

Microbiome Workshop

Canada Future Directions in IBD
Hot Topics from Bench to Clinic to Policy

via Calgary, Canada

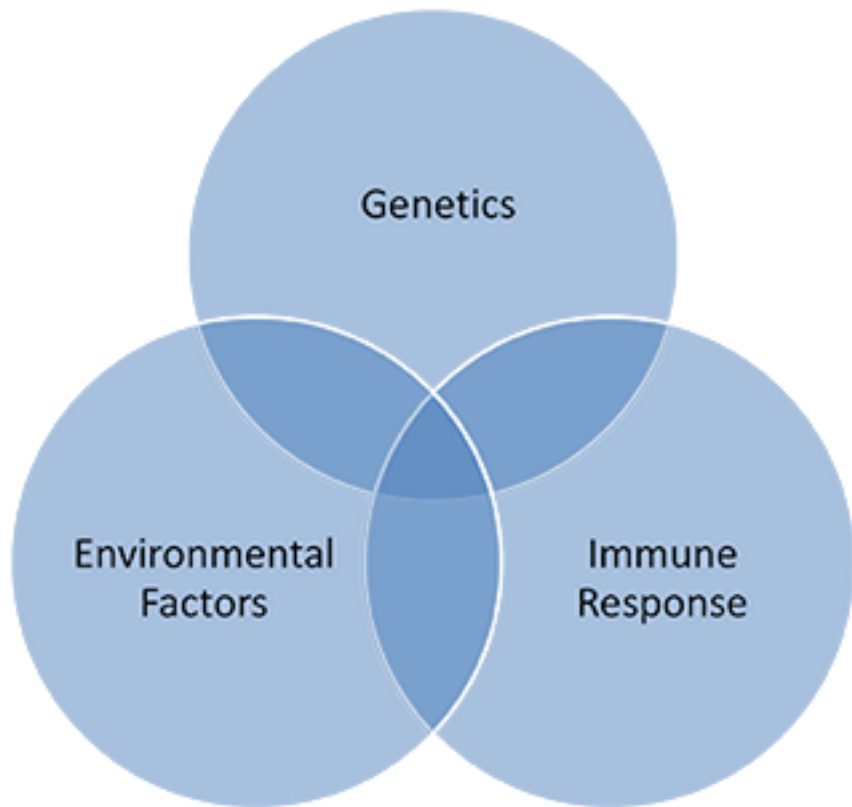
07-November-2020

Kathy McCoy

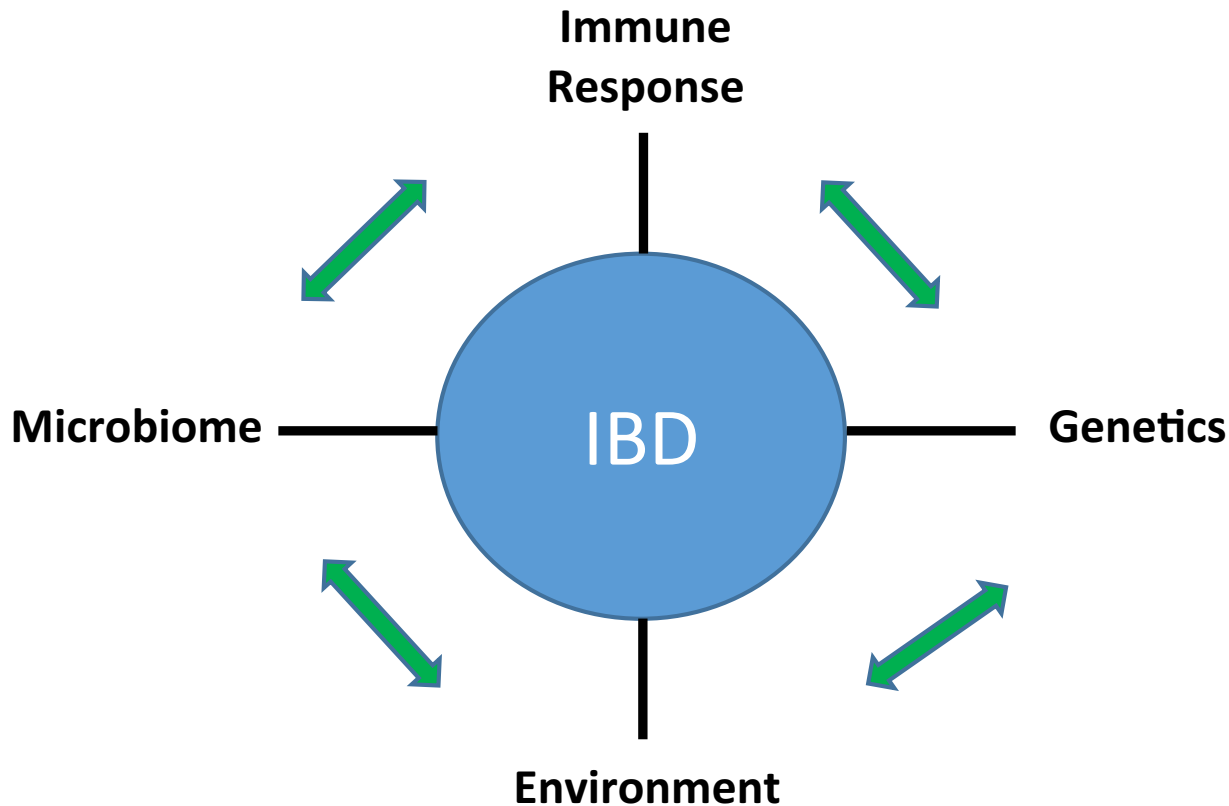
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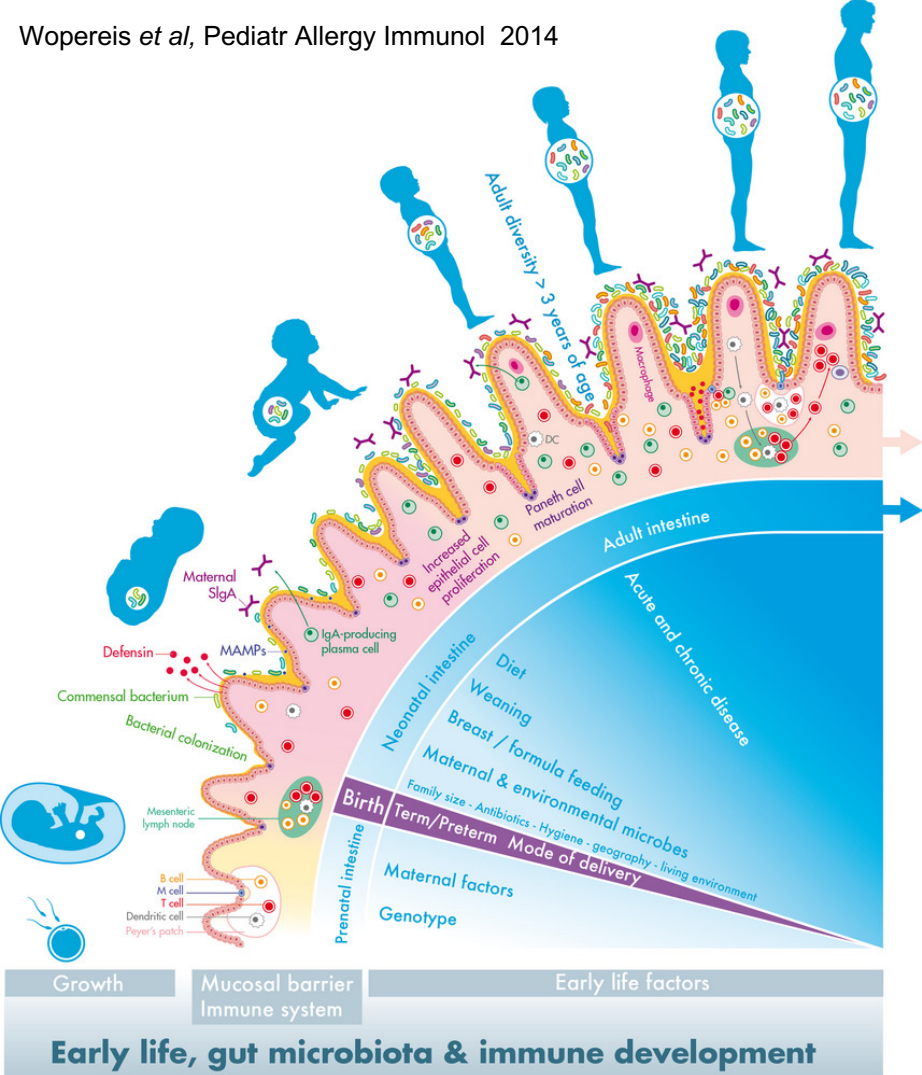
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IBD develops through complex interactions

