

# Gut Microbiome, Diet, and Cancer Immunotherapy



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## Learning Objectives

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- ✓ Describe the role of the gut microbiome in cancer progression and strategies to exploit it to aid cancer therapy.
- ✓ Discuss ongoing studies examining the role of the food-gut axis in immunotherapy treatment.
- ✓ Explain how diet affects the microbiome and can modulate responses to immunotherapy.

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# Human Microbiome

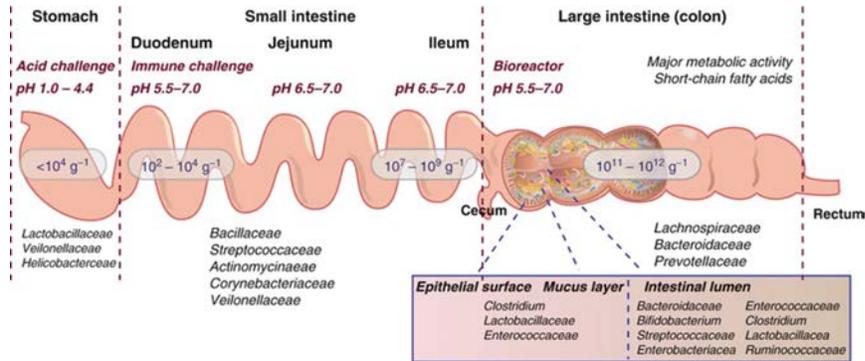
Organisms living in gut, mouth, skin, and other body parts acquired from the environment at birth



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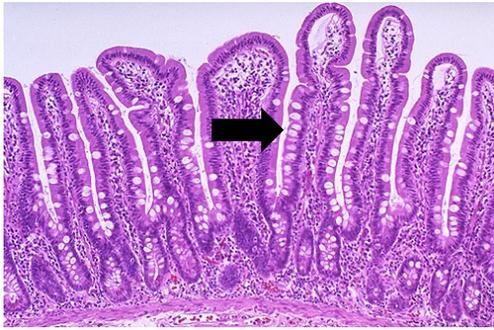
# Gut Microbiome

~99% of human microbes exist in the GI tract

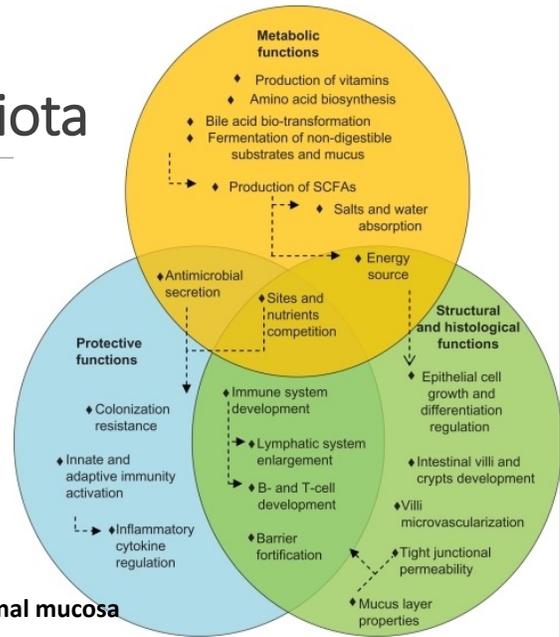


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## Function of Gut Microbiota



About 60% of the body's immune cells are present in the intestinal mucosa



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## Important Role of Gut Microbiota

- Nutrient and mineral absorption
- Synthesis of enzymes, vitamins, and amino acids
- Production of short-chain fatty acids (SCFAs)
- Fermentation byproducts acetate, propionate, and butyrate are important for gut health
  - Provide energy for epithelial cells
  - Enhance epithelial barrier integrity
  - Provide immunomodulation and protection against pathogens

