Review

Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery

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Background: **The pathogenesis of colorectal cancer recurrence after a curative resection remains poorly understood. A yet-to-be accounted for variable is the composition and function of the microbiome adjacent to the tumour and its influence on the margins of resection following surgery.**

Methods: **PubMed was searched for historical as well as current manuscripts dated between 1970 and 2017 using the following keywords: 'colorectal cancer recurrence', 'microbiome', 'anastomotic leak', 'anastomotic failure' and 'mechanical bowel preparation'.**

Results: **There is a substantial and growing body of literature to demonstrate the various mechanisms by which environmental factors act on the microbiome to alter its composition and function with the net result of adversely affecting oncological outcomes following surgery. Some of these environmental factors include diet, antibiotic use, the methods used to prepare the colon for surgery and the physiological stress of the operation itself.**

Conclusion: **Interrogating the intestinal microbiome using next-generation sequencing technology has the potential to influence cancer outcomes following colonic resection.**

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Introduction

Despite improvements in surgical technique and postoperative surveillance, colorectal cancer recurrence after pathologically confirmed complete resection remains a significant problem. Recurrence affects at least 40 per cent of patients, typically occurring within the first 3 years[1–3]. Historically, disease recurrence has been attributed to tumour stage, grade, presence of obstruction or perforation at presentation, presence of lymphovascular invasion, and the ability to achieve an R0 resection[4,5].

Although many factors, both genetic and environmental, can affect disease recurrence, the intestinal microbiome (the microbial community membership, structure and function) has not been viewed as an active participant. With the development of advanced intestinal sampling and analysis of both nucleic acids (RNA sequencing) and protein products (transcriptomics), the intestinal microbial community has emerged as a key component not only in tumorigenesis, but also in disease-free survival after surgery. Much of the initial investigation into the microbiome's role in colorectal cancer recurrence has been sparked by clinical studies in which local recurrence has been shown to be much higher in patients who developed anastomotic complications[6]. The focus of the present study was how the intestinal microbiome has influenced our understanding and management of colorectal cancer, with a particular focus on recurrence.

Methods

PubMed was searched for historical as well as current manuscripts dated between 1970 and 2017 using the following keywords: 'colorectal cancer recurrence,' 'microbiome,' 'anastomotic leak,' 'anastomotic failure' and 'mechanical bowel preparation'.

Microbiome and tumorigenesis

At birth, the gut is first colonized and then stabilized through adaptation with four dominant phyla: Firmicutes, Bacteriodetes, Proteobacteria and Actinobacteria. Depending on environmental conditions, genetics, the host's immune system, diet, and early exposure to infection or antibiotics, the presence and dominance of these species becomes highly varied among healthy individuals[7].

With further advances in molecular techniques and bioinformatics analysis, a more complete understanding of what constitutes flux of a healthy microbiome is emerging to define what constitutes a pathological disturbance in the microbiome[8]. Such dysbiosis, or disturbance in microbial community membership, structure or function, can consist of a loss of specific beneficial bacteria or a critical loss of diversity among the beneficial bacteria. This produces a state termed a pathobiome, defined as loss of the health-promoting microbiome with a predominance of disease-producing pathogens[9,10].

Several studies[11–13] have demonstrated an overabundance of *Fusobacterium*, *Alistipes*, Porphyromonadaceae, Coriobacteridae, Staphylococcaceae, *Akkermansia* and Methanobacteriales, and lack of *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, *Faecalibacterium*, *Roseburia* and *Treponema* in patients with colorectal cancer. Although these microbes may be associated with colorectal cancer, their causal relationship with disease remains to be clarified. To address this, Baxter and colleagues[14] analysed the tumour burden in germ-free mice that were subjected to a chemical carcinogen and given a faecal transplant with a sample from either a patient with colorectal cancer or a healthy patient. Mice that had a microbiome dominated by Gram-negative *Bacteriodes*, *Parabacteroides*, *Alistipes* and *Akkermansia* had a higher tumour burden, regardless of whether the faecal transplant was from the colorectal cancer donor or the healthy patient. In this model, the presence of species within the *Clostridium* genus had a negative correlation with tumour count[14]. A European study[15] reported similar findings after analysing stool samples following colonoscopy. Patients with colorectal cancer were more likely to have an abundance of the Gram-negative phylum of Fusobacteria and a decrease in the Gram-positive phylum of Actinobacteria. The presence of *Fusobacterium* also showed a positive correlation in biopsy samples of adenomas compared with biopsies of normal tissue[16]. This bacterium is thought to activate the FadA adhesin, which binds to an extracellular domain of E-cadherin, triggering invasion and activating WNT signalling, leading to promotion of tumour growth[17]. Additionally, it can inhibit T cell-mediated immune responses against colorectal cancer cells[16,18,19]. The abundance of *Fusobacterium nucleatum* DNA has also been correlated positively with advanced disease stage and higher colorectal cancer-specific mortality[20]. *Bacteriodes fragilis* is another bacterium that is associated with poor disease-free survival in patients with colorectal cancer[20], and has been shown to cleave E-cadherin and enhance WNT/B-catenin signalling while also increasing the expression of MYC[21].

