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How do probiotics and prebiotics function at distant sites?

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REVIEW ARTICLE

Abstract

The realisation that microbes regarded as beneficial to the host can impart effects at sites distant from their habitat, has raised many possibilities for treatment of diseases. The objective of a workshop hosted in Turku, Finland, by the International Scientific Association for Probiotics and Prebiotics, was to assess the evidence for these effects and the extent to which early life microbiome programming influences how the gut microbiota communicates with distant sites. In addition, we examined how probiotics and prebiotics might affect the skin, airways, heart, brain and metabolism. The growing levels of scientific and clinical evidence showing how microbes influence the physiology of many body sites, leads us to call for more funding to advance a potentially exciting avenue for novel therapies for many chronic diseases.

Keywords: probiotics, prebiotics, skin, airways, vascular

1. Introduction

It may seem far-fetched to some that microbes play a role in programming the host's health trajectory, including and beyond the immune components, but microbiome mining is certainly suggesting this to be possible. The extent of bacterial colonisation is more surprising than long thought, with areas like the stomach, breast tissue, bladder and even brain having some sort of indigenous microbiota (Branton *et al.,* 2013; Lewis *et al.,* 2013; Marshall and Warren, 1984; Urbaniak *et al.,* 2014a). Exposure to bacteria and their by-products has been shown to occur during foetal development (Aagaard *et al.,* 2014; Collado *et al.,* 2016), during delivery (Reid *et al.,* 2011) and early feeding regime (Del Chierico *et al.,* 2015; Rautava, 2016) and is modified by antibiotic exposure, all of which (Bokulich *et al.,* 2016) shape the microbiota composition and host's tolerance.

We now know that the composition and quantity of ingested food influences which organisms dominate the mucosa and

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lumen, and whose metabolites shape disease processes. It is suspected that these effects not only alter our risk of chronic ailments, but may prime us for lethal diseases in later life.

The enormous interest in probiotics and prebiotics in recent years has been driven, to a large extent, by the belief that these products can manipulate the microbiota and/or their metabolic imprint (Kolmeder *et al.,* 2016; McNulty *et al.,* 2011). To date, the ability of probiotics to induce meaningful and lasting changes to the existing microbiota composition appears limited, but metabolically their administration has been shown to confer an effect (Sanders, 2016). It remains unclear why probiotic strains are poor colonisers, with some exceptions (Maldonado-Gómez *et al.,* 2016), although faecal microbiota transplant (FMT) studies have suggested that strains may survive and persist if they are transported in a milieu close to what they experience in the host, and if there are unoccupied niches in the recipient (Fuentes *et al.,* 2014). As more FMT studies are reported, we will learn the extent to which this modulation of the intestinal microbiome influences sites distant from the gut. For the present review, we explored how the administration of probiotics and prebiotics to the gut might affect the skin, airways, heart, brain and metabolism.

2. Skin

Is the skin the most improbable site for orally administered probiotics to affect? In order to protect the body from exposure to toxic microbes and substances, as well as ultraviolet (UV) radiation, the skin's ability to survey temperature and antigens is aided by a network of small blood vessels containing muscle fibres controlled by the sympathetic nervous system. Thus, the ability of bacteria in the gut to influence the skin could occur through molecules carried by the blood and nerves. The superficial plexus also allows a way for immune cells to enter the tissue thus offering a further opportunity for modulation of skin by bacteria via the immune system. This is not as easy to conceptualise as the way that the vagus nerve, linked to the gut and other sites colonised by microbes (Reid and Burton, 2016), appears to be a primary means of transferring signalling molecules. Nevertheless, the avenues of access are present to affect the skin.

There is evidence that orally administered probiotics can affect the human skin, even if mechanistic explanations are lacking. Skin inflammation is believed to occur in atopic dermatitis when defective skin and gut barrier function result in exposure to too many environmental triggers and an inappropriate immune response (Flohr and Mann, 2014). Clinical outcomes with oral probiotics for the acute symptoms of atopic dermatitis have been inconsistent (Boyle *et al.,* 2008), although individual studies have shed light on plausible mechanisms. In a study of 220 children with atopic dermatitis, administration of *Lactobacillus paracasei* GMNL-133 and/or *Lactobacillus fermentum* GM090 substantially reduced the SCORAD atopic dermatitis grades and improved quality of life, but the only mechanistic marker noted was lower interleukin (IL)-4 (Wang and Wang, 2015). It would be interesting to see if anti-IL-4 or anti-IL-13 drugs could help atopic patients who are taking probiotics.

