HOUSES OF PARLIAMENT
PARLIAMENTARY OFFICE OF SCIENCE & TECHNOLOGY

POSTNOTE

Number 574 May 2018

The Microbiome and Human Health

There is increasing evidence that the microbial communities on and in the body – the human microbiome – have important implications for human health. This POSTnote examines what is known about the human microbiome and the diseases and conditions linked to it. The note then describes interventions to modify the human microbiome and examines the issues raised by their use and by microbiome research more generally.

Overview

- The microbiome refers to all of the different microbes (including bacteria, viruses and fungi and their genetic information) that live in a particular environment.[1]
- The human microbiome plays a key role in human health; for example it aids the digestion of food and protects from disease.
- New sequencing technologies have given researchers new tools to examine the different human microbiomes, for example the gut microbiome.
- The microbiome is established during infancy, but can change in response to factors such as diet, the environment and antibiotic use.
- Disturbances in the microbiome are linked to medical conditions such as infection with *Clostridium difficile*, Inflammatory Bowel Disease (IBD) and potentially to obesity.
- There is potential to exploit knowledge of the microbiome to produce new treatments.

Background

Recent years have seen the development of a range of new tools that facilitate microbiome research (see Box 1).[2] This has stimulated interest in the application of microbiome research across a variety of sectors, including agriculture,[3] the marine environment[4] and human health.[5,6,7] There is significant commercial interest in the microbiome market[8,9] which is projected to reach up to $2.2 billion by 2025.[10]

There is increasing evidence that the human microbiome is important to human health.[11] For example the human microbiome plays a role in processing food and producing vitamins, and regulating hormones and weight gain. It also helps to program the immune system and protect individuals from disease.[12] Variations in the microbial composition are linked with a wide range of medical conditions.[11] Interventions to alter the composition of the human microbiome may represent potential new treatments for such conditions (see Pages 3 and 4 for details).[13]

Box 1: New technologies for microbiome research

Microbiology research has traditionally relied on isolating and growing individual microbes (such as bacteria, viruses and fungi) in the laboratory.[1] The development of faster and cheaper DNA sequencing technologies and a range of associated techniques have given researchers powerful new tools to investigate complex microbiomes without the need to grow them in the laboratory. These tools include:

- Metagenomics - the study of genomic DNA (the complete set of DNA contained in an organism) obtained from microorganisms. This is the main technology that has driven the field forward.
- Other new technologies include metaproteomics that enable researchers to look at all the proteins present in a microbiome and metabolomics which allows the study of all the biochemicals produced in a given system.

These tools allow researchers to catalogue the microbial composition of a microbiome in terms of the range and type of species present. They also facilitate the study of complex interactions between a host organism (for example a human) and its microbiome and between the various components of a microbiome.

The human microbiome

The human microbiome comprises microbes from a range of different sites in the body including the gut, skin, lung, mouth and reproductive tract.[11] The human microbiome

contains far more genetic information than that contained collectively in human cells[11] and provides functions that human cells cannot perform for themselves. For example, the gut microbiome produces enzymes which aid the digestion of food.[14,15] Because its composition and functions may be modified by dietary or antibiotic interventions, the gut microbiome is the most studied and is the main focus of this note.[16] There are a range of projects investigating the diversity and function of the human microbiome. Two of the largest such projects are:

- The US Human Microbiome Project Consortium, which examined the microbiome of 242 adults in a range of locations on the human body. It discovered a large amount of diversity, even amongst healthy adults.[17]
- The European Metagenomics of the Human Intestinal Tract Consortium involved academics and industry from eight countries including the UK.[18]

In general, such studies suggest that a microbiome comprising a wide range of microbes is often (but not always) associated with positive health outcomes.[19] The following sections outline the various factors that affect the establishment and composition of the human microbiome throughout the life course, although it is widely recognised that this is a developing area where much remains to be firmly established.