Impact of neoadjuvant therapy

Colorectal cancer is commonly treated with cytotoxic agents, such as 5-fluorouracil (5-FU), capecitabine and oxaliplatin, that interfere with DNA replication[22]. Platinum-based antineoplastic therapeutics such as oxaliplatin cause severe toxicity in multiple organ systems, including intestinal, renal and auricular. Its toxicities also affect the intestinal microbiome via damage to the rapidly regenerating intestinal mucosal cells, breaching immunological barriers, and altering environmental cytokines and inflammatory markers. Although the presence of a gut microbiota is not necessary for oxaliplatin to penetrate the tumour and induce genetic damage, the production of reactive oxygen species and antitumour effects requires the presence of certain bacterial species, such as *Lactobacillus acidophilus*, for cisplatin-induced inflammatory gene expression[23]. Mouse studies have shown that the gut microbiota may modulate local immune responses, in turn affecting chemotherapy and immunotherapy[24–27]. Yu and co-workers[28] found that autophagy-related pathways are enriched and activated in patients with colorectal cancer and a high amount of *F. nucleatum*, promoting colorectal cancer chemoresistance. *F. nucleatum* has been found to attach to the host epithelial E-cadherin, promoting colorectal carcinogenesis via the fusobacterial adhesion FadA[17]. *F nucleatum* has also been found to mediate chemoresistance through targeting specific micro-RNA and autophagy elements. Its direct association with colorectal cancer recurrence has even been posited as a method of predicting patient outcomes or modifying chemotherapeutic regimens, such as the inclusion of capecitabine and oxaliplatin, for patients with a high burden of *F. nucleatum*[28].

Chemotherapy resistance in non-malignant cells is well described[29]. When Geller *et al.*[30] co-cultured human dermal fibroblasts with colorectal cancer cell lines, the cancer cells were found to be more resistant to the chemotherapeutic drug gemcitabine. It was found that *Mycoplasma hyorhinis* exposure to human dermal fibroblasts resulted in the metabolism of gemcitabine into its deaminated and inactive metabolite 2′,2′-difluorodeoxyuridine, rendering the chemotherapeutic ineffective. In a cursory exploration of 27 bacterial species, 13 were found to eliminate the effect of gemcitabine on human colorectal cancer cells[30]. A broad understanding of the chemotherapeutic resistance conferred by changes in the microbiota awaits further exploration.

Radiotherapy is genotoxic for tumour cells, but affects non-targeted and non-irradiated cells through changes in inflammatory and immune reactivity, as well as genomic instability[31,32]. Gap junction proteins are disrupted and mediators such as reactive oxygen species, nitric oxide,

cytokines and exosomes are released[33–37]. Although there is interplay between the mechanisms of the microbiota and the effects of radiation therapy, there are several crossovers that warrant consideration. The abscopal effect, wherein distant metastases regress with irradiation of the primary tumour, is an immune-mediated response requiring the activation of antigenic presenting dendritic cells and immune T cells, interactions that have long been known to be deeply influenced by the microbiome[25,26,38]. The clinical effects of radiation therapy include oral mucositis, diarrhoea, enteritis and colitis, which are manifestations of and precursors to microbiotal disruption[39,40].