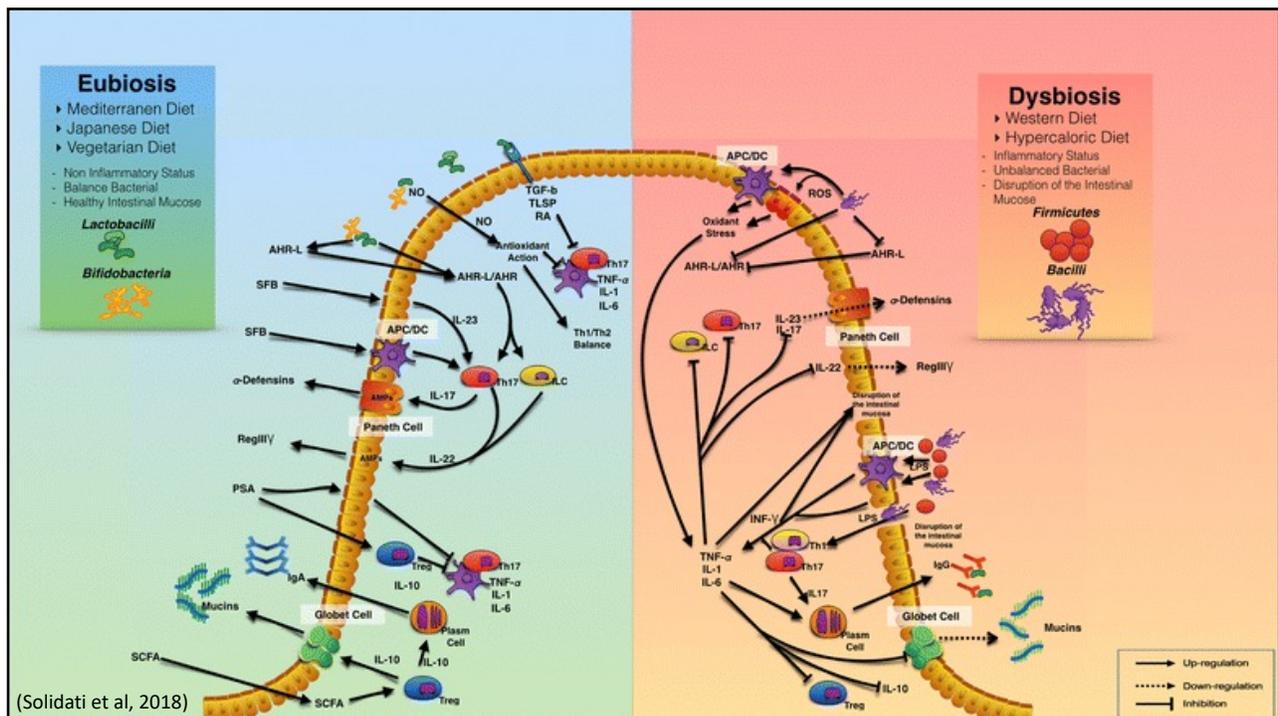
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**Dysbiosis** = Reduction in microbial diversity and a combination of the loss of beneficial bacteria such as Bacteroides strains and butyrate-producing bacteria such as Firmicutes<sup>10</sup> and a rise in pathobionts<sup>12</sup> (symbiotic bacteria that become pathogenic under certain conditions), including Proteobacteria, which encompasses gram-negative Escherichia coli.

- In addition to inflammation, there is some evidence that in the gut, microbiota is involved with the development of colorectal cancer.
  - Dysbiosis may not be the most important factor, products of interaction between diet and the microbiome may play a role also.
  - High-protein diets are thought to result in the production of carcinogenic metabolites from the colonic microbiota that may result in the induction of neoplasia in the colonic epithelium.

(Carding et al., 2015)

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## Ongoing Studies and the Role of the Food-Gut Axis and Immunotherapy

- Retrospective study of 360 patients with advanced renal cell carcinoma (RCC) and non-small-cell lung cancer (NSCLC)
- Treated with the single use of anti-PD1 or anti-PD-L1 monoclonal antibody or combination
- Patients who received antibiotics within 30 days of starting immunotherapy had significantly reduced survival benefit from ICI.
- It was speculated that the gut dysbiosis, a perturbation of the microbial community, induced by antibiotics might decrease the gut microbiota diversity, shift the microbiota composition, and probably eradicate the most immunogenic bacteria to unleash the therapeutic potential of immunotherapy.

