The gut microbiota and its impact on cancer treatment side effects

Side effects related to cancer treatments and the use of antibiotics are a significant burden to many people with cancer. There is emerging evidence indicating a link between the gut microbiota and the severity of these side effects. Dr Hannah Wardill and researchers at the University of Adelaide, Australia, provide novel insights into the pathogenesis of treatment complications, including diarrhoea, weight loss, anorexia, infection, and fever. The team explore and focus efforts on the potential of faecal microbiota transplantation (a 'poo transplant') to restore favourable gut microbiota and thus prevent and reverse these negative effects.

The human gut microbiota is comprised of a diverse number of microorganisms including bacteria, viruses, archea, and fungi. Astonishingly, it is estimated that there are over 1,000 different bacterial species colonising the gut, falling into two broad categories: commensal bacteria, and pathogenic bacteria.

Commensal bacteria and the human gut are an example of a mutualistic relationship, in which both species benefit from and influence one other. Commensal gut bacteria process materials that are indigestible, help prevent colonisation of the gut by pathogens, and interact with the host immune system. In exchange, the host provides nutrients and an environment in which to live and flourish.

The number of bacteria in the human gut is staggeringly high. With such abundance, the genetic material of the microorganisms (the microbiome) is more than the human genome. Furthermore, there is high individual variability in microbiota composition, sparking an interest among researchers as to how this unique characterisation can affect our health and risk of disease.

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Research shows that diseases such as cancer, autism, depression, and Parkinson's disease, among others, are associated with particular microbiota composition illustrating the far-reaching effects of gut microbiota in the body.

Dr Hannah Wardill and the University of Adelaide Supportive Oncology Research Group research team have conducted several pioneering animal studies to understand the role of gut microbiota in developing chemotherapy-induced side effects.

HOW CANCER THERAPY DAMAGES THE GUT

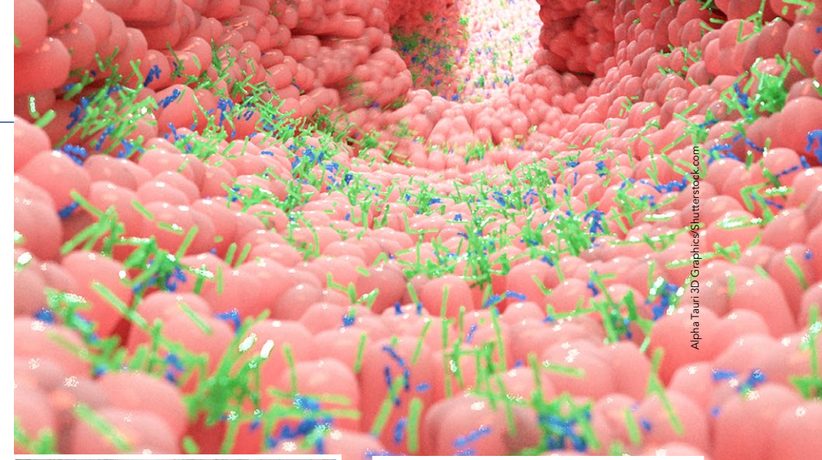
Damage to the lining of the gut or 'mucosal barrier injury' (MBI) caused by anti-cancer drugs is a major problem for people undergoing cancer therapy, and their care teams. Disruption to the mucosal barrier can result in leakage of pathogenic bacteria into the bloodstream, potentially resulting in sepsis. Symptoms such as diarrhoea can have serious physiological and psychological impacts for patients, impacting their ability to go about their daily lives. Furthermore, such disruption may make treatment intolerable to patients, forcing dose reductions or delays in their treatment and thus impacting their likelihood of remission.

Many cancer treatments have been shown to alter the composition of the gut microbiota both acutely and chronically, leading to decreased commensal bacteria populations and susceptibility to opportunistic pathogens. Because of the microbiota's potent control over the immune system, understanding how this contributes to MBI and associated symptoms is an area of great scientific interest.

A study by the research team focused on toll like receptor (TLR) signalling, specifically the role of TLR4, in MBI caused by irinotecan (a chemotherapy drug used in the treatment of solid tumours). TLRs are membrane proteins which recognise substances and alert the immune system, triggering a response. TLR4 recognises gram negative bacteria and eliciting an extreme immune response which exacerbates intestinal injury initially caused by irinotecan.

The researchers explored this in wild type and TLR4 knockout rodents (in which the TLR4 gene is deleted). The study was the first to demonstrate that deletion of TLR4 decreases apoptosis (programmed cell death) of crypt epithelial cells as well as reducing the symptoms and histological markers of intestinal injury. Additionally, the study revealed a corresponding novel finding of improved pain markers in TLR4 knockout rodents, confirming the hypothesis that TLR4 has a dual role in mediating irinotecan intestinal injury and pain. By blocking the communication between gut microbiota and the immune system via TLR4 deletion, the study confirms the role of gut microbiota in drug-related intestinal injury and the development of side effects. The data highlights TLR4 as a potential therapeutic target pending further research on any potential concomitant effects.

