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DIET AND IMMUNITY: TARGETING THE GUT MICROBIOTA

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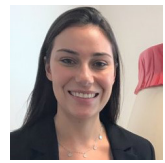

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The term 'microbiota' refers to the community of microorganisms living in and on the human body. In particular, the community of microorganisms living in the gastrointestinal tract is termed the 'gut microbiota'.

Our relationship with the gut microbiota is symbiotic; we provide an environment for the microorganisms in which to live and nutrients for them to feed on. In turn, they participate in several functions that are important for human health, such as fermentation of non-digestible dietary fibres, production of vitamin K and prevention of colonisation by pathogenic microorganisms.[1]

The gut microbiota also plays an important role in the development and homeostasis of the immune system.[1] The gut is the largest immune organ of the body, with over half of all immunologically active cells in the body located around the gut.[2] This structure is termed the 'gut-associated lymphoid tissue' (GALT) and sits beneath the mucous layer comprising a single layer of epithelial cells, the lamina propria, and muscularis mucosae, which together separate the gut lumen from the circulatory system.[3]

The immune system samples antigens from the foods we consume and microorganisms we come in to contact with, which allows the body to differentiate between what is safe (determining what we can tolerate) and what is potentially harmful (triggering an appropriate immune response).[4]

The relationship between the gut microbiota and immune system is important throughout life. Early life events, such as mode of delivery (vaginal vs caesarean section)[5] and mode of feeding (breastfed vs formula fed),[6] can influence which microbes colonise the infant gut and, therefore, the development of the immune system. As we age, many factors can affect both our gut microbiota and immune health. Here we explore some of these factors and, in particular, if dietary interventions targeting the gut microbiota can be harnessed to mediate the negative effects on the immune system.

AGEING AND VACCINE RESPONSE

Although the gut microbiota remains relatively stable throughout adulthood, changes have been observed in older

adults. Studies have shown that there is greater inter-individual variation and often report a reduced diversity and a shift in the dominant species present in the gut microbiota of older adults.[7,8]

Analysis of the gut microbiota of elderly Irish adults (aged 65 years and older) identified a phylum level shift in the Firmicutes:Bacteroidetes ratio, shifting from predominantly Firmicutes in younger adults to Bacteroidetes in older adults.[8] These changes are largely driven by dietary intake, which correlates to where people are living: older adults living in the community have a gut microbiota more similar to young adults, which reflects a more healthy, diverse diet; in contrast, older adults living in residential care have the greatest difference in their gut microbiota mirrored by a change in their diet towards one that is less diverse with a low fibre and a moderate to high fat intake.[9]

As we age, there is a natural decline in immune function. This is in part driven by involution of the thymus and a reduced production of naïve T-cells available to respond as effectively to new infections and vaccinations.[10] As a result, older adults are at higher risk of becoming infected and suffering from complications associated with infections, such as influenza (flu). In the UK and Ireland, the flu vaccine is offered free of charge to at-risk populations, including those 65 years old and over, as a preventative step against flu infection.

Because of the close interplay between the gut microbiota and immune system, researchers have explored dietary interventions that target the gut microbiota as a potential strategy to improve vaccine efficacy. A systematic review and meta-analysis of 20 randomised controlled trials, with a total of 1979 participants, investigated the administration of either prebiotics and probiotics alone or in combination (synbiotics) in subjects receiving the flu vaccine, and found significantly improved seroconversion rates compared with those in the control group, particularly in healthy older adults (H1N1 strain Odds Ratio (OR)=2.93 [95% CI = 1.47-5.87, $p<0.005$], H3N2 strain OR=3.68 [95% CI = 1.11-12.25, $p<0.05$], B strain OR=2.69 [95% CI = 1.51-4.78, $p<0.005$]).

These results suggest that dietary strategies targeting the gut could be effective approaches to improve efficacy of the flu vaccine in healthy older adults, although the authors acknowledge that larger randomised-controlled trials focusing on optimal dose, duration and effect of synbiotics are required to validate this.[11]

SMOKING AND IMMUNITY

Cigarette smoke is an immunosuppressant and can impair the body's immune defences.[12] In a large-scale cohort study of 12,249 participants, it was found that current smokers had a significantly lower natural killer (NK) cell activity compared with non-smokers and former smokers ($p=0.039$ and $p<0.001$, respectively), and that NK cell activity decreased as the number of cigarettes smoked per day increased – even after adjusting for age and sex.[13]