In a study of patients with atopic dermatitis, adults taking *Lactobacillus salivarius* LS01 showed reduced symptoms, reduced production of Th2 cytokines which exacerbate symptoms, and a maintenance in production of Th1 cytokines which are protective (Drago *et al.,* 2011). These findings support an immune mediated concept and indicate the beneficial effects are not restricted to specific species.

In vitro studies with *L. paracasei* strain NCC 2461 (ST11), predicted improved skin barrier function and water retention (Gueniche *et al.,* 2010), and follow-up studies in which women received two month supplementation with this strain showed decreased sensitivity and barrier function recovery (Gueniche *et al.,* 2014).

However, a meta-analysis of studies on probiotics to treat eczema showed no reduction in symptoms (Boyle *et al.*, 2009). There was significant heterogeneity across studies in terms of the probiotic species used and the dosing regimen. Those started after childbirth were not significantly better than placebo. If a probiotic was to work, it might confer its protective effect through early exposure *in utero* resulting in changes lasting through maturation of the immune system (Rautava, 2012). But, human studies are clearly needed to prove this.

The gut barrier function appears to be impaired in a number of skin conditions, suggesting oral probiotics might affect skin health (Nermes *et al.,* 2011). Adults with atopic dermatitis treated with a combination of *L. salivarius* LS01 and *Bifidobacterium breve* BR03 showed improved SCORAD scores and less plasma lipopolysaccharides, indicating reduced microbial translocation (Iemoli, 2012). This is interesting as one might have thought that a more permeable gut lining would have allowed more secreted molecules from probiotic strains to reach the skin. However, it seems that probiotics might alleviate eczema (Rosenfeldt *et al.,* 2003) in infants by reducing intestinal permeability (Rosenfeldt *et al.,* 2004). Another mechanism could be that the molecules secreted by lactobacilli or induced by their presence in the gut, travel to the skin and therefore influence the skin and gut barrier function. To examine this, we need to know more about the metabolites of these lactobacilli and examine blood for molecules that may be mediators of these effects. The recent identification of a blood microbiome certainly offers a means for gut microbes to influence distant sites, including the skin (Potgieter *et al.,* 2015).

The mechanisms of probiotics in atopic dermatitis may be relevant in other skin conditions of uncontrolled inflammation. Hand dermatitis is the most frequently observed skin disorder in adults and will affect 15% of people at some point in their lives (Thyssen, 2010). Hand dermatitis is a syndrome grouping multiple presentations and aetiologies of inflammation, including irritant, allergic, and atopic dermatitis. An open-label study in 30 adults showed that ingesting a probiotic mixture containing *Lactobacillus acidophilus* CL1285, *Lactbacillus casei* LBC80R and *Lactobacillus rhamnosus* CLR2 daily significantly reduced skin inflammation within 2 weeks (Modified Total Lesion Symptom Score, left hand, P=0.015, right hand, P=0.033) and improved the Physician Global Assessment in 54.5% of subjects after 12 weeks (Gulliver, 2012). There have been very few studies of probiotics and prebiotics in the treatment of this condition but there is a good rationale for future research.

The nature of skin ailments is such that one treatment approach is unlikely to impact them all. For example, psoriasis has an inflammatory component, but it is primarily a chronic autoimmune condition in which skin cells are overproduced and dead cells build up into silvery-white scales. The finding that increased systemic inflammatory markers, such as plasma levels of C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α) and IL-6 is shared by ulcerative colitis and psoriasis patients, suggests the barrier dysfunction known at the gut level might be also present at the skin (Groeger *et al.,* 2013). The ability of probiotic *Bifidobacterium infantis* 35624 to reduce plasma CRP and TNF-α in psoriasis further indicates a therapeutic effect by a different species, although no changes in symptomatology were examined in this study. Decreasing TNF-α and IL-4 may not be sufficient if, as has been suggested, Th17 is the main inducer of inflammation in psoriasis (Krueger, 2012) and possibly also cardiovascular diseases linked to this condition (Eppinga *et al.,* 2014). Interestingly, there are reports indicating that probiotic supplementation induces a low-grade inflammation with elevated subclinical levels of CRP during infancy, which was subsequently associated with a reduction of eczema (Viljanen *et al.,* 2005a,b). Thus, it further emphasises that the effects of probiotics differ between strains and that it matters what strain you use, and when in the lifespan, in specific diseases.

