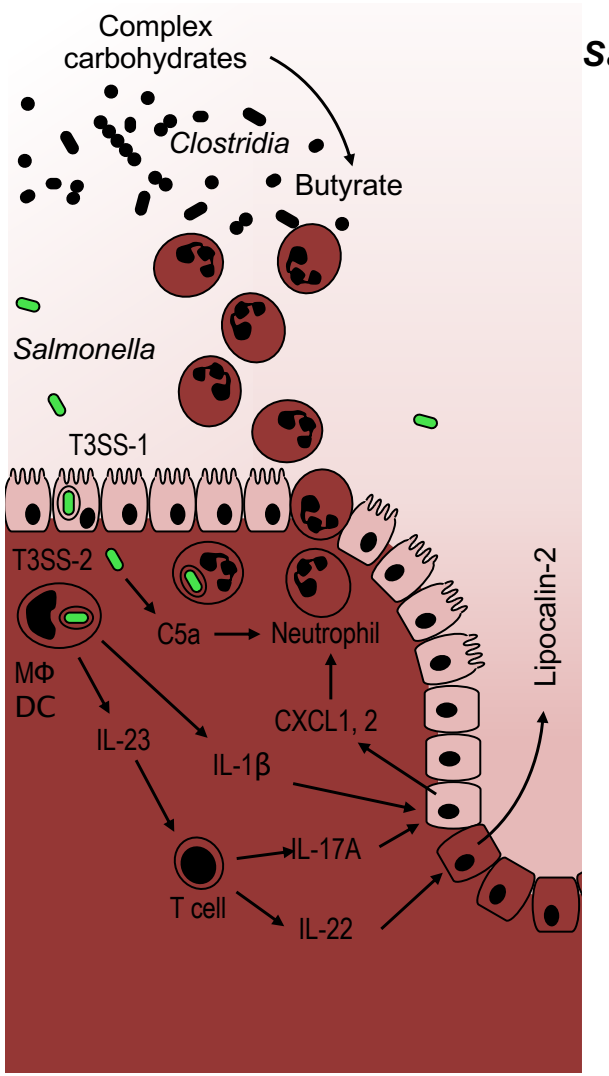


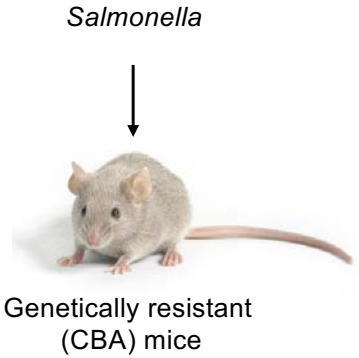
Salmonella virulence factors trigger inflammation

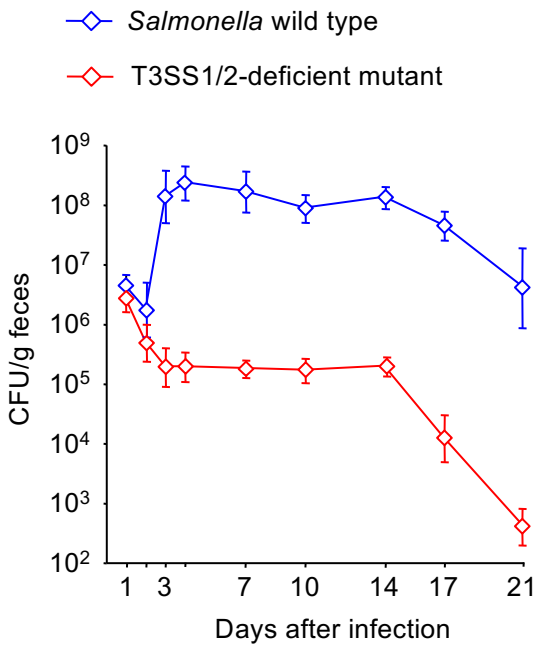


2016 CH&M 19:443

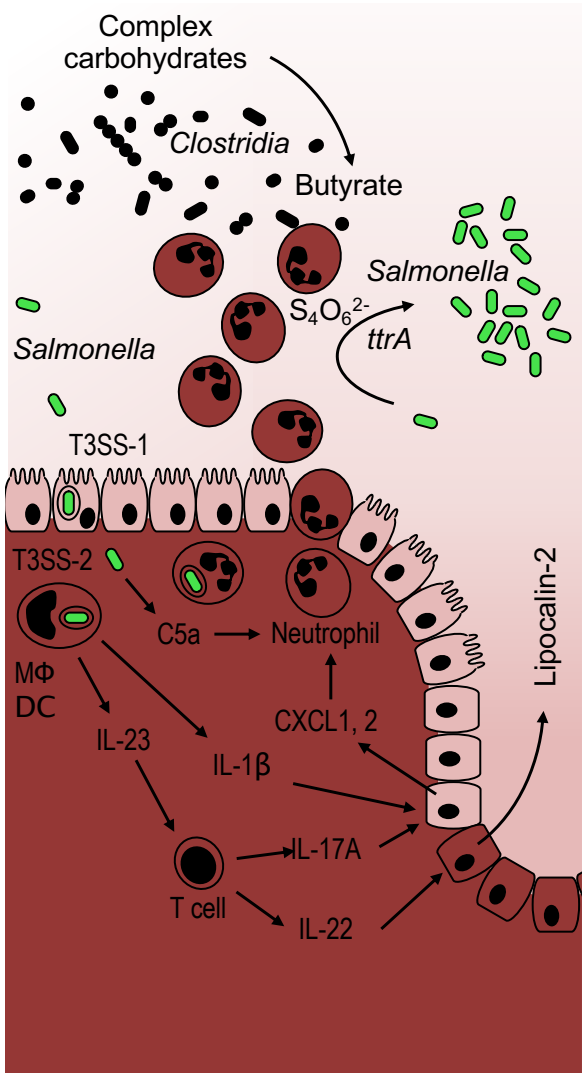
Salmonella virulence factors enable the pathogen to engraft in the microbiota





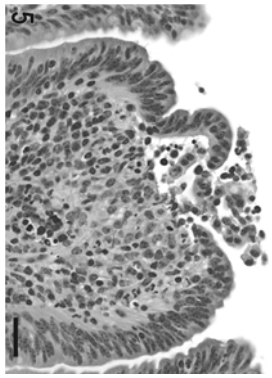


2016 CH&M 19:443



Phagocytes alter habitat filtering in the intestinal lumen

Sebastian Winter



$^{-}O_3S\text{-}S\text{-}S\text{-}SO_3^{-}$ + 2[H]