Cigarette smoking does not only affect the tissues and organs of the human body, but also the human gut microbiota. A cross-sectional study, including 758 men, found a significant difference in beta diversity (a measure of how samples differ from one another) of the microbiota between current smokers and both never and former smokers ($p=0.017$ and $p=0.011$, respectively). Current smokers had a significantly increased proportion of the phylum Bacteroidetes and a decreased proportion of the phyla Firmicutes and Proteobacteria compared with never smokers.[14]

As smoking has been shown to negatively affect both the immune system and gut microbiota, researchers have explored whether targeting the gut microbiota through diet can positively impact immune status. Male smokers receiving *Lactobacillus casei* Shirota daily for three weeks had significant increases in NK cell activity.[15] Whilst people should be encouraged to abstain from smoking for overall health, this

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study shows how dietary interventions may improve the immune status, specifically the NK cell activity of smokers.

OBESITY AND INFLAMMATION

Individuals with obesity experience impaired immune function, which is particularly evident in the current pandemic: individuals with obesity have a greater risk of acquiring COVID-19, requiring hospitalisation, and having poorer outcomes and higher mortality rates compared with non-obese individuals.[16]

Obese individuals show an accumulation of pro-inflammatory immune cells in adipose tissue, which increases inflammatory cytokines – serum CRP, IL-6 and TNF-α – resulting in chronic low-grade inflammation.[16,17] The gastrointestinal tract and its microbiota have been suggested as drivers of this inflammation.

Lipopolysaccharide (LPS) is a component of the cell wall of gram-negative bacteria. Translocation of LPS from the gut into the circulatory system, termed *endotoxemia*, activates an inflammatory response.[18,19] Whilst most research has been conducted in animal models, evidence shows that high-fat diets induce changes in plasma LPS levels and increase inflammation.[20] Interestingly, when the gut microbiota is altered using broad-spectrum antibiotics, mice show a reduction in plasma LPS levels and endotoxemia following a high-fat diet, which suggests an important role for the gut microbiota in this relationship.[21]

Following the evidence from animal studies that shows the gut microbiota can play a role in diet-induced inflammation, the research in humans is growing, with positive outcomes following increased fibre intakes.

A study investigating the effect that dietary fibres have on inflammation in individuals with overweight or obesity found that consuming three servings per day of wholegrains or fruit and vegetables significantly reduced LPS-binding protein ($p<0.05$ and $p<0.01$, respectively) and markers of inflammation; TNF-α (wholegrains group $p<0.001$) and IL-6 (fruit and vegetables group $p<0.01$).[22]

Specific dietary fibres that are known to have direct effects on the gut microbiota have also been researched for their role in endotoxemia. Prebiotic supplementation (16g inulin/oligofructose mix) daily for three months lowered serum LPS whilst also modifying the gut microbiota, including increasing Firmicutes and Actinobacteria, in obese women.[23]

ANTIBIOTICS AND INFECTIONS

The human microbiota is able to maintain symbiosis by monitoring microorganisms at the epithelial cell surface, thereby limiting pathogen translocation and tissue inflammation.[24] However, antibiotic perturbation of the microbiota can disrupt the integrity of these intestinal defences.

Once an antibiotic treatment has ended, the microbiota may present a certain degree of resilience and be capable of restoring its microbial composition. However, the initial state often does not entirely recover and antibiotic-induced changes in the microbiota may remain after long periods of time.[25,26]

Antibiotics will continue to be an important tool in fighting pathogenic bacteria to avoid infection; however, strategies are required to ensure integrity of the human microbiota and in turn its immune response. The administration of live bacteria through probiotics and faecal microbiota transplantation (FMT) holds promise in improving resilience of the microbiome to antibiotic treatment.

A systematic review with meta-analysis, including 21 randomised controlled trials, compared placebo or no treatment with co-administration of *Saccharomyces boulardii* and antibiotics. There was a reduced risk of antibiotic-associated diarrhoea from 18.7% to 8.5% (Risk Ratio (RR)= 0.47; 95% CI: 0.38-0.57), and sub-group analyses showed this was significant for both children (RR=0.43, 95% CI: 0.3-0.6) and adults (RR=0.49, 95% CI: 0.38-0.63).[27] Probiotic administration may be an effective strategy against dysbiosis, but more specific data are needed to determine the most effective probiotic for particular patient as well as disease groups, especially as individual variation in the composition of the gut microbiota is apparent.[28]

