Gut Biogeography of Bacterial Microbiota

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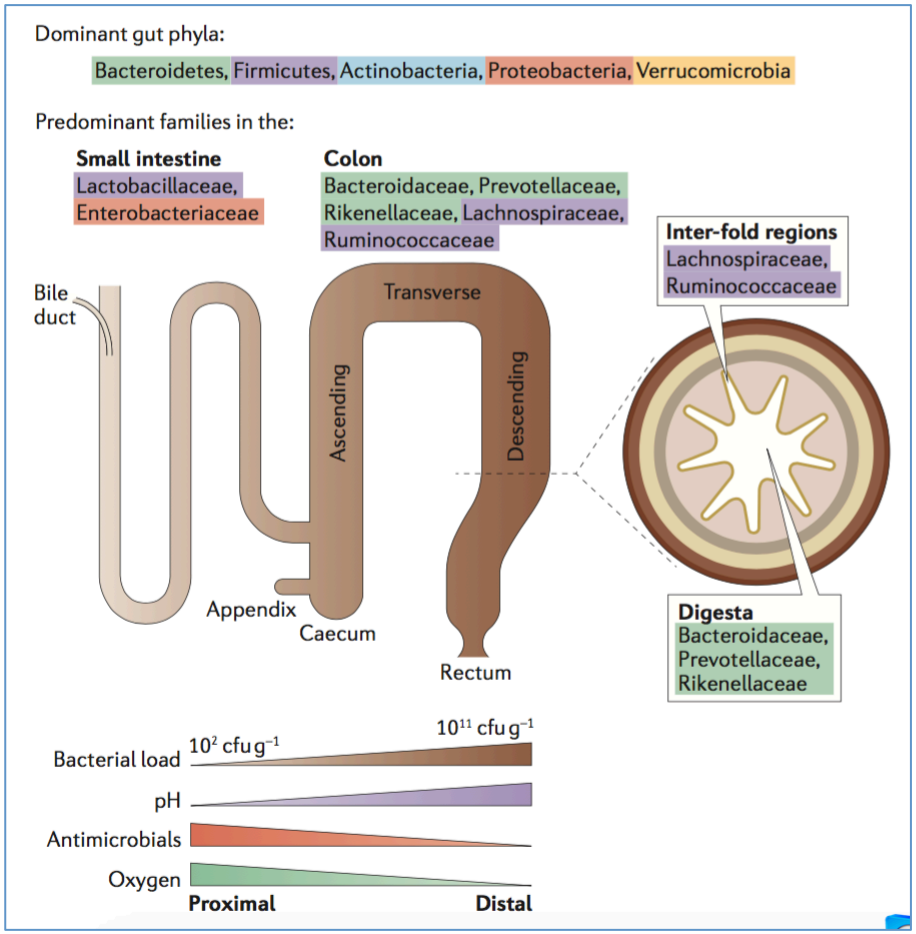
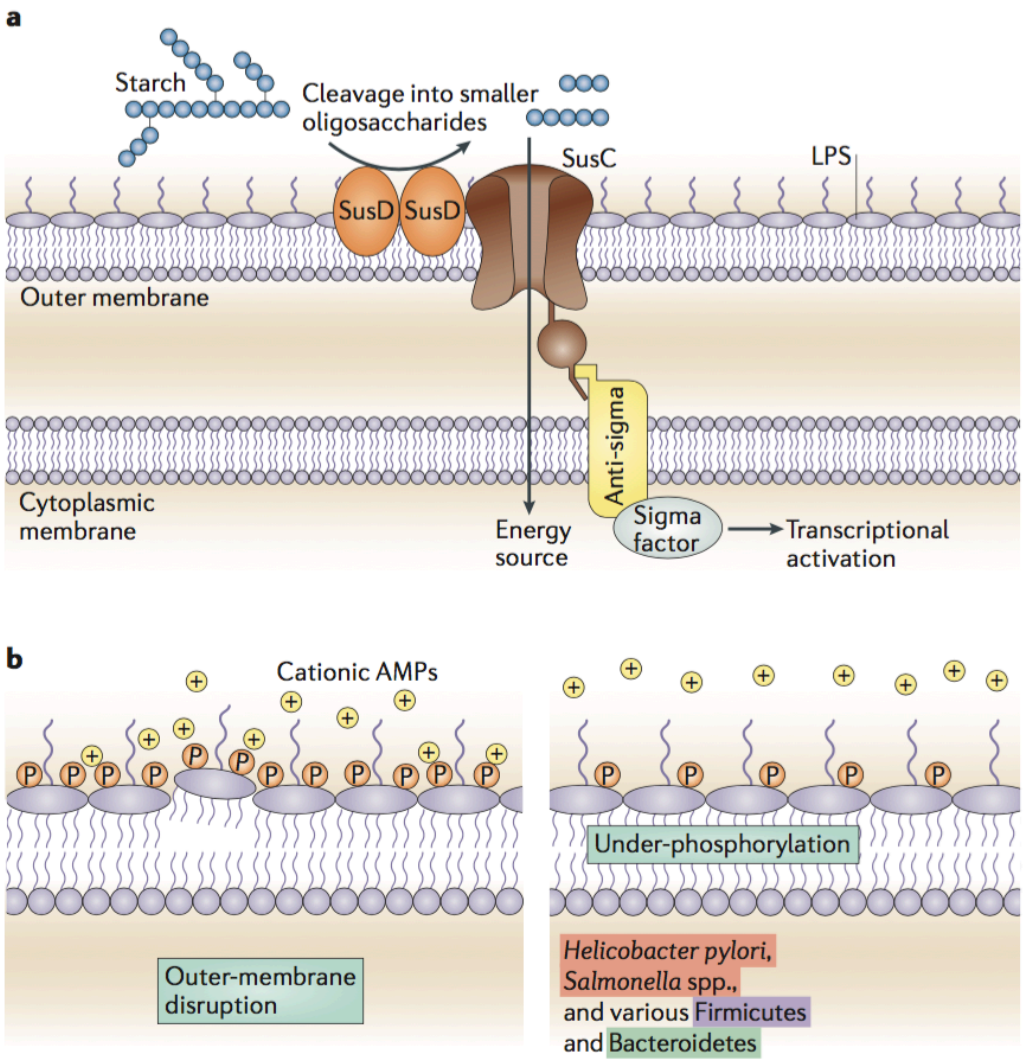
Humans and other mammals harbour a complex gastro- intestinal microbiota that includes all three domains of life (Archaea, Bacteria and Eukarya). This extraordinary symbiosis, formed by a series of exposures to environ- mental factors, is initiated on contact with the maternal vaginal microbiota during birth. Abrupt changes during the first year of life follow a pattern that corresponds to gestational age in both mice and humans, which suggests that strong deterministic processes shape the composition of the microbiota during development. These population shifts may be explained by influences from the diet, the developing immune system, chemical exposures and, potentially, the founder effects of initial colonizers. Founder effects are not well understood in the mammalian gut, but the profound changes in host gene expression that occur in response to microorgan- isms and also the great potential for syntrophic interactions between bacteria suggest that early colonizers would have long-term effects on the establishment of the microbiota. The immune system imposes selective pres- sure on the microbiota through both innate and adaptive mechanisms, such as antimicrobial peptides, secreted immunoglobulin A (sIgA) and other contributing factors (see below). **However, current research suggests that diet has the greatest impact on microbiota assembly**.



