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Review

The Microbiota and the Relationship with Colorectal Cancer: Surgical Complications—A Review

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Abstract: Colorectal cancer (CRC) is one of the most common cancers and represents a major global health burden. While genetics are implicated in a portion of CRC patients, most cases are sporadic. A new possibility of tumor initiation and promotion might be microbiome composition. It was recently shown that bacteria from the gut microbiome might be used as biomarkers for CRC detection, especially *Fusobacterium nucleatum, Peptostreoptococcus stomatis, Parvimonas mica, Solobacterium moorei,* and *Peptostreptococcus anaerobius.* Conversely, the healthy gut microbiome is mostly colonized by Bacterioides (*Bacterioides fragilis*, *vulgatus*, *uniformis*), Firmicutes (*Clostridium* spp., *Ruminococcus faecis*, *Enterococcus faecium*), and Actinobacteria (*Bifidobacterium bifidum*). Some strains of gut bacteria favor tumor promotion through DNA and RNA damage (directly or through interaction with other known food carcinogens) and through local immune inhibition. It is possible that bacteria (e.g., *Bacillus polyfermenticus*, *Alistipes shahii*, *Lactobacillus casei*) exist with protective functions against tumor promotion. Despite current advances in colorectal cancer treatment, especially in the medical oncology and radiotherapy domains, surgery remains the mainstay of curative treatment for colorectal cancer patients, even in the oligometastatic setting. Surgical complications like anastomotic leakage, excessive blood loss, abscess, and abdominal sepsis can reduce 1-year and 5-year overall survival and increase the recurrence rates for these patients; therefore, we reviewed currently published data focusing on the relationship between gut microbiota and postoperative complications for colorectal cancer patients.

Keywords: colorectal cancer; microbiota; anastomotic leakage; infectious complications; adhesions

1. Introduction

Colorectal cancer (CRC) is one of the most common cancers and represents a major global health burden. The latest statistics show a worldwide incidence of 1.93 million CRC cases in 2020, with almost one million deaths [1]. While genetics are implicated in a portion of CRC patients, most cases are sporadic. In some situations, well-known risk factors such as high lipid intake, high body mass index, lack of exercise, and alcohol

consumption might be present. A series of steps are involved in the process of oncogenesis, as reviewed by Hanahan, including inflammation, microenvironmental changes, and immune inhibition [2]. Moreover, in the context of the intestinal digestive tract, a special role is played by the local flora. Given the presence of the rich intestinal flora, a new possibility for influencing tumor initiation and promotion might be microbiome composition [3,4]. Blood group type can be associated with some malignancies, as proved by the study of Gaube A. et al., while in colorectal cancer, the results reported by Khalili et al. do not support an association between ABO blood group and risk of colorectal cancer [5,6].

There are many findings regarding the microbiome in relation to gut health, inflammatory responses, type 2 diabetes, and even mental health [7–9]. The digestive microbiome is composed of millions of microorganisms and each segment of the digestive tract has its own bacterial composition. These organisms obtain nutrients from dietary components, and, in turn, they contribute to the production of gases, acetate, propionate, and butyrate. Most of these bacteria come from the Gram-negative Bacteroidetes and Firmicutes. The latter phylum produces butyrate, which is associated with inflammatory response modulation, has a role in cell proliferation and differentiation, and also has anti-neoplastic functions [10,11]. Other less abundant bacteria such as *Bifidobacterium*, *Escherichia coli*, and *Akkermansia muciniphila* are present and have a larger impact on health. *Bifidobacterium breve* was shown to decrease the severity of diarrhea, alleviate celiac disease, and even influence the outcomes of neurological disorders and mental disorders [12–14]. *Akkermansia muciniphila*, by producing a thick mucus, helps to form a barrier on the intestinal wall and modulate local immune receptors [15].