Tetrathionate

Oxygen radicals

Salmonella ttrSR ttrBCA

Enhanced growth

Transmission

$S\text{-}SO_3^{2-}$ + $2H^+$

Thiosulfate

Colonic mucosa

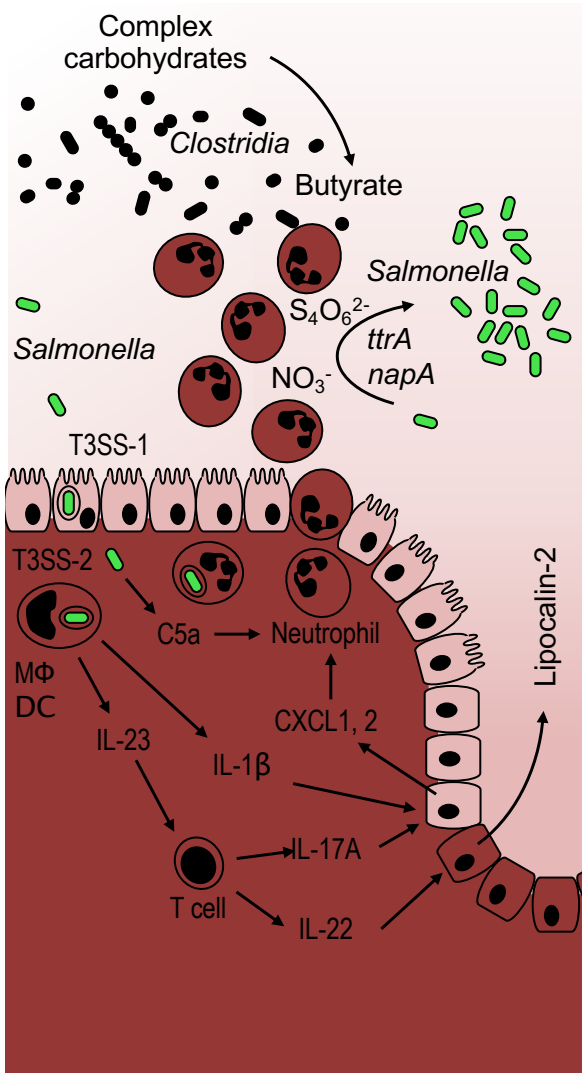
H_2S

Hydrogen Sulfide

Gut microbiota

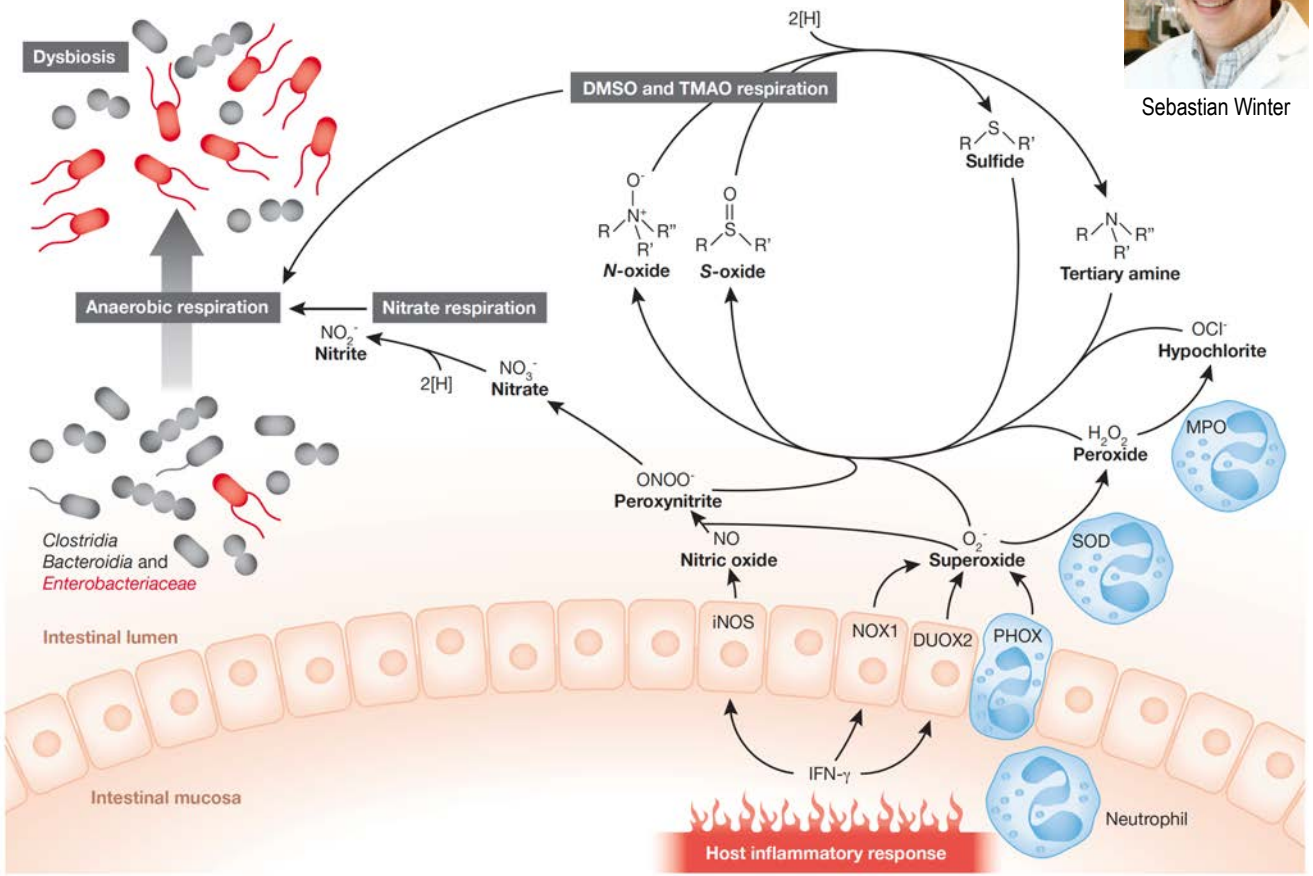
Tetrathionate enrichment

2010 Nature 467:426

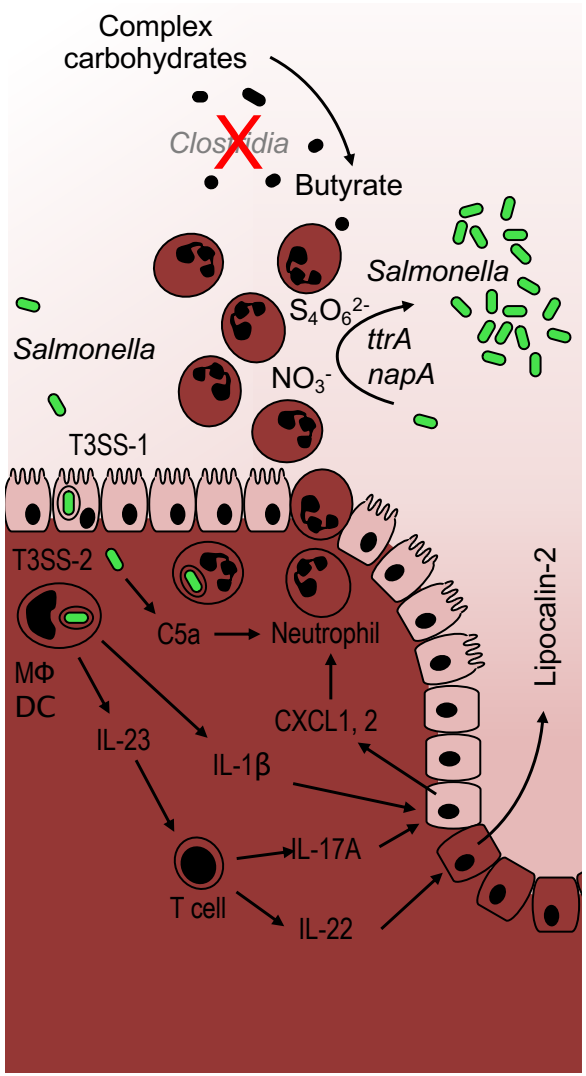