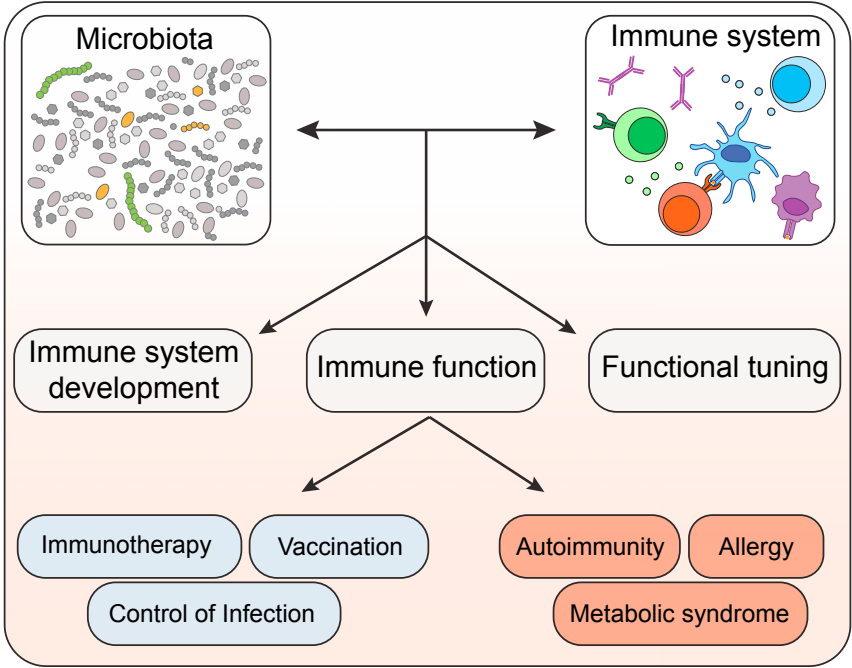


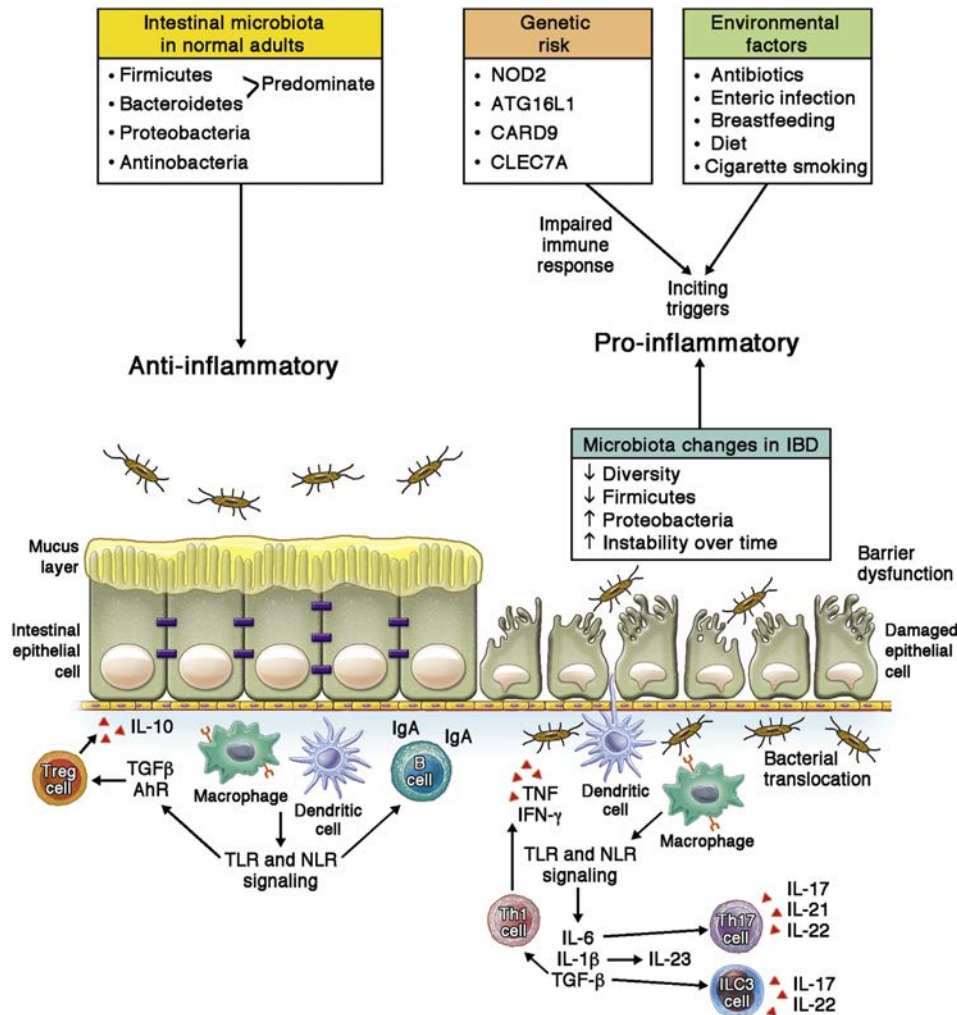
IBD develops through complex interactions





Microbiota drives immune education





Pathogenesis of IBD: Genetic, environmental, and immune impacts on microbiome

Microbial-derived Metabolites are Key Intermediates in Communication between the Gut Microbiome and Host Immune System