Wardill and colleagues have also developed a breakthrough translational animal model of melphalan-induced MBI which accurately reflects the clinical interplay between the gut and immune system in people with blood cancer. This patient population is particularly vulnerable due to the intensity of melphalan treatment, which is often given at very high doses to ablate their immune system and resident cancer cells. Using this model, Wardill and her team confirmed the role of cytotoxic injury in inducing MBI, including the mechanisms involved (such as changes to microbial composition, recruitment of neutrophils and subsequent inflammation). Importantly, this model showed that MBI causes a hostile environment that cannot support commensal bacteria, resulting in pathogenic blooms. Such events can cause bacteria to translocate into the blood thus causing bloodstream infections and fever. The team recently used this model to identify and target aberrant inflammatory responses using the drug anakinra, which was able to strengthen the mucosal barrier and control febrile events. This research was undertaken at University Medical Centre Groningen in collaboration with Radboud University Medical Centre (The Netherlands). This drug has now moved into Phase IIB trial led by Prof Nicole Blijlevens, who has spearheaded the concept of febrile mucositis for more than a decade.



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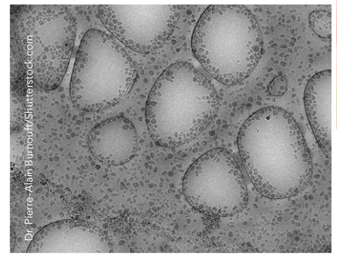
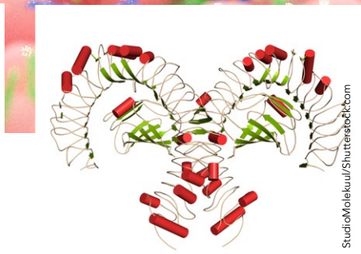


Dr. Pierre-Alain Bunnoth/Shutterstock.com

Irinotecan is a chemotherapy drug, here shown in liposome.



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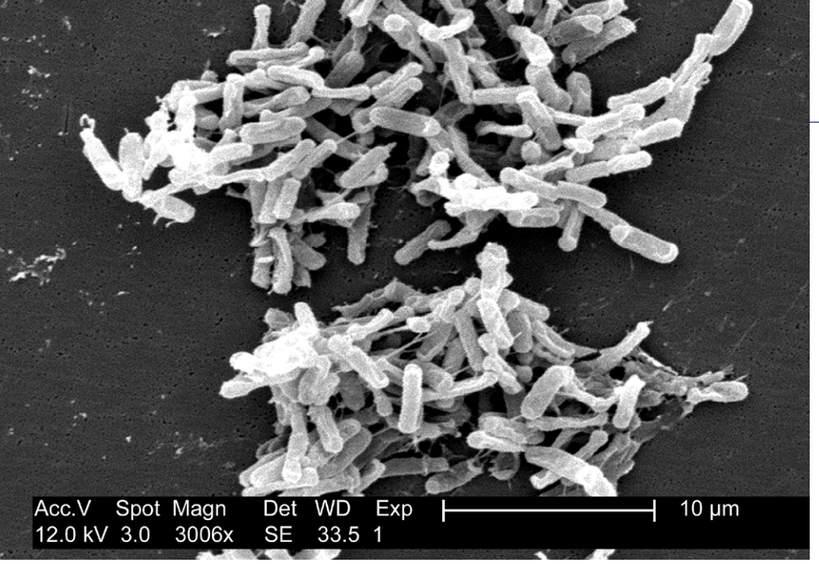
TLRs alert the immune system and trigger a response.

THE POTENTIAL FOR FAECAL MICROBIOTA TRANSPLANTATION

With the mounting evidence suggesting the microbiota is a critical mediator of multiple side effects, including diarrhoea, pain and infection, has prompted enthusiastic investigation of how to maintain a healthy gut microbiota during cancer treatment. Naturally, some of the earliest efforts focused on the use of probiotics, however, the lack of evidence for the benefits of probiotics is driving researchers to focus efforts on other therapies. One such potential therapy is faecal microbiota transplantation (FMT). This procedure involves transplanting faecal matter into the gut to alter or restore the gut microbiota. In healthy individuals, autologous FMT administered following antibiotic use (which disrupts the microbiota, decreasing diversity) has been shown to restore microbial diversity in the gut. Of interest, FMT was more effective than probiotics, with probiotics actually delaying restoration of their native microbiota.

