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Editorial

CIENT PERIODIQUE

The Human Microbiome: The Extraordinary Biology of the Microbes that Live in and on Us

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Introduction

It seems that not a week goes by without a new finding being published, claiming how the microorganisms that live within and on us, affect different facets of our health. Perhaps most encouraging is the growing recognition by clinicians of the role of the microbiome in the development of, and protection from some debilitating or even fatal diseases such as cancer, diabetes and numerous inflammatory diseases (see for example, news of the recent knighthood for Prof Mel Greaves who has demonstrated a possible role for the microbiome in the development of Acute Lymphoblastic Leukaemia (ALL) in children [1]). The microbiome is the term we use to describe the entire population of microorganisms that live within and on our bodies. This brief article explores how we arrived at our current understanding of the human microbiome and touches on some of the many diseases that have been shown to be influenced by alterations in its composition.

Our ability to study the microbiome has only recently become possible, thanks to two critical innovations and discoveries: Next Generation DNA sequencing technology (NGS) and the use of 16S rRNA DNA sequence as a taxonomic tool. Until the advent of the 21st century, we were constrained by the use of traditional microbiological tools such as culture media and microscopy to explore the microbiota living in our gastrointestinal, respiratory, genitourinary tracts and skin.

Traditional methods allowed us to culture those microorganisms that are relatively easy to grow *in vitro*. However, we had not appreciated the complex needs of many of the microorganisms that reside within us. Indeed, some organisms will only grow in the presence of other microorganisms due to mutualistic interactions. Moreover, some microorganisms grow rapidly in the laboratory whereas others may take days, making accurate estimates of population sizes difficult.

The development of 16S rRNA sequencing as a taxonomic tool was first published in the 1980s by Carl Woese [2,3]. All living organisms capable of protein synthesis possess ribosomes. These complex organelles comprise several subunits, composed of protein and RNA. The DNA sequences encoding the ribosomal subunits are highly conserved between different organisms. However, there are certain domains within the subunits where mutations are tolerated. Woese sequenced the 16S rRNA genes from different prokaryotes (18S rRNA in eukaryotes) and showed that by aligning these sequences, he could correlate closely-related organisms with the presence of particular mutations; the more distantly related the organisms, the more the mutations differed. Woese also demonstrated how 16S (18S) rRNA sequencing can be used in phylogenetics to study the evolutionary progression of life [3]. Building on from this work, databases containing the 16S rRNA sequences of different microorganisms have been developed which may be interrogated by researchers [4]. Nowadays, researchers may simply send their 16S rRNA sequences to a database and quickly receive the identity of their unknown organism(s) without performing any of the cultural and phenotypic tests associated with more traditional microbiological methods, within seconds.

The first whole-genome DNA sequence was published in 1995 from *Haemophilus influenzae* (Fleischmann 1995); the first eukaryote genome sequence (*Saccharomyces cerevisiae*) followed a year later in 1996 [5]. An initial limitation to this technology was the immense cost and time taken for whole-genome sequencing. Moreover, lack of bioinformatic tools and data storage were also important limiting factors. However, numerous DNA sequencing platforms have become available, ranging in price and throughput but it is now possible for even small laboratories to purchase NGS technology with the power to sequence a bacterial genome overnight. A consequence of this power is the ability to extract DNA from complex mixtures of microorganisms such as stool samples, PCR-amplify the 16S rRNA sequences from each organism and sequence them using NGS. The software can access the 16S rRNA databases and automatically look-up the identities of each 16S rRNA sequence to generate a list of all the organisms present within the sample and provide information about the population sizes of each species of microorganism.

The Microbiome in Health and Disease

During pregnancy, the baby is in a sterile environment. However, during birth, as the baby travels through the vagina, it becomes "inoculated" with bacteria that live in the mother's vaginal canal. Many of these bacteria, known as Lactic Acid Bacteria (LAB), are known to play crucial roles in the initial colonisation of the baby's gastrointestinal tract. Babies born by Caesarean section are not inoculated with these bacteria so their intestines often become colonised by other types of bacteria. We now know that the LAB play some important roles in colonising the intestine and protecting the baby from colonisation by harmful bacteria. Moreover, the LABs are important in "programming" the baby's immature immune system, 'training' it how to respond to the many bacteria that eventually colonise the intestines. This should be considered alongside the recent findings by Greaves and colleagues in their work on childhood ALL [6].

Greaves argues that growing up in excessively clean environments actually impedes the normal development of the immune system, resulting in the increased likelihood of inappropriate responses following exposure to some microorganisms. The LABs also help digest foods containing complex carbohydrates and produce a number of antimicrobial substances such as bacteriocins that limit the growth of undesirable or harmful microorganisms such as *Clostridium difficile*.