Bacteria are likely not the only instigators of skin reactivity, and a disrupted barrier may allow fungi to invade and avoid the normal anti-microbial peptides, secretory antibody and complement system defences. The presence of a Cys-reduced form of S100A7/psoriasin (redS100A7) antifungal factor has been suggested to allow the host to resist such fungal infection (Hein *et al.,* 2015). Studies in the unique setting of the Antarctic have shown an increase in fungi on the skin in expedition participants, believed to be due to interferences with local immunity and dysbiosis of the normal skin microbiome due to stress, recycled air and antiseptic agents (Moiseyenko *et al.,* 2016).

The approach to skin health may in future include lysates from probiotic bacteria, not only for local application but also *per oral* (Kim *et al.,* 2015). It may comprise use of orally administered strains specifically selected for their ability to up-regulate claudin and other tight junction proteins in the gut (Bergmann *et al.,* 2013), reduce sulphide and ammonia compounds (Naidu *et al.,* 2002), inhibit staphylococcal pathogenesis (Li *et al.,* 2011) and produce metabolites that increase skin hydration and decrease inflammation. Fibromyalgia, characterised by musculoskeletal pain and tenderness and fatigue, emphasises the skin-brain-gut access (Bowe and Logan, 2011), so probiotic strains producing neurochemicals may also prove to be of interest.

3. Programming at birth

The establishment of microbiome communities throughout the body has its origin in early human life, from exposure to microbes carried by sperm, to those that reach the uterus, amnion and placenta. Such studies have been carefully done with best efforts to rule out environmental contamination, but more are required to generate conclusive proof. Still, such early contact is likely only priming the host to a microbial world, whereas the bulk of colonisation occurs after birth and full development of the organ system and hormones that support reproductive capacity. Our understanding of which microbes affect which developmental stages and sites is primitive at best. The study which showed that at least one species, *Bacteroides thetaiotaomicron*, can modulate nutrient absorption, angiogenesis, and postnatal intestinal maturation, albeit in a mouse model (Hooper *et al.,* 2001), provided an indication of what is possible. But, the origin of this organism prior to entry into the new-born is unknown, and colonisation is left to chance, suggesting that either other species perform the same tasks, or the infant's developmental pathway has some deficiencies in its programming if certain bacteria are not present.

Probiotics and prebiotics are approved in a number of countries for administration to new-borns, to prevent necrotising enterocolitis, reduce the risk of eczema, treat colic or simply to supplement formula (AlFaleh and Anabrees, 2014; Braegger *et al.,* 2011; Francavilla *et al.,* 2016; Zuccotti *et al.,* 2015;). The benefits of these microbes on respiratory and skin health have been documented, but beyond influencing the immune system and intestinal permeability, the mechanisms have not been fully explored. For example, which specific strains and metabolites are critical and how do they program immunity? If the beneficial strains are not administered, what pushes the responses toward a less healthy path?

The microbial composition of breast milk also plays a role in programming the host, and likely in organ development, but again beyond the role of human milk oligosaccharides, specific mechanistic understanding is lacking. Human milk contains a wide range of bacterial types, and with so many confounders it will prove challenging to correlate species with distant site effects. One would imagine that ingesting a range of bacteria even in low counts per ml, would lead to a high diversity infant gut, yet, it is dominated by bifidobacteria and therefore is defined as low diversity and linked to reduced risk of certain chronic illnesses in adulthood (Goldsmith *et al.,* 2015). On the other hand, a low diversity of gut microbiota in one month old infants has been suggested as a marker for asthma (Abrahamsson *et al.,* 2014). This is difficult to equate, and raises questions about branding low and high diversity microbiota profiles with disease states. It is surely the composition and function of the microbes and risk factors of the host that are more important indicators than diversity itself.

