The Microbiome and Toxicology

Background

The microbiome is the sum of microorganisms that are resident in, or on, all of us, on surfaces which are in contact with the environment such as the skin and perhaps less obviously the lung (air contact) and the gastrointestinal tract or gut (food). The microbiome is an integral part of all of us. The microbiome consists of bacteria, fungi and viruses and these can fall into three categories 1) mutualists (benefit themselves and host) 2) commensals (benefit themselves but not the host and, 3) pathogens (benefitting themselves but harming the host). Species vary depending on where they are located: on the skin aerobes will be found, while in the gut where the oxygen content is low anaerobes are located.

We are born without a microbiome (there is some debate about this, but generally this is the current majority opinion) and it is established at birth and it's composition influenced by the route of birth. The microbiome further changes throughout life influenced by our environment, age and genetics. The microbiome is not a passive passenger to our lives but an active contributor.

As an example, the gut microbiome is an important component of the overall capacity of humans to metabolise chemicals. Additionally the gut microbiome produces much of the energy on which the gut is reliant; estimated at approximately 70%. The gut microbiome is influenced by our diet, with gut bacterial species for a sugar-high, western diet being quite different from those found in the gut of a person dependent on a more fibrous diet. Similarly antibiotics do what they *say on the can*, and a single course of antibiotics can profoundly affect the composition of the gut microbiome for many months, even years, after cessation of therapy (see below).

Genetics plays a part in the composition of the microbiome. Identical (monozygotic) twins have the same genetics. If living together these individuals will have the greatest similarity of any two individuals, in terms of their microbiomes. When they start living apart then the microbiomes start to diverge, reflecting environmental influences. For both of these reasons unrelated individuals living apart have the most divergent microbiomes.

What has driven the current increased interest in the Microbiome?

The existence of the microbiome has been recognised for a long time. There is however renewed interest in this field due to new and improved research methods, which have enabled a better understanding the microbiome. New genome sequencing techniques allow a rapid elucidation of the diversity of the microbiome, and enable identification of a wider range of microbiome species than was possible using microbiological culture techniques. Additionally, suitable samples are generally accessible from the skin and other such surfaces directly, from the gut via the faeces and from the lung by mouth swabs. Notwithstanding some debate about how well the species found in these samples represent the true microbiome of the areas they are posited to represent, they nonetheless indicate some of the changes occurring in these body compartments as the result of a human's exposures, or altered environment. This new technology, which enables more detailed studies, is driving much of the current interest in the microbiome.

Antibiotics and the Microbiome.

Antibiotics are selective toxins: that is, they exhibit toxicity to some cells/organisms but not to others. In the case of antibiotics, they are toxic to certain bacteria, including those in our microbiome, but not to the cells of our body. We take antibiotics for help to overcome infections. This antibiotic exposure though can change our microbiome. Bacteria in our bodies which are susceptible to the antibiotic will be killed, along with those causing the disease. What happens then is that bacteria which are resistant to the antibiotic, will grow into the space left. This will profoundly change the nature of the microbiome. Furthermore, recovery to the pre-treatment normal does not happen quickly after cessation of antibiotic use, but can take years. This means that the effect of the antibiotic on our bodies lasts for a long period after its use. This could result in further disease or altered phenotype (physical characteristics), for example a differential microbiome metabolism of environmental xenobiotics (chemicals).

Metabolism and the Microbiome

The gut microbiome is responsible for many metabolic reactions that are vital for the excretion for many xenobiotics. Changes in the microbiome can then greatly affect the type and capacity of that metabolism. One of many examples is the antidepressant, nitrazepam. 30% of nitrazepam is metabolised by the gut microbiome to the amine and acetylated metabolites. After antibiotic treatment to alter the composition of the microbiome, gut metabolism to these metabolites drops to 2%. This, therefore, alters the exposure of the whole organism to the parent compound potentially changing the risk profile https://pubmed.ncbi.nlm.nih.gov/1925980/