In addition to the clinical features mentioned above, radiotherapy is a known risk factor for anastomotic leak, having been determined to triple the rate of anastomotic failure[41]. Radiation has been shown to induce endothelial cell dysfunction, marked by increased permeability, detachment from the underlying basement membrane and apoptosis[42,43]. The reduced vascular density and thickening of the intimal layer result in some parenchymal tissue not receiving perfusion[44], creating an ischaemic environment known to deplete health-promoting obligate anaerobes such as *Bacteroides* and Clostridia, while allowing facultative anaerobes such as *Lactobacillus* and Enterobacteriaceae to flourish[45]. In a mechanism similar to how anastomotic tissues select for microbes that express enhanced virulence, irradiated tissue can be expected to do the same given its resultant vascular damage, killing of rapidly proliferating epithelial cells and mucositis[46]. The commensal intestinal bacteria and their Toll-like receptors (TLRs) are known to be necessary for the regulation of intestinal homeostasis, with its interaction with the nuclear factor (NF) κB pathway protecting intestinal epithelial cells from radiation-induced apoptosis[47].

The authors' laboratory has demonstrated using *in vivo* animal modelling that preoperative radiotherapy plus inoculation with *Pseudomonas aeruginosa* leads to a significant incidence of anastomotic leak compared with radiotherapy alone. Phenotype analysis of the original inoculating strain *versus* the strain recovered from the anastomotic tissues after irradiation demonstrated an alteration in pyocyanin production, enhanced swarming motility, high collagenase production and a destructive phenotype against epithelial cells (apoptosis, loss of barrier function, cytolysis). Comparative genotype analysis revealed a single nucleotide polymorphism mutation in the *mexT* gene, and its replacement led to reversion of the preinoculation/irradiation phenotype[48]. Work in *Drosophila* has shown that intestinal infection with *P. aeruginosa* activates the c-Jun N-terminal kinase (JNK) pathway, which leads to apoptosis of enterocytes and proliferation of stem cells[49].

Impact of surgery

Although it is likely that patients with colorectal cancer harbour a pathobiome that plays a significant role in tumorigenesis, the role, if any, that this may play in recovery from surgery and/or recurrence remains to be clarified. Using a reverse transcriptase–quantitative polymerase chain reaction, Ohigashi and colleagues[50] reported that obligate anaerobes such as *Clostridium coccoides*, *C. leptum*, *B. fragilis*, *Bifidobacterium*, *Atopobium* and *Prevotella*, bacteria important in maintaining gastrointestinal homeostasis[51], are diminished following colorectal cancer surgery. In contrast, pathogens associated with surgical complications such as the facultative anaerobes, Enterobacteriaceae, *Enterococcus* and *Staphylococcus*, as well as the aerobe *Pseudomonas*, were observed to be increased after surgery. The functional impact of this response was considered to be significant, given the additional finding of depletion of short-chain fatty acids (SCFAs), which serve as a key energy source for colonocytes. SCFAs are well established bacterial exoproductions that maintain epithelial barrier function, prevent infection, suppress ammonia absorption and promote apoptosis in tumour cells[52–54]. The extent to which these changes are predictive of complications and tumour recurrence is presently unknown.

Anastomotic leak and colorectal cancer recurrence

Anastomotic leak is known to have a significant impact on hospital costs, length of stay, morbidity and mortality[55–57]. The incidence varies from 1 to 19 per cent depending on definitions and types of anastomosis[58–60]. Reported local recurrence rates of colorectal cancer vary between 1 and 23 per cent, with recurrence affecting an average of 8 per cent of surgical patients[61]. Curiously, the majority of recurrences are perianastomotic, occurring in the extramural tissue, and only 12 per cent occur intraluminally[62,63]. The molecular mechanisms for this finding remain unknown. A number of studies[6,55,64] have shown that anastomotic leak is associated with increased local recurrence and reduced disease-free survival in patients with colorectal cancer. Although this could be due to a delay in adjuvant therapy, several mechanistic theories are worthy of discussion in the context of the microbiome: implantation of exfoliated tumour cells on to the anastomotic site, metachronous carcinogenesis and inflammation-mediated carcinogenesis[65–67].