It is well established that faecal microbiota transplantation (FMT), which involves the transfer of faecal microorganisms from a healthy donor to a patient, shows successful outcomes

in *Clostridioides difficile* infections (CDI).[29] In a systematic review with meta-analysis, including 37 studies, highlighted that FMT was more effective than the antibiotic 'vancomycin' in resolving recurrent and refractory CDI (RR=0.23, 95%CI: 0.07-0.80). A significant difference was observed between lower gastrointestinal (GI) and upper GI delivery of FMT of 95% (95%CI: 92%-97%) and 88% (95%CI: 82%-94%) respectively (*P*=0.02). This analysis shows that FMT is a promising strategy against opportunistic, antibiotic-resistant bacterial infections.[29]

Probiotics and FMTs bring new opportunities to manage pathogenic infections treated with antibiotics while limiting damage to the microbiota.

CONCLUSION

The interplay between the gut microbiota and immune system is important throughout life, but there are many factors that can impact on this relationship. Dietary interventions that target the gut microbiota show promise as strategies to improve immune status.

References

1 Jandhyala et al (2015). *World Journal of Gastroenterology* 21(29): 8787-8803
2 InformedHealth.org (2020). What are the organs of the immune system? [Online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK279395/ [Accessed 21 October 2020]
3 Peled et al (2016). *Blood* 128(2): 2395-2402
4 Chassaing et al (2014). *Biomedical Journal* 37(5): 246-258
5 Francino (2018). *Annals of Nutrition and Metabolism* 73 (Suppl 3): 12–16
6 Ho et al (2018). *Nature Communications* 9: 4169
7 Woodmansey (2006). *Journal of Applied Microbiology* 102(5): 1178-1186
8 Claesson et al (2011). *PNAS* 108 (Suppl 1): 4586-459
9 Claesson et al (2012). *Nature* 488(7410): 178-84
10 Gui et al (2012). *Ageing and Disease* 3(3): 280-290
11 Lei et al (2017). *Nutrients* 9(11): 1175
12 Qui et al (2017). *Oncotarget* 8(1): 268-284
13 Jung et al (2020). *Journal of Cancer Prevention* 25(1): 13-20
14 Lee et al (2018). *Journal of Clinical Medicine* 7(9): 282
15 Reale et al (2011). *British Journal of Nutrition* 108: 308-314
16 Popkin et al (2020). *Obesity Reviews* doi: https://doi.org/10.1111/obr.13128
17 de Heredia et al (2012). *Proceedings of the Nutrition Society* 71: 332-338
18 Pendyala et al (2012). *Gastroenterology* 142(5): 1100-1101.e2
19 McLaughlin et al (2017). *Journal of Clinical Investigation* 127(1): 5-13
20 Cani et al (2007). *Diabetes* 56(7): 1761-1772
21 Cani et al (2008). *Diabetes* 57(6): 1470-1481
22 Kopf et al (2018). *Nutrition Journal* 17: 72
23 Dewulf et al (2013). *Gut* 62(8): 1112-1121
24 Belkaid and Hand (2014). *Cell*, 157(1): 121-141
25 Dethlefsen and Relman (2011). *PNAS*, 108(1): 4554-4561
26 Jernberg et al (2007). *The ISME Journal* 1:56-66
27 Szajewska and Kołodziej (2015). *Alimentary Pharmacology & Therapeutics* 42(7): 793-801
28 McFarland et al (2018). *Frontiers in Medicine* 5: 24
29 Quraishi et al (2017). *Alimentary Pharmacology & Therapeutics* 46(5): 479-493

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Questions relating to: *Diet and immunity: targeting the gut microbiota* *Type your answers below, download and save or print for your records, or print and complete by hand.*	
Q.1	Give two examples of functions of the gut microbiota.
A	
Q.2	What phylum level change is observed in the gut microbiota of older adults?
A	
Q.3	What dietary interventions improved seroconversion rates in individuals receiving the flu vaccine?
A	
Q.4	How does the composition of the gut microbiota differ in current smokers compared to former/ never smokers?
A	
Q.5	What innate immune cell, in particular, has shown to be suppressed in those who smoke cigarettes?
A	
Q.6	What component of gram-negative bacteria can cause endotoxemia?
A	
Q.7	How many servings of wholegrains or fruits and vegetables were shown to reduce inflammation?
A	
Q.8	After an antibiotic treatment, does the gut microbiota completely restore itself?
Q.9	What are two promising intervention strategies that can be used to improve resilience of the microbiome to antibiotic treatment?
Please type additional notes here . . .	