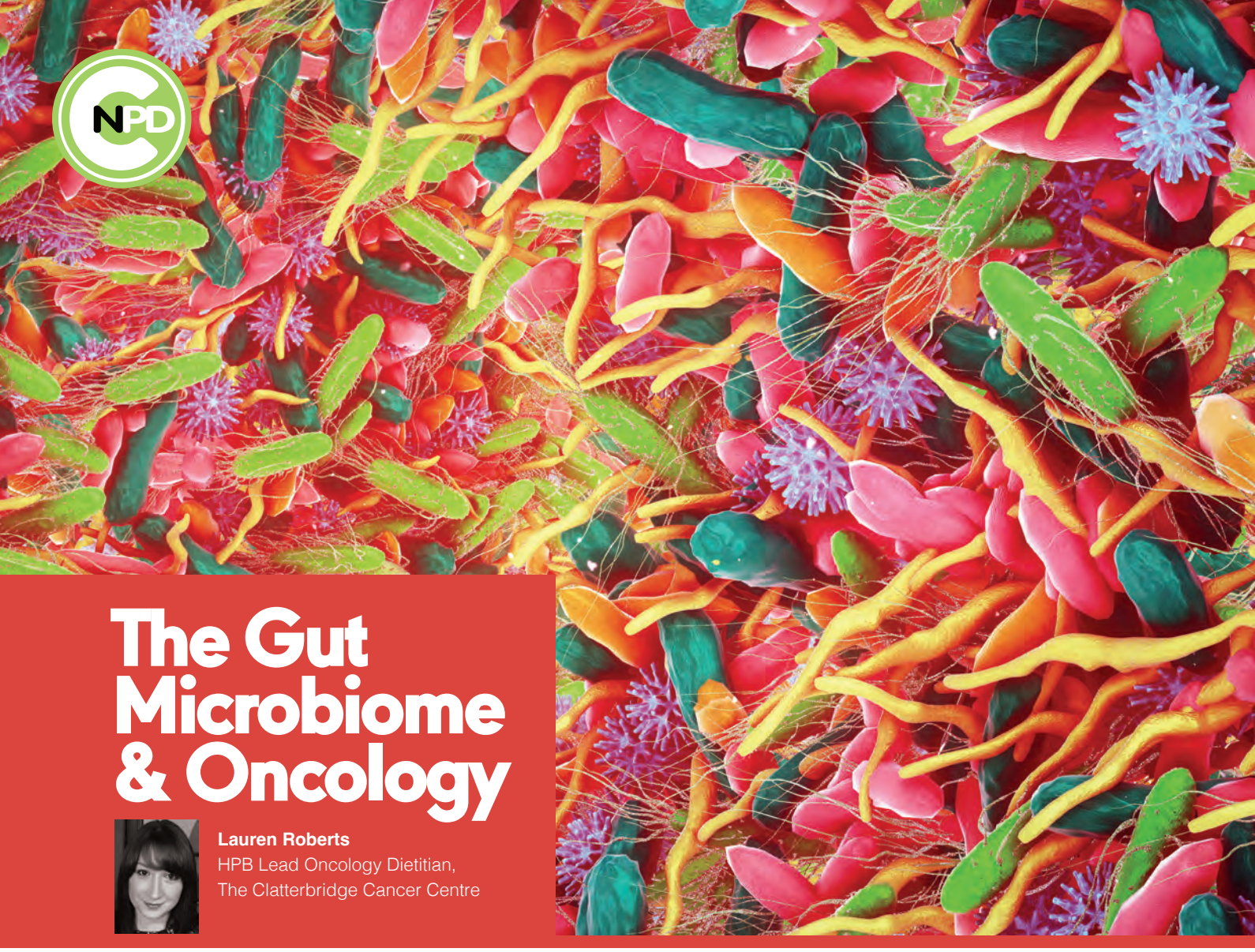

The Gut Microbiome & Oncology

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The human gastrointestinal tract is a reservoir of a complex and dynamic population of microorganisms (the gut microbiota) mainly containing bacteria, as well as viruses and fungi, which exert a significant influence on the host during homeostasis and disease.[1] The composition of the gut microbiome is susceptible to changes, with many factors, such as stress, poor diet, gastrointestinal diseases and obesity, leading to imbalances.[2] These imbalances can lead to proinflammatory immune responses and are thought to initiate disease processes, like cancer.

