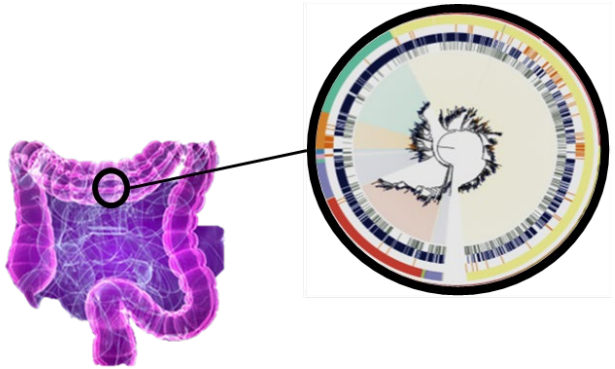
Crohn's and Colitis Canada
Crohn et Colite Canada

SATURDAY, November 5, 2022
Canada Future Directions in IBD

The Microbiome in IBD: What makes the gut abnormally inflamed?



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Surette Laboratory
Microbiome and Infectious Disease Research

FARNCOMBE
Farncombe Family Digestive Health Research Institute

IMAGINE
Inflammation, Microbiome & Alimentation: Gastro-Intestinal & Neuropsychiatric Effects

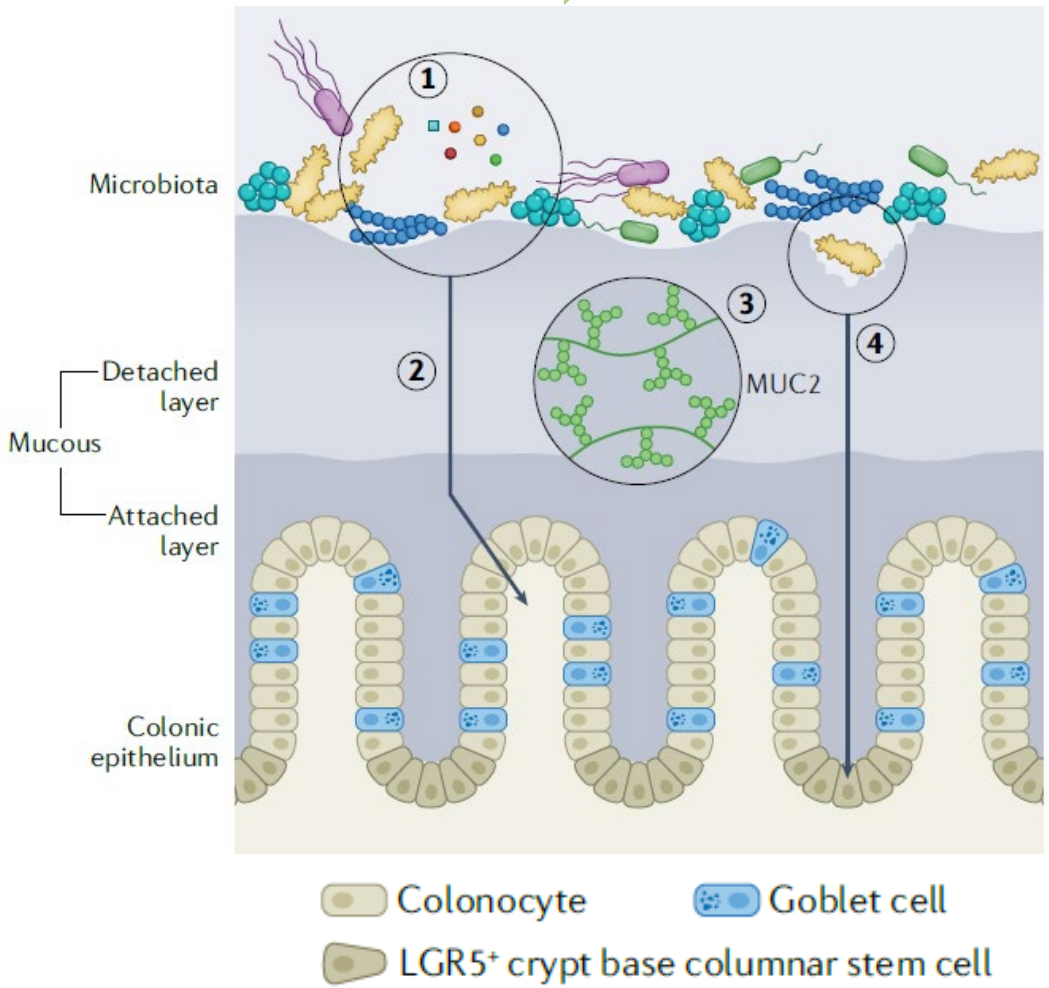
McMaster University

How the microbiome and microbiome derived products contribute to inflammation in IBD

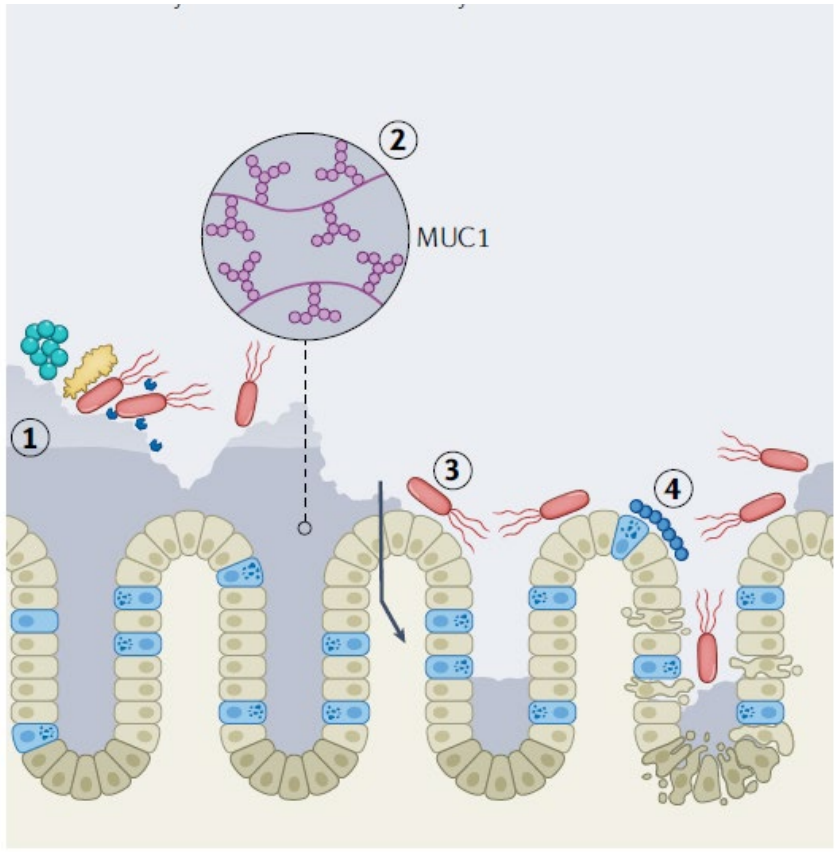
- **PAMPS, PRR and Innate Immunity**
- **Bile acid metabolism and the microbiome**
- *Tryptophan metabolites and serotonin*
- *Short chain fatty acids and branched short chain fatty acids*
- **Microbiome produced enzymes** *(e.g. protease and carbohydrate active enzymes)*

