Role of mucositis in predicting gut microbiota composition in people with cancer

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Purpose of review
Disruption of the precious ecosystem of micro-organisms that reside in the gut – the gut microbiota – is rapidly emerging as a key driver of the adverse side effects/toxicities caused by numerous anti-cancer agents. Although the contribution of the gut microbiota to these toxicities is understood with ever increasing precision, the *cause* of microbial disruption (dysbiosis) remains poorly understood. Here, we discuss current evidence on the cause(s) of dysbiosis after cancer therapy, positioning breakdown of the intestinal mucosa (mucositis) as a central cause.

Recent findings
Dysbiosis in people with cancer has historically been attributed to extensive antibiotic use. However, evidence now suggests that certain antibiotics have minimal impacts on the microbiota. Indeed, recent evidence shows that the type of cancer therapy predicts microbiota composition independently of antibiotics. Given most anti-cancer drugs have modest effects on microbes directly, this suggests that their impact on the gut microenvironment, in particular the mucosa, which is highly vulnerable to cytotoxicity, is a likely cause of dysbiosis. Here, we outline evidence that support this hypothesis, and discuss the associated clinical implications/opportunities.

Summary
The concept that mucositis dictates microbiota compositions provides two important implications for clinical practice. Firstly, it reiterates the importance of prioritising the development of novel mucoprotectants that preserve mucosal integrity, and indirectly support microbial stability. Secondly, it provides an opportunity to identify dysbiotic events and associated consequences using readily accessible, minimally invasive biomarkers of mucositis such as plasma citrulline.

Keywords
microbiome, microbiota, mucosa, mucosal barrier injury, mucositis

INTRODUCTION

The gastrointestinal tract is inhabited by a diverse ecosystem of micro-organisms – collectively referred to as the gut microbiota – comprising bacteria, viruses, fungi and the lesser known anchea and helminths. Over the past decades, an immense surge in research activity has focused on characterizing and understanding this unique ecosystem and its impact on host health and disease [1▪]. Certainly, in the early stages of our understanding, the gut microbiota was surrounded by exceptional hype and hyperbole, with astronomical estimates on the number of micro-organisms present in the human body suggesting they outnumber human cells by ~10-fold [1▪]. More recently, this hype has been replaced with more realistic insights and it is now considered that the human colon houses ~500 g of microbial material with bacterial cells outnumbering human cells by ~30% [2▪]. Despite this re-evaluation, the contribution of the gut microbiota to host health is profound and, because of the highly dynamic nature of the gut microbiota, alterations in its composition are increasingly recognized to contribute to numerous diseases affecting both the gastrointestinal tract and distant sites such as the brain [3,4].

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KEY POINTS

- The gut microbiota is dynamic and subject to exceptional modification from a variety of factors.
- Anti–cancer therapies disrupt the gut microbiota, increasing toxicity risk and severity.
- The intestinal mucosa provides physical niches and nutrients to support resident gut microbes.
- Intestinal mucositis and mucosal barrier injury is emerging as a key driver of gut microbiota disruption.
- Interventions targeting the gut microbiota may be enhanced with paralleled efforts to protect the intestinal mucosa.

In the context of cancer and its treatment, the gut microbiota has been an area of intense focus and growth [5,6]. A growing body of evidence from both preclinical and clinical studies has shown various anti-cancer therapies, namely radiotherapy and chemotherapy, alter the composition of the gut microbiota [7,8▪▪]. Although these changes differ and reflect the nuances of the specific clinical context under investigation, they are generally characterized by a decrease in microbial richness and diversity compared with healthy controls and pre-therapy samples. These changes are ultimately driven by a loss in key commensals, especially those more vulnerable to oxidative stress, and the subsequent expansion of more virulent enteric pathogens [9]. These pathogen 'blooms' are enabled by the physical loss of commensals, thus decreasing colonization resistance, as well as a decrease in luminal short chain fatty acids which serve to acidify the luminal environment and in turn, restrict pathogen growth [10▪▪,11]. The consequence of these changes is a microbial ecosystem that produces higher levels of endotoxin (lipopolysaccharide) – a potent immune stimulant capable of triggering the production of damaging proinflammatory cytokines [12,13].