The gut microbiome & cancer

It is thought that the gut microbiome has a dual impact on cancer, contributing to both development and treatment. Mechanisms such as inflammation, immune regulation, metabolism and genotoxicity dysbiosis, defined as an imbalanced gut microbiota, have been implicated as major drivers of cancer development. The main pathogenic processes are thought to be due to reduced intestinal barrier integrity, persistent inflammation, immunological dysfunction and metabolic abnormalities. These processes disturb systems such as the gut-brain and gut-liver axes, exacerbating systemic dysfunction and driving disease development.[3] The gut microbiome has been linked with the pathogenesis of cancers, including breast, colorectal, ovarian and prostate cancers.[4]

Diet & the gut microbiome

Diet plays an important role in regulating the microbiome over the long and short term. Varying compositions of diet can lead to changes in microbiota profiles; an unbalanced diet consumed over a long period of time, coupled with an unhealthy lifestyle can leave traces of evidence on the microbiota. Studies have demonstrated that individuals that are overweight or obese tend to have a lower diversity of gut microbiome.[5]

Long-term dietary patterns, such as the consumption of vegetables, fibre and omega-3 fatty acids, are associated with increased microbial diversity and an increased abundance of short chain fatty acid (SCFA) fermenters, such as butyrate, acetate and propionate, with positive effects on the host's metabolic functions. Fibre rich diets have been shown to increase commensal bacteria and support with modulating inflammation, gut integrity and tumorigenesis.[6]

The types and amounts of SCFAs are determined by the composition of gut microbiota and quantities of dietary fibres consumed. Non-digestible complex carbohydrates, also named microbiota-accessible carbohydrates (MACs), can be found in cereals, fruits and vegetables, with inulin and oligofructose found in garlic, onions, artichokes, asparagus, bananas and chicory root. There is growing evidence that MACs being made available for gut microbiota as prebiotics promote the growth of *Lactobacillus* and *F. prausnitzii* to metabolise into SCFAs.[5]

Probiotics

Probiotics are defined as *'live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.'* Strains like *Lactobacillus* and *Bifidobacterium* have demonstrated potential in cancer prevention and therapy by modulating immune responses, reducing inflammation and increasing gut barrier integrity.[3, 7, 8]

It is thought that probiotics contribute to the increase in daily production of SCFAs. The presence of SCFAs in the lumen of the large intestine, for instance, have been demonstrated to inhibit the growth of pathogens (e.g. *Salmonella Typhimurium* in the presence of propionate and butyrate). Studies have demonstrated that butyric acid is associated with the prevention of colorectal cancer by improving the intestinal barrier through the increase in mucus production and the proliferation of healthy cells.[9] Slizewska K, *et al.*[2] summarised the anti-carcinogenic activity of probiotics:

- Modification of the intestinal microbiota composition
- Metabolic activity of the intestinal microbiota
- Production of compounds with anticarcinogenic activity, such as SCFAs and conjugated linoleic acid
- Improvement of the intestinal barrier
- Inhibition of cell proliferation and induction apoptosis in cancer cells
- Influence on other mutagenic and carcinogenic factors
- Binding and degradation of carcinogenic compounds present in the intestinal lumen
- Immunomodulation
- Improvement of the intestinal barrier
- Influence on other mutagenic and carcinogenic factors.

Prebiotics

Prebiotics are unique dietary components that selectively feed beneficial gut bacteria through fermentation. Common types of prebiotics include inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and resistant starches. They act as fuel for these microbes to help support a healthy and diverse gut microbiome. Prebiotics are metabolised by bacteria in the colon, producing SCFAs. As discussed earlier, these SCFAs (acetate, propionate and butyrate) serve as an energy source for colonocytes (colon cells) and contribute to overall health. It is thought that they also help support gut bacteria composition and function, favouring the growth of beneficial strains, such as *Bifidobacterium* and *Lactobacillus*.[10]

Symbiotics

Symbiotics combine probiotics and prebiotics, yielding synergistic benefits with key mechanisms of action being:[11]

- Stabilising microbial diversity, enriching *Lactobacillus* and *Bifidobacterium*, and suppressing dysbiosis, therefore lowering cancer risk
- Enhance NK cell, macrophage and Treg activity, reduce proinflammatory cytokines and promote SCFA-mediated HDAC inhibition, leading to apoptosis and oncogene suppression
- Bind mutagens, suppress bacterial pro-carcinogenic enzymes, induce apoptosis, inhibit angiogenesis and even modulate hormone-driven cancers
- Potentially alleviate treatment-related side effects (e.g. mucositis, dysbiosis, fatigue).