Recently, the scientific corpus regarding the gut microbiome and its role in health modulation has consistently increased due to better sequencing algorithms and improved hardware tools such as "bacteria for identification and quantification" [16,17]. A method for microbiome profiling is to use targeted amplicon sequencing. This method uses universal primers for highly conserved DNA such as the 16S ribosomal RNA subunit (rRNA) which is encoded by ribosomal DNA (rDNA). This target is present in all bacteria and, in this method, it is amplified by polymerase chain reaction (PCR). Another method is to use metagenomic sequencing, which involves the analysis of the entire genomes of all bacteria from a given site using a shotgun approach [18,19]. These sequencing techniques create a new challenge relating to the analysis of large data sets. Methods for analysis and visualization such as alpha diversity (maximum species richness) and beta diversity (comparison of bacterial communities) are applied via software solutions such as QIIME, Mothur [20,21].

It is possible that bacteria from the gut microbiome might be used as biomarkers for CRC detection, especially *Fusobacterium nucleatum*, *Peptostreoptococcus stomatis* and *anaerobius*, *Parvimonas mica*, and *Solobacterium moorei* [22–25]. Conversely, the healthy gut microbiota mostly consists of Bacterioides (*Bacterioides fragilis*, *vulgatus*, *uniformis*), Firmicutes (*Clostridium* spp., *Ruminococcus faecis*, *Enterococcus faecium*), and Actinobacteria *(Bifidobacterium bifidum)*. It has been shown that some strains of gut bacteria favor tumor promotion through DNA and RNA damage (directly or through interaction with other known food carcinogens) and through local immune inhibition [26–28]. There is also the possibility that protective bacteria (e.g., *Bacillus polyfermenticus*, *Alistipes shahii*, *Lactobacillus casei*) against tumor promotion exist, as reviewed by Zitvogel et al. [29].

Despite current advances in colorectal cancer treatment, especially in the chemotherapy, target therapy, immunotherapy, and radiotherapy treatment modalities, surgery remains the mainstay curative treatment for colorectal cancer patients, even in the oligometastatic setting [30–32]. Surgical complications like anastomotic leakage, excessive blood loss, abscess, and abdominal sepsis can reduce 1-year and 5-year overall survival and increase the recurrence rates for these patients [33]; therefore, we reviewed currently published data focusing on the relationship between gut microbiota and postoperative complications for colorectal cancer patients. We have summarized in Table 1 the main

postsurgical complications along with the prevalent bacteria involved in these processes and their possible effects.

Table 1. Summary of prevalent bacteria found in association with main postsurgical complications. Impact Negative—the microbial agents are associated with increased risk for postsurgical complication. Impact Positive—the microbial agents are associated with decreased risk of postsurgical complication.

Postsurgical Complication	Microbial Agents	Impact
Anastomotic leakage (AL)	*Ruminococcus*, *Blautia*, *Roseburia*, *Coprococcus*, *Acinetobacter Iwoffi*, *johnsonii*	Negative
	Bacteroidaceae and Lachnospiraceae families	Negative without C-seal
	Faecalibacterium prausnitzii	Positive
	Enterococcus faecalis	Positive
Infectious complications	*Clostridium butyricum*, *Bacillus mesentericus*, *Enterococcus faecalis*	Positive
	E. coli, *P. aeruginosa*, *Enterococcus* spp.	Negative
Postoperative ileus	*E. coli*, *Veillonella*, *Rastonia*, Proteobaceria, Bacteroidetes	Negative
	Faecalibacterium, *Actinobacteria*, Firmicutes	Positive
Postoperative adhesions	*E. coli*, *Lactobacillus*	Negative
Malignant transformation	*Fusobacterium nucleatum*, *Bacteroides fragilis*	Negative
	Bifidobacterium	Positive

