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Review

Gut microbiota controlling radiation-induced enteritis and intestinal regeneration

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Cancer remains the second leading cause of mortality, with nearly 10 million deaths worldwide in 2020. In many cases, radiotherapy is used for its anticancer effects. However, radiation causes healthy tissue toxicity as a side effect. In intra-abdominal and pelvic malignancies, the healthy bowel is inevitably included in the radiation field, causing radiation-induced enteritis and dramatically affecting the gut microbiome. This condition is associated with significant morbidity and mortality that impairs cancer patients' and survivors' quality of life. This Review provides a critical overview of the main drivers in modulating the gut microenvironment in homeostasis, disease, and injury, focusing on gut microbial metabolites and microorganisms that influence epithelial regeneration upon radiation injury.

Highlights

By controlling the diet–gut microbiota–host triangle, the scientific community could uniquely contribute to public health.

Radiation causes intestinal dysbiosis, decreases the diversity of the gut microbiota, and significantly impairs intestinal health.

Short-chain fatty acids and microbial tryptophan catabolites act as radioprotectors.

The use of diets, fecal microbiota transplants, and the administration of specific microbial strains and gut microbial metabolites look to be promising therapies for treating or preventing radiation-induced enteritis.

Radiotherapy causes deleterious intestinal side effects

The main task of the digestive system is to transform food into nutrients and energy to maintain life. The gastrointestinal (GI) tract is a twisting channel within the digestive system that transports food from the mouth to the rectum. As soon as the oral bolus reaches the stomach through the esophagus, the stomach wall releases enzymes and hormones that digest the food and break it down into nutrients. After 3 h, the chyme moves into the duodenum, which mixes food with enzymes and bile to digest it and make nutrients available for absorption in the lower regions, such as jejunum and ileum, where millions of intestinal villi absorb nutrients. Ultimately, leftovers, such as fibers, phytochemicals, lipids, and proteins, reach the colonic region. The intestine also contains microorganisms (Box 1), including bacteria, archaea, fungi, and viruses, that live in the digestive tract and constitute the gut microbiome [1]. By biotransforming available nutrients, the gut microbiota produces spatial and temporal-specific **gut microbial metabolites (GMMs)** (see Glossary) that are affected by environmental factors, such as the diet, and may interact in a healthy or toxic fashion with our intestinal epithelial cells (IECs) [2–5].

The effects of ionizing radiation on the intestine and other tissues were first reported by David Walsh in 1897 [6] 2 years after the discovery of X-rays by Wilhelm Roentgen [7]. Unfortunately, radiotherapy in the abdomen, pelvis, or rectum affects the function of the digestive system and the gut microbiome. The development of successful strategies for cancer treatment has rapidly increased the cohorts of irradiated cancer survivors, approximately 12 million in Europe [8], and will likely keep growing. Roughly 50% of cancer patients undergo radiotherapy, and half are irradiated in the abdominal or pelvic cavity, typically as a treatment for cervical, prostate, colon, or pancreatic cancer [9]. Despite progress in developing more precise radiotherapy techniques, up to 90% of patients undergoing radiation therapy in the abdomen, pelvis, or rectum develop **radiation-induced enteritis** due to the proximity of the GI tract to the pelvic organs (Figure 1). Initially, radiation triggers apoptosis of proliferative cells and denudes the intestinal mucosa. As a result, radiation causes inflammation. Patients initially suffer acute enteritis that is typically resolved without any further treatment due to the high regenerative potential of the intestine

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Box 1. Gut microbiota and implications in human health

The human intestine harbors a complex ecosystem of microorganisms [108] that have coevolved with its host over millions of years of evolution [19]. This complex ecosystem plays a critical role in maintaining gut health. In a healthy gut environment, the gut microbiome is characterized by a diverse community of beneficial microorganisms that help digest food, produce GMMs, and maintain a healthy immune system [4]. During the centuries, however, the gut microbiota has undergone substantial remodeling due to antibiotic use, improved sanitation, cesarean sections, infant formulas, and western dietary patterns. This environmental pressure has selected microbial taxa, and, in turn, molecular signals. The loss of ancestral microbial signals could encode a misregulation of important systems, including intestinal regeneration, immune function, and metabolism. This microbial shift could contribute to the broad spectrum of non-communicable and chronic diseases, including cancer.

In colorectal cancer, the gut microbiome undergoes significant changes, which may contribute to the development and progression of the disease. The gut microbiome in colorectal cancer is characterized by reduced diversity of bacteria and a shift toward potentially harmful bacteria. A cross-cohort study has shown that *Fusobacterium nucleatum*, *Solobacterium moorei*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *Peptostreptococcus stomatis,* and *Parvimonas* spp. were more prevalent in colorectal cancer patients [19]. These specific microbial strains have been associated with inflammation, tumor growth, and the evasion of the immune system in colorectal cancer [109,110]. The gut microbiome could contribute to the progression of the disease by creating an environment that facilitates cancer growth via GMMs. In a healthy gut environment, the gut microbiome produces SCFAs, such as butyrate, acetate, and propionate, which have anti-inflammatory properties and are crucial in maintaining gut health. However, in colorectal cancer, the production of SCFAs is reduced, and there is an increase in the production of toxic metabolites, such as trimethylamine, p-cresol sulfate, LPS, and secondary bile acids [111,112]. By controlling the diet–gut microbiota–host triangle, personalized nutrition could thus push the limits of nutrition and microbiome research and make a unique contribution to public health.

