The microbes thriving in our bowels

Hidaya Aliouche

The gigantic and diverse community of microbes that thrive in our guts are known collectively as the gut microbiota. Hidaya Aliouche investigates how we have managed to establish and maintain a largely mutually beneficial relationship, but how its collapse can produce catastrophic effects on our health

Exam links

AQA Cell recognition and the immune system; Digestion and absorption; Populations in ecosystems
Edexcel A Biodiversity; Responses to infection; Barriers to infection
Edexcel B Biodiversity; Response to infection
OCR A Communicable diseases and the immune system; Biodiversity
OCR B Biodiversity; The immune system
WJEC Eduqas Biodiversity; The human gut; The immune response

Key words

Microbiota
Microbiome
Bowel disease
Symbiosis
Metabolites
Short-chain fatty acids

The human body is teeming with trillions of microorganisms including bacteria, protoctists and fungi. They make up a super-community called the **microbiota**. A distinct term — the **microbiome** — indicates the collection of microbial genomes. Despite their microscopic size, the collective mass of the microbiota is significant, with some 38 trillion bacteria providing the average human with an additional biomass of 1.4 kg. Microbiota have co-evolved throughout thousands of years alongside their human hosts. They perform an array of largely beneficial functions and in return the host provides the nutrients and niches necessary for the survival of the microbes.

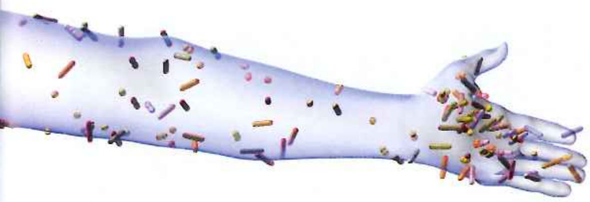
Complexity and variability

Gut microbes are complex and highly variable both within and between individuals. They change in response to internal and external variables. Many genetic and environmental factors shape our microbiota, including age, diet, lifestyle, antibiotic exposure and even the way we were born, through the birth canal or via caesarean section.

With the teeming mass of microbes colonising our bodies, you might expect the immune system to do what it does best — attack and destroy. But this is not the case, as one consequence of this co-evolutionary partnership is tolerance of the host towards the gut microbiota. The gastrointestinal barrier is a great example of the way this tolerance works.

The gastrointestinal epithelial barrier

The gastrointestinal barrier comprises mucus-covered layers of cells that separate the contents of the gut, including the microbiota, from the surrounding tissues (see Figure 1). The barrier prevents an immune response to the microorganisms. Physical defence — prevention of the microbes entering the rest of the body — is assured by tightly packed intestinal epithelial cells and mucus. The mucus has a loose outer layer that houses the microbiota and a tighter-knit inner layer, which they cannot breach.



