The Microbiome: Bacterial Soldiers Fighting Against Infectious Disease

Elle Campbell

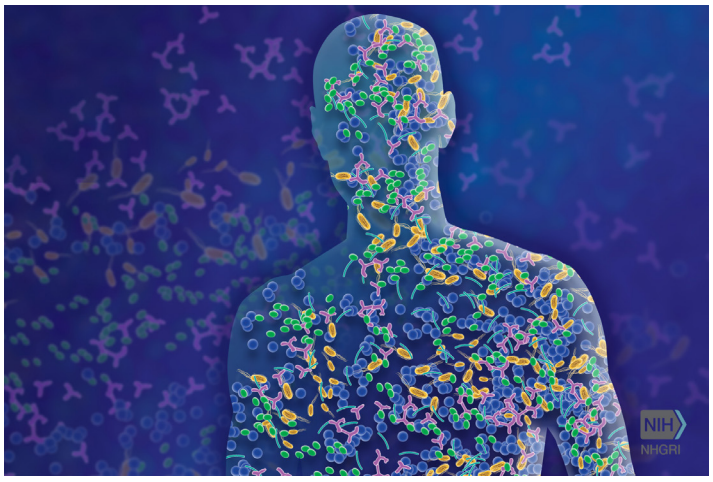
Bacteria are our companions, working with our immune system to fight crime. So, is utilising our knowledge about the bacteria in our gut the answer to fighting infectious diseases? As people, we are composed not only of our own human cells but also trillions of bacterial cells. This community of bacteria are commonly referred to as the microbiome, which resides in the human gut. Highly integrated in human health and disease, the microbiome primes and works with our immune system to fight off incoming infectious diseases. The microbiome also acts as a living barricade to incoming pathogenic bacteria, killing them before they cause disease (Falony et. al., 2019). Therefore, altering the microbiome through a process called microbiome engineering has become an attractive option for treating infectious diseases.

While the human immune system is our bodies' main defence mechanisms against disease-causing bacteria, our gut microbiome regulates this process, preventing these mechanisms from getting out of control and causing harm to our bodies. This process involves maintaining the resilience of gut lining by enhancing the connection of these cells and the production of protective mucus, which can trap foreign bacteria (Liu et. al., 2018).

Studies on the gut bacteria in mice found that mice with no bacteria at all have a smaller intestinal surface area which is poorly developed (Jandhyala et. al., 2015). Other studies saw that this underdevelopment can be prevented by feeding mice with bacteria such as *Lactobacillus rhamnosus*, which can enhance the formation of tight junctions between cells and even enhance the production of IgA, which is an antibody which can tag harmful bacteria in the blood, so that they can be recognised by other immune cells (Yan et. al., 2017).

The microbiome has also been linked to enhancing the production of regulatory T (Treg) cells, which are the primary cell type involved in regulating the immune system (Thomas and Versalovic, 2010). Therefore, the abundance of Treg cells has been linked to the occurrence of autoimmune and inflammatory diseases, where the immune system gets out of control and causes damage to human cells (Lourenço and La Cava, 2011). Again, in mice models, researchers have shown that bacteria such as *Lactobacillus reuteri* can increase the number of Treg cells, so reducing the number of other immune cells that could potentially cause excessive inflammation (Liu et. al., 2013).

The microbiome also directly competes with pathogenic bacteria within our gut. This interaction involves producing compounds that directly harm pathogenic bacteria or competing for resources such as nutrients and space (Mohajeri et. al., 2018). Many broad-spectrum antibiotics target universal processes in bacteria such as blocking cell wall and protein production. For that reason, administration of antibiotics affects the abundance of multiple types of bacteria in our stomach, reducing the stability and overall diversity of this community (Langdon et. al., 2016; Willing et. al., 2011).



Accordingly, antibiotic regimes in some cases cause certain bacterial strains to increase in number and cause disease. For example, the bacteria *Clostridium difficile* often resides happily in the gut in relatively low numbers. But after antibiotic administration, *C. difficile* sometimes increases in number and cause inflammation and diarrhoea, which kills around 12,800 people in 2017 (Center for Disease Control, 2019).

A hunt for a new regime of treatments for infectious diseases, which are specific and cause little disturbance to the microbiome, has been underway. In this pursuit, the notion of microbiome engineering has become an attractive option. Microbiome engineering involves altering the bacterial makeup of the microbiome to improve characteristics in the host, including nutrient utilisation and prevention of disease (Foo et. al., 2017).

The most well-known example of this is the consumption of specific live bacterial strains called probiotics, which confer health benefits to humans. Studies have found that administration of probiotics is linked to both a significant reduction in cases of antibiotic-associated diarrhoea and *C. difficile* infections compared to placebos (Szajewska et. al., 2013; Urbańska et. al., 2016; Feizizadeh et. al., 2014).

These probiotics can also be engineered to directly kill pathogenic bacteria and are known as 'smart microbes'. For example, *Lactococcus lactis* was engineered to produce molecules that targeted the bacteria *Enterococcus faecium*, which has been linked to the development of meningitis in the brain of babies (Geldart et. al., 2015). These alterations to the probiotic are often engineered before they are given to patients, yet currently, scientists are trying to develop a method to edit the microbiome while they are still in the human gut.

This method is often referred to as MAGIC and stands for Metagenomic Alteration of Gut Microbiome by In situ Conjugation. This process includes orally digesting bacteria that can transfer DNA with particular traits to bacteria already housed in the microbiome. Even though this technology is in the early stages of development, DNA has been successfully transferred to the microbiome of infected mice. Yet, this technology needs vast improvements before it can treat infectious disease in humans, including increasing persistence of the DNA in the gut and making sure DNA can only be transferred to specific non-pathogenic microbiome strains (Ronda et. al., 2019).

Although probiotics often refer to only a couple of specific bacterial strains, microbiome engineering now commonly involves the acquisition of a whole new healthy microbiome. The only unappealing aspect to this is this basically involves eating someone else's faeces. However, the doctors refer to this concept of 'eating someone else's poop' as a treatment called faecal microbiota transplantation (FMT). FMT involves acquiring filtered faeces from healthy individuals and helps rebalance the microbiome of people with various gastrointestinal diseases (Bakken et. al., 2011).

For treating *C. difficile* infections FMT is highly effective, as a recent meta-analysis showed that 90 percent of patients using this treatment had a complete clinical resolution for *C. difficile* infections (Bakken et. al., 2011). FMT have also been linked to improving symptoms of inflammatory bowel disease, which is a collection of gastrointestinal disease linked to uncontrolled inflammation (Ianiro et. al., 2014). Therefore, even though FMT may be considered a crude alternative to antibiotic treatments, it has shown promising results in treating gastrointestinal diseases.

The microbiome is the environment in which infectious diseases start their lives in the human body and understanding its terrain has given science a new dimension of understanding of infectious diseases' lifestyles. Microbiome engineering gives a glimpse of the future, where utilising our own bacteria could be the answer to winning this fight. But will the public be able to get over the stigma of FMT and consuming live bacteria?

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