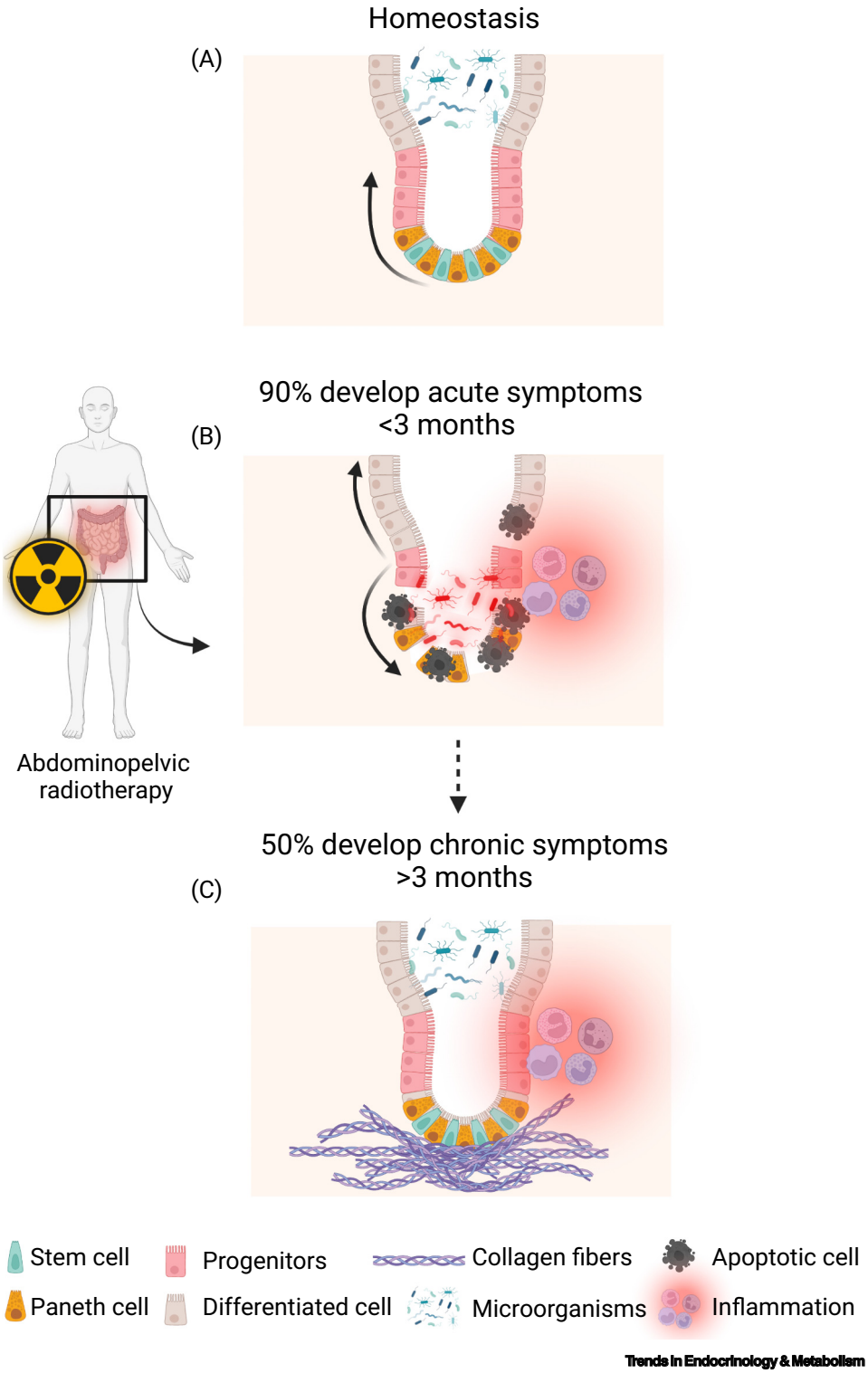
[9]. However, the enteritis symptomatology is dramatic and includes bleeding, malabsorption, diarrhea, abdominal pain, nausea, and vomiting. Moreover, due to the severity of these effects, some patients must interrupt the treatment, jeopardizing the effectiveness of anticancer treatment. Half the irradiated patients develop some form of chronic GI dysfunction [9]. Unfortunately, chronic radiation-induced enteritis is manifested in 50% of irradiated patients [9], and the cellular and molecular causes remain unknown. Unlike in cases of acute enteritis, the subepithelial layers are drastically affected by fibrosis of the intestinal wall. Altogether, these pathologies may cause intestinal obstruction and perforation, thus leading to surgical resection, with 10% of cases resulting in death [10,11]. Sadly, treatments are only palliative, as no medical cure exists [12]. The most commonly adopted approach now is still a reduction in the delivered radiation dose, which may inevitably decrease treatment efficacy [9,13,14]. Due to the widespread application of radiotherapy for cancer, the long-term effects of radiation are now a serious medical issue [15]. Numerous studies have consistently shown that the gut microbiota and its metabolites play a crucial role in regulating epithelial regeneration following injury. These microbial communities and their byproducts are heavily influenced by dietary patterns and lifestyle choices. In this comprehensive review, we provide an up-to-date and insightful analysis of this field, shedding light on the key factors that modulate the gut microenvironment during both homeostasis and injury. Specifically, we emphasize the impact of GMMs and microorganisms in promoting epithelial regeneration, with a focus on their role in mitigating radiation-induced damage.