Phagocytes alter habitat filtering in the intestinal lumen

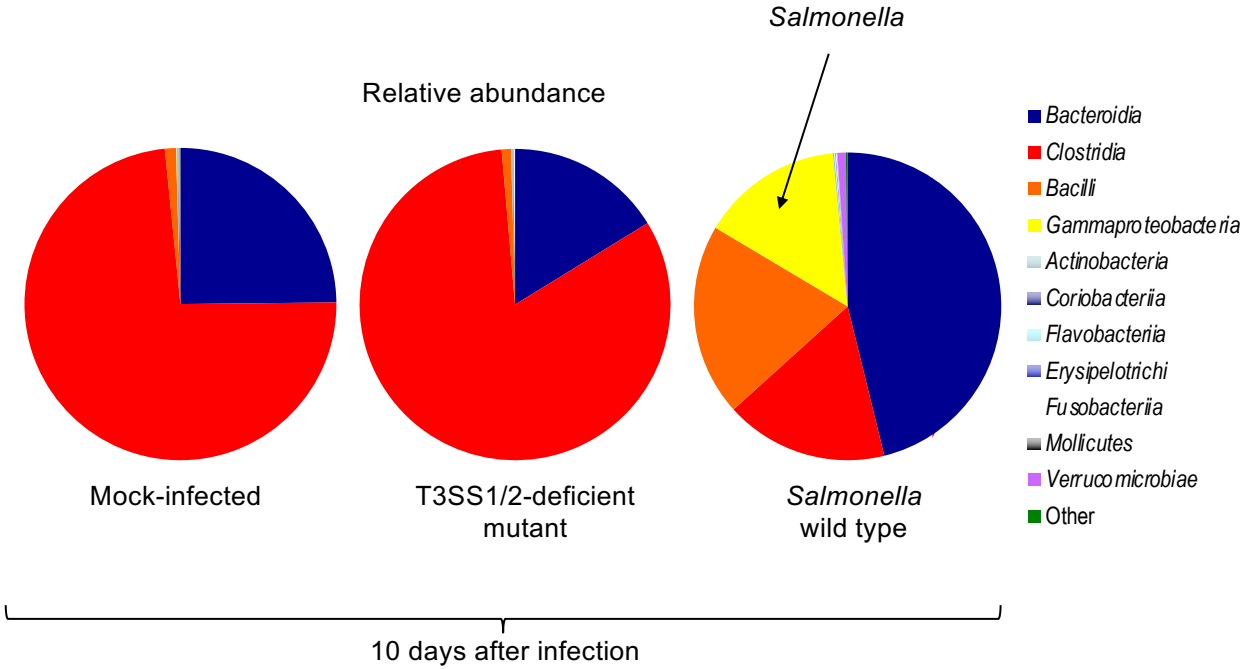
Sebastian Winter



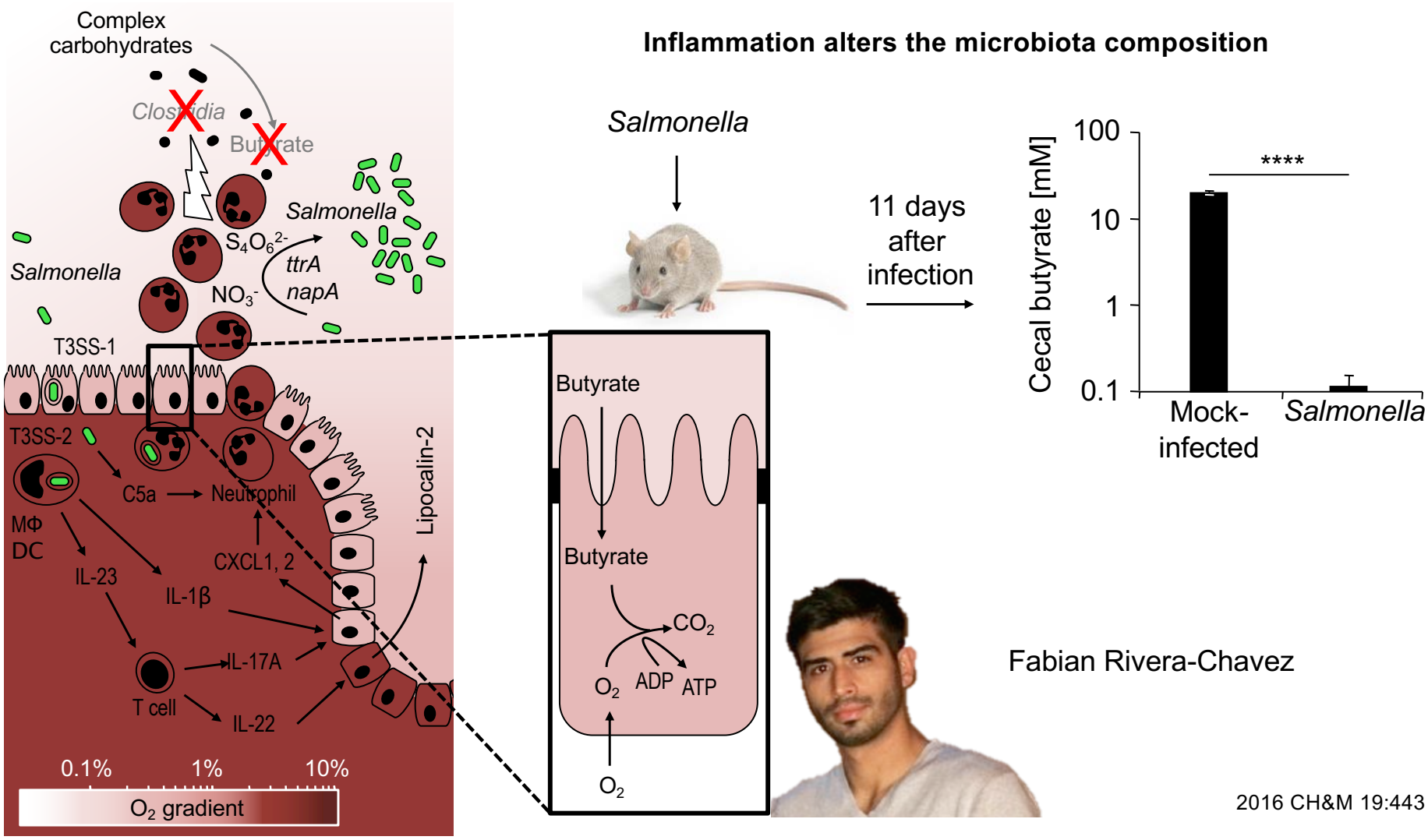
2013 Science 339:708

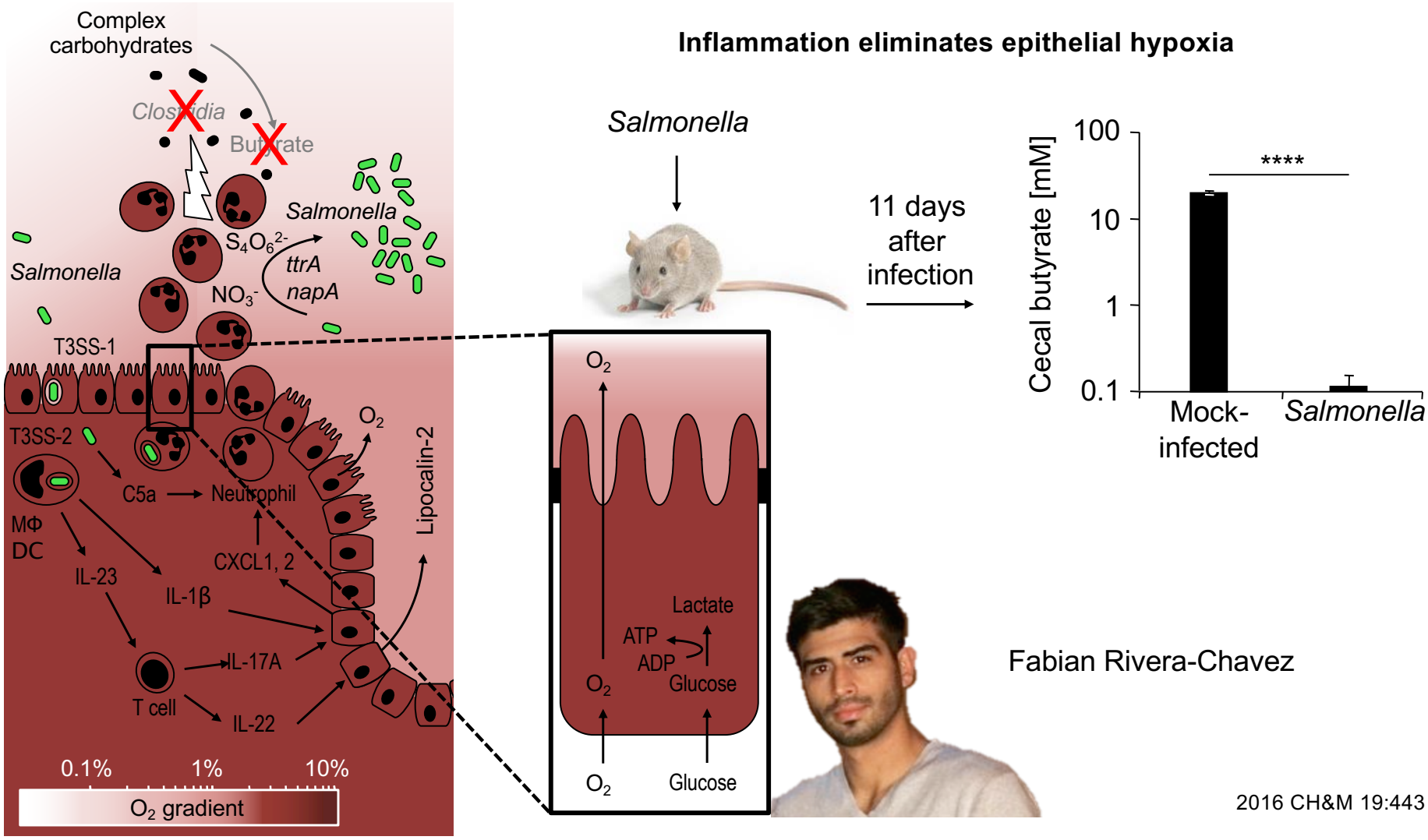


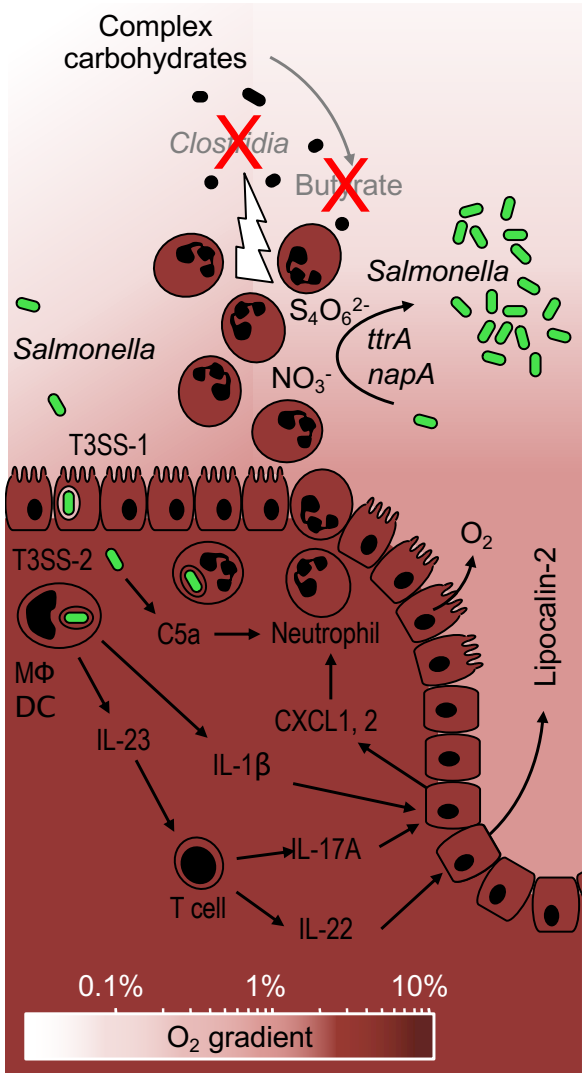
Inflammation alters the microbiota composition



2016 CH&M 19:443

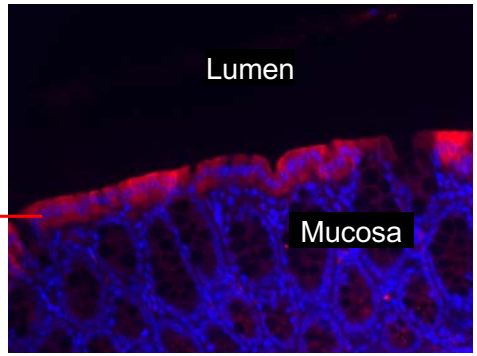

Complex carbohydrates
Clostridia
Butyrate
Salmonella
$S_4O_6^{2-}$
ttrA
napA
NO_3^-
Salmonella
T3SS-1
T3SS-2
C5a
Neutrophil
MΦ
DC
IL-23
IL-1β
CXCL1, 2
Lipocalin-2
IL-17A
T cell
IL-22
0.1%
1%
10%
O_2 gradient
Inflammation alters the microbiota composition
Salmonella
11 days after infection
Butyrate
Butyrate
CO_2
O_2
ADP
ATP
O_2
Cecal butyrate [mM]
100
10
1
0.1
****
Mock-infected
Salmonella
Fabian Rivera-Chavez
2016 CH&M 19:443