Key points to think about along the way

Healthy Homeostatic State



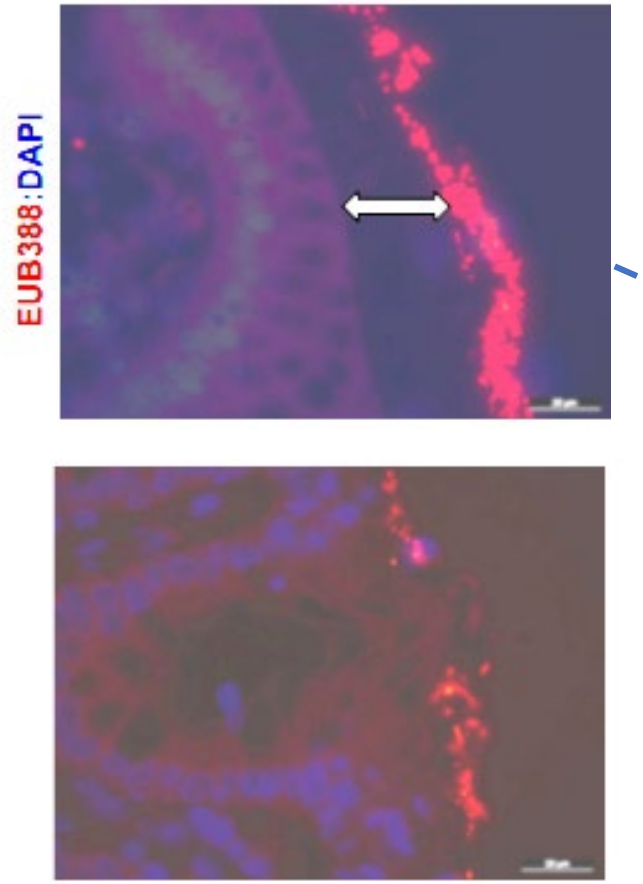
Dysbiotic (*Homeostatic?*) State



Rogers et al Nat Rev Microbiol. (2022)

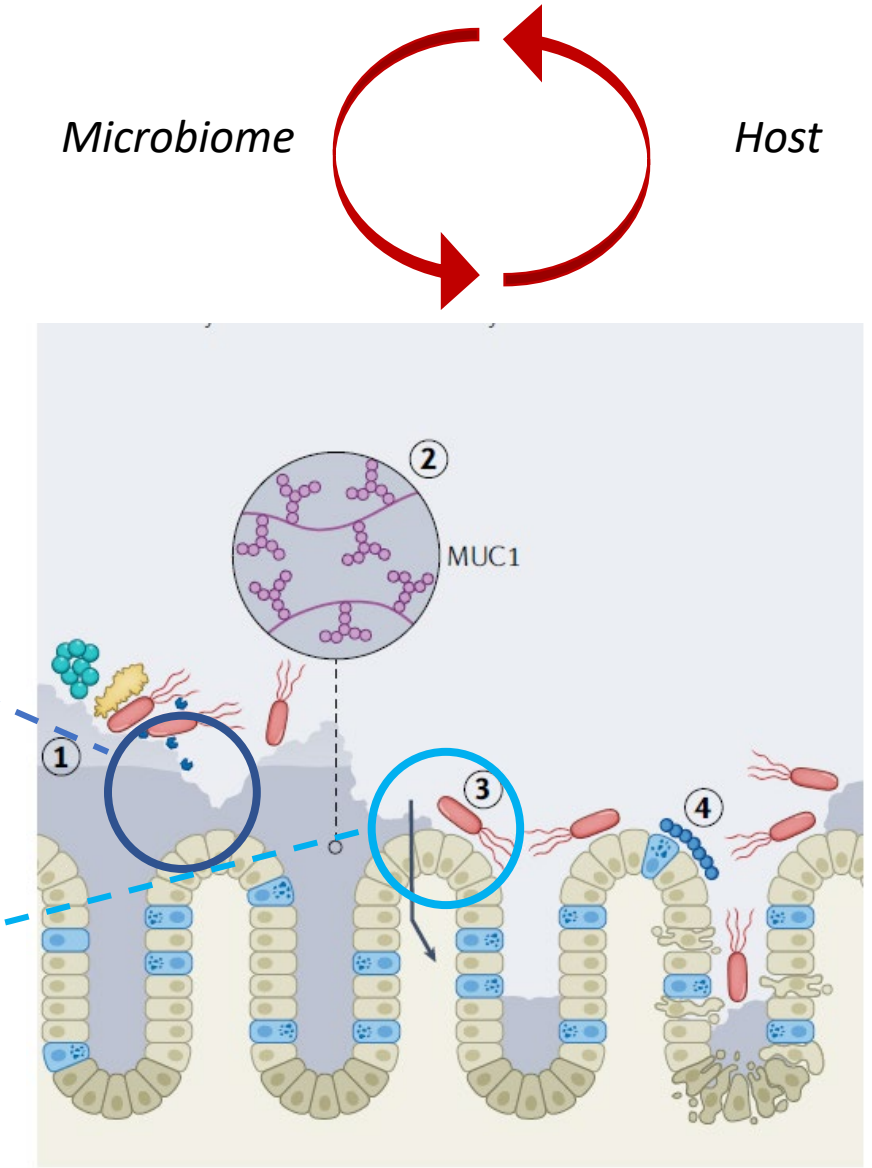
Dysbiotic (*Homeostatic?*) State

Inflamed areas are associated with greater encroachment of bacteria to epithelial cells



Biopsies from non-inflamed and inflamed site from CD patient.