Radiotherapy and the gut microbiota

In homeostasis, microorganisms and IECs communicate bidirectionally and create a harmonious environment that could be defined as healthy due to the absence of GI diseases, and the absence of increased intestinal permeability and mucosal inflammation [16]. However, western dietary patterns, enteric infections, antibiotics, abdominal surgery, and radiotherapy could cause undesirable **dysbiosis** [17] (Box 1). The lack of balance in a microbial community has been associated with potential diseases or even the apparent onset of clinical symptoms [18–20]. Most studies reported that radiotherapy-induced dysbiosis decreased microbiota richness [21–27] (Figure 2). Thus, dysbiosis occurs at the same time as radiation-induced enteritis. However, whether

Glossary

Acellular diet: this diet typically includes highly processed foods that eliminate cellular components, such as whole cells or intact tissues. Acellular food can be high in calories, sodium, sugar, and fats, providing microbial and human cells with more easily digestible substrates and increasing disease risk.
Alpha diversity: a major indicator to describe the diversity of the gut microbiota, referring to the number and abundance of different microbial species or taxa within an individual's gut. Generally, higher alpha diversity is considered a marker of good health, as it suggests a more diverse and robust microbial community capable of performing a range of metabolic functions. On the contrary, lower alpha diversity of the gut microbiota is associated with diseases.
Dysbiosis: disturbance and imbalance of a harmonious composition of gut microbiota. Dysbiosis can change bacterial species diversity and abundance, and alter microbial functionality.
Fecal microbiota transplantation: stool from a healthy donor is transplanted into another patient's GI tract to modulate the gut microbiota, reverting the composition and functionality. The procedure is performed by collecting fecal matter from a healthy donor, removing any solid matter, and then transplanting it into the patient's gastrointestinal tract via colonoscopy, nasogastric tube, or enema. FMT is generally considered safe, although there is a risk of complications, such as infection or allergic reaction.
Firmicutes/Bacteroides ratio: measures the relative abundance of two major bacterial phyla in the human gut microbiota. This ratio is widely accepted to have an important influence on maintaining normal intestinal homeostasis. However, this ratio is just one of many factors (diet, age, and genetics) influencing gut microbiota composition and function.
Gut microbial metabolites (GMMs): the gut microbiota produces a diverse metabolite repertoire by breaking down dietary products and endogenously synthesizing essential cofactors. These metabolites can affect human health, including modulating immune function and regulating metabolism. GMMs represent a promising therapeutic tool for numerous disorders.



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Microbe-associated molecular patterns (MAMPs): molecular structures present in microorganisms, including bacterial cell walls, lipopolysaccharides, peptidoglycans, and flagellin, among others.

Radiation-induced enteritis: side effect of abdominal radiotherapy. Half the irradiated patients will develop some form of chronic gastrointestinal dysfunction, including radiation-induced chronic enteritis, whose symptomatology is characterized by atrophy of the mucosa and fibrosis of the intestinal wall. The symptoms comprise malabsorption, diarrhea, intestinal obstruction of the lumen, and intestinal perforation.