Inflammation eliminates epithelial hypoxia
Complex carbohydrates
Clostridia
Butyrate
Salmonella
$S_4O_6^{2-}$
ttrA
napA
NO_3^-
Salmonella
T3SS-1
T3SS-2
O_2
C5a
Neutrophil
MΦ
DC
IL-23
IL-1β
CXCL1, 2
Lipocalin-2
IL-17A
T cell
IL-22
0.1%
1%
10%
O_2 gradient
Salmonella
11 days after infection
O_2
Lactate
ATP
ADP
Glucose
O_2
O_2
Glucose
Cecal butyrate [mM]
100
10
1
0.1
****
Mock-infected
Salmonella
Fabian Rivera-Chavez
2016 CH&M 19:443

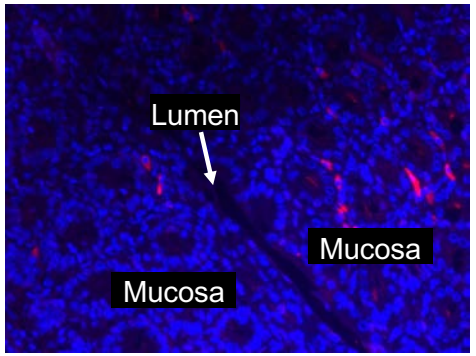


Inflammation eliminates epithelial hypoxia

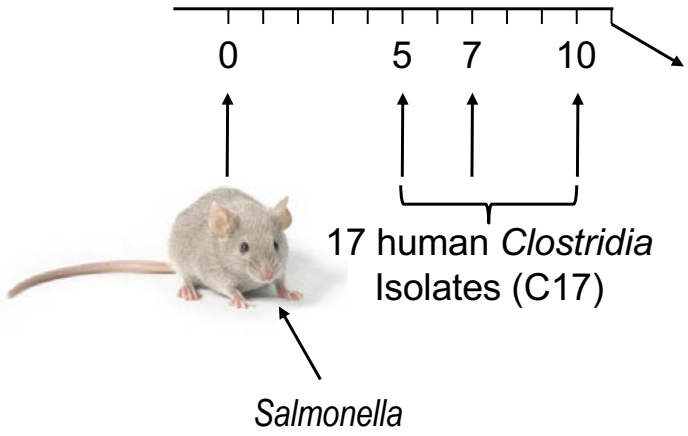
Hypoxia (< 1% oxygen)

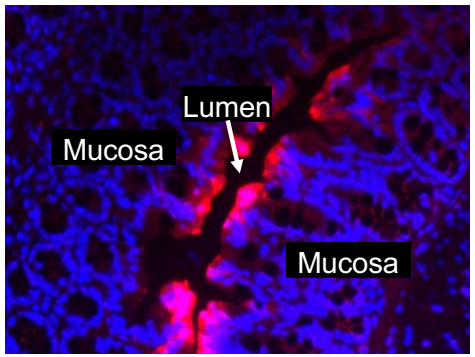


Mock-infected



Salmonella





Salmonella + C17

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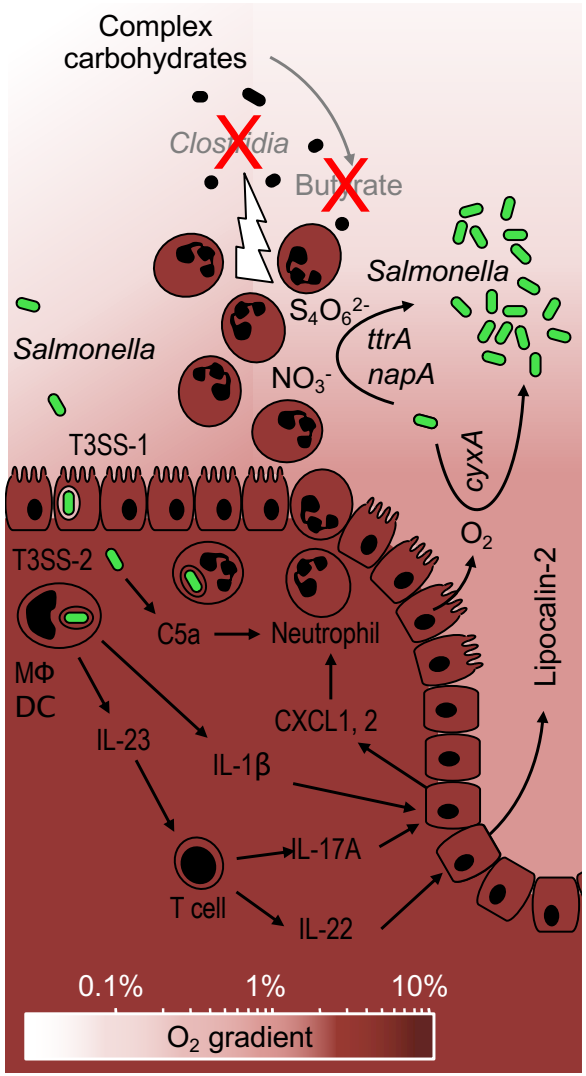
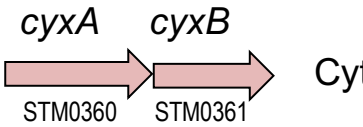
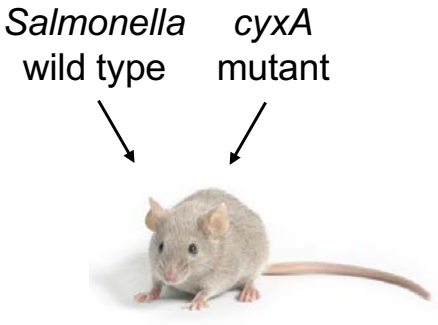
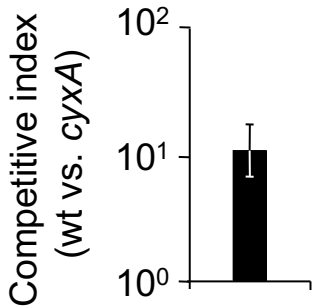