2. Alterations of Intestinal Microbiota Following Colorectal Surgery

There are several factors that could be involved in changes to the composition of the gut microbiota after colorectal surgery. One factor is stress, related to gut microbiota through the microbiome–gut–brain axis. Stress can influence the composition of the microbiome, and the microbiome can influence the host response to stress through immune, endocrine, and metabolic pathways [34]. Another factor is oxygen exposure during colorectal surgery, which could cause a significant depletion of the facultative anaerobes and obligate anaerobes [34]. In 2014, Shogan et al. demonstrated that in rat models, the opening of the bowel caused a loss of "good" obligate anaerobes, such as *Bacteroides*, and a gain of "bad" facultative anaerobes, such as *Enterococcus* [35]. Research on rat models identified that vascular changes secondary to colorectal surgery may cause temporary or permanent ischemia of the neighboring gastrointestinal tract, thus leading to significant changes in the gut microbiota [35]. Using a reperfusion model, the authors found that changes in gut microbiota started to develop 30 min following colic ischemia and reached a peak at 6 h after reperfusion before gradually recovering. This change consisted of an early increase in *E. coli* and *Prevotella* and a later increase in *Lactobacillus*, in line with reperfusion and epithelial healing [36]. Ohigashi et al. conducted the first study to assess the impact of CRC surgery on the fecal microbiota through 16S rRNA-targeted reverse transcription-quantitative PCR (RT-qPCR) analysis. The results demonstrated a decreased abundance in obligate anaerobic bacteria, including members of *Bacteroides*, *Bifidobacterium*, *Clostridium*, and *Prevotella*, which are crucial for intestinal homeostasis, whereas pathogens such as *Enterococcus*, *Pseudomonas*, and *Staphylococcus* were enriched postoperatively [36].

A decreased diversity in the fecal microbiota, such as a lower ratio of Firmicutes and Bacteroidetes to Proteobacteria and increased levels of *Klebsiella*, were found in CRC patients after the surgery compared to pre-operative CRC patients or to healthy individuals [37,38]. This result has two facets—first, a higher risk for an inflammatory response was observed postsurgery, and second, the strains that are known to be

associated with a higher recurrence risk (*Enterococcus*, *Fusobacterium*) were also destroyed [39]. In contrast, a study done by Liu et al. [40] showed that preoperative levels of *Escherichia–Shigella* genera were higher versus levels in postoperative patients, while postoperative levels of *Enterococcus* and *Parabacteroides* were higher.

3. Anastomotic Leakage and Colorectal Microbiota

Anastomotic leakage (AL) is defined as a defect of the intestinal wall at the anastomotic site, leading to communication between the intra- and extraluminal compartments. The severity of anastomotic leakage should be graded according to its impact on clinical management. Grade A anastomotic leakage results in no change in patient management, whereas grade B leakage requires active therapeutic intervention but is manageable without re-laparotomy. Grade C anastomotic leakage requires re-laparotomy [41]. The microbiome is a new and very promising field of research, especially when studying the etiologies of AL in colorectal surgery. Identifying at-risk patients with unfavorable microbiome compositions, comprising pathogens with high collagenase activity, and treating them with appropriate antibiotic regimen (per os, intravenous, or by enema) and/or fecal transplantation if required could help to reduce AL rate [42]. Further, studying the microbiome might help to explain the protective effect of preoperative oral antibiotics on AL rate. Recent evidence supports the hypothesis that AL might result from a local infective complication, resulting in impaired healing at the anastomotic level due to a local increase in collagenase activity [43].

Jasper et al., in a pilot study, collected fecal samples from 16 patients that had C-seal, of which 8 developed AL. Bacterial 16S rDNA of both groups were analyzed using MISeq technique. They found that *Lachnospiraceae* and *Bacteroidaceae* families were higher in patients with AL, especially *Ruminococcus*, *Blautia*, *Roseburia*, and *Coprococcus*. The most important involved bacteria were the mucin-degrading *Ruminococci* (*R. gnavus* and *R. torques*). Another interesting finding in their study related high BMI to the same bacterial family, especially *R. obeum*, although this was not statistically significant ($p = 0.068$). These findings were surprising, given that it was shown that butyrate-producing bacteria were associated with reduced oxidative stress and with decreased risk of inflammation [44,45]. Later, the same authors did a more extensive study on 123 patients after surgery, out of which 63 had C-seal. They concluded that AL in patients without C-seal could be explained by microbiome diversity, specifically higher levels of *Lachnospiraceae and Bacteroidaceae* families [46]. Their findings suggest no association between microbiome and AL in C-seal patients, although the C-seal group had a higher incidence of AL (25% vs. 17%).