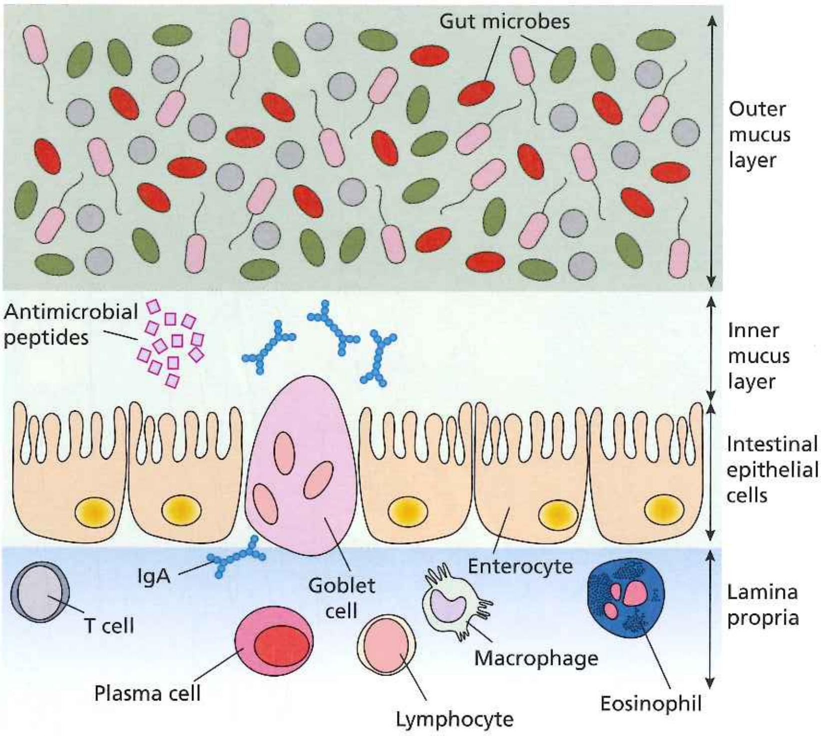


Figure 1 The gastrointestinal barrier. A thick mucus layer overlies the intestinal epithelium. The lamina propria is a layer of connective tissue that houses immune cells including T cells, eosinophils, lymphocytes and macrophages

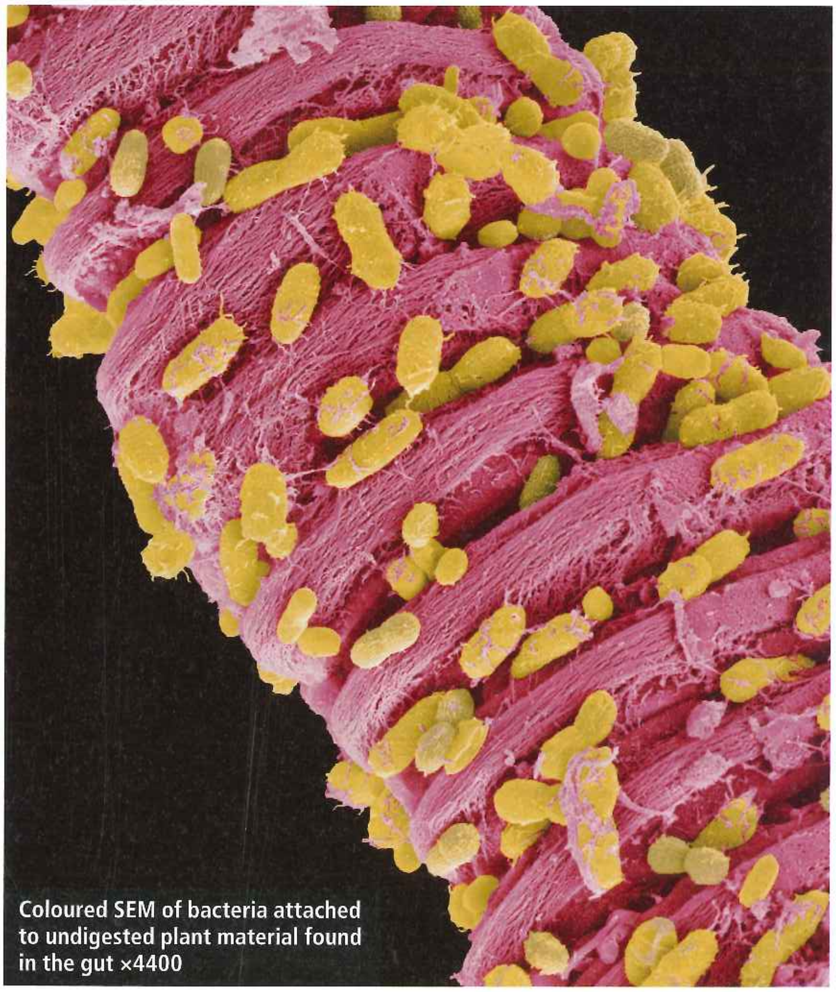
Biochemical defence is provided by bactericidal bile and gastric acids. Antimicrobial peptides, including immunoglobulin A (IgA) secreted by plasma cells, provide further immunological defence at the inner layer. Innate and adaptive immune cells 'patrol' within the connective tissue to quash any microbial breach. The microbiota can nevertheless affect processes within our bodies, by using the molecules it produces to communicate with our cells.