Of note, viable colorectal cancer cells invariably persist in the bowel lumen after surgical resection. These cells are clones of the original tumour and harbour the capability for implantation into remote tissues[68,69]. In nine of ten patients

who undergo surgery for colorectal cancer malignant cells remain on tissues discarded from the circular stapling device[70]. A more recent study[71] demonstrated that over half of patients undergoing a right hemicolectomy for colorectal cancer had exfoliated malignant cells in lavage fluid collected from the anastomotic site. Remarkably, there was no correlation between tumour size or depth of invasion and the presence of residual colorectal cancer cells[71].

Another mechanism of local recurrence that has been suggested is metachronous carcinogenesis or 'field cancerization'[72]. Umeto and co-workers[73] suggested that microenviromental changes in the region of the primary tumour can lead to genetic instability resulting in new tumour growth near the anastomotic site. A third theory relates to the impact of acute-phase reactants and inflammatory mediators on cancer biology. Several studies[74–77] have demonstrated that the presence of inflammatory biomarkers (tumour necrosis factor, interleukin (IL) 1, IL-6, matrix metalloproteinases (MMPs), vascular endothelial growth factor) can lead to tumour progression, metastasis and resistance to chemotherapy. Salvans *et al.*[78] demonstrated that peritoneal liquid samples surrounding a postoperative infection have the ability to enhance proliferation, migration and invasiveness of colorectal cancer cells *in vitro*.

An additional mechanism worthy of discussion is the possible attraction of circulating colorectal cancer cells to sites of inflammation; this could explain the lack of intraluminal tumour recurrence. Circulating tumour cells, a prognostic and predictive factor for progression-free and overall survival[79], can seed multiple organs, but metastatic tumours may grow in only one or a few places[80]. Angiogenic dormancy is a phenomenon by which a balance of proliferation and apoptosis results in micrometastases that do not progress[81,82], suppressing the malignancy to metastatic cells until hospitable perturbations in the microenvironment allow their reactivation. Sites of inflammation promote systemic conditions that continuously recruit inflammatory cells to the tumour mass[75], setting up a cascade of events by which the tumour-promoting effects of immune cells (wound repair, angiogenesis, cell proliferation[83]) can be progressively amplified, resulting in the recurrence of local cancer at the antiluminal surface of the intestine with exposure to circulating tumour cells and a consistently inflammatory environment creating the soil for the seed.

In the context of anastomotic leak and the microbiome, it is possible that many of the above mechanisms act in concert to drive tumour recurrence following colorectal cancer surgery. Once a leak occurs, there is often a long period of inanition, resulting in poor nutritional status, hospital confinement with further exposure to pathogens, the physiological stress of a second operation, and ongoing infection and inflammation, often requiring prolonged exposure to antibiotics and invasive procedures. Under such circumstances, the intestinal microbiome can not only become depleted, but may also be transformed to a pathobiome capable of inducing further anastomotic inflammation and seeding of exfoliated cells to anastomotic sites.

The extent to which an anastomotic leak disrupts the local microenvironment and potentially leads to colorectal cancer recurrence remains to be elucidated. Furthermore, the extent to which loss of the microbiome, the presence of a pathobiome, or both, drive tumorigenesis remains to be clarified. It is now well established that the presence of the normal microbiota plays a key role in maintaining both local intestinal and systemic immune function[24,25]. In addition, the presence of certain highly pathogenic species in the gut, permissively promoted by loss of the competitive exclusion by the normal microbiome (colonization resistance), can directly suppress the immune system[84]. Whether these factors influence exfoliated colorectal cancer cells to implant on to anastomotic tissues and migrate into deeper tissues remains to be fully explored.

Previous work from the authors' laboratory has demonstrated that anastomotic leak can occur when the normal microbiome is depleted and low abundance strains such as *Enterococcus faecalis* predominate. Pathogens such as *E. faecalis* can drive the pathogenesis of anastomotic leak as they possess high collagenase activity and activate (MMP-9), key contributors to tissue breakdown and intestinal inflammation[85]. MMPs are a group of proteolytic enzymes that mediate extracellular matrix degradation and regulate the release of growth factors, chemokines and adhesion proteins[86]. High levels of MMP-9, a gelatinase MMP with type IV collagen as its primary substrate, have been shown to be a marker of invasion and worsen the oncological outcome in patients with colorectal cancer[87–89]. That *E. faecalis* strains seem to play a major role in anastomotic leak pathogenesis and remain present at anastomotic tissues despite current methods of preparing the bowel for surgery[50], suggests that one overlooked element in local recurrence may be suppression of the microbiome and the presence of a highly inflammatory pathobiome. These collagenase-producing strains of *E. faecalis* in a GelE/SprE-dependent manner can interact with resident macrophages and shift cultured mouse colonic epithelial cells to express a mesenchyme-like phenotype with aggressive invasive features, similar to the epithelial mesenchymal transition that is involved in cancer metastasis[90] (*Fig. 1*).