Libertucci et al (2018)



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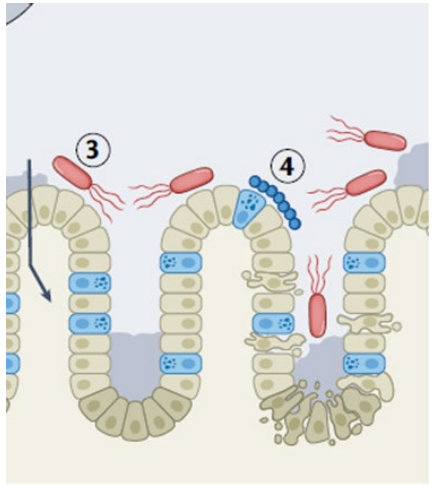
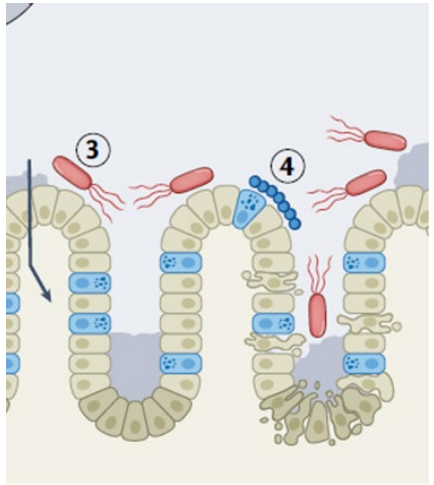


The compromised mucous layer increase access of microbiota to the epithelial layer and comprised barrier

this allows for more PAMP-PRR

Microbiota Gram negative LPS → TLR4 → Inflammation



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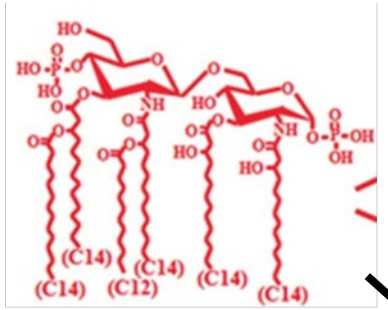


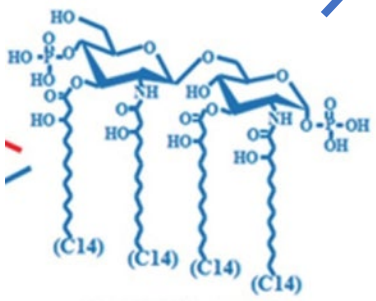
E coli

(Enterobacteriaceae)

Microbiota Gram negative

LPS

TLR4 → Inflammation



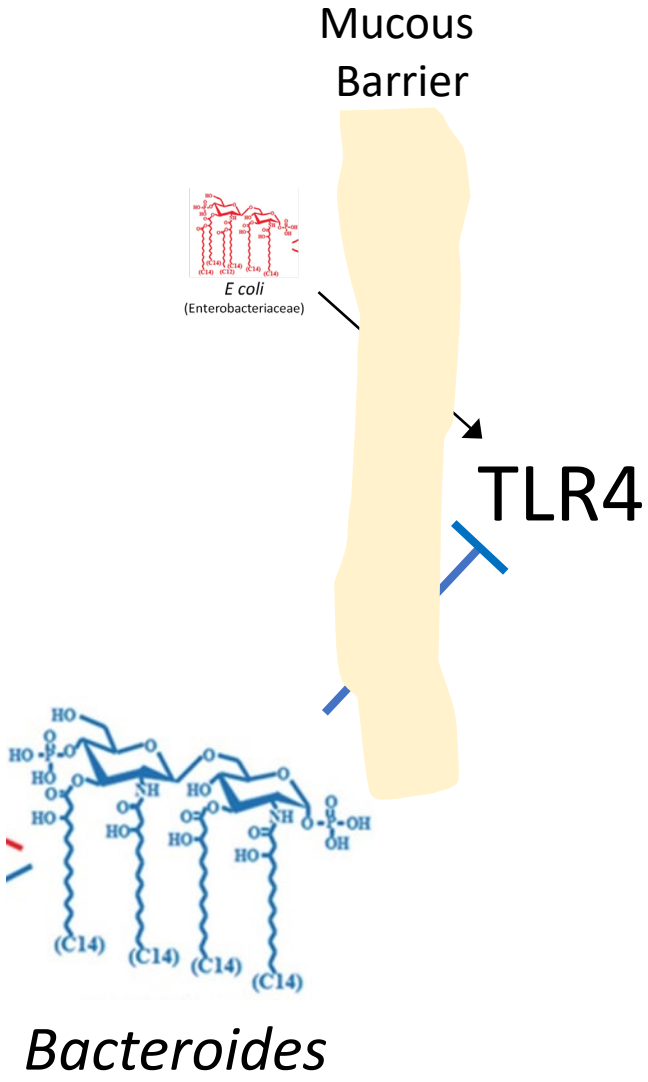
Bacteroides

This antagonistic interaction does not happen with mouse TLR4.