Bacterial communication

The microbiota produces, alters and breaks down many different compounds. Some of these compounds are derived from the microbes themselves, others are from our diets, others are from the components of the mucus. The metabolites are either removed from the body in our faeces or absorbed through the mucus when they reach the epithelial cells. The metabolites can be powerful influencers of the way our bodies function. In a healthy situation, the effects produced by metabolites are beneficial.

Microbiota in health

The biological relationship that describes the interaction between the gut microbiota and the host is called symbiosis (*sym*, together + *bios*, life). This broad term covers several types of interactions



Coloured SEM of bacteria attached to undigested plant material found in the gut ×4400

A diet high in fat and sugar but lacking in fibre reduces the diversity of microbes in the gut

that describe close-living arrangements between organisms. The three types of symbiosis are:

- **mutualism**: the maintenance of a balanced (homeostatic) relationship which is advantageous to both
- **commensalism**: the advantage to one interacting party which does not benefit or harm the other (from *com*, sharing + *mensa*, a table)
- **parasitism**: the advantage to one interacting party to the detriment of the other

A 'healthy' microbiome is one comprising mutualistic and commensal microbes. A healthy microbiome has a variety of species and includes species that can adapt in response to changes in the gut environment.

The proportions and quantities of protein, fats and carbohydrates we consume influence the composition of our gut microbiota. Water-soluble plant substances that cannot be broken down completely by our digestive enzymes are called soluble fibres. These are the optimal food source for the mutualistic bacterial components of the microbiota. Short-chain fatty acids (SCFAs) are the end products of their digestion.

Terms explained

Microbiome The collection of the genes found in all of the microbes that occupy an environmental habitat.

Microbiota A collective term for all the species of microorganisms found in a habitat.

Prebiotics Non-digestible foods that provide a source of nutrition for probiotic microbiota. **Probiotics** are microorganisms that provide health benefits to the host (mutualistic symbionts).

SCFAs are the most extensively studied microbial metabolites and positively influence our bodies in several ways. These include improving how efficiently our bodies digest food for energy or building new compounds (metabolism), improving our immune cell function and preventing inflammation.

Soluble fibres are a type of **prebiotic** — a non-digestible foodstuff which selectively stimulates the growth of the types of gut bacteria beneficial to our health. A diet rich in prebiotics results in a gut with considerable microbial diversity, which in turn results in a vast range of metabolites, with multiple benefits to the host.

Research shows that consumption of processed foods, notorious for their high fat and sucrose content and lack of complex carbohydrates, reduces the diversity of the microbiota in both mice and humans. For example, when exposed to a low-fibre diet, microbes that break down fibrous material are forced to switch to other substances. The breakdown of some of these, such as amino acids, can produce harmful compounds that have been implicated in diseases such as colon cancer and intestinal bowel disease. There are even links between the gut microbiota and obesity, although the exact cause-and-effect relationship is controversial (see Box 1).

Box 1 Is the microbiota to blame for obesity?

Studies in mice have shown that microbes can directly affect weight change. In one study, microbes from lean mice transferred to obese counterparts prevented further weight gain, but the opposite transfer failed to induce weight gain in lean mice. The reason for this difference is because of the effect of diet. The mice were fed plant-based diets. Some of the microbes in the lean mice, which were absent in the obese mice, can digest fibre. When the microbes of the lean mice were transferred to the obese mice, the fibre-digesting species could make use of the dietary fibre and flourish, outcompeting the obese microbial species and preventing weight gain. On the other hand, when the mice were given unhealthy, low-fibre diets, transfer of microbiota from lean mice to obese recipients failed to prevent weight gain, because there was no available fibre for them to establish and grow their population. This illustrates that the success of gut colonisation by lean-associated microbiota is dependent on fibre-rich diets. So, although microbes matter, so do we — we provide the external factors that affect their ability to thrive.