In another study by Palmisano et al., 49 stool samples were analyzed from 27 healthy subjects and 22 patients that had surgery for colorectal cancer, out of which 5 developed AL. They found that the second group had significantly higher levels of *Bacteroides* family bacteria (*Bacteroides fragilis* and *Bacteroides faecis*) compared to healthy subjects (1.5% vs. 0.2% and 1.9% vs. 1.3%). Within the second subgroup, microbiome composition was different between patients that developed AL vs. those that did not— there was a higher level of *Acinetobacter Iwoffi*, *johnsonii* in AL patients, while other species had higher incidence in non-AL patients—*Barnesiella intestinihominis* (4%, $p < 0.05$) and *Faecalibacterium prausnitzii* (2%) (Table 1) [47]. Another possible association with AL risk was shown for the *Bifidobacterium* genus (odds radio 3.96, CI = 1.50–10.51) [48]. It was shown that *Bifidobacterium* inhibits PTGS2 expression, which was shown to promote neovascularization [49,50].

These observations suggest that the C-seal influences the microbial composition after its introduction and that this may ultimately impair anastomotic healing [51]. Moreover, the study of Shogan BD et al. demonstrated that *Enterococcus faecalis* leads to the degradation of collagen IV at the anastomotic level through activation of matrix metallo-proteinase (MMP)-9. In the same study, topical antibiotherapy administered by enema and targeting *Enterococcus faecalis* was shown to reduce AL to 0%, whereas intramuscular

Cefotixin—commonly used for elective surgery prophylaxis—did not reduce collagenase activity or AL risk [52]. Regarding MMP, in a study from Stumpf et al., a lower collagen type I/III ratio and higher expression of MMP-1, -2, and -9 in biopsies of patients with impaired anastomotic healing was found when compared to controls [53]. All these data suggest that an unfavorable microbiome comprising collagenase-inducing pathogens and neovascularization modulation might impair anastomotic healing and result in AL, and that changes in the local microbiome caused by surgery might worsen the situation of patients with already unfavorable microbiome profiles [54].

4. Infectious Complications

Surgical site infection (SSI) following colorectal surgery is a frequent complication associated with increases in morbidity, medical expenses, and mortality. The estimated incidence rate of SSI following colorectal surgery is currently considered to be up to 20%. The most common causative pathogen is *Staphylococcus aureus* (*S. aureus*), which is responsible for 20% of SSIs and, due to high use of antibiotherapy, methicillin-resistant *S. aureus* [55].

The overall surgical site infection rate was found to be 9.6%, of which 5.5% were incisional surgical site infections and 4.1% were organ/space surgical site infections. Patients with rectal cancer had a two-fold increased risk for surgical site infection compared to colon cancer patients. Surgical site infection was associated with lower disease-free survival. In patients that developed SSI, *E. coli* and *P. aeruginosa* were the agents found in patients with colon cancer, while *E. coli* and *Enterococcus* spp. were found in patients with rectal cancer [36,56].

In a study by Naoya Aisu et al., 165 CRC patients were divided into two groups, with one group (n = 75) receiving probiotic tablets with *Clostridium butyricum*, *Bacillus mesentericus*, and *Enterococcus faecalis* while the other group did not. Following the rate of surgical site infections, the authors found that in the nonprobiotic group, 16 patients developed SSI compared to only 5 cases in the probiotic group (p = 0.016), thus showing a statistically significant decrease in SSI with probiotic administration [57].