Healthy State

Low Enterobacteriaceae

High Bacteriodes

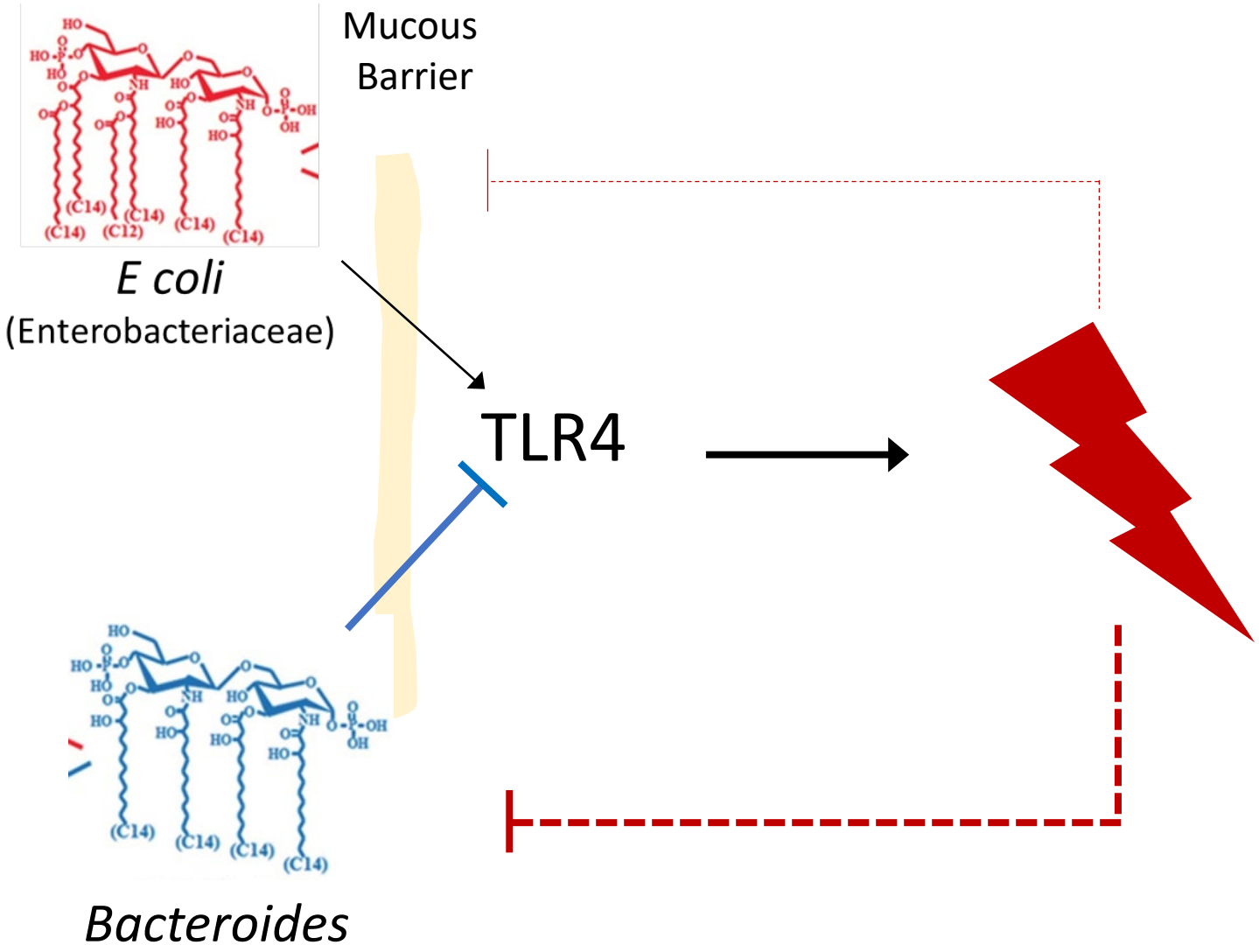


Low Inflammation

Disease State

Enterobacteriaceae increase

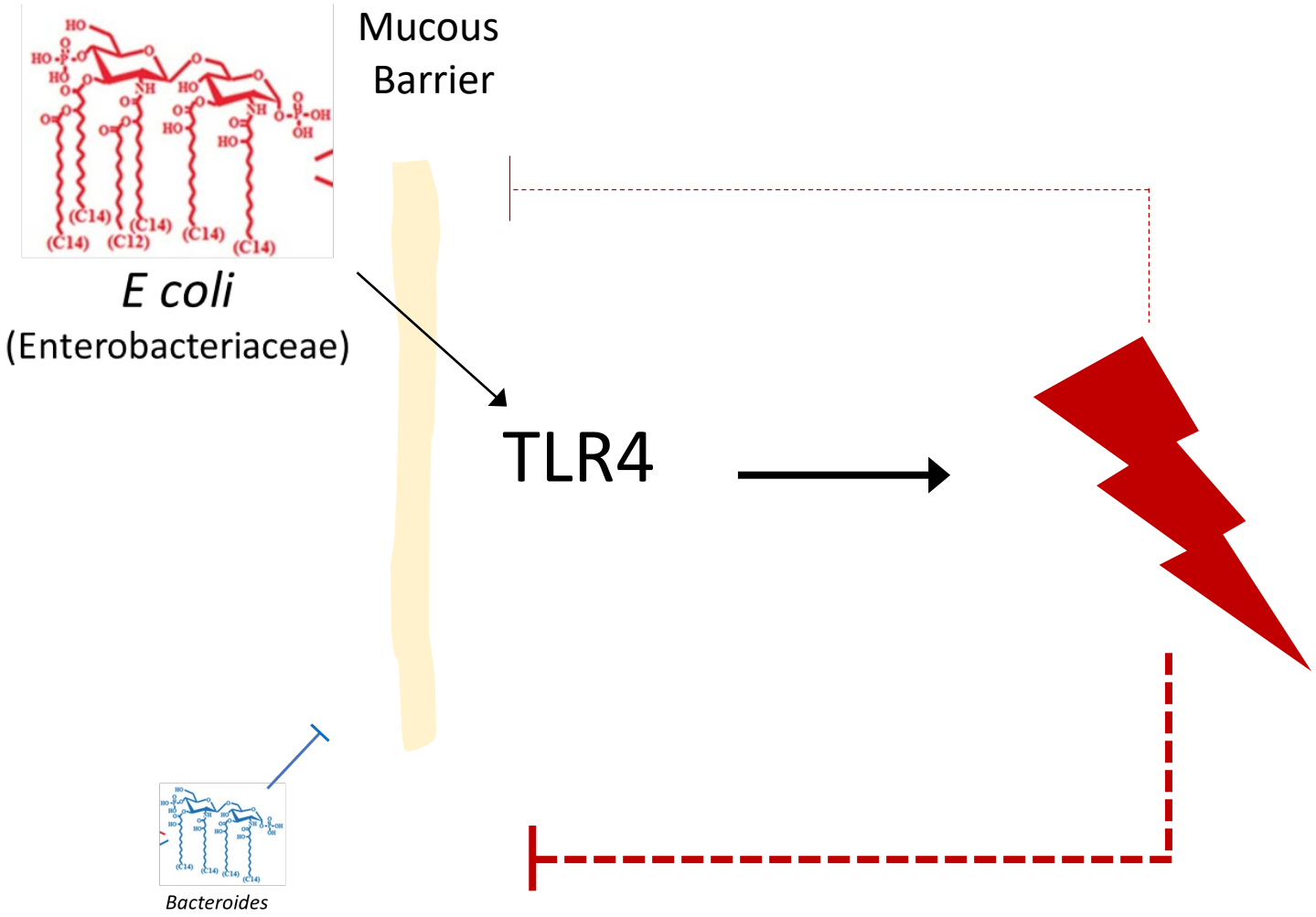
Bacteriodes decrease



Disease State

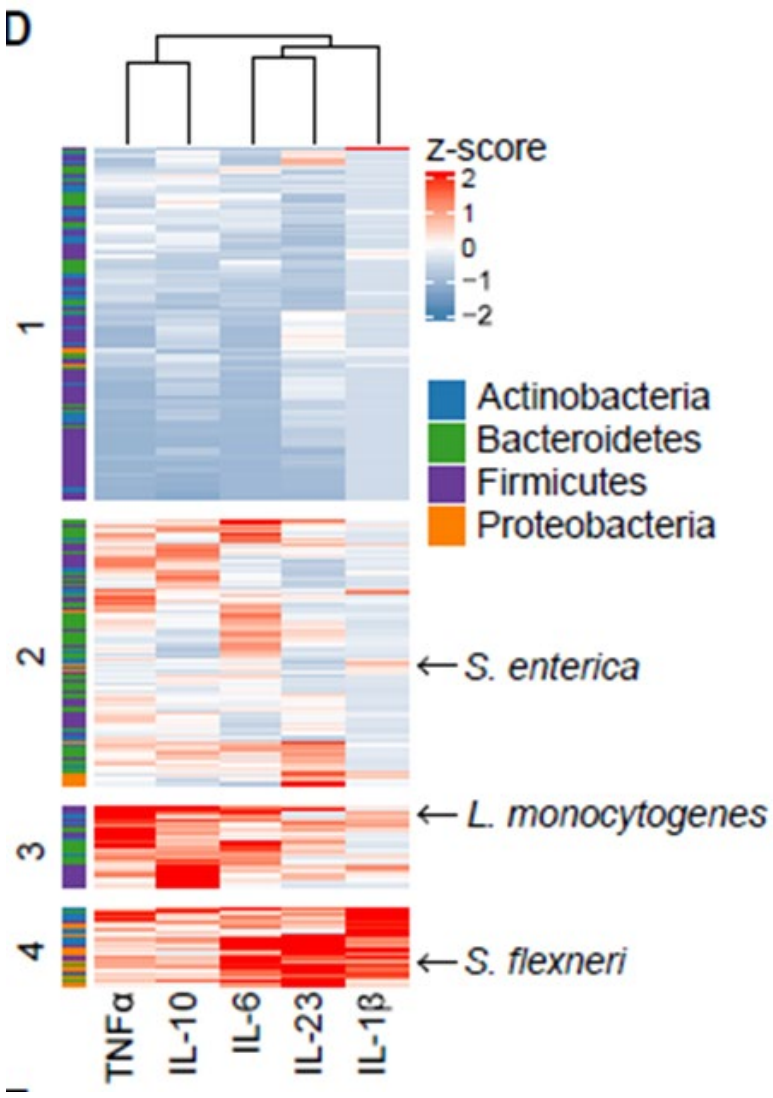
Enterobacteriaceae increase

Bacteriodes decrease

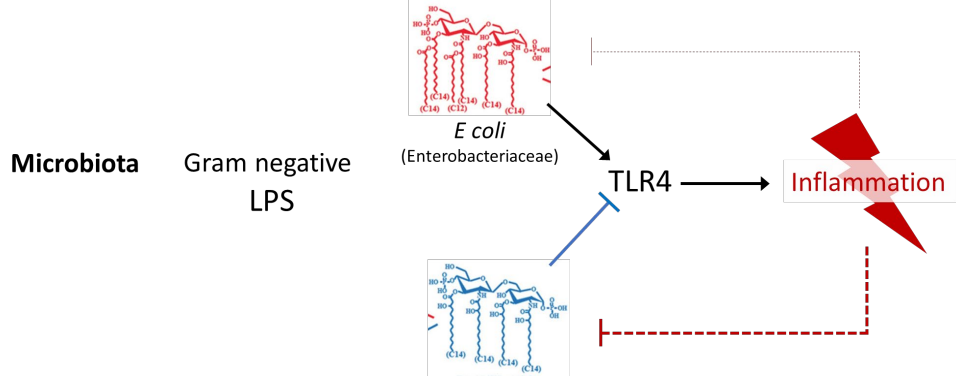


Positive feedback loop - homeostatic

Of course it is not always this simple…



Co-culture of bone marrow-derived dendritic cell (BMDC) with commensals



- 277 unique human gut strains representing 4 phyla
- Patterns of innate immune responses are enriched but not specific to defined taxa
- There is variability at the species/strain level