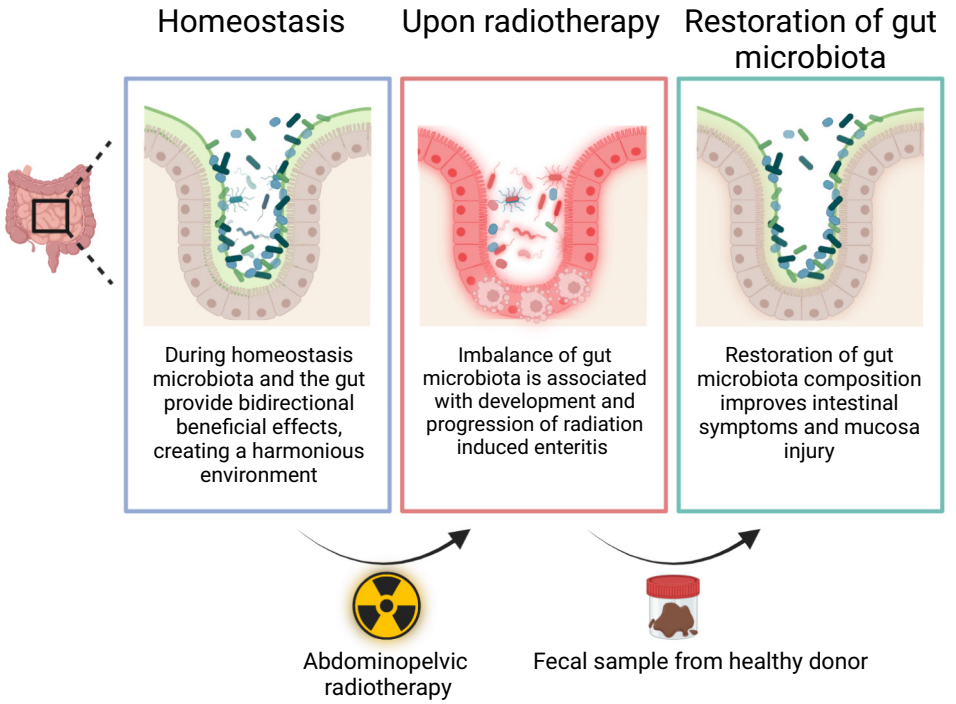

Figure 2. Radiation injury causes dysbiosis, which correlates with acute radiation-induced enteritis severity. In mice, symptomatology of radiation-induced enteritis can be improved using fecal transplantations that restore gut microbiota composition if this is conserved in humans and remains poorly characterized.

dysbiosis plays a role in establishing radiation-induced enteritis and enhancing the severity, or contrary to this, merely correlates with the disease, remains poorly characterized. Furthermore, one major problem of studying the microbiome after radiotherapy is that in some cases, patients are receiving a combined treatment of radiotherapy, chemotherapy and intensive use of antibiotics which may also lead to microbiota dysbiosis [28–31]; therefore, it is difficult to establish the causality between radiotherapy and gut dysbiosis.

In this frame, several research studies [23,24,32] have demonstrated that patients who developed acute diarrhea after radiotherapy had significant changes in the composition of their gut-microbiota compared to healthy volunteers or treated patients that did not develop acute diarrhea. The literature has underlined that patients who progressed to diarrhea had significantly lower microbial **alpha diversity** and **Firmicutes/Bacteroides ratio** compared with those who did not develop diarrhea, suggesting that microbial taxa may be a predictive marker of diarrhea induced by radiation. Indeed, Clostridia, linked to promoting regulatory T cell expansion and protection from colitis and allergic diarrhea [33], was significantly less abundant in patients who developed radiation-induced enteritis and diarrhea. On the contrary, a higher alpha diversity

Figure 1. The clinical course of patients undergoing radiotherapy to the abdominopelvic region and consequential development of radiation-induced bowel injury over time. During steady-state crypt, intestinal stem cells and progenitors divide to produce the differentiated progeny (A). Upon radiation injury, progenitors and stem cells are depleted, causing tissue inflammation, and regeneration evolves via surviving intestinal stem cells and dedifferentiation of progenitors and differentiated cells (B). Three months after radiotherapy treatment, 50% of the patients develop gastrointestinal disorders, including chronic radiation-induced enteritis that eventually leads to fibrosis (C).

was positively correlated with better patient-reported GI function [22,24,25]. Although these studies provide vital evidence for a link between gut microbiota, radiotherapy, and post-radiotherapy diarrhea, unfortunately, they do not shed light on the mechanistic relationship between gut microbiota and radiation enteritis. Therefore, it is clear that diarrhea is concomitant with changes in the gut microbiota. However, whether these changes cause those symptoms remains elusive.

The importance of gut microbiota in health and disease is a growing interest [34,35], and many therapeutic strategies to restore the balance of the intestinal ecosystem have been implemented [36,37]. These strategies include the administration of probiotics, prebiotics, symbiotics, phage therapy, and **fecal microbiota transplantation (FMT)** (Figure 2). Recently, the latter has been suggested as an attractive therapeutic strategy for restoring gut microbiota composition [38]. Ding and collaborators attempted to establish a cause–effect link between gut microbiota and radiotherapy side effects by performing an FMT on five patients with radiation enteritis [39]. Three of the five patients highlighted increased microbial diversity quantified by Shannon's diversity index after the transplant. Additionally, FMT led to satisfactory amelioration in rectal hemorrhage, fecal incontinence, diarrhea, and abdominal and rectal pain. However, it is worth noting that the specific strains altered remain unknown. Moreover, there were several limitations to that study, including (i) the lack of appropriate untreated controls; (ii) the low number of patients analyzed; and (iii) the clarification of changes in patients' symptoms and gut microbiota, whether those symptoms come from the FMT or represent the natural course of the disorder was not addressed. Therefore, it is difficult to establish the causality of FMT in the symptom improvement.