Babies born by Caesarean section may eventually become colonised by LABs, especially if they are breast-fed but it is also likely that they will develop very different gut microbiota and this can sometimes have long-term consequences for the health of a person. Thanks to NGS, we have been able to correlate the presence and absence of several groups of bacteria with several serious, chronic diseases such as Irritable Bowel Disease, Crone's Disease, Necrotising Enterocolitis, obesity, type II diabetes, autistic spectrum disease and neurodegenerative diseases such as Parkinson's Disease [7-13]. Some researchers have been experimenting by taking the vaginal secretions from the mother and smearing them over her new-born baby to deliberately colonise the infant with "beneficial" bacteria. Intriguingly, it has been shown that some components of breast milk cannot be assimilated by the newborn infant eg fructo-oligosaccharides, but are in fact metabolised by LABs. Thus, the breastmilk is also designed to feed and encourage the growth of the types of bacteria that are so important for the healthy development of the baby [14].

A common feature of diseases such as some cancers, obesity, type II diabetes, irritable bowel syndrome and Crone's disease, the microbiome has been implicated in causing chronic inflammation [6,7,9,10]. The mechanisms leading to inflammation are well documented and it is thought that during inflammation, the influx of neutrophils results in the release of inflammatory cytokines and reactive oxygen and nitrogen species which are intended to destroy potential pathogens. However, the reactive oxygen and nitrogen species also cause a certain amount of collateral damage to the host including DNA damage with the potential to promote tumorigenesis [10,15]. It is therefore tempting to speculate that several different diseases could be controlled using a well-chosen group of probiotic organisms that have been shown to reduce inflammation in the gut (cited in [7]).

What Determines Which Bacteria Live in Our Intestines? Can We Change Our Microbiomes?

Factors important in determining the composition of our microbiomes include diet, genetics of the individual and early colonisation during birth /*post-partum*. We now know that the typical Western diet does not encouraging the growth of the "beneficial" bacteria. A good diet should contain plenty of fibre and plant matter such as fruit and vegetables and fish. The typical Western diet is rich in refined ingredients such as sugars, fats, salt and protein and this encourages the growth of very different microbiomes to those seen in people living on relatively unrefined diets eg in the Far East, Africa etc. Moreover, diet influences the diversity of the microbiota with high-fibre, low fat diets, resulting in greater diversity. Up to this point, most researchers have concluded that no single organism /group of organisms is responsible for determining the health and wellbeing of a person; it is the combined effect of many diverse organisms although we now have a better idea of the groups of organisms associated with inflammatory diseases and healthy gastrointestinal tracts.

One of the extraordinary findings that has been made in recent years follows from analysis of metabolites produced by some organisms in the gastrointestinal tract. It has been shown that some organisms release small psychoactive molecules such as gamma-amino butyrate (GABA), serotonin and dopamine which act upon neuronal receptors in the brain, to affect mood and the feeling of well-being [16]. Intriguingly, it is now being speculated that the reason why some people find foods rich in fats, sugars and salt, highly addictive is because these foods encourage the growth of organisms such as *Candida* sp, *Streptococcus* sp, *Escherichia coli* and *Enterococcus* sp which produce serotonin [16], leading to a feeling of well-being (or a 'high'). The idea that our behaviour might, to some degree be under the control of the microbiota within the gastrointestinal tract raises exciting opportunities for treatment of dietary disorders and mental health through the administration of probiotic supplements (cocktails of beneficial microorganisms that can be ingested with food) rather than treated pharmacologically. For example, bacteria such as members of the family *Porphyromonadaceae* and LABs convert dietary fibre to short-chain fatty acids such as acetate and butyrate that reduce inflammation (cited in 10).

Outlook

With relatively easy access to NGS technology and bioinformatics tools, microbiologists and other researchers are being empowered to ask questions that had never previously been considered. Diseases where no obvious cause had been identified, are now being shown with varying degrees, to be affected by the microbiome. Of course, use of NGS and 16S rRNA sequencing is only a first step to answering many of the questions regarding how our microbiomes affect our health. These experiments simply inform us what organisms we need to look at in more detail and study their interactions with the host. This raises several important questions that should be considered when treating any condition:

1) If a patient is given antibiotics to treat an infection, what are the potential long-term consequences and how can they be mitigated?

2) Can we treat more chronic conditions by altering the patient's microbiome through dietary alterations / addition of prebiotic supplements to encourage the growth of desirable organisms /probiotics to introduce microorganisms with known beneficial properties?

3) Can we reduce the usage of antibiotics and therefore problems of antibiotic resistance by using probiotic organisms instead?

4) Can we reduce the West's voracious appetite for antidepressants and other powerful and sometimes expensive drugs by altering a person's microbiome?

5) Can we address the rapidly escalating mental health problems such as anxiety, stress, depression and autism that affecting our young people, by controlling their diets and thus their microbiomes?

As microbiologists, our challenge is to apply our knowledge and skills to advance this rapidly growing field. We must use it to improve the lives of the many people who may be unwittingly harming themselves through their lifestyle choices which are adversely affecting the delicately balanced microbiomes in and on their bodies.

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