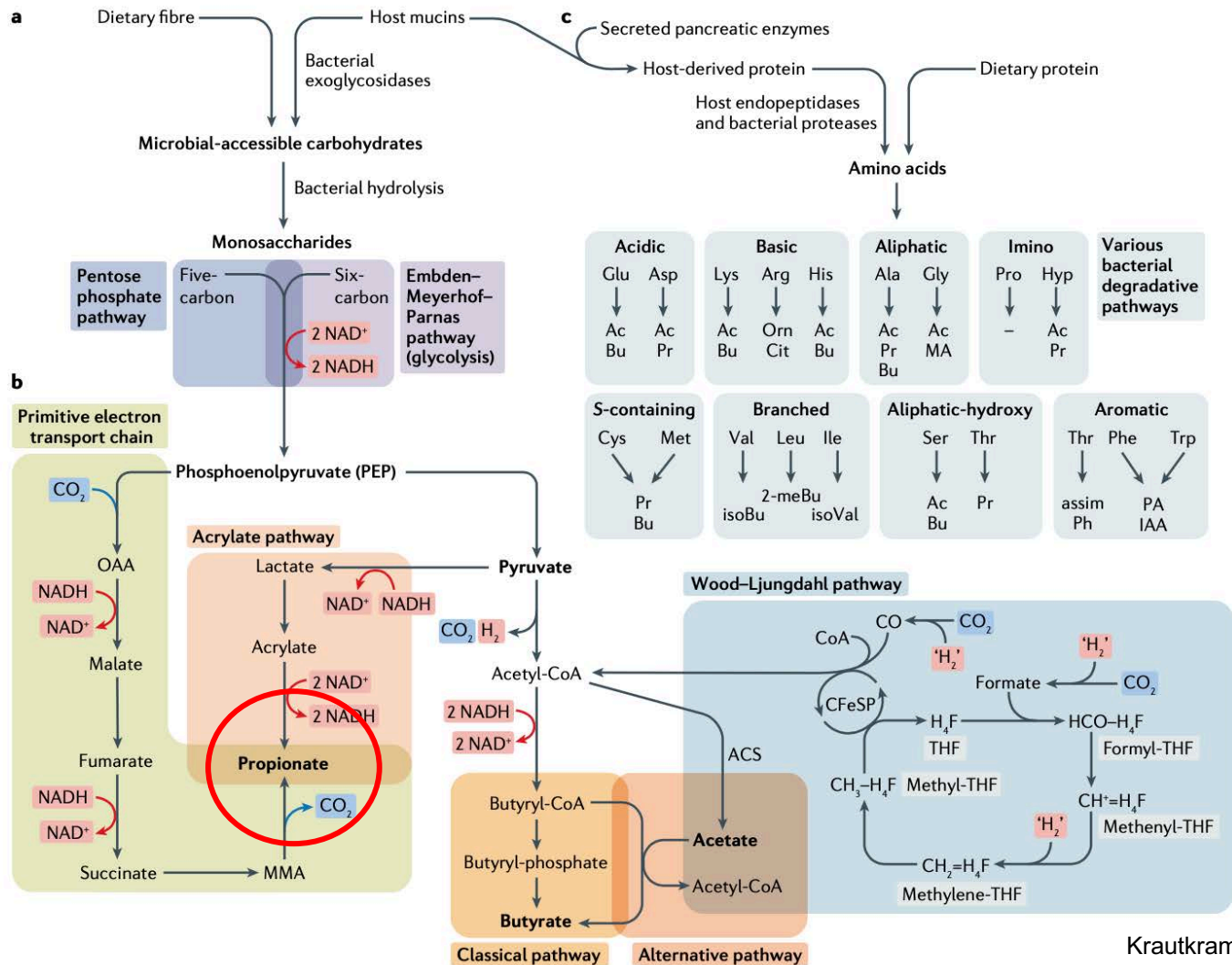
Gut Microbiota

The diagram illustrates the mechanisms of gut microbiota in maintaining intestinal homeostasis and regulating immune responses. Key pathways and interactions include:

- SCFAs (Short-Chain Fatty Acids):**
 - Butyrate:**
 - Acts on **GPR43** and **GPR109a** on intestinal cells, leading to **Energy↑** and **Inflammation**.
 - Acts on **HDAC** and **NFκB** in intestinal cells, leading to **IL-18** production and **Intestinal Homeostasis**.
 - Acts on **HDAC** in **DC Mφ** (Dendritic cells/Macrophages), leading to **Neutrophil Chemotaxis**.
 - Acts on **Goblet cells**, leading to **Mucin↑**.
- Diet tryptophan:**
 - Acts as **AHR ligands** on intestinal cells, leading to **TJ** (Tight Junctions) and **IL-18** production.
 - Acts on **AHR** in **ILC** (Innate Lymphoid Cells), leading to **IL-22** production.
- Bile Acids:**
 - Acts on **FXR** and **TGR5** on intestinal cells, leading to **Proinflammatory Genes** and **IL-18** production.
- Bacteroides fragilis:**
 - Acts on **TLR2** on intestinal cells, leading to **IL-10↑** and **IL-17↓** production.
- Immune Cell Interactions:**
 - IL-18** (red dots) is produced by intestinal cells and acts on **DC Mφ** and **Naive T_{reg}** cells.
 - IL-22** (purple dots) is produced by **ILC** and acts on **DC Mφ**.
 - IL-10** (blue dots) is produced by **CD4⁺** cells and acts on **Naive T_{reg}** cells.
 - FOXP3** is produced by **Naive T_{reg}** cells and acts on **DC Mφ**.

Blautia hydrogenotrophica,
Clostridium spp.,
Streptococcus spp.