Probiotics, prebiotics & symbiotics in cancer therapies

Pro-, pre- and symbiotics may potentially be efficacious in reducing complications associated with chemotherapy, radiotherapy, immunotherapy and surgery in patients with cancer. Pro-, pre- and symbiotics can modulate host metabolism and gut microbiota and potentially help prevent cancer and modulate the adverse effects (AEs) of treatment. Numerous studies on this role have reported inconsistent results, although evidence of their use in modulating AEs resulting from oncology therapies. However, it is still unknown whether pro-, pre- and symbiotics might also upset microbiota balance, increasing potential infection risk in immunocompromised patients with cancer.

Chemotherapy

Increasing evidence suggests that the gut microbiome is associated with chemotherapy outcomes and undesirable events. Currently, there are few effective biomarkers available to predict and/or proactively manage chemotherapy-induced side effects.[4] Gastrointestinal toxicities, including chemotherapy-induced diarrhoea, is one of the most common side effects of chemotherapy, leading to suspension or attenuation of many treatment regimens, which can have a negative influence on prognosis, potentially resulting in mortality. It is thought that a possible contributing factor to diarrhoea is that the normal protective gut microflora is altered.[12]

Tong J, *et al.*[13] examined the changes in gut microbiota in 18 ovarian cancer patients that had undergone surgery and chemotherapy. The study found that the composition and diversity of intestinal microbiota postoperatively significantly differed from that preoperatively. It revealed that certain bacterial genera *Ruminococcus* ($p < 0.05$), *Ruminococcaceae unclassified* ($p < 0.01$), *Desulfovibrio* ($p < 0.05$), *Clostridiaceae unclassified* ($p < 0.001$) and *Lactobacillus* ($p < 0.05$) significantly correlated with gastrointestinal reactions. However, the validity and reliability of study results are questionable due to the small sample size with no robust regimen for the frequency stool samples were taken pre, post op and during chemotherapy, and other variables (e.g. antibiotic use) likely influencing results in the post-operative period.[13]

The efficacy of a high potency multi-strain probiotic on chemotherapy-induced diarrhoea in cancer patients receiving fluropyrimidines and/or irinotecan-based therapy was investigated in a phase II/III, randomised, double blind, placebo-controlled trial. 291 patients were included in the study with primary endpoint being incidence of grade 3 and grade 4 diarrhoea. Enrolled patients were randomised to receive 1 sachet (900 billion CFU/sachet of 4 strains of *Lactobacillus*, 3 strains of *Bifidobacteria* and 1 strain of *Streptococcus thermophilus*) or a placebo (corn starch), starting 14 days before chemotherapy and continued till two weeks after end of chemotherapy cycle [3]. Both the study and the control group had similar cancer site and chemotherapy regimens, with body weight between the two arms comparable at all visits. The study concluded that there was a limited role of the probiotic in reducing incidence of severe chemotherapy-induced diarrhoea. However, it was able to significantly reduce all grades of diarrhoea episodes, levels of vascular endothelial growth factor, faecal calprotectin and clusterin, suggesting probiotics may be useful as an adjunct in managing chemotherapy induced diarrhoea.[14]

A network meta-analysis further suggests that symbiotics reduce surgical site infections, pneumonia, sepsis, hospital stays and antibiotic use, which was also supported in another study reporting similar results with the use of perioperative administration of symbiotics significantly reducing postoperative infection rates in 91 patients with colorectal cancer. The study highlighted that given infections are common in individuals with cancer on treatment and the role of the gut microflora in immunity, pro-, pre- and symbiotics need to be evaluated not only for their infection prevention efficacy, but also for their safety.[15, 16]

The safety of using probiotics was evaluated in a previous systematic review that included 1530 participants, with results not raising any safety issues with probiotic use. The study suggested that probiotics may help reduce the severity and frequency of diarrhoea in patients with cancer and the need for antidiarrheal medication. Within the study, there were 105 AEs among consumers of probiotics and 145 among non-probiotic consumers. However, given the heterogeneity of the malignancies and treatment regimens included, it was difficult to ascertain which AEs were specifically associated with probiotic consumption. The study found no deaths were attributed to probiotic-associated infections in the intervention groups.[17]