Dysbiosis: a microbial catastrophe

The harmonious relationship between the host and the gut microbiota can be disrupted. Dysbiosis is a shift in the composition of the microbiota that produces a deleterious imbalance. Dysbiosis manifests itself in several ways — beneficial species can decline, harmful species increase, or overall microbial diversity declines. These changes can cause malfunction of the gastrointestinal barrier. If the gut barriers are breached, microbes are exposed to cells of the immune system. The immune cells will recognise the microbes as foreign by the antigens found on their cell surfaces. This triggers an immune response, which results in inflammation, causing direct harm to the gut tissue and preventing the efficient absorption of nutrients. A failure to re-balance the gut microbiota will eventually lead to disease.

Changes in the microbiome have been linked to an enormous list of conditions that includes ulcerative colitis, atherosclerosis, anxiety, rheumatoid arthritis, diabetes and allergies (as we will see in the next issue of Biological Sciences Review). Many of these links are merely correlations and it is not yet clear whether alterations in the microbes are the cause or consequence of the condition. We often do not know if one species is to blame or several. Scientists are still working to determine causal links but this has not stopped efforts to remedy catastrophic shifts.

Curative poop-pills

Attempts to control the microbiota date back thousands of years. In the fourth century, patients suffering with diarrhoea were given 'yellow soup', made from the fermented stool of healthy people. Fast forward to today, microbiota-based therapies are a lucrative business, and, thankfully, faeces can be delivered via a small pill.

Whole microbiome transplants involve the introduction of faecal microbiota from healthy individuals to patients suffering from a microbiota-associated disease. Termed faecal microbiota transplantation (FMT), this approach has proved successful in the treatment of antibiotic-resistant strains of the bacterium *Clostridium difficile*. Across the world, start-up companies are investigating the use of FMT in treating inflammatory bowel diseases and even cancer. But faeces is a potential source of infection and its microbial composition changes every time it is produced, so both reproducibility and accuracy are problematic.

The understanding of how and why FMT is successful remains a mystery. The use of microbial transplants in the treatment of disease is in its infancy. Some scientists argue that its efficiency is limited as it is likely that transplanted species are unable to compete with the well-established host species. FMT is usually last on the list of treatment options — more commonly, antibiotics are used.

Other creative approaches being investigated include trying to target and destroy specific bacterial strains or switching off particular genes within a strain. There is even research to see whether gut bacteria can be engineered to produce drugs that can be released directly in the gut. As research continues into the causative mechanisms connecting our microbiome to our health, we will no doubt see more creative uses for microbiota, and improvements in therapeutic applications.

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Further reading and viewing

Watch a TedEd video, 'How the food you eat affects your gut', by gastroenterologist Dr Shilpa Ravella: **https://tinyurl.com/y9f2fw59**

Read an entertaining article charting one journalist's journey into uncovering the power of microbiota: **https://tinyurl.com/hvkx3gk**

Listen to a BBC podcast on 'That Gut Feeling': **www.bbc.co.uk/programmes/b07ff0hl**

Find out more about FMT: **https://tinyurl.com/y7m9mnem**

Visit **www.gutmicrobiotaforhealth.com/en/home/**, a platform for information and debate surrounding the importance of gut microbiota for health.

Key points

- The gut microbiota is the collection of a diverse set of microorganisms in our intestines. Their collective genomic contents are called the microbiome.
- The co-evolution of humans and microbiota has resulted in a mutually beneficial partnership. We provide food and shelter, and the microbiota enact a variety of functions — breaking down otherwise non-digestible foods, developing, shaping and regulating our immune system and protecting against invasion by harmful microbes.
- Maintaining the integrity of the gut barrier is essential to prevent the immune system from attacking the microbiota.
- One of the biggest factors affecting the composition and function of our microbiota is our diet. A varied diet, with plenty of whole fibre-rich foods, is linked to a diverse, healthy microbiome.
- Sometimes the partnership breaks down and there is a shift in the composition of the microbiota that results in breakdown of the gut barrier and the onset of inflammation, arthritis, obesity, diabetes and intestinal bowel disease.