Inflammation eliminates epithelial hypoxia



Cytochrome *bd*-II oxidase





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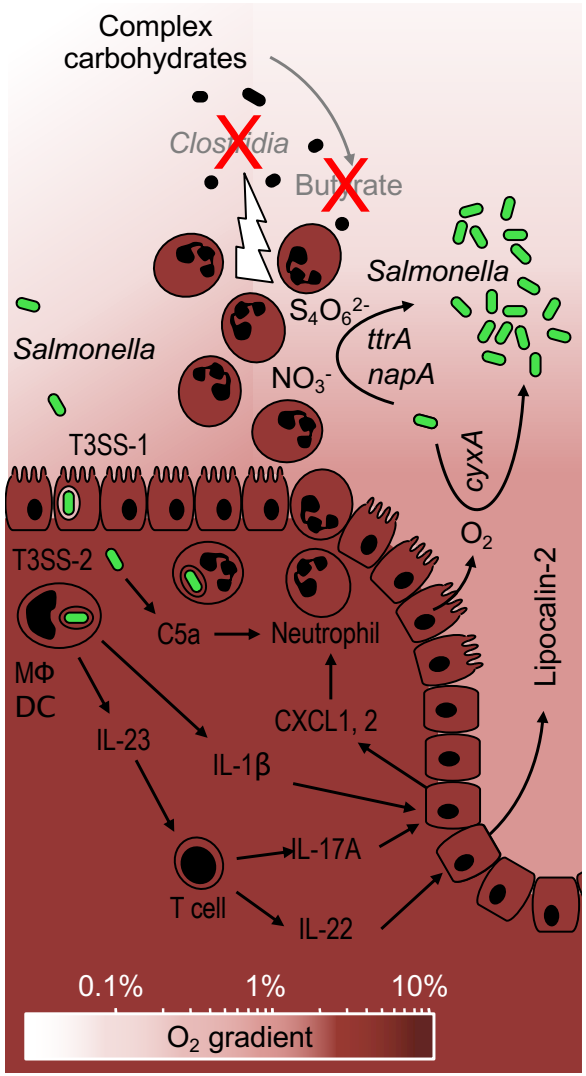
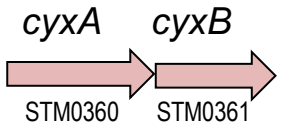
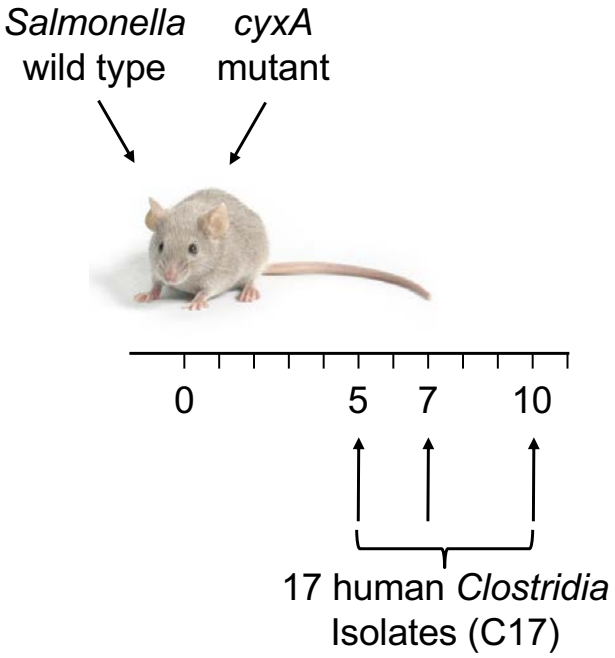
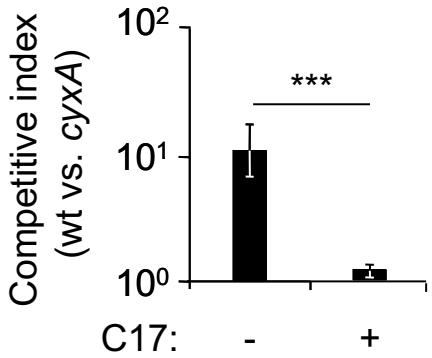


Inflammation eliminates epithelial hypoxia



Cytochrome *bd*-II oxidase





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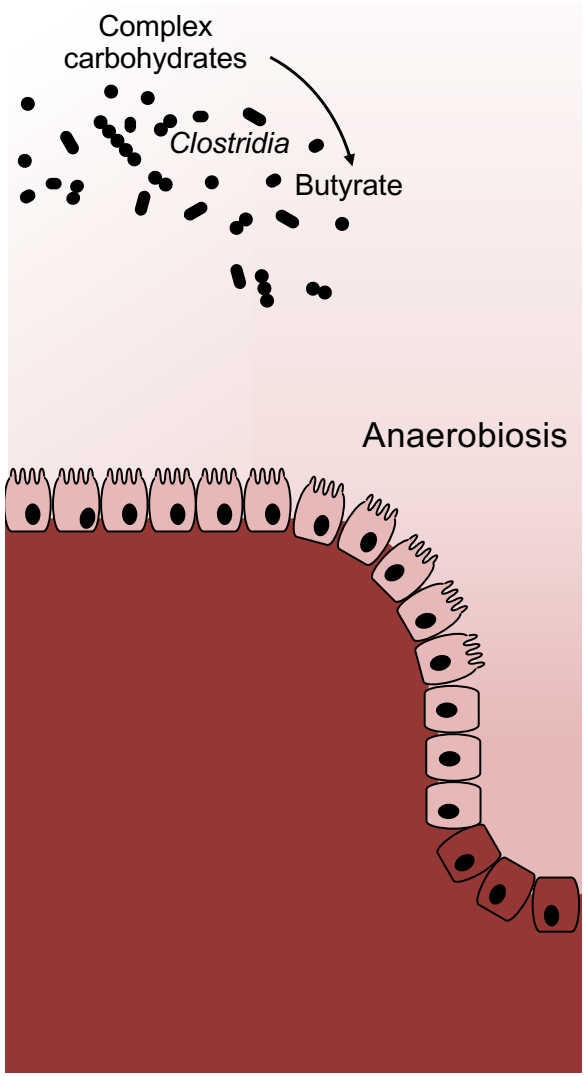
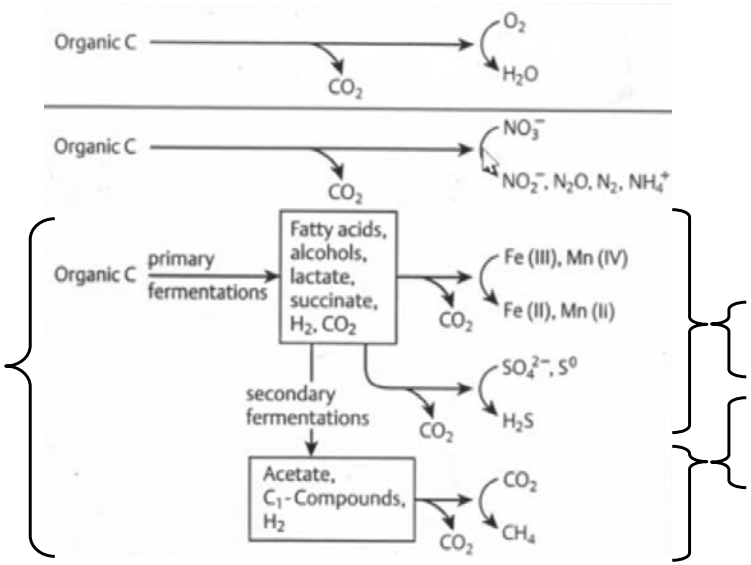