Microbial habitats in the human lower gastrointestinal tract. The dominant Proximal bacterial phyla in the gut are Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobia. The dominant bacterial families of the small intestine and colon reflect physiological differences along the length of the gut. For example, a gradient of oxygen, antimicrobial peptides (including bile acids, secreted by the bile duct) and pH limits the bacterial density in the small intestinal community, whereas the colon carries high bacterial loads. In the small intestine, the families Lactobacillaceae and Enterobacteriaceae dominate, whereas the colon is characterized by the presence of species from the families Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae and Ruminococcaceae (colours correspond with the relevant phyla). A cross-section of the colon shows the digesta, which is dominated by Bacteroidaceae, Prevotellaceae and Rikenellaceae, and the inter-fold regions of the lumen, which are dominated by Lachnospiraceae and Ruminococcaceae. cfu, colony-forming units.



Bacterial colonization determinants. Several factors affect the localization of bacteria within the gastrointestinal tract, including the ability to utilize different glycans and to resist antimicrobial peptides (AMPs). **a** Starch utilization system (Sus)-like systems in *Bacteroides* spp. allow the utilization of complex polysaccharides from the diet or the host. The figure shows a generalized schematic of a Sus-like system. Homologues of SusD and other outer-membrane lipid-anchored enzymes bind and cleave the glycans (such as starch) into smaller oligosaccharides, which are then imported by the SusC-like outer-membrane transporter. Interaction with the cognate glycan often leads to transmembrane signalling to activate gene regulatory mechanisms, such as a two-component system or a transmembrane anti-sigma factor that releases and activates a sigma factor. Downstream transcriptional regulation allows *Bacteroides* spp. to respond to the local availability of glycans.