There are multiple sources from which microbes colonise post-natally, including the delivery room and environment, and familial handling. The range of these microbes is likely quite large and certainly influenced by the hospital and home environments, nutrition, and lifestyle of the parents. There may come a time when different microbes are administered at different time-points to positively influence specific developmental processes. The ability of these compositions to perform the required functions within the confines of the microbes already present, will be interesting to see. Certainly, this is not to disregard the importance of the intrauterine environment in promoting beneficial intestinal function, which places an enormous emphasis on promoting the general health of child-bearing aged adults. If the end result is stopping the rise in chronic diseases or the rapid shifts that cause NEC or other diseases, encouraging acquisition and colonisation by beneficial microbes will benefit many children throughout their life course. At the very least, efforts to reduce antibiotic use in early life where possible, or negate their disruptive effects on the infant microbiome are recommended along with exposing the infant to mother's microbiome through vaginal birthing and exclusive breast feeding.

4. Airway health

Most airway problems tend to arise in the young and elderly, the former through allergy and the latter through poor mobility, immunosenescence, and exposure to viral and bacterial pathogens. Low gut microbiota diversity during the first month of life has been associated with asthma in school age (Abrahamsson *et al.,* 2014). However, no study with oral supplementation with probiotics has yet been shown to reduce asthma (Azad *et al.,* 2013; Fiocchi *et al.,* 2012; Vliagoftis *et al.,* 2008).

A short term intervention with probiotic *L. rhamnosus* GG seemed to be effective in children with cystic fibrosis, to re-set the gut microbiota found in these children to ones more like the healthy controls (Bruzzese *et al.,* 2014). Probiotics have been shown to reduce the number of participants experiencing episodes of acute upper respiratory tract infections, as well as the mean duration of an episode, and antibiotic use (Hao *et al.,* 2015).

Until recently, the airway was considered to be sterile in healthy individuals. However, there is growing evidence supporting at least transient colonisation in normal healthy lungs of adults (Dickson *et al.,* 2016). Furthermore, it has been reported that new-born infants acquire an airway microbiome during birthing, and that the composition of this microbiome affects subsequent lung diseases (Lal *et al.,* 2016). This study was based upon tracheal aspirates and suctioning in the first hours of life. The results imply colonisation occurred in the uterus or during labour, but the timing is difficult to prove. As the organisms identified included *Firmicutes, Proteobacteria*, *Actinobacteria, Bacteroidetes, Tenericutes, Fusobacterium, Cyanobacteria*, and *Verrucomicrobia*, all of which could have come from the birthing canal and maternal faecal contamination, it is feasible that probiotic strains could be administered orally and vaginally to the mother to influence the organisms passed on to the infant.

It would be much more difficult, ethically and logistically, to try and administer beneficial living microbes to the upper respiratory tract of older infants who have a more-established microbiome. One potential cohort could be young infants (<1 year) with a *Haemophilus*-dominant airway profile who are hospitalised for acute and severe bronchiolitis (Hasegawa *et al.,* 2016). It may be feasible to aerosolise a microbiota mix, or administer orally or intra-nasally in liquid form, to these infants, to try and displace the *Haemophilus*. In older children and adults, lozenges might be useful and affect the oropharynx which is a main source of airway organisms. The transient nature of the lung microbiome (Madan *et al.,* 2012) could potentially help the probiotic organisms colonise or at least re-establish a healthy microbiome.

Probiotic bacteria that produce compounds like D-tryptophan, might be good candidates to prevent chronic immune diseases like asthma (Kepert *et al.,* 2017). In one study, 100 µl containing 13 strains of lactobacilli and bifidobacteria in sterilised honey and bee-pollen sprayed into each nostril, was shown to be safe but did not change the commensal microbiota profile (Mårtensson *et al.,* 2016). A mouse study showed that oral administration of *Streptococcus thermophilus* CCFM218 resulted in strong suppression of airway inflammation characterised by reduced inflammatory cell infiltration and Th2 cytokines in lung tissues (Zhang *et al.,* 2015). One wonders if this success

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will carry over to humans, given that *S. thermophilus* is a starter organism for yogurt rather than a probiotic strain *per se*. Based upon a literature review, Licciardi *et al.* (2012) proposed that probiotic bacteria could prevent lung pathogenesis by enhancing mucus secretion, production of secretory IgA, improving epithelial barrier function, and activating dendritic cells can trigger Th1, Th2, and Th17 and regulatory T cells and B cells.

