Microbiome Therapeutics Need for Better Tools

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This issue of the UTMJ seeks to highlight aspects of microbiome research. The general sentiments of my clinical colleagues towards the microbiome and its importance to human health, is still primarily as a reservoir of infection or research novelty. While some accept that microorganisms may have contributed to the problems, we must consider that some may also be part of the solution. Perhaps such sentiments are understandable given the fast moving pace of research studies now linking almost every human body system to having some kind of interaction with the microbiome. Even within this issue, researchers present microbiome work relating to their interactions beyond their primary colonizing sites and possibly having an influence upon atherosclerosis, circadian rhythmicity and liver disease amongst others. Indeed, our own work looks at the influence beyond the intestinal microbiome to urological health and we believe that the intestinal tract microbiome is linked to chronic kidney disease, kidney stones, urological cancers and microbiome modifiers, like antibiotics, can create profound changes to the host.[1,2] It is likely the hospital of the future will offer advanced personalized diagnostic and treatment options. If this is to occur then a considerable amount of information will be required not only from the person's own genome, metabolic and clinical outputs, but also from their own microbiome. Once this information is attained, the microbiome may have to be modified to alleviate the condition. However, we are currently limited to some basic tools such as probiotics, prebiotics (like oligosaccharides), antibiotics and faecal transplants.

Some major paradigm shifts have occurred in the last five years, led by Canadian-based research groups. Examples include the microbiome's role in metabolism, inflammation and obesity, the brain-gut axis and the false concept of internally-sterile humans, to name a few.[3, 4, 5] The latter is particularly interesting with microbiomes being described in regions important within the human body such as bladder, breast and even placenta. In other areas we have seen studies on type I diabetes (T1D) and type II diabetes (T2D), with microbiome diversity changing before clinical disease occurrence in T1D,[6] and the microbiome being an earlier predictive indicator of likely disease progression than host genome for T2D.[7, 8]

Microbiome therapeutics looks to modify bacterial populations for human benefit and can encompass dietary agents like prebiotics, probiotics or even drugs that are specifically modified by microbial metabolism. At present the largest thrust is probiotics. However, in chronic diseases, using single- or multi-strain probiotic bacterial strains is a bit like trying to recolonize the fauna of a decimated jungle with one or two domesticated animals. For example, probiotics have been tried without success thus far in humans in an attempt to control the presumed immune inflammation promoted by a leaky gap junction/gut barriers in T1D.[9] In reality few probiotics ever persist after dosing and can also be quite different physiologically and genetically from their original isolates.[10] In addition, while many probiotic strains may be intestinal in origin, they are usually restricted to organisms with a history of use in food, typically only lactobacilli or bifidobacteria, often representing minor components of the intestinal tract. It is amazing that they have efficacy for anything but many do and a guide to clinical probiotic supplement exists specifically for Canada, relating to indication, dosage and evidence.[11] However, most intestinal bacteria which currently "roam free" will never see their use as probiotics, given the regulatory and safety requirements needed to bring to market, although the probiotics market is valued as high as $30 billion USD.[12]

To treat more chronic diseases using microbiome therapeutics, it may require the ultimate multi-strain bacterial application in the form of a fecal transplant (FT). Canada is a world leader in implementing FT for the treatment of refractory *Clostridium difficile* (CD) infection. While a bit of a sledge hammer approach, usually involving a blender and a fecal sample, somehow it has the ability to modulate the intestinal microenvironment which has become altered by infection, antibiotics or some other kind of insult. How does it work? No one knows exactly, but it seems to take enough of the functional aspects of someone's healthy system to "reset" an ailing one. Given the success with CD, researchers are itching to trial the concept in chronic diseases where the microbiome may play a role, from arthritis to colitis.

Alarmingly, the power of the technique has also been seen, in that undesirable phenotypes such as obesity (not to mention disease) can be transferred shown in FT mouse models. Some careful consideration of donors will be required, given that certain chronic diseases with intestinal links may not be seen for decades after treatment. Thus, risk-benefit assessments are required before its use. In April 2013, the FDA

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classified FT (and probiotics for clinical outcomes) as Investigational New Drugs; similarly in Canada it is restricted to the treatment of refractory CD infection. There has been some caution to avoid rushing in to use FT and alternatives; therefore, like the more eloquent synthetic stool has been developed in Canada, paving the way for "designer microbiome" transplants.[13]

There is no doubt that the microbiome is of immense importance for health, diagnostic and bioprospecting purposes. While some still question the role of this vast collection of bacteria that have co-evolved with us over millions of years, those who are more pragmatic are starting to consider it as an organ in its own right, perhaps one of the most complex in the body, considering its functional genomic output is much greater than our own. At present we have a few crude tools to change the microbiome if it goes "haywire", however, one day we may see specific targeted therapies and drugs. It is likely that these may involve nonconventional approaches, such as having fermenters bubbling away with patients bacteria in the basements of hospitals, "reconditioning" patients microbiomes for their re-implantation to complement their other clinical treatments.

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