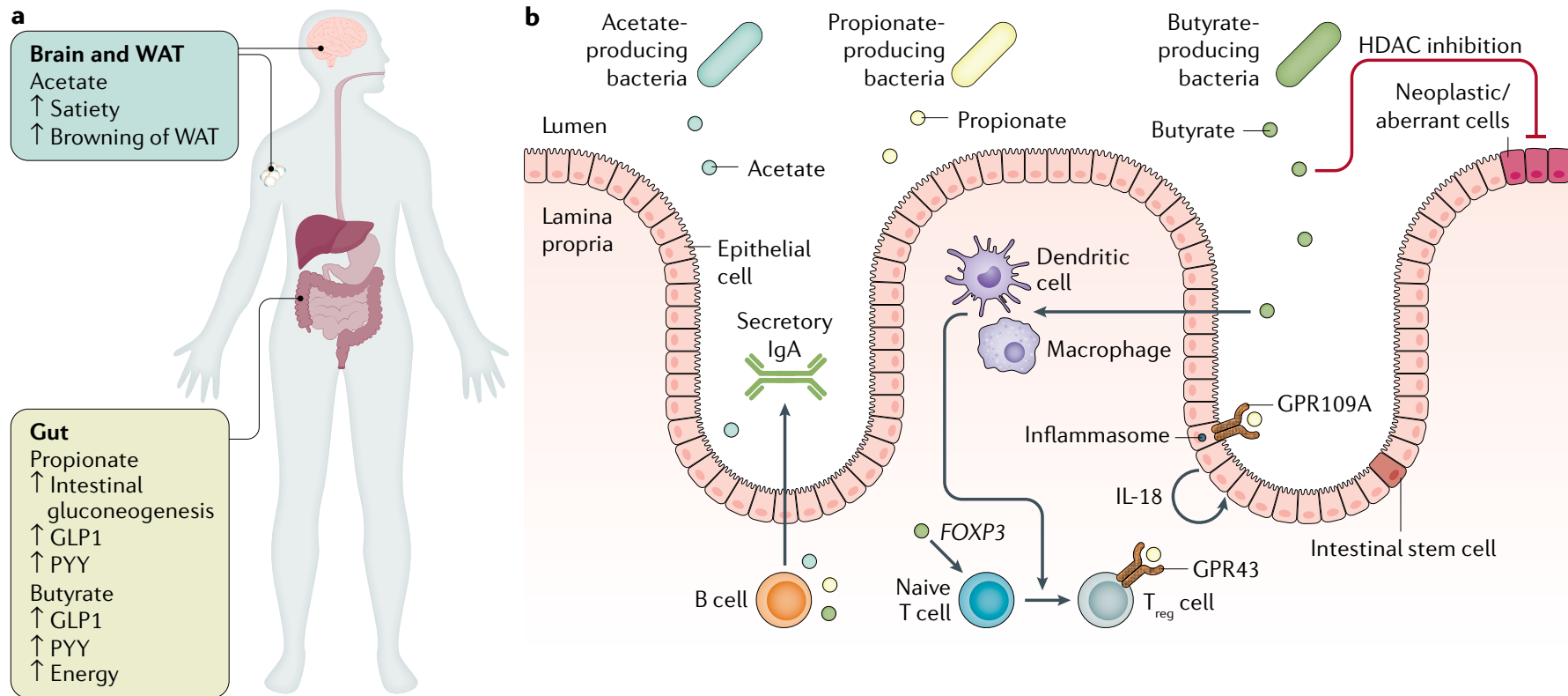




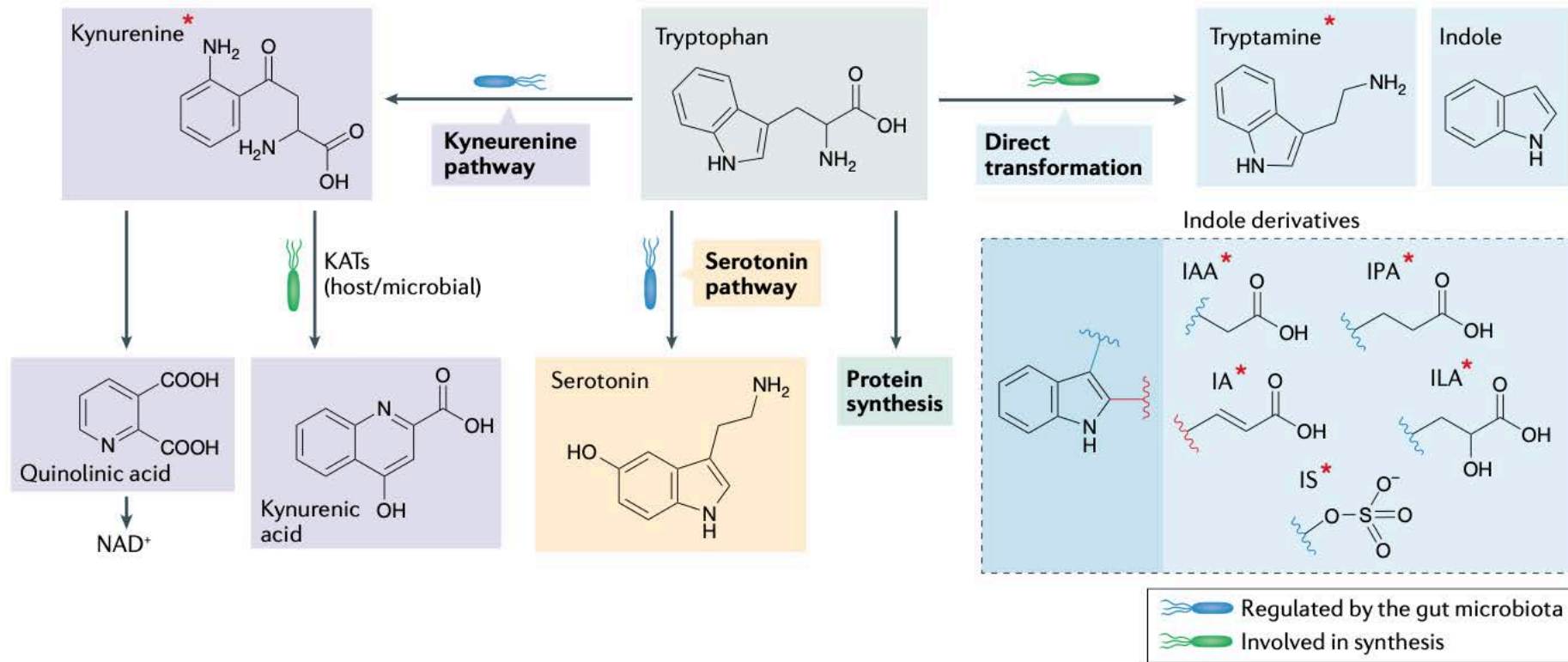
Microbial Fermentation: Carbohydrates and Proteins

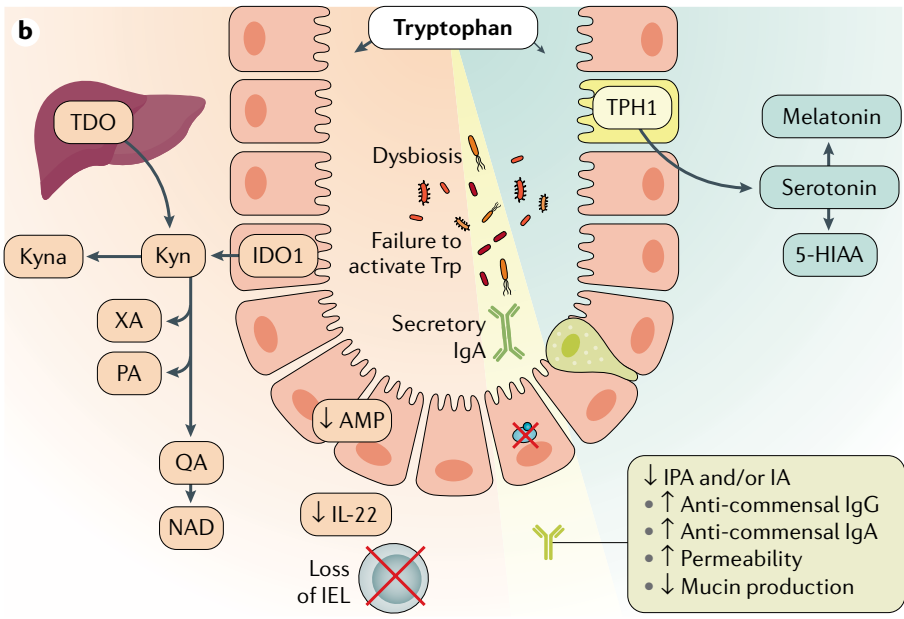
Coprococcus catus
Eubacterium hallii
Megasphaera elsdenii
Veillonella spp
Bacteroides spp.
Dialister spp.
Phascolarctobacterium succinatutens,
Veillonella spp
Roseburia inulinivorans
Ruminococcus obeum
*Salmonella enterica*2