Generally, the interplay between bacterial strains is complicated and the colonization of tissue with some types of strains might inhibit new strains' development (competitive exclusion) [58]. This seems to be the case for methicillin-resistant staphylococcus aureus (MRSA). Strains of *Lactobacillus* and *Bifidobacterium* were found to inhibit MRSA growth in vitro as well as in vivo [59,60]. Liu Guanwen et al. showed that *Lactobacillus rhamonsus* isolated from human milk inhibited the growth of *S. aureus* in vitro as well as in animal models through α tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) decrease [61].

One other possible mechanism might involve surgical stress, which could promote contamination of microbiota with skin bacteria and lead to the disruption of the local T lymphocytes, thus creating an increased risk of SSI [56,62,63].

5. Postoperative Ileus

Postoperative ileus (POI) is a temporary gastrointestinal motility disorder characterized by nausea, vomiting, inability to eat, and lack of flatus and stool [64]. It has been found that 10–30% of patients have increased morbidity and prolonged hospitalization due to postoperative ileus.

Serotonin, a key neurotransmitter in the digestive tract neurons, with a role in motility and contractility, is modulated by the components of the microbiome and it might be involved in POI production. In a meta-analysis, Drake et al. concluded that serotonin agonists along with μ-receptor opioid agonists reduced the duration of POI. [65] Moreover, a link between microbiome composition and serotonin modulation exists. This relation is due to the stimulation of the colonic enterochromaffin cells by local flora, which in turn leads to the activation of 5-hydroxytryptamine (5-HT) biosynthesis; some bacteria

might even directly produce 5-HT [66,67]. It is possible then that the microbiota influence the length of postoperative ileus.

Another possible factor that might influence POI seems to be the composition of the gut microbiome through the modulation of motility and local inflammation response [68]. One such example comes from a study from Ye Jin et al. in which two patient cohorts that had CRC surgery were analyzed [38]. They found that Firmicutes-to-Bacteroidetes ratio and Fusobacteria were lower in patients with ileus versus those without, while *Escherichia–higella*, *Veillonella*, and *Ralstonia* were present in higher levels in the patients that developed postoperative ileus. *Faecalibacterium* was also significantly reduced in the former group [69]. The authors introduced a second cohort in their study and used *Faecalibacterium* levels as a biomarker to predict the development of postoperative ileus. The AUC obtained for the validation cases was 0.79, a finding that could be used to validate other independent cases using the same model.

In another study on rectal cancer patients that had surgery, Shogan et al. found that patients that developed postoperative ileus had increased levels of Proteobacteria and Bacteroidetes and decreased levels of Actinobacteria and Firmicutes. These changes depended on the postoperative day, with abundance increasing with the number of postoperative days. Moreover, they considered possible confounding variables such as previous intestinal surgery, steroid use, and preoperative chemotherapy/radiotherapy and none were found to affect postoperative ileus risk, thus underscoring the role of microbiome composition in this postsurgical complication [70].

In a study on mice, Pohl et al. described a connection between CD103+, CD11b+ cells, and microbiota which might regulate postoperative ileus. A substantial reduction of interleukin-12 (IL-12) and Nitric Oxide Synthase (iNOS) was identified, and this was seen as a contributor to postoperative ileus following gut microbiota depletion with oral antibiotics [71].

6. Postoperative Adhesions

Peritoneal adhesions are pathological bonds that occur usually between the omentum, loops of bowel, and the abdominal wall. They are mostly induced by surgical procedures in the peritoneal cavity, and their prevalence after major abdominal procedures has been evaluated at 63–97%. Colorectal surgery has proven to be the most significant type of surgery that may cause intra-abdominal adhesions [72].