FMT may be performed to prevent or treat an intestinal disorder, with proven efficacy in *Clostridium difficile* infection and positive results found in ulcerative colitis trials. There is, however, caution for its use in oncology due to a potential risk of infection in such immunocompromised patients and extensive research is required to address these concerns. The research team published a comprehensive review of FMT in the journal *EBioMedicine*, discussing its potential applications in oncology and recommendations in immunocompromised recipients. This FMT work was undertaken at the

Injury to the intestinal lining or 'mucosal barrier injury' is a major problem for people with cancer, and their care teams.



FMT has proven highly effective in treating intestinal disorders such as *Clostridium difficile* infection.

University Medical Centre Groningen (The Netherlands). The rationale for its use, potential benefits in preventing cancer treatment related side effects and prevention of associated complications such as bloodstream infections are outlined. Importantly, Wardill and her colleagues emphasise that FMT in immunocompromised patients may in fact decrease their infection risk, with low microbial diversity itself a risk factor for infection. Although promising, the use of FMT in cancer patients to treat therapy induced side effects requires a great deal more research to thoroughly assess its safety and efficacy before it is implemented as an adjunctive therapy.

This study provides a rationale to investigate methods of enhancing the composition of the microbiota, before starting cancer therapy

As part of Wardill's research pipeline conducted at the University Medical Centre Groningen (the Netherlands), she investigated how antibiotics and FMT impact the severity of MBI. In the *European Journal of Cancer*, the team published the first study showing that the microbiome directly influences MBI caused by the chemotherapy drug, methotrexate. The study aimed to understand the effects of antibiotics and FMT on MBI and related symptoms. Results revealed that antibiotics administered before chemotherapy disrupted the microbiota, impeding the recovery of the intestinal lining and exacerbating symptoms, namely diarrhoea. Importantly, when FMT was performed after antibiotics, it enhanced mucosal recovery and reversed the aforementioned negative effects of antibiotics. This study provides a rationale to investigate methods of enhancing the composition of the microbiota, especially in people who may have been exposed to antibiotics, before starting cancer therapy to mitigate treatment side effects.

Interestingly, the success of the FMT was associated with the presence of the core rodent gut bacterium, *Muribaculaceae* (S24-7). Although this species is not abundant in humans, the researchers suggest that colonisation of the gut by core human bacteria would be comparable and may indicate successful FMT in humans. This research highlights the therapeutic options of targeting/altering the microbiota, both before chemotherapy to shift colonisation to a favourable composition, and after chemotherapy to aid recovery of mucosal injury and lessen symptoms.

TECHNOLOGY ADVANCES AND FUTURE DIRECTIONS

Given the team's finding that the composition of the microbiota before chemotherapy is associated with treatment side effects, they are now interested in how the microbiota can be harnessed to predict individual treatment responses. Another research team has investigated the use of an electronic nose and a technology called Field Asymmetric Ion Mobility Spectrometry (FAIMS) and an e-nose to identify people at risk of intestinal symptoms undergoing radiotherapy. An e-nose can analyse gaseous biomarkers from human samples such as breath, blood, sweat, urine, and in this case faeces to capture the types of bacteria present in someone's gut.

Many people with pelvic malignancies undergoing radiotherapy experience gastrointestinal symptoms including diarrhoea, bleeding and pain. It is suspected that more susceptible individuals have an altered gut bacteria composition at the time they receive radiotherapy. Using e-nose and FAIMS, the team aimed to determine if there were differences in the stool odour profile between patients who had severe gastrointestinal symptoms compared to those who had minimal/no gastrointestinal symptoms. Interestingly, both e-nose and FAIMS detected differences in the odour profile and thus gut microbiota composition between the two groups, both before and after radiotherapy. This indicates a difference in the composition of gut bacteria between the groups.

The authors suggest this could be used in the future to potentially identify patients at risk of developing severe gastrointestinal symptoms, but larger studies are needed first. Research into cancer and the gut microbiota is thus a rapidly growing area of interest and key studies by the team at the University of Adelaide show the importance of gut microbiota composition during cancer treatment and its relationship with the development of side effects.

Photo Credit: The Hospital Research Foundation

Behind the Research

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Research Objectives

Dr Hannah Wardill and her team research the role of gut microbiota in the development of cancer treatment side effects.

Detail

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Bio

Dr Hannah Wardill leads the Supportive Oncology Research Group at the University of Adelaide, a dynamic and multidisciplinary group dedicated to improving the health and wellbeing of people affected by cancer. Her group has a strong focus on how the gastrointestinal microenvironment can be better supported to improve outcomes of cancer therapy.

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Personal Response

Can you tell us if/how any recent advances in biomedical technology and methodology have furthered your understanding of the role of gut microbiota in the development and severity of cancer therapy or antibiotic-induced side effects?

"We have seen huge advances in our ability to accurately access the composition and functionality of the microbiota, and these techniques are now highly accessible to most researchers. We are using genomic and functional microbiota analyses to better understand how the microbiota changes in response to cancer therapy, and link preclinical and clinical projects to deliver translational outcomes."