This is an isolated example but illustrates an important point that needs to be considered in hazard (toxicity) testing where the microbiome can alter the response of the organism to the substance under test. This can happen even when all other characteristics of the individuals, for example genetics, are the same or similar. An example of this has been observed with galactosamine, a liver toxin. A cohort of Sprague Dawley rats were exposed to galactosamine and some individuals responded very differently in terms of the severity of the liver toxicity seen. This response was entirely dependent on the composition of the microbiome of individual rats, leading to categorising the rats into “responders” and “non-responders” https://pubmed.ncbi.nlm.nih.gov/19821561/

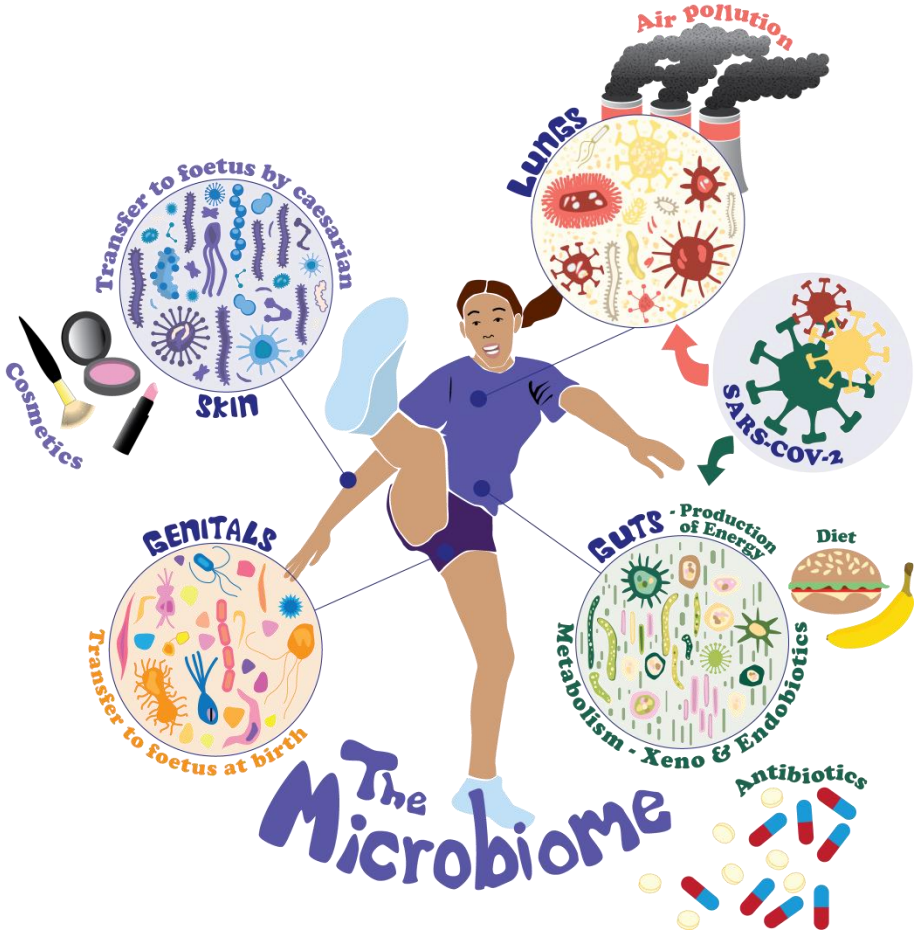
A further question needs then to be asked: how can the influence of the human microbiome be represented in toxicology testing? This is an area where a lot more research is needed. Not least for *in vitro* testing systems, where it is difficult to represent the microbiome, particularly that of the gut, which is largely dependent on low oxygen conditions. These conditions are difficult to reproduce for in vitro testing purposes and they do not favour the growth of mammalian cells in culture.

Environmental Microbiome

Outside of the body we also need to consider other microbiomes which occur in the surrounding environment and may impact human health. Their composition, and whether these species have a beneficial or adverse effects on health, will be dependent on many variables such as atmospheric temperature and moisture.

For the Future

Our understanding of our internal and external microbiomes is proceeding at a rapid pace. It is clear that both can have profound effects on human health, wellbeing and on an individual’s response to other environmental stressors. Furthermore, it is becoming clear that there is a need to consider the microbiome when assessing human risks from exposure to chemicals or drugs.



The Microbiome - potential influence on susceptibility to toxicity and impact on human health

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