b Cationic AMPs in the small intestine, which also pass into the colon via the faecal stream, disrupt bacterial outer membranes by interacting with negative charges on their surface. By removing phosphate groups (P) from the lipid A of lipopolysaccharide (LPS), pathogens and commensals alike — such as *Helicobacter pylori*, *Salmonella* spp. and various Firmicutes and Bacteroidetes members — reduce the negative charge on their membranes and evade attack by cationic AMPs

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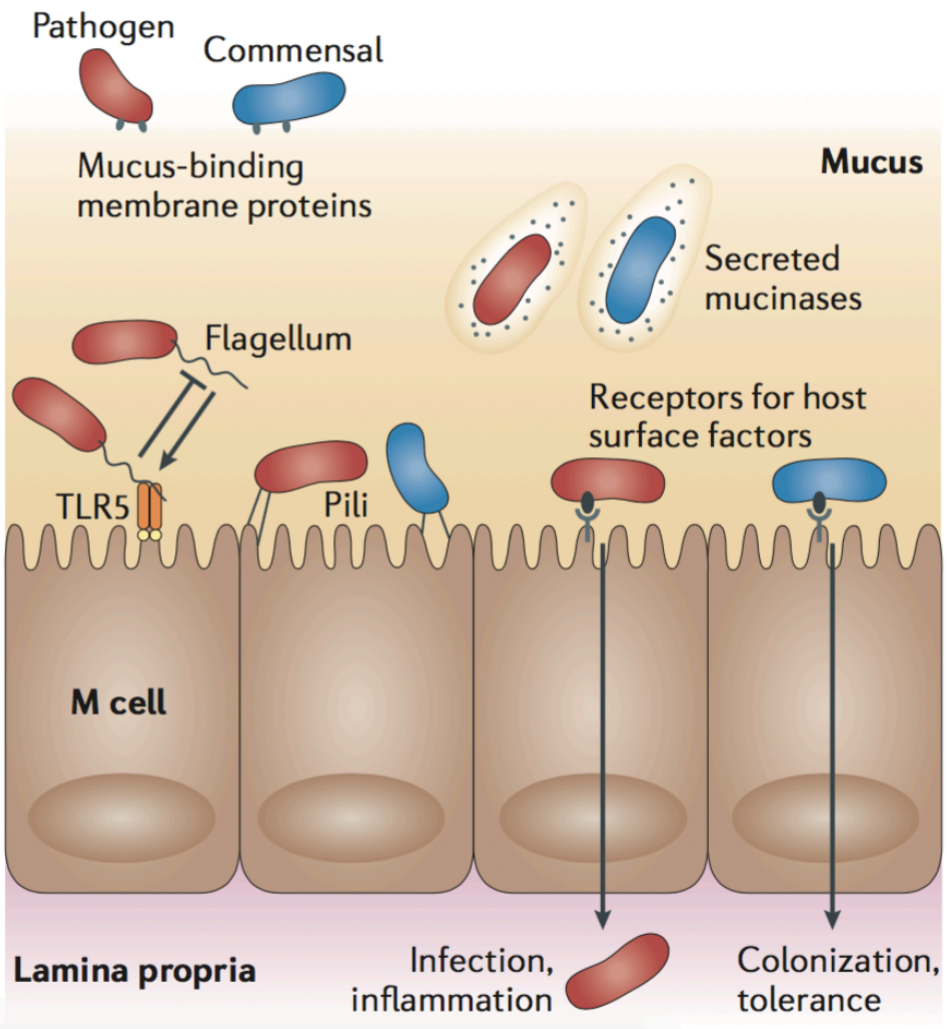
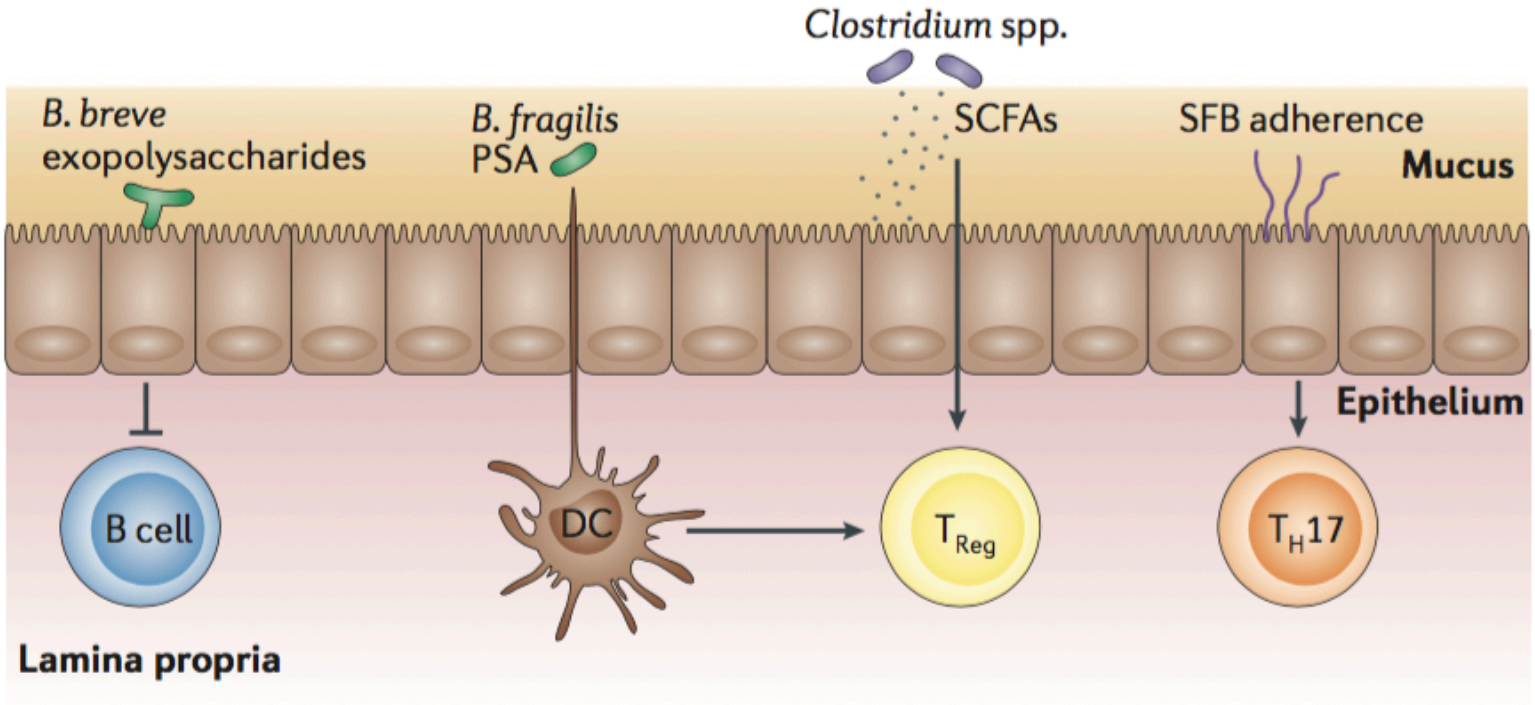