There is evidence that the gut microbiota can influence the lungs, but the key organisms may not be the target of current prebiotic compounds. A pilot study using prebiotic Bimuno-galactooligosaccharide (B-GOS) supplementation on hyperpnoea-induced bronchoconstriction (HIB), a surrogate for exercise-induced bronchoconstriction, and airway inflammation found significant alleviation of inflammatory markers (Williams *et al.,* 2016). Though the effect is hypothesised to be mediated by the gut microbiota, the mechanisms have not been identified.

5. Cardiovascular health

The number one killer in developed countries, cardiovascular disease, has been attributed to atherosclerosis, with inflammation and plaque deposition within the arterial walls. Traditional fermented cheese whey has been shown to have significant anti-atherosclerotic potential, likely modulating lipid metabolism and protecting an atherosclerotic aorta in rabbits (Nabi *et al.,* 2016). The mechanisms proposed included reducing C-reactive protein, VCAM-1 and ICAM-1 and increasing high density lipoprotein (HDL-C) ($P<0.05$). Another study using fermented milk supplemented with *Bifidobacterium lactis* HN019 resulted in not only lowering of total cholesterol and low-density lipoprotein (LDL) and TNF-α, but also body mass index (Bernini *et al.,* 2016). The ability of probiotic strains to improve the cholesterol profiles and thereby lower the risk of cardiovascular disease has been known for some time. This is one of the many ways in which probiotics can improve cardiovascular health, as reviewed by Ettinger *et al.* (2014).

Organisms expressing bile salt hydrolases (BSH) promote the deconjugation of bile acids in the gut, one mechanism by which probiotics can affect cholesterol metabolism. Additionally, some organisms have been shown to incorporate cholesterol in their cellular membrane or convert cholesterol to coprostanol, a non-absorbable sterol. One product containing BSH-active *L. reuteri* NCIMB 30242, can lower LDL-cholesterol levels, by 11.6%, as well as C-reactive protein in hypercholesterolemic adults (Jones *et al.,* 2012). Bile acid deconjugation has been implicated in several key transcriptional changes in circulation, liver and the GI tract. Of note, the colonisation of mice with active BSH was shown to reduce weight gain, plasma cholesterol and liver triglycerides as well as increase intestinal gene expression of adenosine triphosphate-binding cassette G5/G8 transporters (Joyce *et al.,* 2014). Furthermore, the exopolysaccharide producing *Lactobacillus mucosae* DPC 6426 has previously been shown to attenuate dyslipidaemia and atherogenesis in an apolipoprotein-E deficient mouse model (London *et al.,* 2014). The market for cholesterol-lowering drugs is substantial, but while statins claim to reduce the risk of myocardial infarction and stroke by 25%, some patients may prefer probiotics without the statin side effect, even though the cholesterol lowering effect is not as profound (Thushara *et al.,* 2016).

A meta-analysis has shown that probiotic therapy can lower fasting blood glucose and thereby counter one of the major risk factors for cardiovascular disease (Nikbakht *et al.,* in press). An animal study showed that probiotic *L. rhamnosus* could remodel the heart post-infarction, through increasing the adiponectin-leptin ratio (Gan *et al.,* 2014).

With cardiovascular disease still the main killer in developed countries, it behoves us to find accessible effective alternatives to statins and beta blockers, which along with dietary modifications and exercise, could reduce the numbers of fatalities and morbidities. Studies are recommended to compare pharmaceutical agents with probiotics, and profile the gut microbiome at the same time to see if certain patterns correlate with better outcomes. As the gut microbiome can significantly alter the ability of a drug to be adsorbed and specific bacteria can actively degrade common drugs (Spanogiannopoulos *et al.,* 2016), these gut organisms will undoubtedly become an important parameter to consider and modulate in determining the efficacy of a drug. Likewise, chemotherapy can induce dysbiosis in the gut (Montassier *et al.,* 2015) and in human milk (Urbaniak *et al.,* 2014b), which can lead to further complications in drug efficacy.

6. Effects on the brain

The ability of gut bacteria to influence the brain is one of the most fascinating areas of microbiome science today. The vagus nerve appears to be a key routing for the effects (Forsyth *et al.,* 2014), but the actual presence of bacteria in the brain itself seems more and more likely, albeit in very low quantities (Branton *et al.,* 2013). Indeed, viruses, *Chlamydia* and *Spirochaetes* have been clearly linked to Alzheimer's (Itzhaki *et al.,* 2016) and Parkinson's disease (Scheperjans *et al.,* 2015). To what extent this array of microbes influences cognition, information processing and responses, and by what mechanisms, needs to be investigated with haste. Neglect has been a result of funding agencies failing to embrace radical ideas, and people not being convinced that the brain may not be sterile.