SCFAs and effect on immune system



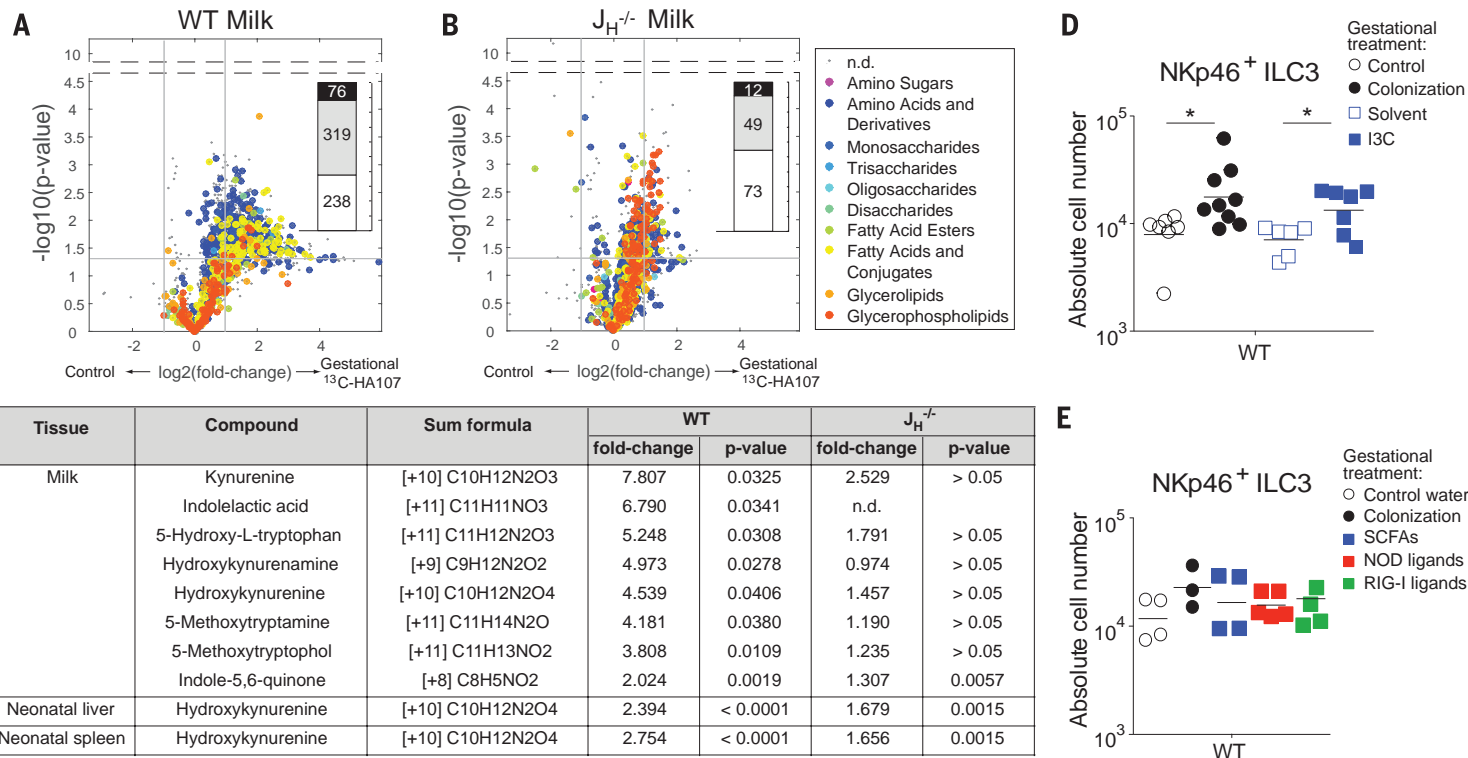
Microbiome and Tryptophan Metabolism





■ Kynurenine pathway
 ■ Indole pathway
 ■ Serotonin pathway

Maternal microbiome drives early postnatal innate immune development



Microbiome and immune education

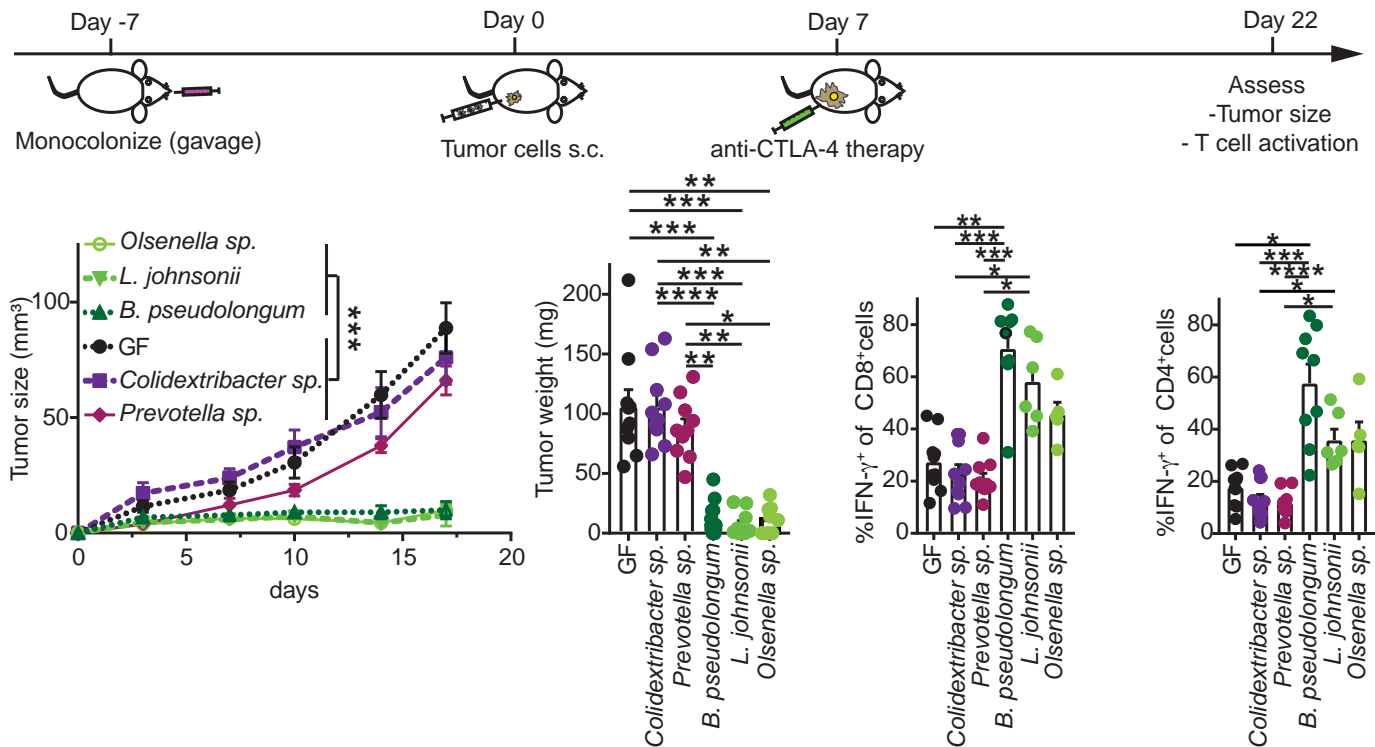


Gut Microbiota

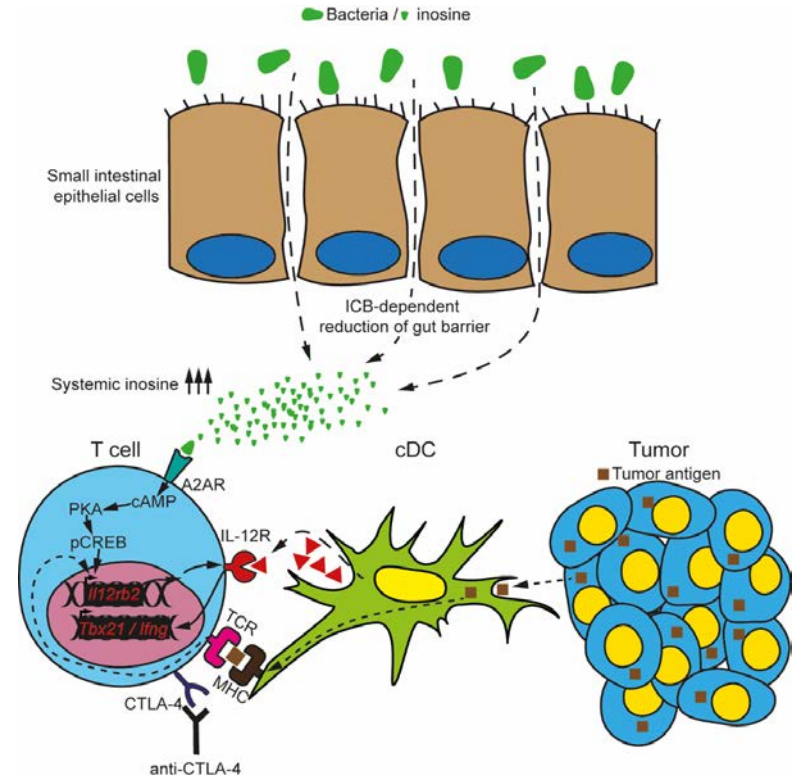
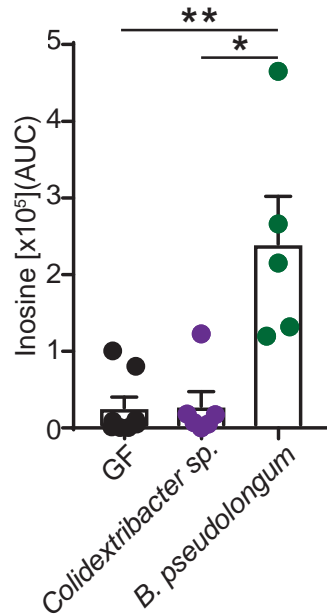