Bacterial access to the epithelium. Bothbacterial pathogens and commensals (or mutualists) have the ability to cross the mucus layer and access the gut epithelium. Lectins and other mucus-binding proteins facilitate initial interactions with the mucus layer. Mucinases and proteases are used to degrade mucus, allowing bacteria to 'eat' their way through, whereas some pathogens (such as Salmonella spp.) use flagella to swim through the viscous mucus. Toll-like receptor 5 (TLR5) sensing of flagellin effectively leads to inhibition of flagellum biosynthesis for most bacteria in the gut. Adherence to the tissue is achieved by both commensals and pathogens through pili, lectins and other outer-membrane proteins that target ligands on the epithelial cell surface. Adherence facilitates gut colonization for both commensals and pathogens, and also allows tissue invasion by pathogenic bacteria. Microfold cells (M cells) are specialized immune sentinel epithelial cells that detect gut bacteria and are also exploited by many pathogens as a means of translocation across the epithelium.



Immunomodulation by commensal gut bactera Commensal gut bacteria induce immunomodulation via interactions with epithelial cells and antigen-presenting cells (such as dendritic cells (DCs)), and via the production of signalling metabolites. The exopolysaccharides of adherent Bifidobacterium breve reduce the production of inflammatory cytokines to dampen B cell responses. The capsular polysaccharide of Bacteroides fragilis, polysaccharide A (PSA), and the short-chain fatty acids (SCFAs) produced by many Clostridium spp. (and species of other genera) stimulate the production of the anti-inflammatory interleukin-10 (IL-10) by regulatory (TReg) T cells. Segmented filamentous bacteria (SFB) intercalate between the microvilli of epithelial cells and stimulate the development of T helpe cells, which are important for mucosal immunity to extracellular pathogens