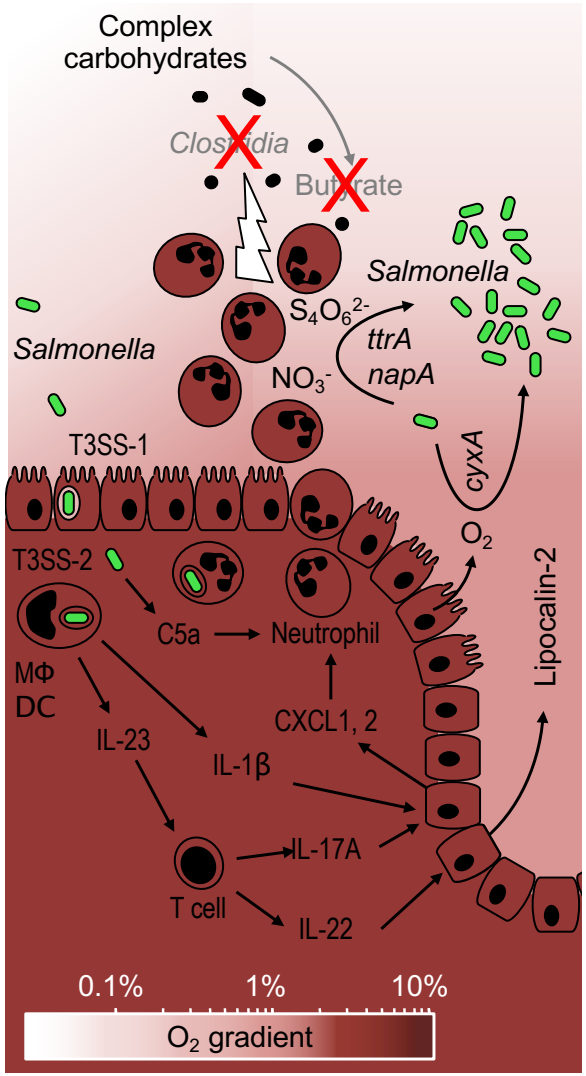
Inflammation triggers a state of abnormal habitat filtering in the colon

Colon during homeostasis



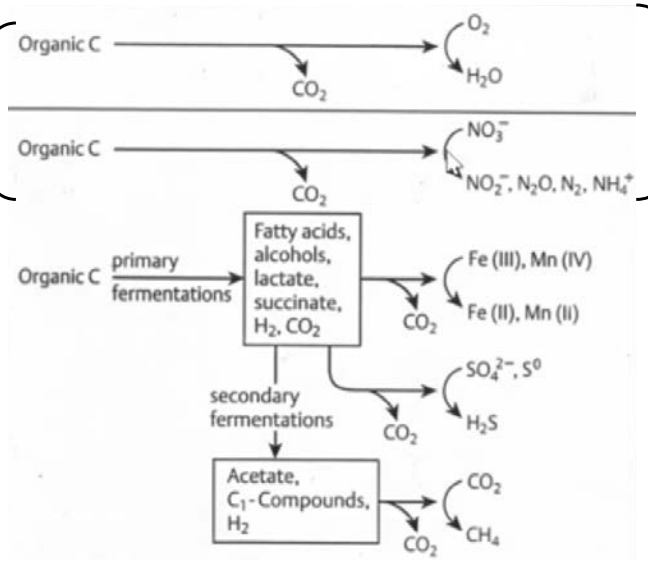
Lake sediment

Bernhard Schink



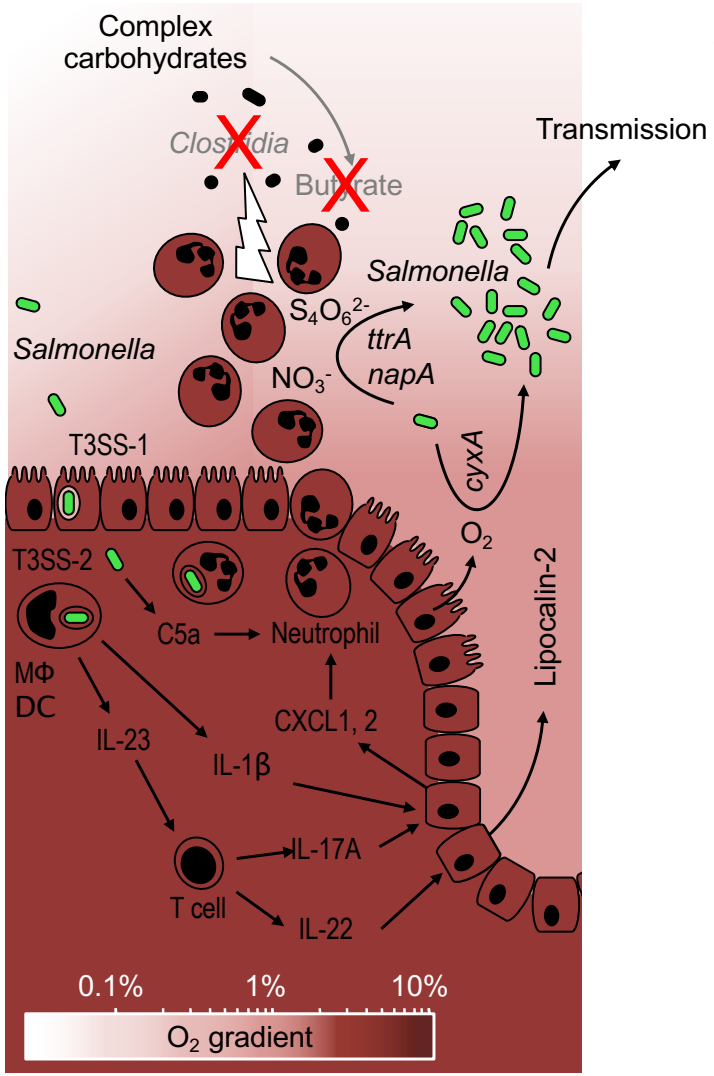
Inflammation triggers a state of abnormal habitat filtering in the colon