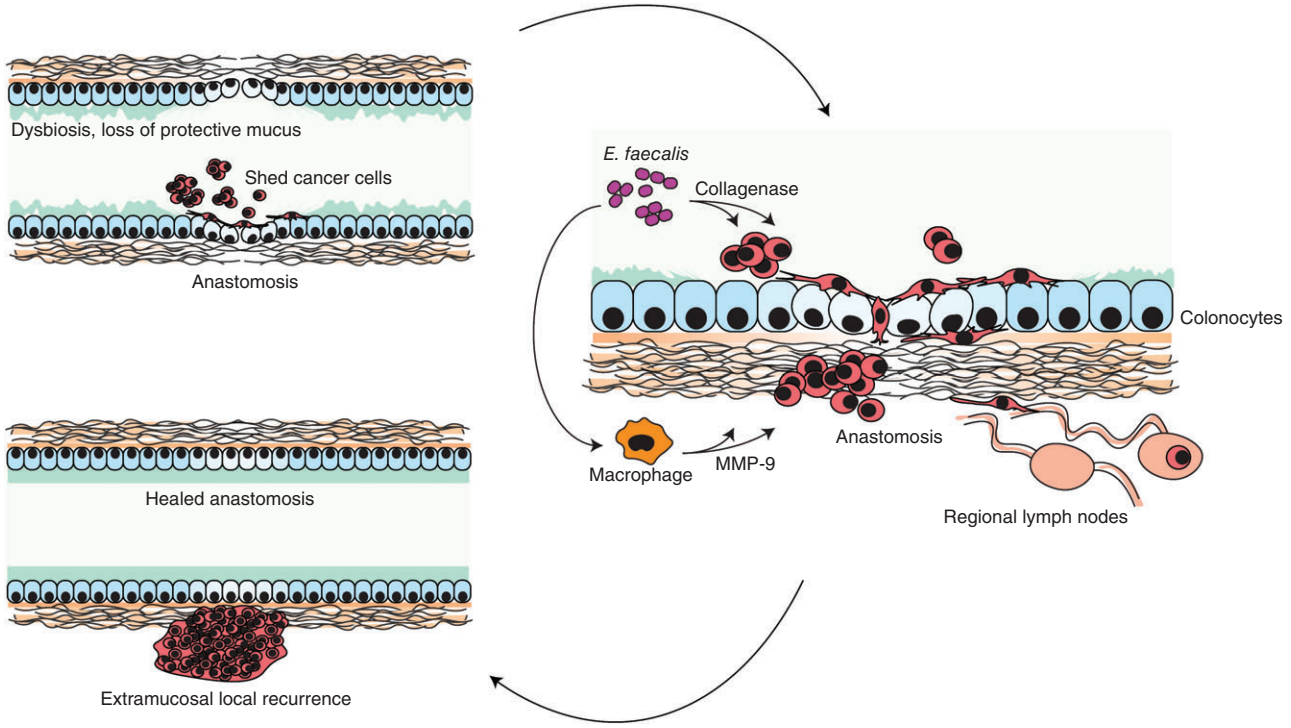

Fig. 1 Hypothesized mechanism of colorectal cancer recurrence following surgical resection. Across the continuum of care to treat colorectal cancer (preoperative chemoradiotherapy, antibiotics, surgical resection), a unique environmental context is created that promotes colonization by collagenase-producing microbes (*Enterococcus faecalis*) followed by implantation of cancer cells, which are shed continuously both during and after surgery. High collagenase-producing microbes may activate local macrophages such that anastomotic healing is impaired in a manner that promotes shed cancer cells to implant and migrate to extramucosal sites, leading to local tumour recurrence. MMP, matrix metalloproteinase

