Gut Microbiota: Who is there?

- All mucosal surfaces are colonised with bacteria
- The intestine is a preferred site – over 70% of all bacteria are found in the colon
  - large organ
  - rich in nutrients
- Longitudinal: bacteria increase in number and composition changes from proximal to distal GI tract
Gut Microbiota: Where are they?

- Latitudinal: bacterial composition also differs between lumen, mucus, and attached to epithelium
Gut Microbiota: Where do they come from?

- Initial exposure occurs during passage through birth canal
- During first year of life, heavily influenced by mother and environment
Gut Microbiota: Where do they come from?

- Microbial stability is established after 1 year
- Composition continues to be influenced by environment; antibiotics, diet, genetics, inflammation, hygiene, lifestyle
Gut Microbiota in Health

- Increases the metabolic capacity of the host.
  - Digestion of otherwise unused food components.

  ![Diagram of metabolic pathways and microbial interactions]

  - Vitamin synthesis (e.g., Vitamin K)
  - Production of short chain fatty acids
  - Completion of the bile-salt cycle

  ![Diagram showing bile-salt cycle]

Protect the host from colonization with pathogenic bacteria (Colonization resistance)
Gut Microbiota in Health: Innate immune system

- Microbiota regulates intestinal immune responses primarily through the production of pathogen-associated molecular patterns (PAMPs) and metabolic by-products.
Gut Microbiota in Health: Adaptive immune system

- Microbiota stimulation leads to B cell switch to IgA, regulatory T cell induction, T cell differentiation to Th17
Gut Microbiota in Disease: IBD

- Genetic and environmental factors induce impaired barrier function
- Translocation of bacteria and bacterial products
- Immune activation and proinflammatory cytokine production
- Chronic inflammation leads to tissue destruction and complications
Gut Microbiota in Disease: GIT malignancies

- Three categories of microbiota-induced carcinogenesis
  - Disproportionate pro-inflammatory signaling at the GIT mucosa, leads to increased sloughing and repair of epithelium, which can ultimately lead to neoplasia and malignancy
Gut Microbiota in Disease: GIT malignancies

- Three categories of microbiota-induced carcinogenesis
  - Certain microbial species can have direct or indirect (through host cell activation) cytotoxic effects on cells
  - Microbial metabolism can produce by-products toxic to epithelium; repair in injury can lead to neoplastic transformations
Gut Microbiota in Disease: Obesity and metabolic syndrome

- Chronic low-grade inflammation is associated with obesity and metabolic dysfunction (insulin resistance)
- Gut microbiota (and diet-induced changes in microbiota composition) may contribute to low-grade inflammation

Fig. 14.2 Main mechanisms of action for gut microbiota components and their interactions with dietary lipids in the context of inflammatory processes leading to obesity-associated metabolic dysfunction (insulin resistance). LPS from Gram-negative bacteria activate TLR4/MyD88/NF-κB and MAPKs/JNK pathways in epithelial and immunocompetent cells activating inflammatory mediator synthesis, inflammatory cell recruitment and activation of the underlying lymphoid tissue, thus contributing to inflammation. Dietary lipids (saturated fatty acids) increase the expression and activation of innate immune receptors (TLR4, TLR2 and inflammasome) and contribute to translocation of bacterial products (LPS, PGN, etc.) by transcellular and paracellular pathways that activate immunocompetent cells in the gut-associated lymphoid tissue and in peripheral tissues. HFD-induced microbiota imbalances leading to inflammatory cytokine production also alter tight-junctions between enterocytes, increasing paracellular permeability to bacterial antigenic products. Bacteria and bacterial antigenic products can also translocate via M-cells and reach peripheral tissues via DCs. TLR2 recognizes lipoteichoic acids from Gram-positive bacteria and also LPS from Gram-negative bacteria, acting synergically with TLR4 triggering inflammation via NF-κB and JNK pathways. NOD1 and NOD2 proteins recognize bacterial peptidoglycan (PGN) and mediate insulin resistance in different tissues via activation of common signaling transduction pathways (MAPKs), expression and production of pro-inflammatory cytokines/chemokines, and impairment of insulin signaling.
Gut Microbiota in Disease: Allergic Disease

- Massive increase in prevalence of allergic diseases in Westernized countries (>20% over 10 year period)
- Allergic disease is attributed to both genetic predisposition and environmental factors
- Genetic drift over such a short period of time cannot explain increased incidence of disease
- Westernized life-style has introduced several environmental risk factors that disturb the homeostatic balance of gut microbiota
  - Excessive antibiotic use, especially during early life (or even during pregnancy)
  - Shift towards more formula-fed babies
  - Shift towards greater numbers of babies born via Caesarean section
  - Western diet