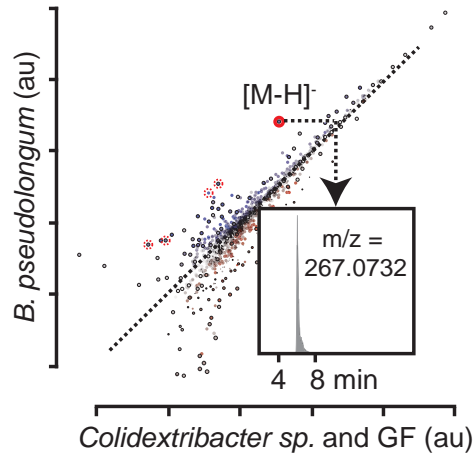
SCFAs (Butyrate, Acetate, Propionate) → GPR43, GPR109a → Energy↑, Inhibition of autophagy, Inflammasome activation, HDAC, FOXO3↑, NFκB, Mucin↑ (Goblet cell), AMP, NLRP6 inflammasome, IL-18, AHR ligands, Diet tryptophan, Bile Acids, FXR, TGR5, TJ, AHR, ILC, IL-22, Proinflammatory Genes, Mφ, DC Mφ, Neutrophil Chemotaxis, HDAC, DC Mφ, Neutrophil Chemotaxis, IL-18, Intestinal Homeostasis.