Maternal microbiome

There is debate over when the human microbiome first starts to develop.[20,21] The current consensus is that the infant microbiome starts at birth with microbes coming into contact with the infant through the birth canal.[22,23] Babies who are delivered via caesarean-section harbour a different microbiome to vaginally-delivered babies.[24] In the longer-term, caesarean-delivered babies may be more likely to develop allergies and autoimmune disease,[25,26] likely due to microbiome-associated immune regulation.[27]

Infant nutrition

Another factor known to influence the microbiome in infancy is nutrition.[28] Research has shown a close match between the bacterial species found in a mother's milk and around her breasts and those found in her infant's microbiome.[29] It is also established that sugars in breast milk promote the growth of certain bacteria involved in programming the immune system.[30,21] In babies who are formula-fed, the bacterial communities appear to take longer to establish than babies who are breast-fed.[31] There are currently projects attempting to make formula milk more closely resemble breast milk.[32]

Antibiotic exposure

There is evidence from animal experiments that antibiotic exposure early in life may have a long-term effect on health. For example, research in mice suggests that repeated use of antibiotics can result in metabolic changes that increase the risk of obesity in adulthood.[33] Data collected from humans so far reflects this, with early antibiotic use associated with later-life weight gain and asthma.[34] There is considerable debate about the clinical pros and cons of treating pregnant women and newborn babies with antibiotics. Antibiotics are deemed necessary in certain circumstances. For example, pregnant women with a ruptured amniotic sac are given the antibiotic erythromycin as clinical trials have shown that this improves outcomes for both mother and child, such as a reduction in chronic lung disease in the infant.[35,36] However, a recent study suggests that this antibiotic use may have a detrimental effect on the beneficial bacteria present in the birth canal.[37] Some researchers and clinicians are concerned that antibiotic use at this stage may have a negative effect on the developing microbiome with unknown longer-term health impacts.[37] However, long-term research is required to assess the overall benefits and disadvantages of antibiotic use in pregnant women and newborn babies.

In adults the microbiome is relatively stable. However, recurrent use of antibiotics can disturb the microbiome with negative impacts on health. The long-term use of antibiotics to treat cases of recurrent tuberculosis (TB) may diminish the patient's microbiome. In some cases the lung microbiome becomes dominated by fungal species that results in symptoms similar to the initial TB.[38]

Diet and environment

Studies on identical twins in different environments have shown that they develop widely differing microbiomes.[39] Such studies indicate that environmental factors play a greater role in shaping the microbiome than genetics.[40] Other studies have looked at links between different types of diet and the diversity of the microbiome. For example an increase in the risk of colon cancer in African Americans compared to South Africans has been shown to be largely linked to diet[41]. Changes to the diet (low or high in protein, vegetarian or vegan) can affect the composition of the microbiome both in the short-term and longer-term.[42]

Ageing

The microbiome naturally changes with age and becomes less diverse.[43] However, one study found differences in microbiome diversity between elderly populations living in care compared to those in community settings.[44] A follow-up study in 2016 indicated that this may be due to diet, but also other environmental factors and disease.[45] The European NU-AGE consortium is investigating whether changes in the ageing microbiome are directly caused by ageing or by age-related changes in innate immunity or loss of skeletal muscle mass.[46] Better understanding of the factors affecting the microbiome during ageing could lead to interventions to promote healthy ageing.[45] For example, the ELDERFOOD project in Ireland is examining the effect of dairy foods on microbiome composition in elderly people and aims to develop products to protect against disease.[47]

Conditions linked to the microbiome

Evidence of associations between the gut microbiome and a range of diseases have been found. Evidence of whether the composition of the microbiome is the cause of a disease or merely an effect of disease is more difficult to obtain. The

following sections outline the conditions which are currently most closely linked to the gut microbiome.

Clostridium difficile (*C. difficile*) infection

Infection with *C. difficile* can be a life-threatening condition, and in 2007 was responsible for 4,056 deaths in the UK.[48] *C. difficile* infection occurs in patients who have undergone multiple antibiotic treatments that disrupt their gut microbiome.[49,50] This allows opportunistic and harmful bacteria like *C. difficile* to dominate the gut microbiome.