A pioneer animal study investigated a mice population that recovered from high-dose total body radiation and lived average life spans [40]. In this study, 'elite-survivors' harbored a distinct gut microbiota compared with age-matched controls. The authors identified in the elite-survivor group higher abundances of Lachnospiraceae and Enterococcaceae. To confirm the relationship between gut microbiota and radioprotection, germ-free (GF) and specific pathogen-free (SPF) C57BL/6 mice were transplanted with stools from elite-survivors or age-matched controls. After radiation, animals containing elite-survivor microbiome were able to reduce clinical scores and expand survival rates compared to GF and SPF controls. The elite-survivor microbiome was enriched with Lachnospiraceae. Both Lachnospiraceae and Enterococcaceae increased the production of SCFAs (see following text), but also could have regulated the immune system, produced vitamins, and protected against pathogens. In another study, by performing 16S rRNA, Kim and colleagues showed that after γ-irradiation exposure, the genus *Alistipes* increased in the large intestine and the genus *Corynebacterium* in the small intestine [41]. Both genera have been associated with GI pathological conditions that may contribute to diarrhea and irradiation injuries. Although this study considered the spatial distribution of microorganisms, the sample size was relatively small, and the irradiation effect was not analyzed over time. Analyzing the gut microbiota spatially and longitudinally over time (before, during, and after irradiation) would provide more detailed information on how microbial communities evolve at taxonomical and functional levels (see Outstanding questions).

In summary, several studies have investigated how the gut microbiota is affected by radiotherapy in animal models and humans. Nevertheless, the different techniques applied to characterize the taxonomic distribution, types of samples (fecal samples versus biopsies), various doses and duration of radiation exposure, different time points after irradiation, and reduced sample size constitute a remarkable limitation to interpreting the results collectively. Therefore, the homogenization of criteria would significantly improve the comparison of different datasets and translate these findings into clinical practice. Considering that the gut microbiota varies between mice and is influenced by many factors, we recommend using a large sample size to increase the

statistical power and a longitudinal sample collection of biological fluids and tissues over time to compare better between healthy and irradiated animals. The same applies to clinical trials where control and treated participants must receive standardized radiation doses and diets followed by a longitudinal sampling to reveal the role of the microbial strains and GMMs.

Gut microbial metabolites ruling intestinal regeneration

Recent *in vitro* and *in vivo* studies have shown that microbial strains and GMMs modulate epithelial regeneration upon injury (Box 2).

In vitro studies

Using mouse intestinal organoids (IOs) (Box 2), several groups have shown that the probiotic *Lactobacillus reuteri* promoted intestinal proliferation via the Wnt signaling pathway [42,43], thus indicating that probiotic treatment could be used as a nutritional strategy to reduce ulceration inflammation and enhance intestinal regeneration. Probiotics, such as *L. reuteri* might alleviate radiation side effects. However, how probiotics exert beneficial effects on IECs remains unclear (Figure 3). A research study investigated a potential interaction between **microbe-associated molecular patterns (MAMPs)**, such as muramyl dipeptide, and murine IOs [44]. This study showed the ancestral symbiosis between mammals and their intestinal microbiota. ISCs express the cytosolic innate immune sensor, nucleotide-binding oligomerization domain-containing protein (NOD)2, that can interact with MAMPs. Firstly, IOs treated with ligands for NOD2 led to an increase in organoid number and size [44]. Secondly, murine IOs that were treated with lactate derived from bacteria displayed significantly increased $Lgr5^+$ (ISCs) and organoid growth, suggesting there may be specific MAMPs that interact with the host cells to modulate the ISC response [45]. However, all MAMPs do not promote regeneration, which is the case of LPS that triggers inflammation. In another study using mouse IOs, the authors claimed that LPS induced differentiation toward secretory lineages [46]. This experiment could have mimicked the release by shedding or through bacterial lysis of LPS after radiation and the role of this glycoconjugate on IECs. However, readouts were quantitative PCR; therefore, it is difficult to unravel if there were changes in the gene expression of particular markers or, contrary to this, the number of specific lineages was affected.

These experiments indicate that MAMPs interact with IECs. However, many of these studies present a key limitation: the lumen of the intestinal organoids faces inwards. The correct polarity of the gut must be considered for experiments with MAMPs, GMMs, and microbial strains. Therefore, beyond the fact that organoids represent a simplified model and always require *in vivo*

Box 2. Intestinal regeneration

The intestinal epithelium, the most frequently renewing organ in adult mammals, is composed of crypts of Lieberkuhn connected to villi, which are finger-like protrusions. The cells facing the lumen are epithelial cells, categorized into five kinds of mature cells, including enterocytes, goblet cells, enteroendocrine cells, Paneth cells, and tuft cells. All these mature cells are derived from $Lgr5^+$ ISCs, which reside at the crypt base and harbor self-renewal and differentiation capacities [28]. In response to injury, the ISC niche adapts to ensure epithelial regeneration beyond the homeostatic state. The epithelial restitution is achieved by the proliferation of active ISCs ($Lgr5^+$) or via dedifferentiation of progenitors, and committed cells that acquire a fetal-genetic program to *de novo* produce ISCs [113].

IOs recapitulate many properties of the intestine, including the heterogeneity of the cellular composition, appropriate physiology, region-specific features of the intestine, and self-renewal dynamics [114]. These self-organized 3D structures provide a powerful tool to study mouse and particularly human intestinal biology, opening new horizons to explore the diet–gut microbiota–host triangle and intestinal regeneration [115–117]. Whether the gut microbiome and GMMs play a role in intestinal regeneration remains poorly characterized. In fact, we are just beginning to address how the exceedingly complex microbial communities and their derived GMMs influence epithelial repair and regeneration using mouse models. Recent *in vitro* and *in vivo* studies have demonstrated that gut microbiota and GMMs are essential in epithelial regeneration upon injury.