- Combinations of Toll-like receptor (TLR) ligands model some, but not all, responses to commensals

Spindler MP et al (J Faith lab) Cell Host & Microbe (2022)

When is a microbe (or product/pathway) **necessary** *vs* **sufficient** *for a phenotype*

Germ Free Mice

Deficit in Tregs and Th17 cells

Atarashi et al (2013) distinct group of *Clostridia* isolated as spores → Restores Treg development

Gaboriau-Rothiau et al (2009) murine specific SFB → Restores Th17 development

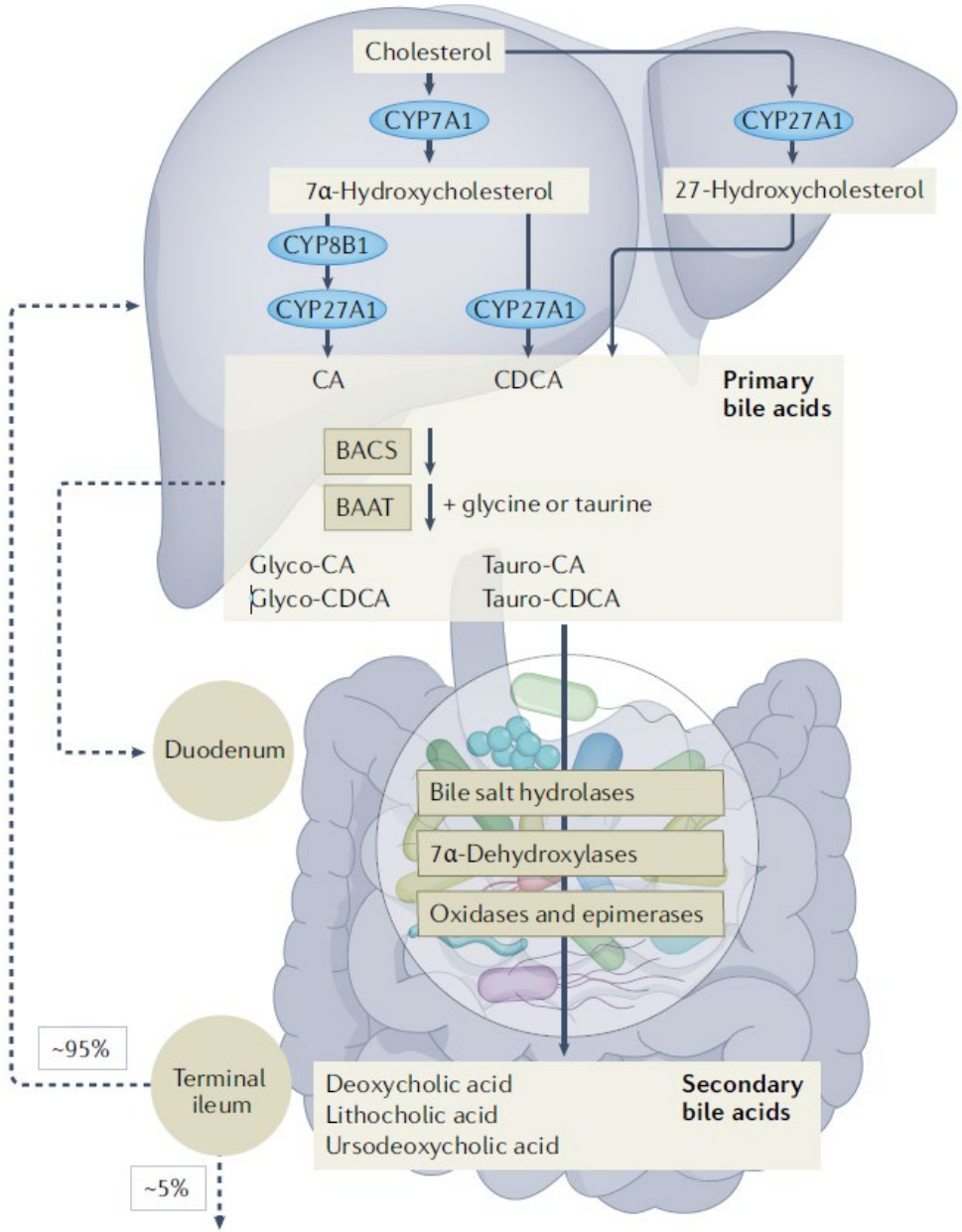
Any of these bacteria are sufficient but not necessary to induce the specific cells in this murine model - i.e. ***functional redundancy*** with respect to immune maturation.