Bacteroides fragilis (PSA) → TLR2, CD4⁺, IL-10↑, IL-17↓, Inflammation, GPR43, T_{reg}, Naive, FOXP3, T_{reg}, GPR109a, DC, IL-10.

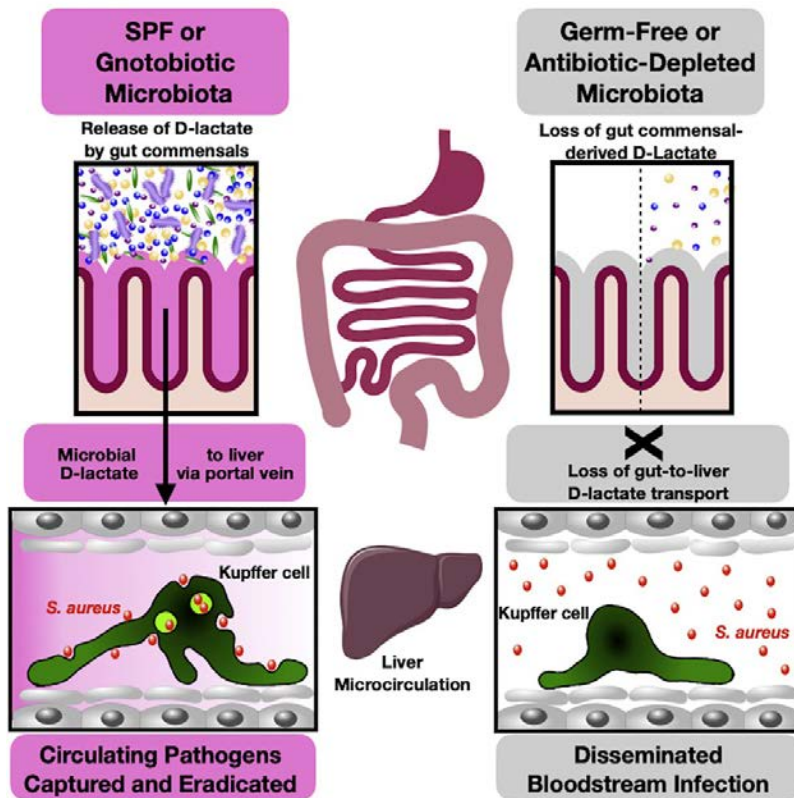
Specific bacteria can boost ICB efficacy



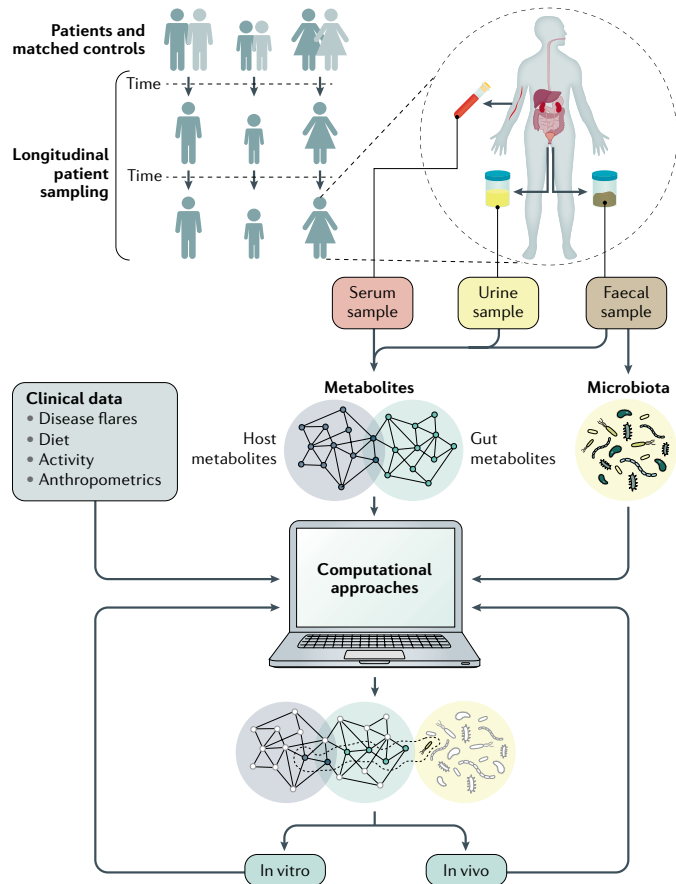
Identification of a bacterial-derived metabolite



Microbial-derived D-lactate programs intravascular immune firewall



Discovery of microbiome-metabolome in IBD



International Microbiome Centre (IMC)



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Canada Foundation for Innovation
Fondation canadienne pour l'innovation