Many of the conditions emanating from the brain, creep upon us slowly and methodically, and thus while massive

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resources went immediately to create a vaccine for SARS, that in fact was not needed, allocation of resources to brain diseases has mainly been prioritised by patient-funded organisations. It is time to make microbiome-brain health a funding priority. The number of people affected is too sizeable not to do this.

Is it a surprise that microbes can find their way to different parts of a tissue rich in nutrients and niches for them to survive? Rather, the surprise is that we have not discovered this sooner, and that the organisms for some reason rarely proliferate to the point of easy detection. Could it be that some species exist in certain niches to perform tasks essential for human behaviour and well-being? Like the thyroid, limited in size, set in a specific location, and with a defined purpose.

It will not be long before we find out the extent of microbial presence in the brain, as neurosurgeons are now sampling different regions and scientists are exploring microbial profiles. Some conditions, like autism, anxiety, depression and attention deficit disorder, may be 'programmed' in early life. Others, like Parkinson's disease, Alzheimer's disease, post-traumatic stress disorder, dementia, and schizophrenia may have later triggers. Collectively, these conditions emanate from different regions of the brain: the hippocampus (memory), amygdala (emotion and reward), frontal lobe (working and emotional memory), among others, are influenced by various pathways and systems such as the vagus nerve, blood stream (hormones, metabolites, others), immune & lymphatic systems or endothelia. Blood-brain barrier integrity, or dysfunction, may indeed also play a major role in pathogen translocation or influence into the brain.

What we do know, mostly from animal models, is that bacteria in the gut can influence anxiety and memory (Luczynski *et al.,* 2016), and their metabolic by-products can induce disorders such as autism spectrum-like behavioural responses (Shultz *et al.,* 2015). As one might expect, chronic antibiotic use, which is not uncommon in humans, causes dysbiosis in the gut and deficits in spatial memory, increased visceral sensitivity and more depressive-like behaviours (Hoban *et al.,* 2016). This was correlated with altered CNS serotonin concentration, changes in the mRNA levels of corticotrophin releasing hormone receptor 1 and glucocorticoid receptor, and changes in expression of brain derived neurotrophic factor. This further emphasises the viewpoint of Blaser (2011) that antibiotic use can have dangerous long term consequences.

This once again raises the question of whether beneficial microbial supplementation can reset the microbiome – essentially the basis for probiotics. Patients are known to be self-administering donor faeces in the hope of treating many brain-related conditions, but without proper controls it will be difficult to know if any are successful and why. Without adequate testing of the donor faeces, some of the organisms, such as viruses, *Chlamydia* and spirochaete may inadvertently be transferred to the patient and make their condition worse at a later point in time.

If probiotic strains are to be used, several considerations are needed. If it is discovered that live bacteria are present in the healthy brain and the species differ from those of patients suffering from a brain condition, how might one alter the disease-related one? Obviously, antibiotic administration is one route, assuming the drugs reach the brain and targeted species. Another might be to administer probiotics orally and see whether the strains reach the brain via the blood or if their metabolites induce changes (Pinto-Sanchez *et al.,* 2017). Actually injecting small numbers of live organisms directly into a region of the brain will seem radical now, but we should not rule it out in the future. Selection of such inocula into the brain or indeed the gut, may be based upon the neurochemicals they produce, the direct or indirect interaction with or invasion of, host cells, the anti-inflammatory reaction they induce, and the ability of signalling molecules to navigate the vagus nerve and neuronal pathways.

Probiotic *L. acidophilus* NCFM has been shown to induce expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells, and mediate morphine-like analgesic functions in the rat gut (Rousseaux *et al.,* 2007). Interestingly, no confirmatory reports in humans have followed this work, despite the ten year gap. The *L. rhamnosus* JB-1 strain was identified for its neurobiotic properties, namely reducing GABA(Aα2) mRNA expression in the prefrontal cortex and amygdala, increasing GABA(Aα2) in the hippocampus, and reducing stress-induced corticosterone and anxiety- and depression-related behaviour (Bravo *et al.,* 2011). However, this has not so far translated to reducing anxiety in humans (Kelly *et al.,* 2016), perhaps another unfortunate result of using mice to predict human outcomes. The potential for this strain to reverse stress-induced gut dysmotility has been recognised, again in mice (West *et al.,* 2017), but translation to humans remains to be proven. It is out of the scope of this review to discuss the relevance of certain animal studies to humans, but clearly if humans are the ultimate target, clinical studies are the only true way to know if a therapy has merit.