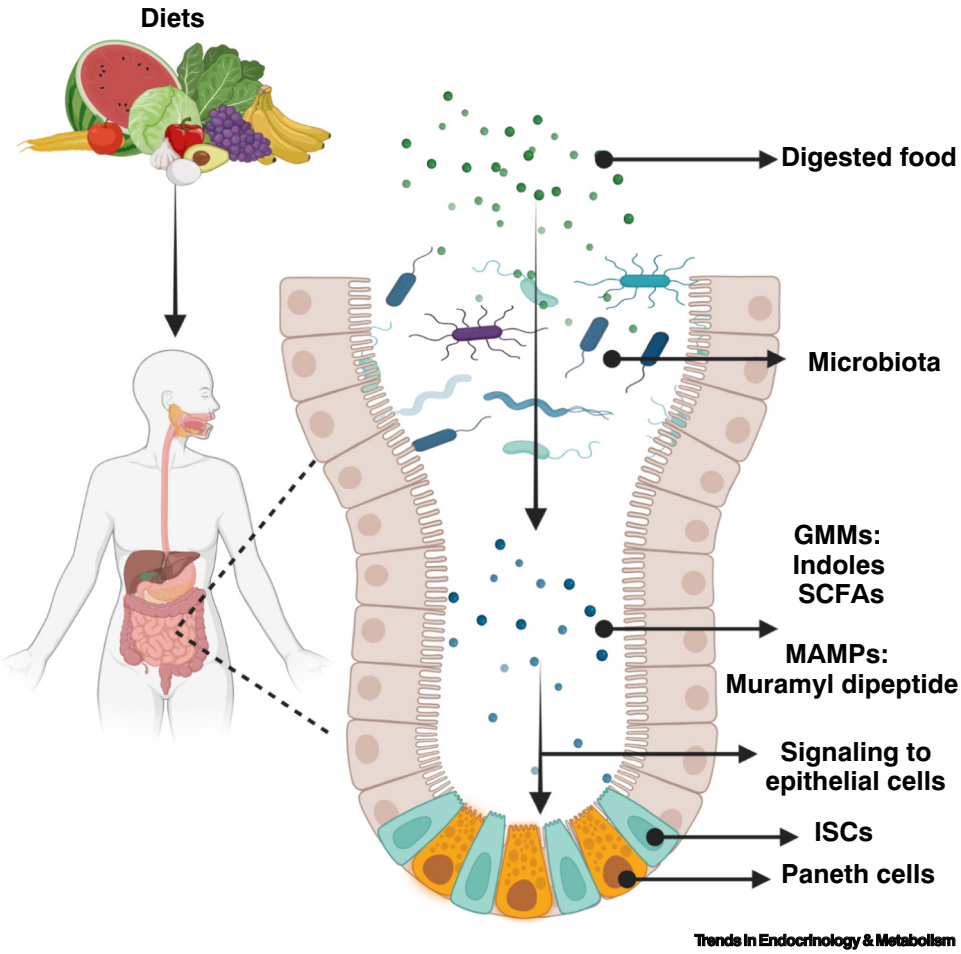

Figure 3. Diet–gut microbiota–host triangle. The gut microbiome shapes the chemical structure, lifespan, bioavailability, and biological activities of most of the compounds ingested via diet, releasing gut microbial metabolites (GMMs). Microorganisms also shed molecular structures known as microbe-associated molecular patterns (MAMPs). Both GMMs and MAMPs orchestrate intestinal stemness and differentiation on intestinal epithelial cells.

validation [47,48], microbial strains, MAMPs, and GMMs must be exposed to the apical membrane to avoid impairing the interpretation. This problem could be addressed by performing microinjections into the intestinal organoid lumen [49,50], which requires time and instrumentation, or by exposing 2D organoid monolayers [51,52] to microbial strains, MAMPs, or GMMs.

In vivo studies

Several *in vivo* studies indicate gut microbiota–cell interactions influencing epithelial repair and regeneration. As described in the preceding text, Guo and collogues investigated a population of mice that recovered from high-dose radiation to live an average lifespan. Most importantly, this research demonstrated that GMMs might act as radioprotectors [40]. Propionic acid, a SCFA produced by the fermentations of dietary fibers [53,54], significantly increased the survival rate, mucus thickness, crypt length, attenuated radiation-induced loss of granulocyte–macrophage progenitors and reduced intracellular reactive oxygen species (ROS) levels in bone marrow stem cells. Microbial tryptophan catabolites, such as indole-3-carboxaldehyde and kynurenic acid, raised considerable survival rates too. These GMMs have been strongly associated with the intake of fiber-rich foods [55,56]. In this frame, Cui and colleagues proved that FMT increased

the survival of irradiated animals [57], and in a follow-up study, the same group claimed that some of the effects induced by FMT were mediated via a GMM, indole 3-propionic acid [58], which has recently demonstrated to boost chemotherapy [59] and barrier functionality [5,60–62]. These findings provide insight into the crucial significance of the gut microbiota–gut epithelium axis in generating signals to protect against radiation, demonstrating that GMMs could prevent the adverse side effects of radiation exposure.