Faith et al 2014, Sefik et al 2015, diverse group of Clostridia and Bacteroides.
Tan et al 2017, a very diverse group of taxonomically distinct bacteria

Bile Acids and Bile Acid Metabolism in IBD

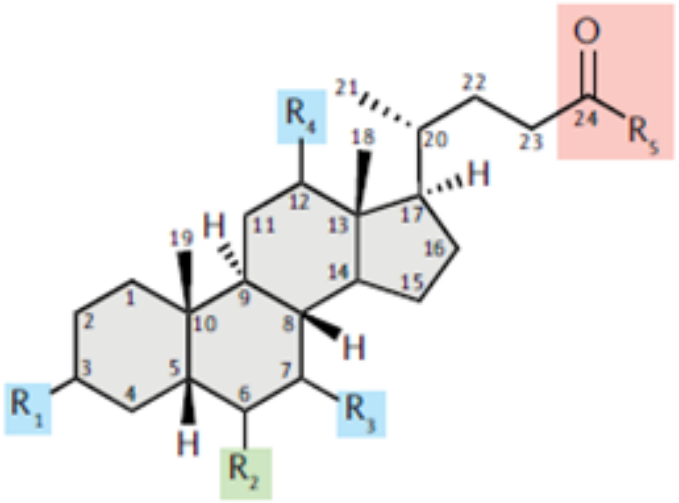
- Bile acids are amphipathic cholesterol metabolites that solubilize dietary lipids in the small intestine and required for their absorption
- Bile acids are also sensed and regulate their own biosynthesis, as well as lipid and glucose homeostasis, and immune signalling
- Gut microbiota metabolizes bile acids secreted into the duodenum into secondary bile acids
- In healthy guts, 95% of the bile acids (1° and 2°) are readsorbed in the terminal ileum and recycled in the liver

Enterohepatic circulation of bile acids



Collins SL et al Nat Rev Microbiol (2022)

Bile Acids and Bile Acid Metabolism in IBD



General structure of bile acids.

- R_1-R_4 are sites of dihydroxylation of oxidation
- R_5 is the site esterification, amidation, deconjugation

There are a large number of bile acid derivatives known and likely many more to be discovered.

The Metabolomics Innovation Centre (UofA) targeted bile acid analysis quantifies 76 compounds.

Because bile acids can also be signaling molecules very low abundant derivatives could be potent agonists of antagonists.

Bile Acids and Bile Acid Metabolism in IBD

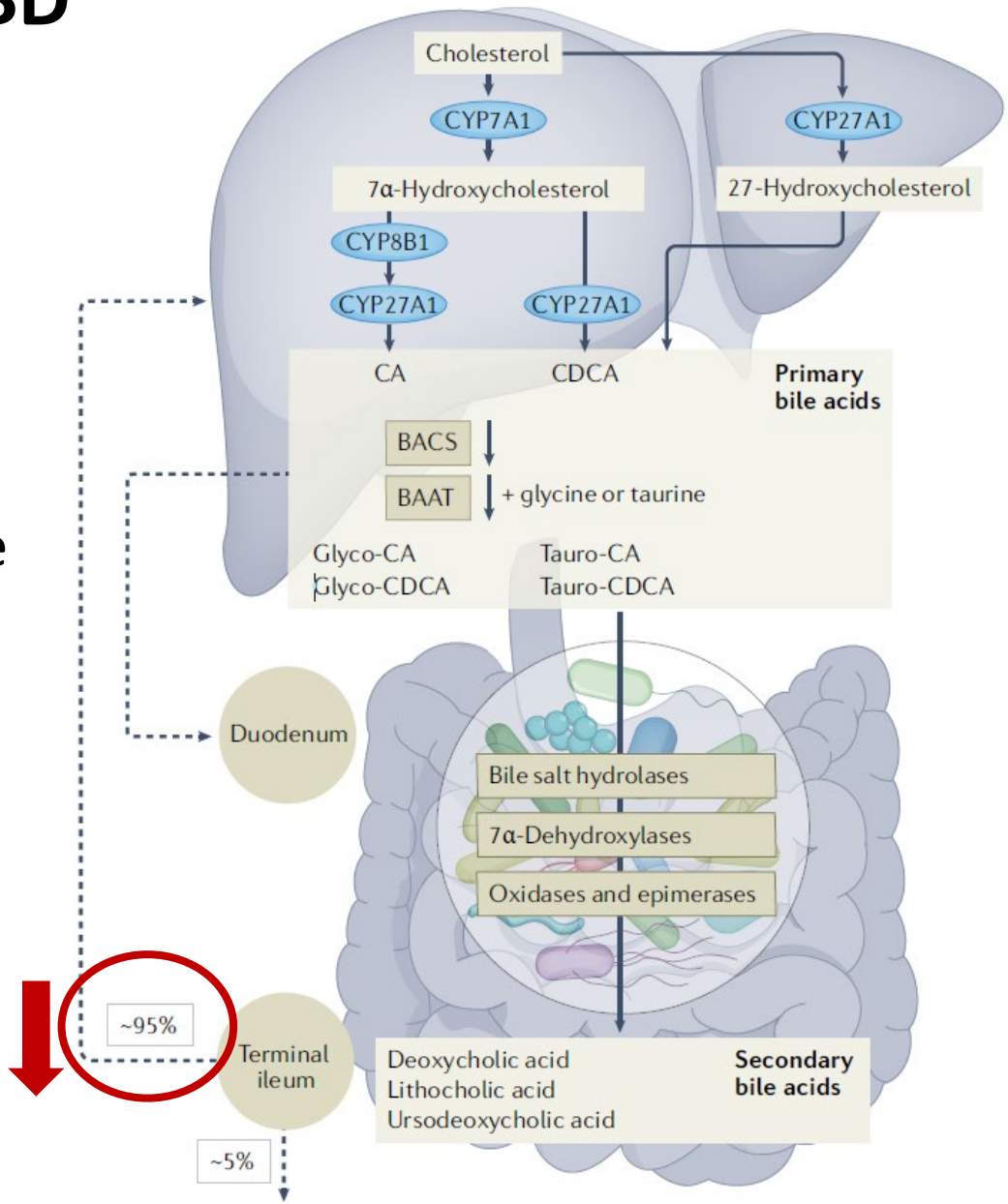
Bile acid metabolism is dysregulated in IBD, enterohepatic circulation is decreased with active disease.

This at least in part due to increase transit rate which mean lower microbial load and less time to metabolize bile.

Elevated levels of conjugated BAs and amino acid-conjugated bile acids and reduced levels of secondary BAs in their stool.