Peritoneal irritation by infection or surgical trauma can induce a local inflammatory response, with an imbalance in fibrin deposition/degradation leading to peritoneal adhesions. More specifically, a factor in response to tissue damage during abdominal surgery is the local migration of fibroblasts, which tends to induce extracellular matrix production. Matrix metalloprotease can reverse this response and normal healing is then reestablished. Disturbance of this balance leads to peritoneal adhesion formation and microbiota might modulate these responses [72]. It was shown that nonsteroidal anti-inflammatory drugs mitigate the inflammation in animal models, although it is not yet clear if these findings are consistent in human patients [73,74].

An experimental study on such modulation was done by Bothin et al., wherein the authors compared germ-free rats (GF) with ex-germ-free rats contaminated with *E. coli* or *Lactobacillus*. They found that GF rats had decreased peritoneal adhesion formation compared to rats contaminated with *E. coli* or *Lactobacillus*. The authors concluded that the probable bacterial leakage might be the main culprit [75]. These findings are also consistent with other results in animal models in which antibiotherapy was found to neutralize most microbiome composition, leading to a decreased risk of adhesion formation [76]. Other similar important findings showed an association of lower serotonin production with short-chain fatty acid synthesis in GF mice [77,78].

7. Long-Term Outcomes

Patients that have surgery for CRC usually develop complications in the long term, and it has been found that microbiota can also influence these. Two types of bacteria have been shown to be involved in the pathogenesis of new colorectal cancers and adverse outcomes—*Fusobacterium nucleatum* (*F. nucleatum*) and *Bacteroides fragilis* (*B. fragilis*). It seems that *F. nucleatum* is associated with an increased risk of malignant transformation, as was shown by Flanagan et al. Enterotoxigenic *B. fragilis* was found in abundance in patients that had low-grade dysplasia compared to healthy individuals. Lin et al. studied long-term metabolic alterations after CRC surgery. They found that patients with right hemicolectomy had a higher risk of intestinal dysbiosis, as shown by a lower Firmicutes/Bacteroidetes ratio, higher levels of Fusobacterium, and lower levels of *Faecalibacterium prausnitzii* compared to the patients with lower anterior resection.

In the study by Flanagan and colleagues, shortened recurrence-free survival was demonstrated in CRC patients with higher levels of *F. nucleatum*. The presence of enterotoxigenic *B. fragilis* in the colonic mucosa was associated with a higher colorectal cancer stage [79]. Additionally, Wei et al. concluded that the 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, the authors identified that *B. fragilis* can induce NF-κB signaling and release of inflammatory cytokines. Thus, one intervention that can shape the microbiome before surgery and potentially downstage colorectal cancer is mechanical and antibiotic bowel preparation [80].

On the other hand, it was shown that *Bifidobacterium* might stimulate a local antitumor immune response through effects similar to that of programmed cell death protein ligand 1 (PD-L1) or through death protein 1 (PD-1) and enhanced CD8+ T cells, which might offer a more favorable outcome in patients with CRC [81]. These effects on immune modulation might work in synergy with anti-PD-1/PD-L1 monoclonal antibodies given to patients that are PD-L1 positive or who have microsatellite instability [82].

Kosumi et al. showed that the number of *Bifidobacterium* was related to the number of signet-ring cells, a finding that should be confirmed by future studies. The study showed no association between the number of intratumor bacteria and local immune response. The hypothesis was given that the cancerous cells might utilize the lactic acid and acetate produced by bacteria and, given the new tumoral milieu, the protective effect of *Bifidobacterium* might be mitigated [46].

8. Conclusions and Future Perspectives

Many important findings are available regarding the gut microbiota in relation to gastrointestinal tract health and even to mental health. To date, some findings have supported the idea that bacteria (e.g., *E. faecalis*, *P. aeruginosa*, *Lactobacillus*, *Faecalibacterium*, *Enterococcus faecalis*, and *E. coli*) might influence postsurgical events such as anastomotic healing, infectious complications, ileus, and adhesion formation, while strains such as *Bifidobacterium* might be used to improve local immune response in healthy individuals and to prevent future colorectal oncologic events. It seems that the context of bacterial composition is important, as was hypothesized in the study of Kosumi et al. where *Bifidobacterium*, normally known to provide local antitumor properties, promoted tumor growth in patients with CRC and, possibly, the presence of signet-ring cells.