Inflamed colon

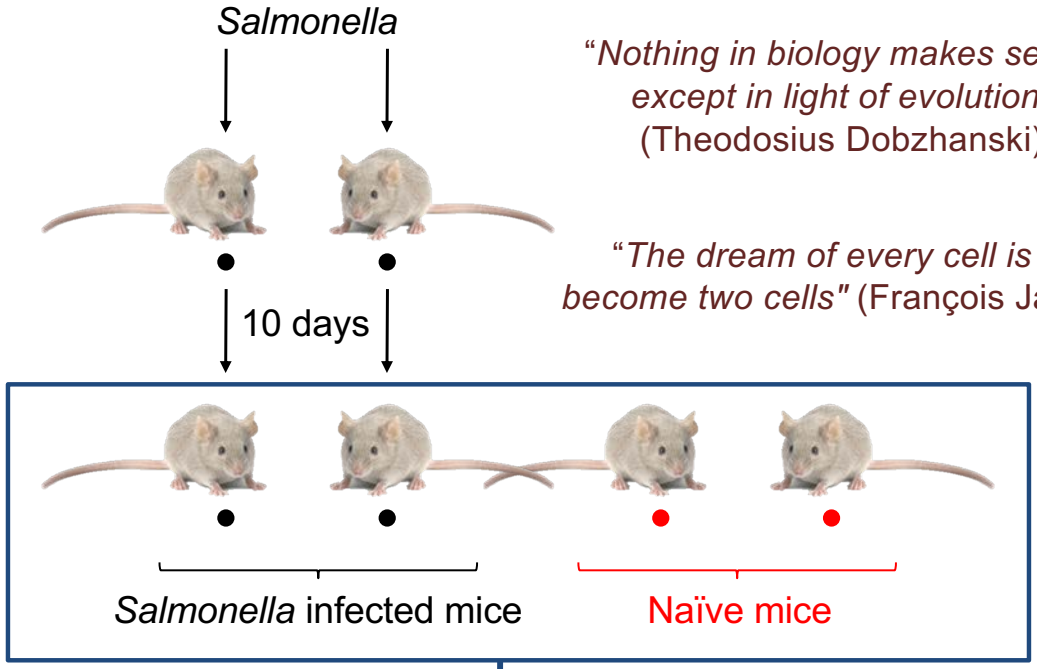


Lake sediment

Bernhard Schink



The principle driving force of natural selection: transmission

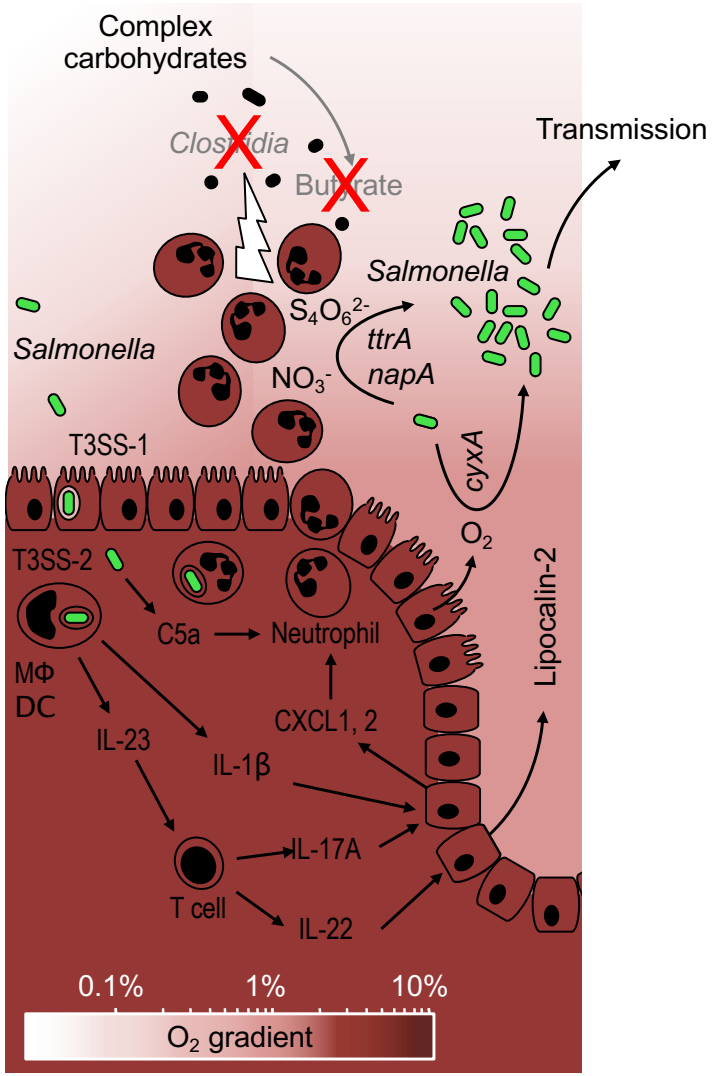


"Nothing in biology makes sense except in light of evolution" (Theodosius Dobzhanski)

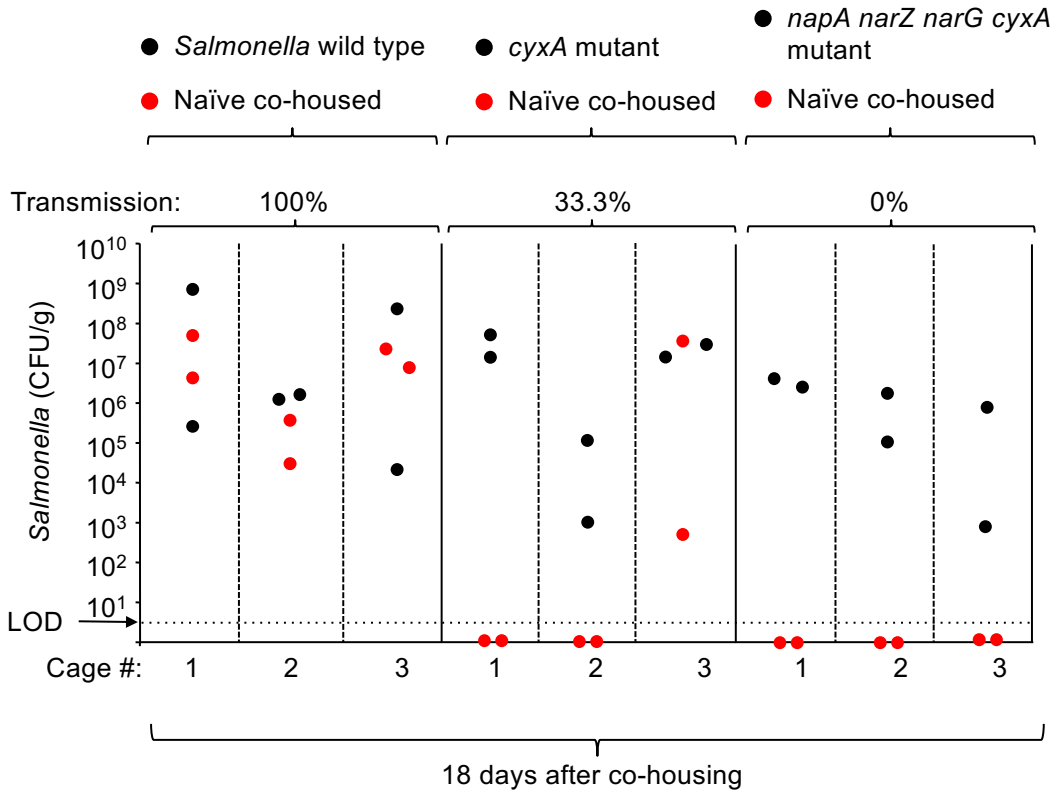
"The dream of every cell is to become two cells" (François Jacob)

Co-housing for 18 days

Assess *Salmonella* transmission



The principle driving force of natural selection: transmission



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The downside of ecosystem engineering: a new nutrient-niche comes with new competitors