Lee and collogues revealed how lactic acid-producing bacteria, including *Bifidobacterium* and *Lactobacillus*, support intestinal epithelial cell regeneration. Symbiont-derived lactate is sensed by G-protein-coupled receptor 81 on Paneth and stromal cells to promote regeneration in a Wnt3/β-catenin-dependent manner. In addition, the authors showed that lactate preadministration protects mice exposed to radiation- and chemotherapy-induced intestinal damage [45]. This agrees with a recent publication that shows that gut microbiota promoted ISC self-renewal [63]. In this study, the authors illustrated a complex crosstalk among gut microbiota, intestinal nerve cells, intestinal immune cells, and ISCs. The authors determined valeric acid an another SCFA, promoted Tph2 expression in enteric serotonergic neurons by blocking recruitment of the NuRD complex onto the Tph2 promoter. At the same time, 5-hydroxytryptamine activated prostaglandin (PG)E2 production in a $PGE2^{+}$ macrophage subset through its receptors HTR2A/3A. Subsequently, PGE2 via binding its receptors EP1/EP4 promoted Wnt/β-catenin signaling on ISCs to accelerate self-renewal.

The Thaddeus S. Stappenbeck laboratory recently demonstrated that a specific GMM modulated the epithelial regeneration upon injury [64]. Deoxycholate (DCA), one of the most abundant secondary bile acids in humans produced by intestinal microorganisms [65,66], promoted repair phases via PGE2 regulation. DCA levels were locally diminished in the wound during barrier re-establishment, boosting PGE2 production and barrier re-establishment. However, during the wound channel formation phase transition, DCA levels increased to inhibit PGE2 production and promote crypt regeneration. Note that abnormally high levels of DCA have been associated with dysbiosis and diseases, such as colorectal cancer [67]. In addition, a long-term high-fat diet (HFD) in mice impaired the intestinal mucosal barrier by damaging ISCs. An HFD increased the concentration of DCA and decreased the secretion of interleukin-22, which plays an important role in the proliferation, repair, and regeneration of ISCs [68].

Further support for the role of gut microbiota in tissue regeneration comes from a study that claimed that an injured inflammatory environment shifted the microbial composition near the site of the wound bed, including the enrichment of *Akkermansia muciniphilia*, which contributed to the enhanced repair of mucosal wounds [69].

The diet–gut microbiota–host triangle has demonstrated that gut microbiota and GMMs modulate intestinal stem cell behavior (Figure 3). Therefore, this field constitutes a novel and exciting paradigm to develop non-invasive treatments for cancer patients and survivors of radiation enteritis (see Outstanding questions). However, whether the reported effects of these microorganisms and GMMs on intestinal stemness and differentiation are equal on healthy, damaged, and cancerous cells remains to be seen. This is of relevance to implementing the previously-mentioned results into clinical practice. Here research comparing the effects of GMM in healthy, injured and tumorigenic tissues is highly required.

Dietary patterns modulate intestinal stemness and regeneration

The balance between self-renewal and differentiation of ISCs is essential for intestinal epithelial homeostasis and can be regulated by dietary patterns, nutrients, microbial communities, and

GMMs. Nutritional interventions profoundly influence the composition of the gut microbiota in mice and humans [70]. During the last few decades, several diets promoting gut health have been proposed using animal models, including calorie restriction [70,71], intermittent fasting [72,73], ketogenic diets [74,75], protein restriction [76], and essential amino acid restriction [77]. Although these diets hold promise and have shed light on paramount mechanisms, such as the mechanistic target of rapamycin (mTOR) [77,78], they were scarcely implemented for cancer patients and survivors that suffer radiation-induced enteritis.

Calorie restriction is defined as energy intake, 60–80% of average caloric intake, without causing malnutrition. Caloric restriction and fasting effectively increase lifespan and promote tissue regeneration by improving adult stem cell function in several tissues [79–81]. Several studies have shown that Paneth cells, a crucial part of the ISC niche, were targeted by caloric restriction. First, Paneth cells increase in number, and, in turn, this increases the number of ISCs and their regenerative potential [82–84]. At the molecular level, caloric restriction diminishes mTOR complex 1 activity in the Paneth cells and, as a result, increases secretion of cyclic ADP ribose that promotes ISC self-renewal [82,84,85]. Thus, a calorie restriction acts via a non-cell-autonomous mechanism over the stem cells. A recent study claimed that intestinal epithelial autophagy is required for the regenerative benefit of calorie restriction. Williams and colleagues reported that luminal levels of primary bile acid glycocholic acid were modulated by epithelial cell autophagy during calorie restriction with direct effects on epithelial stem cell function [86]. This study used a small sample size, and the significant variability within the groups makes it challenging to arrive at definite conclusions. Similarly, fasting promotes IEC regenerative capacity after damage by preserving ISC function [83,87–90]. For instance, a fasting-mimicking diet can effectively ameliorate the symptoms and pathogenesis of inflammatory bowel disease caused by dextran sulfate sodium by reducing the inflammation of the intestine, promoting the regeneration and repair of the damaged intestinal epithelium, and stimulating a protective gut microbiota [88,90]. Furthermore, 24-h fasting increased surviving crypt number and promoted the organoid-forming capacity in ISCs and crypts [83].