The strain-dependency of probiotics has been illustrated in studies showing that *B. longum* 1714 was able to reduce stress, anxiety, depression-like behaviours and improve cognition in mice (Savignac *et al.,* 2014, 2015). This has been translated into humans, via a study of 22 volunteers in whom there were subtle improvements in hippocampus-dependent visuospatial memory performance, and enhanced frontal midline electroencephalographic mobility following four weeks of daily consumption of *B. longum* 1714 (Allen *et*

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al., 2016). This opens up potential new avenues to manage drug treatment-resistant patients.

In another case, a combination of strains has been tested in humans to reduce cognitive reactivity to sad mood (Steenbergen *et al.,* 2015). While some effect was noted, it is unfortunate that the basis for strain selection seemed to be 'the more the better' rather than what each actually could do, and no samples were taken in this study to explain the mechanisms leading to this effect. In an Iranian study of patients with major depressive disorder using three strains, 8-week treatment showed benefits in Beck Depression Inventory, decrease in serum insulin, and plasma glutathione concentrations, but not lipid profiles (Akkasheh *et al.,* 2016). Preclinical studies have shown the potential for prebiotic galacto-oligosaccharides (GOS) to increase the expression of key proteins involved in many neuropsychiatric disorders, after feeding in early-life and adulthood, as well as trump brain inflammation and anxiety following inflammation induced by lipopolysaccharides (Savignac *et al.,* 2016). These findings were confirmed in a small human study in which the product reduced the main stress hormone cortisol and attention towards negative bias, a component of anxiety (Schmidt *et al.,* 2015). The studies are small in size and the effects moderate, however, these data do show translatability from preclinical studies to humans and that there are some effects in healthy humans.

The ability of microbes directly or indirectly to stimulate or aid with regeneration of neurons could be a research track worth pursuing given the degenerative nature of many brain conditions. The literature is scarce on this topic, but interestingly sialidases, known to be produced by vaginal pathogens (Schellenberg *et al.,* 2016), have been found to significantly enhance motor function and increase axon sprouting in spinal cord injured animals, through blocking factors that inhibit the regeneration (Mountney *et al.,* 2010). In contrast, providing mice with human milk oligosaccharides containing sialyllactose prevents stress-induced anxiety-like behaviour, changes in intestinal bacteria, and reductions in hippocampal neurogenesis (Tarr *et al.,* 2015). It would be interesting to further study interactions between microbial sialidases, sialylated oligosaccharides, and nervous system functioning. For the treatment of multiple sclerosis, the use of immunoregulators to protect oligodendrocytes from further degeneration and enhance remyelination has been proposed (Rodgers *et al.,* 2013). Since some probiotic strains are efficient immunoregulators, it would be interesting to test them to enhance remyelination. Indeed, studies already suggest that the gut microbiota can influence myelination in the prefrontal cortex (Hoban *et al.,* 2016).

7. Pre-diabetes

In the final topics discussed, the question was asked what foods and microbes should pre-diabetics be eating and why? Current guidelines for prediabetic people are available and include a preference for low-glycaemic index carbohydrates. Inulin derivatives, whole-grain fibres, psyllium fibres and resistant starches (RS) have been long studied for their potential ability to prevent or tackle metabolic syndrome. Recent meta-analyses support the interest for some of these fibres. For instance, the degree of psyllium's glycaemic benefit was shown to be commensurate with the loss of glycaemic control (Gibb *et al.,* 2015). In addition, a higher intake of whole grain was associated with decreased risk of deteriorating glucose tolerance including progression from normal glucose tolerance to prediabetes by mechanisms likely tied to effects on insulin sensitivity (Wirström *et al.,* 2013). While the impact of RS on insulin sensitivity in small sets of various populations has been well-documented (Bindels *et al.,* 2015), the effectiveness of dietary inulin derivatives to control glycaemia still remains a matter of debate (Bonsu *et al.,* 2011). Other dietary interventions, such as the Mediterranean and DASH diets, may also constitute effective additions to a lifestyle-intervention program for prediabetic patients (Esposito *et al.,* 2014).