Bile acids are toxic to bacteria and modification of bile by bacteria are resistance mechanisms. (alter microbial community composition)

Enterohepatic circulation of bile acids



Collins SL et al Nat Rev Microbiol (2022)

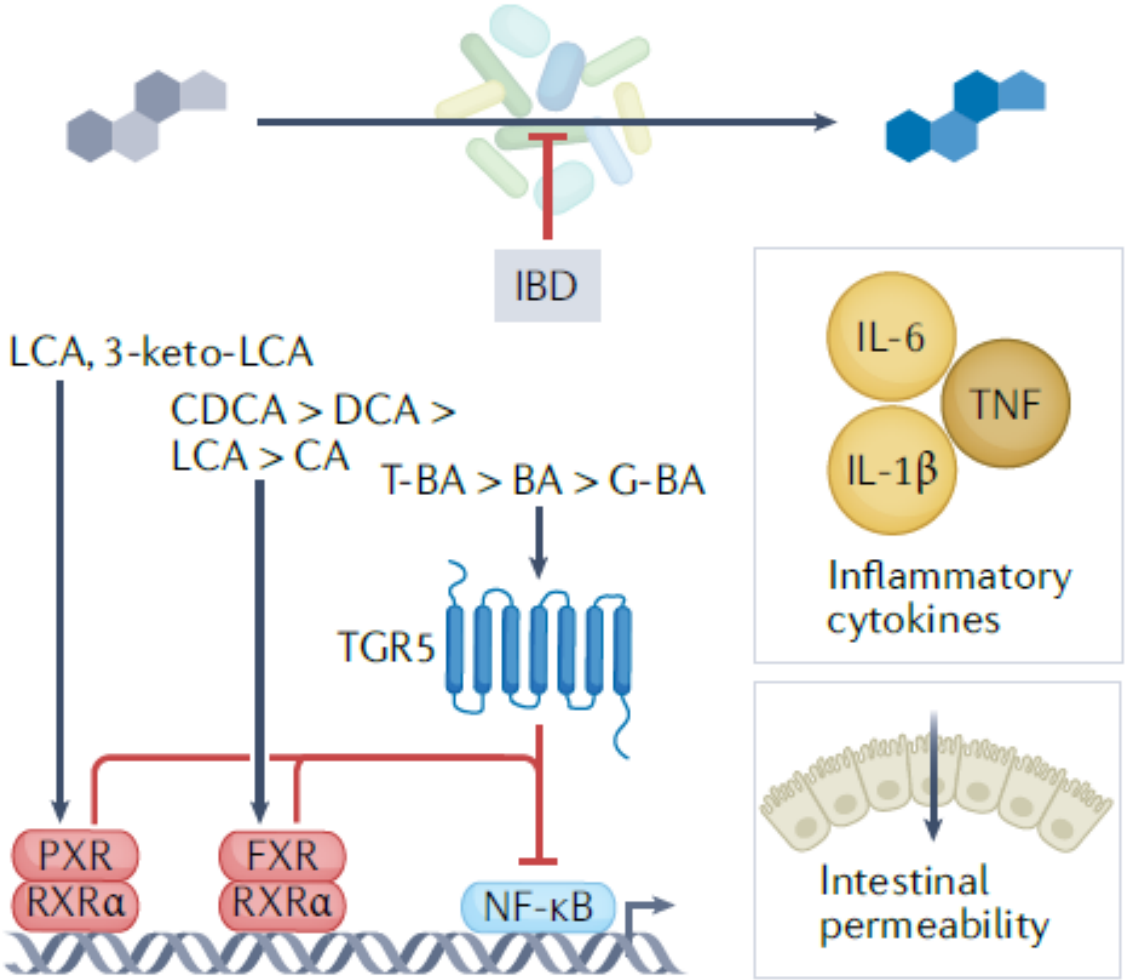
Bile Acids and Bile Acid Metabolism in IBD

As ***signaling molecules***, secondary bile acids activate PXR and FXR receptors on intestinal cells and TGR5 on monocytes.

This leads to reduces inflammatory cytokine production and intestinal permeability by inhibiting NF- κB.

In IBD, the altered bile acid pools result in reduces PXR, FXR, TGR5 activation.

Agonists of FXR and PXR reduce inflammation in murine IBD models.



LCA, lithocholic acid
CDCA, chenodeoxycholic acid
DCA, deoxycholic acid

T-BA, taurine- conjugated
G-BA, glycine- conjugated

Collins SL et al Nat Rev Microbiol (2022)

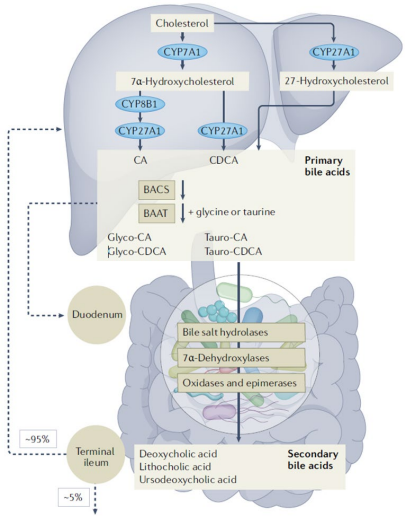
Bile Acids and Bile Acid Metabolism in IBD

Mice and humans have very different bile acid pools

- cholic acid and chenodeoxycholic acid in humans
- cholic acid and muricholic acid (MCA) in mice

The human bile acid metabolites are more cytotoxic and accumulation in the liver → NASH / NAFLD …

Consequently reduction of the cytotoxic effects of bile accumulation is easier to achieve in mouse models than in actual patients

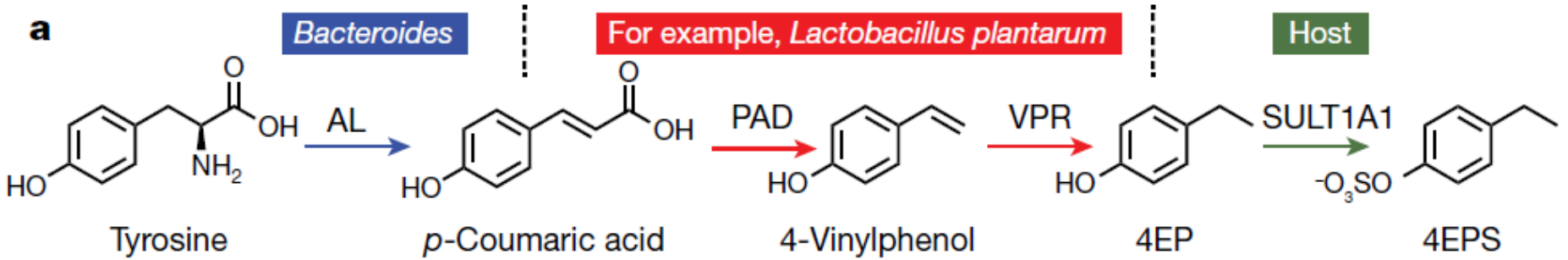


Chiang et al Am J Physiol Gastrointest Liver Physiol 2020

Active microbiome derived metabolites are not always made by a single organism

4-ethylphenyl sulfate (4EPS)