Several studies have demonstrated that the gut microbiota may serve as a prognostic biomarker of survival in patients with colorectal cancer. Flanagan and colleagues[91] demonstrated shortened recurrence-free survival in patients with colorectal cancer with higher levels of *F. nucleatum*. The presence of enterotoxigenic *B. fragilis* in the colonic mucosa was associated with a higher colorectal cancer stage[92]. Wei and co-workers[20] concluded that abundance of *F. nucleatum* or *B. fragilis* was a prognostic biomarker of poor survival, associated with increased levels of inflammatory mediators including MMP-9. In addition, *B. fragilis* can induce NF-κB signalling and release of inflammatory cytokines[93]. Thus, one intervention that has the capability to shape the microbiome before surgery and potentially downstage colorectal cancer is mechanical and antibiotic bowel preparation. The extent to which current bowel preparation methods affect gut microbial community composition, refaunation, overall morbidity and oncological survival remains inadequately studied and largely unknown.

Bowel preparation in the genomic era

Bowel preparation, including the use of oral and intravenous antibiotics, is a topic of much debate in general and colorectal surgery. Historically, the goal was extensive decontamination with mechanical bowel preparation (MBP), which includes mechanical cleansing and oral non-absorbable antibiotics, to prevent anastomotic complications and surgical-site infections. In the 1990s, as outcomes of colonic surgery improved, there was a move to eliminate MBP. Multiple studies seemed to suggest that full MBP, including purgative cleansing and oral antibiotics, was unnecessary. An RCT[94] and a meta-analysis[95] failed to find evidence that MBP decreased postoperative infectious complications.

However, with the ability to mine large databases electronically, more recent studies[96,97] have validated the original practice of MBP combined with oral antibiotics, demonstrating a decrease in anastomotic leak and surgical-site infection rates. The effect of bowel preparation on oncological outcome is largely unknown

and there is conflicting evidence regarding the impact of MBP on the long-term survival of patients with colorectal cancer[98,99]. Among the many reasons for this conflicting evidence is that the scientific basis of the components of the MBP relative to overall efficacy has not been properly elucidated. As such, the current approach of a broad-based 'kill' strategy suffers from the empiricism of its original formulation and its lack of recalibration to the shifting demographics of human populations, their ever-evolving microbiome, and the selective pressures on human pathogens that drive disease.

The inherent flaw of a broad-based intestinal decontamination approach to prepare the bowel for surgery is the lack of recognition that a diverse gut microbiome actually serves to suppress the development of potentially harmful pathobiota and promotes intestinal healing[100]. With next-generation technology, including microbial metagenomics, it is possible to define the scientific basis of a 'bowel prep 2.0'. For example, one might consider gentle cleansing of the bowel along with nutritional supplements and non-microbicidal antivirulence agents[101], rather than mass destruction of the microbiome, as is current practice. Preliminary studies have addressed this issue with selective gut decontamination. In an RCT, Reddy and colleagues[102] studied the prevalence of Enterobacteriaceae after various combinations of MBP, neomycin and/or synbiotics. There was a significant reduction in Enterobacteriaceae in faecal samples and in bacterial translocation after bowel mobilization when the patients were administered synbiotics with neomycin and MBP. However, this selective decontamination and preservation of the intestinal barrier was not associated with postoperative systemic inflammatory response or rate of septic complications[102]. Although the results did not significantly alter septic morbidity, a similar concept is already being implemented with hydration and nutritional supplementation solutions being administered within 2 h of elective surgery, rather than the overnight starvation that was practised in many centres until recently. Several randomized trials have demonstrated that patients consuming preoperative oral carbohydrate supplementation had a shorter hospital stay[103,104], improved metabolic profiles, and attenuated inflammatory responses to surgery[105,106].

Bowel preparation as it relates to colorectal cancer recurrence

These evolving concepts may inform the design of a more targeted bowel preparation solution, with the potential to reduce inflammation and colorectal cancer recurrence rates after surgery. For example, butyrate is produced by bacteria during the breakdown of fibre and carbohydrates. It is a SCFA that is used as a fuel source for colonocytes, and is an inhibitor of histone deacetylases, which suppress the proliferation of colorectal cancer cells[107]. Other additives to 'bowel prep 2.0' might include key nutrients that are known to suppress bacterial virulence among problematic pathogens such as *P. aeruginosa* and *E. faecalis* without affecting their growth, thus allowing the normal microbiota to proliferate and further suppress pathogen virulence. Such an approach has the potential to induce beneficial effects on the mucosal epithelium and underlying immune cells by producing a more balanced, diverse microbiome[108]. It would be interesting to follow the patients studied in the randomized trial[102] that found selective gut decontamination eliminated Enterobactericeae from the faeces. Whether this practice altered the colonic cancer recurrence rates in these patients could then be interrogated.