Given the ability of these microbial changes to create a proinflammatory microenvironment, they have been increasingly investigated for their role in adverse treatment side effects. Data now show that dysbiotic changes in the gut microbiota after cancer therapy coincide with side effects such as diarrhoea [14] and blood stream infection (BSI) [15–17], as well as systemic complications such as graft versus host disease (GvHD) [18–23]. Although only emerging in the literature, it is also suggested that the gut microbiota may also contribute to neuropsychological symptoms [24], including cognitive dysfunction [25], pain [26] and fatigue [27] and other undesirable treatment outcomes such as fear of recurrence [28] and relapse [29]. With this new knowledge at hand, attention has shifted into understanding *how* the gut microbiota can be exploited or targeted to improve outcomes of cancer therapy. Numerous interventional strategies have since emerged, with prebiotics [30,31▪▪,32], probiotics [33–35] and other microbial therapeutics (e.g. faecal microbiota transplantation, FMT [36,37▪▪,38]) all under investigation for their ability to protect or restore the gut microbiota and improve treatment outcomes. However, interventions targeting the gut microbiota are inherently challenging, particularly when used in the context of supportive care. This reflects not only the complexity of the gut microbiota but also the extensive list of variables that must be considered when designing effective microbial interventions [1▪,39]. Ultimately, when designing a microbial intervention, the myriad of variables that influence the gut microbiota, the uptake of exogenous microbes and presence of microbial fuels (i.e. dietary fibre) must be considered to maximize the efficacy of these interventions. Not only should the candidate strain be carefully selected, but also the total microbial load and diversity, route of administration to target the most appropriate region of the gastrointestinal tract (e.g. oral vs rectal) and relevant/context specific contraindications (i.e. is per oral administration feasible in people with oral mucositis?). Further to this, one must consider the actual *cause* of microbial injury in the first place, particularly when delivering live microbes (e.g. probiotics or FMT) to ensure the microbes remain viable in their new environment. Here, we provide a rationale, evidence-based perspective that the intestinal mucosa is critical in shaping the composition of the gut microbiota in people undergoing cancer therapy, positioning mucositis (mucosal barrier injury [MBI]) as a catalyst for microbial disruption.

MUCOSAL-MICROBIAL CROSS TALK

Although dysbiosis is commonly observed in people undergoing cancer therapy, in particular chemotherapy, current evidence suggests that chemotherapy itself is minimally impactful to microbes [40]. This suggests that either secondary biological events or concurrent factors/variables are responsible for driving dysbiosis in people with cancer. Naturally, dysbiosis in people undergoing cancer therapy has been attributed to the widespread and routine use of antibiotics [41]. However, increasingly it is recognized that not all antibiotics are damaging to the gut microbiota. In fact, recent evidence suggests that microbial changes occur *independently* of antibiotics in the context of haematopoietic stem cell transplantation (HSCT) [42,43].

When considering the gut microbiota and drivers of dysbiosis in the context of cancer therapy, the bidirectional interaction between resident microbes and the intestinal mucosa is critical. Recently, Rashidi and colleagues explored this interaction and identified that the microbial genera, *Blautia*, was critical in dictating the integrity of the intestinal mucosa, proposing a model of microbe-to-mucosa communication [44]. Certainly, microbes have the capacity to influence the mucosa, particularly via their ability to produce beneficial metabolites such as short chain fatty acids [45]. These compounds are a major energy source for colonocytes, promoting epithelial proliferation and regeneration, whilst also promoting barrier integrity via their influence on tight junction assembly. However, as recently discussed [46,47], this direction of communication may be more relevant in the context of mucosal/microbial *recovery*, and not necessarily the *initial disruption* of the microbial community. In this context, the influence of the mucosa on gut microbes may be more relevant.

Microbes rely on the mucosa to provide physical niches within which they reside as well as the provision of nutrients [48]. As such, when considering the widespread destruction of the intestinal mucosa caused by many anticancer therapies, clinically referred to as (gastro)intestinal mucositis or MBI, the concept that the integrity of the mucosa dictates microbial composition is compelling. Complementary to this concept is the evidence generated by Shouval and Peeled, each of which show that loss in microbial diversity is dependent on the intensity of the conditioning regimens [42,49▪▪,50]. Varying conditioning regimens induce varying levels of MBI, and thus microbial phenotypes and their associated clinical implications. Of interest, the recent trial conducted by Rahsidi *et al*. investigating FMT for BSI prevention in HSCT recipients did not reach its primary endpoint, that is, FMT did not significantly reduce the incidence of BSI [36]. This may reflect the fact that although microbes were successfully delivered to recipients, their ability to durably colonize the gut may be impacted by persistent mucosal damage. The concept of mucosal-to-microbe disruption is further supported by recent preclinical data which show the gut microbiota can be stabilized after high-dose melphalan (HDM) using anakinra, an interleukin-1 receptor antagonist [9]. Rats treated with HDM and anakinra had a less pronounced citrulline nadir, indicating less severe MBI. Presumably, this results in less mucosal hostility for resident microbes, reduced oxidative stress and thus less severe dysbiosis. Of interest, rats receiving anakinra had fewer febrile events suggesting a lower rate of infection. This reinforces the emerging concept that, contrary to historical belief, BSIs in people with cancer originate in the gut as a result of pathogens translocating across the damaged mucosa. It also adds further strength to this concept by suggesting that the damaged mucosa not only allows the translocation of these pathogens, but also facilitates their initial expansion [10▪▪].