Inflammatory Bowel Disease (IBD)

IBD is a term used to describe two conditions which involve an immune response to the gut microbiome leading to inflammation of the gut: Ulcerative Colitis which affects only the colon (the large intestine), and Crohn's disease which affects the entire gut. Research implicating interactions between the gut microbiome and host with IBD includes:[51]

- Animal studies that show that mice with a genetic predisposition to IBD develop the condition when they are exposed to microbes, but not when raised in a sterile environment.[52]
- Research in IBD patients linking disturbance in the microbiome with episodes of inflammation.[53]
- The fact that antibiotics, drugs that significantly affect the composition of the microbiome, can be used to treat both Crohn's disease and Ulcerative Colitis.[54,55]

Irritable Bowel Syndrome (IBS)

IBS is a common condition which affects 10-20% of the general population.[56] IBS is subtyped according to bowel habit and whether symptoms are diarrhoea-predominant, constipation-predominant or mixed.[57] Evidence linking the gut microbiome with IBS includes:

- studies that show differences in gut microbiome composition between healthy individuals and IBS patients that are related to IBS subtype.[58,59]
- a study that showed a small but significant increase in the rate of IBS among a Canadian community following an outbreak of gastroenteritis, a disease that affects the microbiome causing sickness and diarrhoea.[60]

Colorectal cancer

A wide range of studies have linked colorectal cancer to the gut microbiome.[61] For example, mice genetically predisposed to develop colorectal cancer that are raised in a germ-free environment (and hence do not have a microbiome) do not develop the cancer whereas those raised in an environment where microbes are present do.[62] Additionally, treatment with antibiotics effective against a wide range of bacteria has been shown to lead to a significant reduction in the number of tumours in animal models of colorectal cancer.[61] One study in humans has suggested that colorectal cancer may be associated with a specific type of bacterium,[63] although this has recently been questioned.[64] Researchers are investigating the potential for using various features of the gut microbiome as diagnostic signals for colorectal cancer.[65,66]

Box 2: Priorities for microbiome research

Microbiology research is an interdisciplinary subject. It involves microbiologists and molecular biologists working alongside systems biologists, immunologists, neuroscientists, data analysts and clinical, environmental or marine scientists (depending on the microbiomes of interest). Further research will be required to understand the efficacy and mode of action of the interventions outlined in this briefing. However, the Microbiology Society and other stakeholders have identified a number of priorities for fundamental research needed to underpin further progress in microbiome research.[5] These include:

- increased capacity to manage, analyse and share data
- establishing data inventories and standard study methods to allow comparisons between studies
- improving knowledge of what constitutes a healthy microbiome.

Obesity

Evidence in animal models suggests a link between the microbiome and obesity. Germ-free mice receiving the gut microbiome of an obese mouse develop significantly increased body fat when compared to those receiving the gut microbiome of a lean mouse.[67,68] Other studies in animals suggest that the gastric bypass surgery used to treat human obesity profoundly affects the interactions between microbes and their hosts.[69,70,71] Recent evidence indicates that the relationship between the microbiome and obesity may be more complex in humans.[72,73,74] Conditions linked to obesity, such as type-2 diabetes have also been associated with the microbiome.[75,76,77]

Other conditions

Research is examining potential links between variations in the human microbiome and a range of other medical conditions. While research may indicate that the microbiome is involved in such conditions, it is more difficult to establish whether it is the cause. For example, research is currently looking at the potential links between:

- the diversity of the lung microbiome and the risk of asthma in children.[78,79]
- variations in the vaginal microbiome and assisted reproduction outcomes,[80] the risk of miscarriage[81,82] and the risk of preterm birth.[83,84]
- the human microbiome and cognitive conditions such as anxiety and depression.[85]

Interventions

Researchers are investigating whether interventions targeted at the microbiome can be used to prevent or treat disease. Approaches include drugs, prebiotics, probiotics and faecal microbiota transplants.

Drug development

There is global interest in the commercial potential of the microbiome for drug research with some products in early clinical trials. UK biotechnology companies such as 4D Pharma, Microbiotica and CHAIN Biotechnology are interested in potential applications across a range of conditions.[5,86] The main focus of research is on the development of interventions to affect the composition of the microbiome. While there are currently no such licensed therapies on the market, potential approaches include new

drugs (small molecule drugs) or live biotherapeutics (LBPs, standard preparations containing one or more type of bacteria). There is particular interest in the role of the microbiome in immunotherapies (using the body's own immune system to fight diseases such as cancer). For example, the gut microbiome may modulate responses to:

- cancer immunotherapy in animal studies[87,88]
- anti-tumour immunotherapy in melanoma patients.[89]

All medicines and LBPs will need to obtain market authorisation through the conventional regulatory routes.[90] Companies developing drugs and LBPs will also need to show that they have appropriate facilities for manufacturing them. This authorisation may be more difficult for LBPs due to the more complex nature of these preparations.