Previous work from the authors' laboratory has shown that pathogens with the capacity to proliferate when the microbiota become depleted, such as *P. aeruginosa*, *E. faecalis* and *Serratia marcescens*, can produce collagenase and elicit intestinal inflammation leading to anastomotic leak[48,85]. It was observed that merely providing oral non-absorbable phosphate, a key nutrient that becomes depleted following surgical injury and is known to suppress pathogen virulence, can prevent bacteria-mediated anastomotic leak in animals[109]. Because elements such as SCFAs and phosphate actually promote the proliferation of bacteria, a balanced solution of a 'bowel prep 2.0', containing both nutrients and antivirulence agents, might represent a more scientifically validated approach to preparing the bowel for surgery that allows for purgative cleansing while preserving the important function of the normal microbiota (*Fig. 2*). The application of next-generation technology to analyse the effect of our current approach to preparing the bowel for surgery promises to inform the design of future formulations to prevent surgical-site infections, remote infections, anastomotic leakage and colorectal cancer recurrence.

Applications of current knowledge for the practising surgeon

The promise of precision medicine to interrogate the human genome and deliver personalized therapy based on individual genetic makeup may explain why some patients respond to therapy whereas others do not, and inform novel

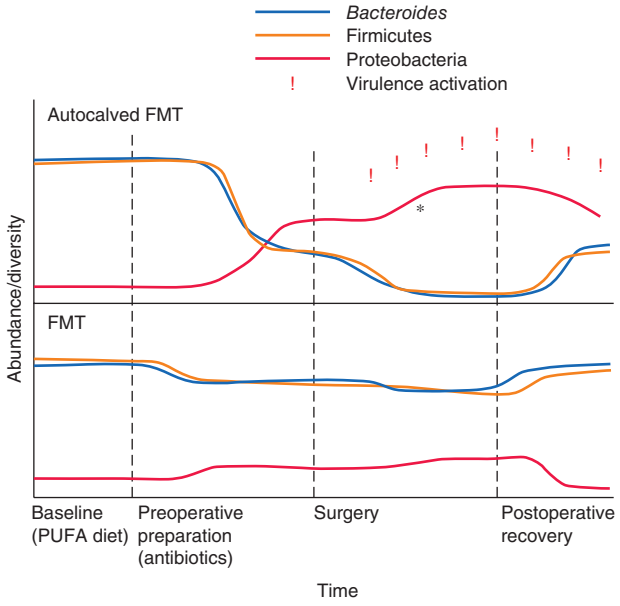

Fig. 2 Theoretical perioperative microbiome disruption. As the body undergoes various stressors, such as antibacterial and purgative preoperative preparation, as well as surgical manipulation, the microbiome changes accordingly. In aggregate, these factors provide stress to the microbiome with a reduction in commensal bacteria and a proliferation of low-abundance γ proteobacteria that cause infection. The point of susceptibility to infection (*) marks a theoretical time point at which the virulence activation of pathogenic bacteria and the suppression of healing-promoting species would make the patient most likely to become infected. It is a vulnerable period that determines whether future postoperative recovery is complicated by microbial dissemination. FMT, faecal microbiota transplant; PUFA, polyunsaturated fatty acids

treatment strategies. Many serious infections following colorectal cancer surgery are a surprise to surgeons who have done their best perform safe and effective procedures. Understanding changes in the human microbiome and the phenotypes they express over the course of high-risk surgery represents the next phase of a genetic approach to inform patient care. Implicit in this approach will be to understand, at a high-resolution molecular level, how best to prepare the bowel in the perioperative period. This will require that we depart from the tradition of empiricism and apply next-generation sequencing in designing future formulations to control the influence of the microbiome on surgical outcomes. This should reduce surgical-site infections, anastomotic leaks and colorectal cancer recurrences through scientific endeavour rather than a traditional conservatist dogma.

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