Radiotherapy

Radiotherapy can lead to radiation-induced side effects which can occur many months or years after treatment. Radiation to the pelvic area can cause changes in bowel habit, which can be permanent and have a significant impact on well-being and quality of life. Wang Z, *et al.*[18] investigated the gut microbiome and radiation enteritis during pelvic radiotherapy and suggested that dysbiosis of gut microbiota may contribute to development and progression of radiation enteritis. This potentially highlights the importance of the gut microbiota and its role as a biomarker in predicting treatment effects.[18]

A randomised double-blind controlled trial analysed the impact of a probiotic supplement (*Lactobacillus acidophilus* LAC-361 and *Bifidobacterium longum* BB-53) on moderate and severe treatment-induced diarrhoea during pelvic radiation in 246 individuals. Patients recorded their gastrointestinal symptoms daily and were reviewed by a registered dietitian and radiation oncologist every week during treatment. The study concluded that standard dose of the probiotic supplement may reduce radiation-induced grade 2-4 diarrhoea at the end of the treatment of patients with pelvic cancer. In patients operated on before radiotherapy, a standard dose of probiotics suggested reduced radiation induced grade 4 diarrhoea. Interestingly, the study highlighted that nutritional intervention by a registered dietitian helped reduce global digestive symptoms, highlighting the role of dietetics in this population.[19]

Jiang C, *et al.*[20] evaluated the effect of a probiotic combination on the severity of oral mucositis (OM), a common, unpreventable complication induced by radio-chemotherapy in patients with locally advanced nasopharyngeal carcinoma undergoing concurrent radio-chemotherapy (CCRT). 99 patients were randomly assigned (2:1) to receive a probiotic combination or placebo with severe OM (grade 3 or higher) as the primary endpoint. Individuals taking the probiotic combination showed a significant reduction in the severity of OM, suggesting that the severity of OM is reduced through modification of gut microbiota.[20]

Immunotherapy

Cancer immunotherapy is an emerging field in cancer treatment, which aims to strengthen or activate immune response against tumour cells. Immune checkpoint inhibitors (ICI's) (e.g. ipilimumab, nivolumab, pembrolizumab, durvalumab, atezolizumab), are frequently used immunotherapy treatments. The gut microbiome has been linked with therapeutic responses to ICIs. Clinical trials are underway to explore the impact of factors such as faecal microbiota transfer (FMT), probiotics, prebiotics and several dietary interventions on patients receiving ICIs. Human studies on the relationship between ICIs and the gut microbiome so far have focused on melanoma, lung cancer and renal cell carcinoma.[21]

An observational study by Spencer, *et al.* reported probiotic intake had no effect on the survival outcomes of 158 patients with melanoma treated with ICI therapy.[22] In contrast, patients with renal cell carcinoma orally supplemented with bifidogenic live bacterial products and treated with dual ICI (nivolumab and ipilimumab) therapy showed longer performance free survival (PFS) than those that were not supplemented.[23]

ICI-induced colitis is a common gastrointestinal side effect complicated with immunotherapy. In human studies, the development of ICI-induced colitis is thought to be associated with decreased diversity and a shift in composition of gut microbiota. For example, in patients with melanoma following anti-CTLA-4 treatment, Firmicutes (e.g. *Faecalibacterium prausnitzii* and *Gemmiger formicilis*) were associated with the occurrence of ICI-induced colitis, while *Bacteroidetes* were associated with no occurrence of colitis.[24]

Prebiotics, like dietary fibre, are generally accepted as safe to alter the microbiota. However, there is no robust evidence that prebiotics protect against ICI-induced colitis. Studies highlight that prebiotics might possibly play a protective role in ICI-induced colitis through the immunoregulatory role of SCFA which could induce colonic Treg proliferation.[25]

Lee KA, *et al.* recommends that individuals undergoing immunotherapy should focus on diversity, variety, plant-based foods, protein and dietary fibre and that individuals before and during ICI should have access to nutrition support.[26]

Faecal microbiota transplantation & immunotherapy

FMT is a method that directly manipulates the recipient's gut microbiome. Donor stool is transferred to the recipient's gastrointestinal (GI) tract to induce therapeutic effects. Early studies suggest that FMT may have therapeutic potential, converting ICI non-responders into responders. The MITRE study will explore and validate a microbiome as a biomarker of efficacy and toxicity in a larger scale prospective study across several different cancer types receiving immune checkpoint inhibitor therapy.[27]

Summary

Understanding the composition and function of the microbiota may support as a biomarker for cancer prognosis, predicting treatment efficacy and potential adverse effects, thereby facilitating personalised medicine strategies for individuals with cancer. Evidence emerging is promising, however, further robust clinical studies are required to support routine application in clinical practice.

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