- increased in plasma of individuals with autism spectrum disorder (ASD)
- increased in murine models of ASD
- impaired oligodendrocyte maturation in mice



Tyrosine rich diets

Plant diets with p-coumaric derivatives

Diversity of conjugates with positive health effects described

Pei et al 2015

Needham et al Nature 2022

Microbiome produced enzymes

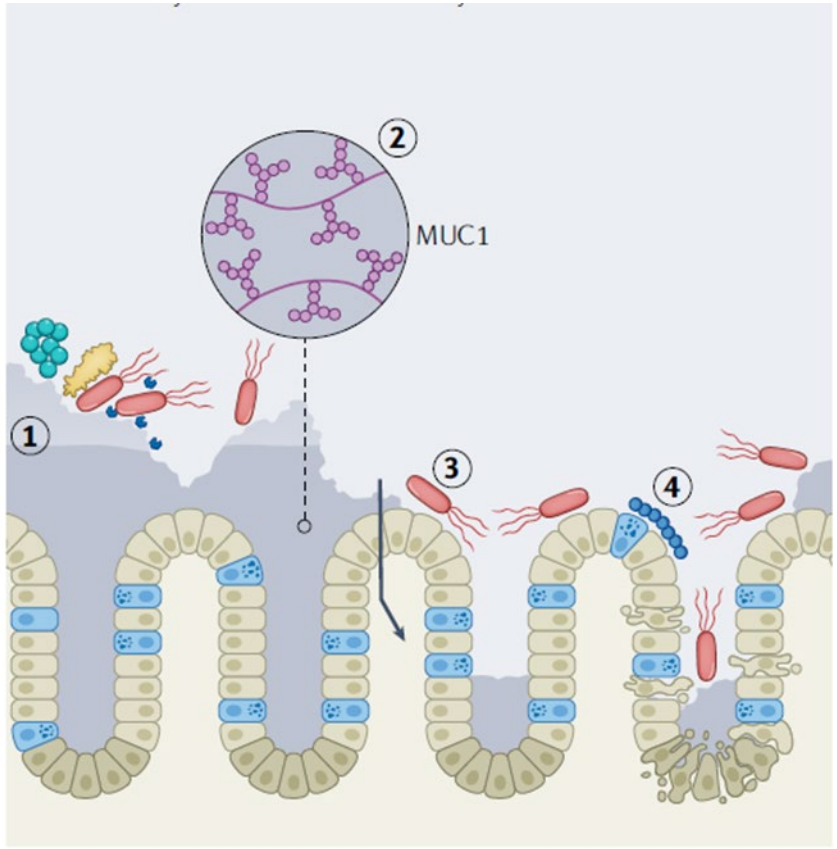
Proteases

In additional to PAMPs and metabolites microbiota produced enzymes can act on host proteins and receptors to modulate response.

Degradation of mucin requires proteases in addition to enzymes that remove carbohydrate moieties.

Galipeau et al (2021) using samples from the GEM study have shown that protease activity is elevated in UC patients even before they present with disease.

Protease activated receptors (PARs) have been shown to be important regulators of intestinal homeostasis and bacterial proteases have been shown to activate PAR and proinflammatory pathways in murine models of celiac disease (Caminero et al, 2019)



Microbiome produced enzymes

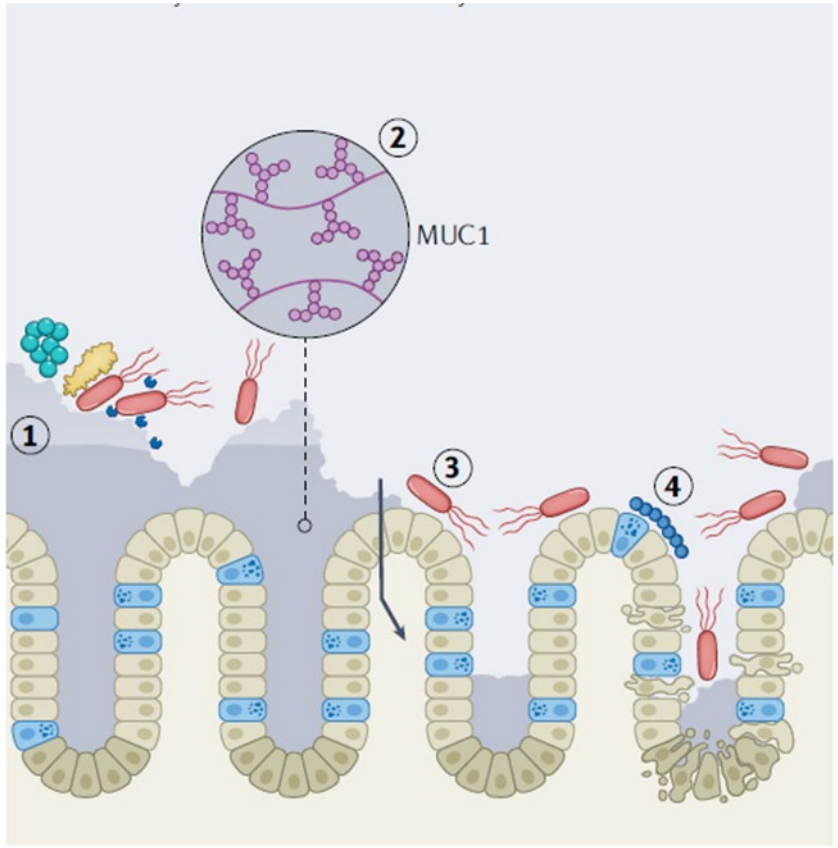
Carbohydrate active enzymes (CAZy)

In additional to PAMPs and metabolites microbiota produced enzymes can act on host proteins and receptors to modulate response.

This group of enzymes is responsible for digestion of complex carbohydrates (e.g. fiber) and extracellular matrix (e.g. mucin).

They can also act directly on host cells and modulate their activity.

Host glycosylation is altered in IBD and bacterial derived CAZy are altered in IBD from metagenomic analysis.



Using culture-enriched metagenomics for in depth profiling of the stool microbiome we observed 10-14,000 different glycoside hydrolases per sample.

We currently under estimate the biochemical complexity of the gut microbiome.

Standard tools are not analyzing the microbiome at a sufficient level of detail that any biologist should be happy with!

Short-read analysis of metagenomic data underestimates biochemical potential and taxonomic complexity.

Metabolites that act as signaling molecules (e.g. bile acid, indole derivatives) are required at levels far below that required for other physiological roles (levels not detected by routine metabolomics).

Variation in PAMPs between bacteria can alter agonist / antagonist activity.

While we generally think of the healthy state as homeostatic, feedback mechanisms may also make disease states stable as well.


We are probably just seeing the “tip of the icebergs” of our understanding of mechanisms of how the microbiome and microbiome derived products promote and suppress inflammation in IBD.
…but the research continues to open new avenues for treatment and early diagnosis.