A nested case-cohort study following subjects for 11 years showed that consumption of yogurt delayed or decreased the risk of type II diabetes (O'Connor *et al.,* 2014). It seems too simplistic to imagine that a yogurt per day can prevent type II diabetes, but the result of this study warrants examination. It suggests that in addition to the effects of menaquinones (vitamin K_2) synthesised by animal tissue and present in the milk, and the low energy nature of the food, lactic acid bacteria may be performing metabolic tasks that modulate glucose and insulin levels. The inherent metabolic properties of bacteria in the gut has led to a number of new candidate probiotic species being identified. Four of these will be discussed in brief.

Akkermansia spp. have been negatively associated with metabolic disorders, appear to express anti-inflammatory attributes, and *Akkermansia muciniphila* which specialises in mucin degradation, has been shown to protect mice from diet-induced obesity and atherosclerosis (Derrien *et al.,* 2016). Despite the species not having a safe history of use in humans, studies are underway to determine its potential to alleviate metabolic disease in overweight and obese people. It seems most likely that the effects will be retained in the gut, but distant site effects warrant investigation given the prevalence of the species in healthy people. The higher abundance of *A. muciniphila* in eczematous infants provides a note of caution, since damage to mucus and the integrity of the intestinal barrier would pose a safety risk for many other diseases (Zheng *et al.,* 2016).

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Likewise, *Faecalibacterium prausnitzii*, reduced in patients with Crohn's disease (Sokol *et al.,* 2008), has been associated with atopy and eczema in infants (Zheng *et al.,* 2016), yet its ability to produce butyrate, along with *Roseburia* spp., has been associated with healthy kidneys. Indeed, both *F. prausnitzii* and *Roseburia* serve as 'microbiomarkers' of healthy kidneys, according to Jiang *et al.* (2016). The depletion of both *F. prausnitzii* and *Akkermansia* spp. in relative abundance in nasal secretions has been associated with a history of acute sinusitis, again attracting interest in propagating these species as probiotics. The problem is that associations and differences in abundance are insufficient to prove cause and effect, and the consequences of applying these bacteria, even to the nose, need to be carefully examined before they could be considered probiotics. Even candidate prebiotic foods, such as amaranth, can stimulate *F. prausnitzii* and *Roseburia intestinalis* (Gullón *et al.,* 2016), thereby providing a means to look for any adverse outcomes at local and distant sites. The approach requires somewhat of a balancing act, as illustrated in a recent paper by Endesfelder *et al.* (2016). In this, they hypothesise that increased abundance of *Akkermansia* to the detriment of *Bacteroides* would result in increased butyrate production from the co-fermentation of acetate, thereby protecting against the development of anti-islet cell autoantibodies.

Another interesting gut organism, *Oxalobacter formigenes*, has the ability to degrade oxalates and reduce the risk of kidney stone formation (Allison *et al.,* 1985; Sidhu *et al.,* 1999). Given the relative absence of the species in at least young American adults (Barnett *et al.,* 2016), the issue is how to deliver and maintain it by providing enough oxalate for its propagation without increasing the risk of the oxalate adsorbing and inducing calculi formation in the kidneys? This is not an easy matter to decipher, but with no reported side effects from *O. formigenes* consumption (Hoppe *et al.,* 2011), further studies should be performed. Having stated that, the lack of effect reported by Hoppe *et al.* (2011) on urinary oxalate secretion following probiotic consumption, is rather disappointing.

8. In summary

There is mounting evidence that microbes at one site can affect the host at other sites. The gut microbiome link with the milieu of the brain, respiratory and urogenital tracts, heart and skin represent exciting discoveries that could lead to new approaches to health maintenance, disease prevention and even treatment. We have taken for granted the ease with which antibiotics adversely impacted bacteria, but these drugs provided evidence that microbiome manipulation is possible. If less damaging methods, such as probiotics and prebiotics and in some cases FMT, can be used to influence local and distant microbial communities, the potential for patient care is enormous. Many of the conditions discussed here are chronic in nature, costly to the healthcare system, and debilitating to the patient and his/her family. The members of this workshop strongly urged funding agencies to prioritise funding for these areas, advocated careful selection of microbial strains, and encouraged identification of well-defined human cohorts to allow acquisition of insightful data.

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