CLINICAL IMPLICATIONS AND OPPORTUNITIES

The clinical implications for this knowledge are significant for a number of reasons. Firstly, if indeed the mucosa is the most influential factor shaping the gut microbiota in people with cancer, this approach suggests that much more consideration should be placed on protecting the mucosa from cytotoxic therapy. Unfortunately, intestinal mucositis is ubiquitous to many anti-cancer drugs due to their affinity for the highly proliferative cells that populate the intestinal mucosa. Currently, there are no universally accepted methods to prevent intestinal mucositis, with only one narrow indication for *Lactobacillus* containing probiotics for pelvic radiotherapy (± chemotherapy) [51,52]. This may reflect the practical challenges with accessing the intestinal mucosa as well as difficulties in developing interventions that protect the mucosa without impairing the intended cytotoxic properties of chemotherapy. However, it may also reflect the fact that intestinal mucositis has fallen victim to low visibility and priority. Given the surge of activity and attention the consequences of microbial dysbiosis have received, especially in HSCT recipients, this may be an opportunity to direct research efforts to intestinal mucositis with the goal of not only reducing its associated symptoms (e.g. malnutrition, diarrhoea), but also the secondary complications of mucositis-associated dysbiosis. Whether this be in the form of purely mucosally-targeted interventions such as anakinra, which has since transitioned into Phase IIB trial [53], or combined therapies that target both the microbes and mucosa simultaneously is yet to be determined.

Combined microbial and mucosal targeting strategies have not been directly investigated to date, however, comparable strategies in which FMT is paired with oral supplementations to improve its efficacy have been explored. For example, a proof-of-concept study showed that FMT paired with oral intake of low-fermentable fibre can increase engraftment of donor microbes to improve insulin sensitivity and metabolic syndrome more effectively than FMT alone [54▪]. In the context of cancer and HSCT, complications such as nausea/vomiting, oral mucositis and low appetite reduce food intake and often necessitate intravenous/

parenteral nutrition (TPN) [55,56]. TPN deprives the gastrointestinal system of important dietary input to maintain the gastrointestinal microenvironment, and hence, evidence shows enteral nutrition promotes microbial recovery in paediatric HSCT recipients compared with standard of care [57], with a recent meta-analysis showing EN reduces GvHD incidence in adult cohorts [58]. To extend the concept of mucosa-initiated dysbiosis and realize the clinical benefits of this concept, the use of excipients/adjuvant drugs that enable the mucosa to regain its ability to regulate and support its associated microbiota should be considered in combination with nutritional or microbial interventions. For example, paneth cells – which secrete antimicrobials to maintain microbiota homeostasis – have been found to decrease in number following conditioning and its deficiency has been observed in GvHD [59]. Both R-spondin [60] and GLP-2 analogues [61] have been shown to accelerate paneth cell recovery and indirectly support microbial composition in the context of GvHD. This reiterates that the microbiota can be modulated by targeting the mucosa, and underscores the potential for mucosal strengthening to enhance efforts aiming to promote eubiosis in people with cancer.

The other major implication, or opportunity, associated with the idea that the mucosa dictates dysbiosis in cancer therapy is the ability to more easily predict events associated with dysbiosis (e.g. BSI). Serial sequencing of the gut microbiota is not feasible to perform in routine clinical practice, with practical obstacles related to sample collection, processing and sequencing. In contrast, there are numerous biomarkers of intestinal mucositis which could be used as surrogate markers to identify or predict. Plasma citrulline is an amino acid exclusively produced by enterocytes, and is commonly used in clinical practice as a biomarker of (gastro)intestinal mucositis [44,62–64]. It can be easily measured in small quantities of blood, or even dry blood spots, allowing rapid and highly accurate insights into the insight of the mucosa and the likely composition of the gut microbiota. In fact, de Mooij *et al.* [65] have shown that citrulline predicts BSI with greater accuracy compared with conventional predictors such as neutrophil counts. Plasma citrulline has also been shown to predict GvHD [66] and other transplant outcomes such as mortality, mucositis and nutritional requirements [67].

CONCLUSION

In summary, there is a complex interplay between the mucosa and resident microbes in the gut. Whilst it is simplistic to assume a single, linear relationship exists between these components of the gut microenvironment, the collateral damage caused to the mucosa cannot be overlooked as a predictor of dysbiosis. This emerging concept therefore highlights the need to consider mucosal strengthening strategies in parallel to microbial interventions, ensuring the mucosa is optimally primed to receive and support donor microbes in a manner that creates durable colonization. Similarly, given the availability of mucositis biomarkers such as citrulline, this approach provides a novel opportunity to identify dysbiosis-associated consequences early in their sequelae with adequate time to intervene.

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Conflicts of interest

There are no conflicts of interest.

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