(Chan, 2020)

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## Gut Bacteria Diversity May Slow Metastatic Melanoma

- Study of fecal samples from 105 patients treated with immune checkpoint blockade
- Patients with higher diversity of bacteria in their digestive tract had longer median progression-free survival (PFS)
- Notable compositional differences existed in the gut microbiome of patients who responded versus those who did not, with the Ruminococcaceae family enriched in responders and the Bacteroidales order enriched in non-responders. Patients who had a high abundance of the genus *Faecalibacterium* (of the Ruminococcaceae family and Clostridiales order) in their gut had significantly prolonged PFS (median not reached), compared to patients who had a low abundance (median PFS of 242 days)
- Abundance of Bacteroidales was associated with more rapid disease progression, with high abundance within the gut microbiome associated with significantly reduced PFS (median 188 days), compared to low abundance (median PFS of 393 days).

(Oncology Times: July 25, 2017 - Volume 39 - Issue 14 - p 32)

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## The Affect of Diet and Supplements on Microbiome and Role in Modulating Responses to Immunotherapy

- Fecal sample study with 113 patients with melanoma
- Higher microbiome diversity was associated with response to therapy—regardless of treatment type—and the gut microbiome did not significantly differ based on age, sex, and body mass index.
- Eating whole grains, fruits and vegetables, and a high-fiber diet was positively associated with bacteria previously shown to confer response to anti-PD-1 treatment. Diets high in added sugars and processed meat were negatively associated with these bacteria.
- In a subset of 46 patients treated with anti-PD-1 immunotherapy, the researchers found that patients who consumed a high-fiber diet were about five times as likely to respond to anti-PD-1 treatment compared to patients who consumed a low-fiber diet.

(Spencer et al, 2019)

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## Nutrients Involved in Modulating Immune Response

**Fiber** intake is associated with increased abundance of potentially beneficial species such as *Akkermansia muciphilia* and *Roseburia* spp, which ferment dietary fibers and produce SCFAs (acetate, propionate and butyrate). SCFAs are important for maintaining epithelial barrier function and regulating mucosal and systemic immunity

**Omega-3 fatty acids** modulate inflammation by inducing a transient increase in some SCFAs-producer bacterial genera and by interacting with the G protein-coupled receptor 120 (GPR120) suppressing tumor necrosis factor alpha and IL-6 decreasing macrophage-induced tissue inflammation.

(Russo et al., 2020)

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## Nutrients Involved in Modulating Immune Response

**Saturated fatty acids, proteins and vitamins** influence the host inflammatory responses through the TLR4 activation, the increase in trimethylamine-n-oxide (TMAO) synthesis and the expression of mucin 2, and the induction of tolerogenic dendritic cells and Tregs' differentiation, respectively.

**Probiotics** show beneficial effects on ameliorating diarrhea and other gut-related damages following anti-cancer therapy, thus re-establishing a healthy GM composition. *Lactobacilli* were administered to cancer patients to re-populate the compromised patients' GM, thus re-establishing the levels and functionality of the commensal bacteria, depleted after the treatment

(Russo et al., 2020)

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## Polyphenols

- Polyphenols are the most effective anticancer compounds as they inhibit NF- $\kappa$ b activation.
  - They likely impede secretion of cytokines usually released in tumor microenvironment.
  - They induce production of anti-inflammatory cytokine IL-10 and polarize immune response toward a tolerogenic pathway.
- ✓ Curcumin
  - ✓ Green tea—Epigallo-catechin-gallate (EGCG)
  - ✓ Quercetin
  - ✓ Resveratrol



(Solidati et al, 2018)

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# Important Patient Education During Immunotherapy Treatment

Be a healthy weight

Be physically active

**Eat a diet rich in whole grains, fruits vegetables, and beans**

**Limit consumption of “fast foods” and other processed foods high in fat, starches, and sugar**

**Limit consumption of red and processed meats**

**Limit consumption of sugar-sweetened drinks**

Limit alcohol consumption

Do not use supplements for cancer prevention