Prebiotics and probiotics

Prebiotics are food ingredients that are used to encourage growth of beneficial bacteria already present in the body in order to confer health benefits.[91] Conversely, probiotics are live microbes which modulate the composition of the microbiome more directly.[92] There are a small number of studies showing that prebiotics can be efficacious: for example a prebiotic has been shown to reduce symptoms in IBS,[93] although this has been questioned by another study.[94] There are more studies of efficacy of probiotics, showing evidence of benefit of some strains in some disorders. Meta-analyses (which combine data from smaller studies to provide a more powerful statistical analysis) show evidence for efficacy for probiotics. For example, probiotics show a weak effect in preventing *C. difficile* infection in patients who are taking antibiotics and may be beneficial in preventing respiratory tract infections.[95,96,97,98]

Faecal Microbiota Transplant (FMT)

FMT is the transfer of faeces from a healthy donor to a recipient to treat a medical condition, usually recurrent *Clostridium difficile* infection. Generally, the transplant may be administered by enema/colonoscopy or via a tube into the small bowel. [99,50] The approach has been shown to be highly effective in treating patients with recurrent *C. difficile* infection.[100,101] Guidelines on using FMT to treat recurrent *C. difficile* infection were published in 2014.[50] However, the exact mechanism of action and long-term effects of FMT are not known and there is at least one study which suggests that the effect may be as a consequence of other components such as bile acids.[102]

The success of FMT in treating *C. difficile* infection has generated interest in using it to treat other conditions. Trials that have been conducted or are on-going include:

- A small-scale trial using FMT to treat IBS that showed improvements in symptoms but did not yield sufficient data to determine efficacy.[103]
- A small-scale trial[104] using FMT to treat chronic liver disease is currently recruiting patients (liver cirrhosis is associated with an altered gut microbiome).[105,106]
- An on-going, larger trial (STOP-Colitis) to assess two routes of FMT delivery in patients with Ulcerative Colitis.[107]

Regulatory issues

Regulation of prebiotics and probiotics

Prebiotics and probiotics are typically regulated and marketed as foods. New species of bacteria for use in probiotics would be subject to a pre-market safety assessment and authorisation under the Novel Food Regulation.[108] The regulatory process for getting approval to make a health claim for a food product also requires:[109]

- approval from a research ethics committee to conduct a trial to provide evidence of a health claim
- consideration of the evidence by the European Food Safety Authority (EFSA)
- if a positive EFSA opinion is given then the European Commission and Member States decide whether to approve the claim.[110]

To date, no probiotic claims have been accepted, and only one claim for a prebiotic, inulin, for maintenance of bowel movements has been accepted by EFSA.[111] Any clinical trial performed to obtain authorisation as a medicine, such as treating a patient with a medical condition with an LBP, would need to be performed in accordance with the Clinical Trials Directive[112]. This will be replaced in 2019 by a new EU Clinical Trial Regulation (POSTnote 561). Evidence from the trial would need to be submitted to regulators (as for any medicinal product) for assessment of safety quality and efficacy prior to the granting of a licence.

Regulation of FMT

FMT was initially regulated under EU human tissue legislation but is now regarded as a medicinal product in the UK. Responsibility for medicines legislation falls to the Medicines and Healthcare Products Regulatory Agency.[113] There are currently no licensed FMT medicines in the UK. Clinicians thus have to obtain FMT on prescription for individual patients,[114] either as an unlicensed medicine, or under an exemption which enables medicines to be prepared in a pharmacy. If FMT is to be used in a clinical trial it could also be subject to clinical trials regulations (see above).[115]

Future research

The UK has an active microbiome research community. For example, public funding in this area comes mainly from the Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council. One of the research aims of the BBSRC is Integrative Microbiome research. The BBSRC with partners has recently invested £75 million in the Quadram Institute.[116,117] One of the four research strands of this institute is Gut Microbes and Health and other research priorities are outlined in Box 2.[116] The National Institute for Health Research has put out funding calls for new therapies based on knowledge of the microbiome[118] and charities such as CORE (which focuses on digestive disorders)[119] and Arthritis Research UK[120] have also funded research in the area.

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to Erin Cullen for researching this briefing, to the BBSRC for funding her parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Pete Border.

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