Unhealthy eating habits, such as HFDs, western-style diets, and **acellular diets** containing excessive ultraprocessed food promote overnutrition and induce a plethora of changes ranging from alterations in enterocyte subcellular structures [91] and erosion of the whole crypt–villus organization [92] to alteration in the composition and physiological performance of the gut microbiota [93,94]. The western dietary pattern has shown to directly boost ISC proliferative activity through enhanced β-catenin signaling and reduce Paneth cell number, leading to increased villi length in the small intestine [95–99] that increases the absorption of nutrients and, in turn, ISCs are highly prone to stem cell exhaustion, an integrative hallmark of aging [100]. Simultaneously, HFD increases the level of bile acids that erode intestinal villi, leaving ISCs more exposed to toxic metabolites [92]. Additionally, HFDs perturb the intestinal cellular hierarchy, and secretory progenitors suffer a switch toward enterocytes to improve lipidic absorption [101]. By using IOs growing efficiency as a proxy of stemness, it has been shown that HFDs enhanced the stemness and reduced the budding capacity of the organoids, indicating a more immature phenotype [95]. Besides increasing the ISCs numbers, HFD also leads to intestinal inflammation that may increase the risk of intestinal cancer development [95,102,103]. In this frame, Mana and coworkers demonstrate that an HFD enhanced intestinal stemness and tumorigenicity through a peroxisome proliferator-activated receptor–fatty acid oxidation program [104]. Paradoxically, both caloric restriction and fasting increase the number of ISCs. However, unlike HFDs, caloric restriction decreases the risk of tumorigenesis [105,106]. Thus, indicating similar phenotypes with likely different molecular mechanisms behind them. Understanding whether a specific diet and microbial community modulate cells specialization along the crypt–villus axis on healthy, injured, and tumorigenic tissues will reveal the functional significance of the specialization of cell types, opening new opportunities to personalize nutrition and prevention (see Outstanding questions).

Few studies performed nutritional interventions in humans treated with radiotherapy, showing contradictory results regarding the incidence of intestinal toxicity [107]. In a meta-analysis, Wedlake and colleagues established a weak correlation between specific diets (e.g., elemental, low- or modified-fat, fiber, and low-lactose) and intestinal toxicity. A reasonable explanation for the contradictory results could be that these studies established correlations between diet and intestinal toxicity without considering the gut microbiome and GMMs, which are the functional effectors. This led to results that needed to be clearer to interpret. Moreover, studies had different endpoints and included different symptom scales, impairing the collective interpretation of the results. More research in this area is needed to standardize nutritional interventions, sample collection, and downstream analysis to improve the quality indicators that can be used to assess the effectiveness of specific diets. Understanding the complex interplay between food and gut microbiota, and health and disease outcomes has enormous potential to perform an evidence-based design of functional foods, prebiotics, probiotics, and GMM interventions for cancer patients and survivors that suffer radiation-induced enteritis.

Concluding remarks

The research discussed in this Review indicates that the diet–gut microbiota–host triangle constitutes a promising therapy to improve quality of life in cancer patients and survivors with radiation-induced enteritis. However, at this moment, more high-quality evidence is needed to implement nutritional interventions in people treated with radiotherapy in the abdominal and pelvic cavities. Key milestones must be achieved before nutritional interventions are translated into clinical practice.

At the molecular level, mechanisms that connect diet to ISCs still need to be fully understood. For this reason, a deeper understanding of these mechanisms using a holistic view that considers diet, gut microbiome, GMMs, and mechanisms in targeted cells will be instrumental to successfully developing helpful intervention strategies in humans for radiation-induced intestinal side effects (see Outstanding questions). It is most relevant to homogenize scientific criteria *in vitro* and *in vivo* studies and clinical trials. This will allow the verification of scientific findings, ensure the accuracy of scientific claims, and promote scientific knowledge advancement.

Altogether, this critical Review pushes forward the diet–gut microbiota–host triangle that will be crucial to develop preventive measures and noninvasive treatments to diminish symptoms in cancer patients and survivors with radiotherapy-induced side effects in the intestine.

Outstanding questions

To what extent does diet revert the gut microbiome in individuals whose microbiome is compromised and do not retain symbionts?

Are the extensive changes that occur as cells specialize along the crypt–villus axis predetermined, or are they subject to environmental regulation (e.g., by microbial strains and GMMs)?

What is the functional significance of the specialization of cell types along the villus–crypt axis?

What are the target cells of GMMs in the regenerative process?

Can we mimic the effects of an FMT by exclusively administrating GMMs and pasteurized microorganisms?

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Declaration of interests

No interests are declared.

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