Regarding the risk of anastomotic leak after colorectal surgery, a lower diversity in microbiota seems to be a prognostic factor for AL but only in patients that have classical surgery. It is important to extend the study on C-seal patients, since in this group no correlation was found with microbiome diversity. On the other hand, intervention studies with antibiotics might shed some light on the causal patterns of some bacterial families and even on the mechanisms involved such as collagen degradation by bacteria. Additionally, given the fact that the increased usage of antibiotics has led to resistant

bacterial strain selection, the possibility of colonization exclusion through butyrate-producing bacteria might deserve further investigation.

Postoperative infections decrease survival in patients and antibiotherapy is necessary. It would be interesting to check whether strains that normally inhibit MRSA would also have the same effect in patients that had CRC surgery, thus reducing the rate of MRSA infections. One study indeed showed that administration of perioperative probiotic tablets in patients that underwent CRC surgery was associated with a significantly lower risk of SSI. Given these results, other similar investigations should be pursued, using the same probiotic agents and others as well.

Postoperative ileus, another important postsurgical complication, might play a role in the development of intestinal dysbiosis, which in turn might lead to microbiome compositions compatible with CRC recurrence. As for the other complications, *Faecalibacterium* levels and Firmicutes-to-Bacteroidetes ratio are associated with this surgical complication. Continuation of this line of research might be necessary to validate the model developed by Ye Jin et al. and to check the role of *Faecalibacterium* as a biomarker for postoperative ileus. Another possibility would be to establish a potential causation relationship by manipulating microbiome composition before and after surgery, for example using either antibiotics or fecal transplant. Along these lines, basic research on the local immune response, as was done by Pohl et al., remains continuously important. Given the immune interplay between bacteria and intestinal mucosa shown by Pohl, the findings of Shogan et al. in which corticosteroids did not seem to influence the risk of postoperative ileus might offer another possibility for investigation. This relationship might be tested using *Faecalibacterium* levels as well as Firmicutes-to-Bacteroidetes ratio as parameters. Another lead might be to determine the role of serotonin in patients with postoperative ileus. Some studies have demonstrated that serotonin agonists decrease the length of the complication; thus, a study using colonization with serotonin-stimulating bacteria or even with serotonin-producing bacteria might be conducted in animal models.

Postoperative adhesion formation, which poses a risk especially for long-term survivors, is modulated by local inflammatory response. To mitigate the risk, NSAIDs might be used, or other drugs that inhibit neovascularization and fibroblast local invasion. Since metalloproteases degrade the extracellular matrix resulting from fibroblasts, some strains of bacteria might regulate this process, as was shown Wei et al. A possible direction for investigation would be to check whether bacteria such as *F. nucleatum* or *B. fragilis*, which are known to modulate MMPs, play a role in this complication. Similarly, buryrate-producing bacteria such as *Faecalibacterium prausnitzii* are known to decrease the inflammatory response and thus might be another avenue for research in conjunction with postoperative adhesion formation. Antibiotherapy effects on the microbiome in this setting could also be investigated, as it was found in animal models that the onset of adhesion formation was slowed.

These findings are mostly from studies involving animal models, and more studies in human patients are needed to establish causative links between different bacterial strains and postsurgical complications.

A great challenge is represented by the amount of data collected from fecal samples, with this kind of analysis requiring expertise and multidisciplinary collaboration between clinical researchers, statisticians, and bioinformaticians. While some associations might be found between composition and a given risk, one needs to consider possible mechanisms for these effects, construct a physio-pathological model, and add in possible confounding variables such as smoking, diabetes, age and frailty, obesity, and medication.

Studies on human patients still cannot directly point to the direction of causation; all these findings seem only to scratch the surface of a vast domain.

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