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CCR Translations

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Prediction and Treatment of Radiation Enteropathy: Can Intestinal Bugs Lead the Way?

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Radiation-induced gastrointestinal toxicity is a significant comorbidity affecting many patients with cancer. Intestinal microbial changes are observed in patients suffering from radiation enteropathy, although a causal relationship with disease activity has yet to be proven. Implementation of bacterial profiling in clinical care could improve recognition and management of this debilitating disease.

See related article by Reis Ferreira et al., p. 6487

In this issue of *Clinical Cancer Research*, Reis Ferreira and colleagues investigated the contribution of bacterial microbes in the complex pathogenesis of radiation enteropathy and suggested that microbial profiles might be relevant in the prediction, prevention, or treatment of radiation enteropathy in the future (1). Many patients with cancer suffer from gastrointestinal (GI) symptoms after radiotherapy treatment, but a better recognition of symptoms, as well as a better arsenal of treatment modalities is needed to care for these patients. New findings in translational microbiome research may serve as a tool in the assessment, identification, and management of patients at risk of radiation enteropathy.

Radiotherapy plays a major role in the treatment and survival of oncology patients, but is accompanied by severe adverse side effects. The intestines and the colon in particular are affected when the pelvis or the abdomen is included in the radiation field, resulting in early (acute) and/or delayed (chronic) radiation enteropathy. While early radiation toxicity generally occurs during treatment exposure and subsides thereafter, delayed radiation enteropathy is now stated to be one of the most common causes of gastrointestinal complaints, with a prevalence reported to exceed even that of inflammatory bowel diseases (IBD; ref. 2). Clinically, IBD and radiation enteropathy share similarities, as both are characterized by bloody stool and diarrhea and both are accompanied by mucosal immune cell infiltrate and inflammation, epithelial barrier breach (in case of acute radiation enteropathy), and fibrosis (in case of chronic radiation enteropathy), as well as alterations in the intestinal microbiota (Fig. 1). Modulation of IBD disease activity through manipulation of the microbiome is now receiving vast attention, and it is therefore only logical that radiation enteropathy should follow suit. The use of probiotics, specific diets and fecal microbial transplants (FMT) have all been advocated for IBD treatment, and may also hold promise for management of radiation enteropathy. The intestinal bacterial community indeed shows clear signs of disbalance post radiation (3–5), although it is not fully understood whether radiation-induced GI symptoms are caused by the disruption of the microbiota or vice versa. An altered bacterial profile prior to radiotherapy was demonstrated in patients who subsequently developed diarrhea, suggesting that preexisting changes in the gut microbiota exist (4). *Coprococcus* was evidently enriched before radiation in patients at risk of radiation enteropathy and may serve as a potential biomarker (5). The innovative microbiota and radiotherapy-induced GI side effects (MARS) study of Reis Ferreira and colleagues expand on these findings by investigating both acute and late effects of radiation enteropathy by using fecal samples from these cohorts in addition to mucosal biopsies from patients with $\geq$1 year of follow-up (1). Importantly, this largest clinical study to date confirmed a trend for lower fecal bacterial diversity prior to development of acute radiation enteropathy and found a nonsignificant pattern in the late radiation enteropathy group.

Mouse models have allowed mechanistic investigation of the microbiota in radiotherapy-induced GI toxicity, and potential treatments thereof. A significant shift in gut microbial composition restricted to the damaged mucosa was shown in irradiated mice (6). Interestingly, germ-free mice that were inoculated with the microbiota of these irradiated mice showed more severe pathologic features following irradiation, demonstrating that bacterial disbalance may drive radiation-induced toxicity. FMT improved GI functionality and intestinal integrity after irradiation in a mouse model, suggesting that resetting the microbiota may be beneficial for the treatment of radiation enteropathy (7). In humans, modulation of the microbial community for the treatment of radiation enteropathy symptoms has so far predominantly been tested with the use of probiotics, which appears to be effective and safe (8). Furthermore, application of low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet was shown to improve symptoms in a small pilot study in radiation enteropathy patients with symptoms of irritable bowel syndrome, but whether the GI microbial community was involved was not investigated (9). Of note, however, Reis Ferreira and colleagues did not identify any specific changes in mucosal microbiota in late radiation enteropathy. Furthermore, when investigating specific fecal taxa, a link between short-chain fatty acids producing bacteria (e.g., *Roseburia, Clostridium IV*, and *Phascolarctobacterium*) and disease severity was observed, which is surprising given that these bacteria are generally associated with

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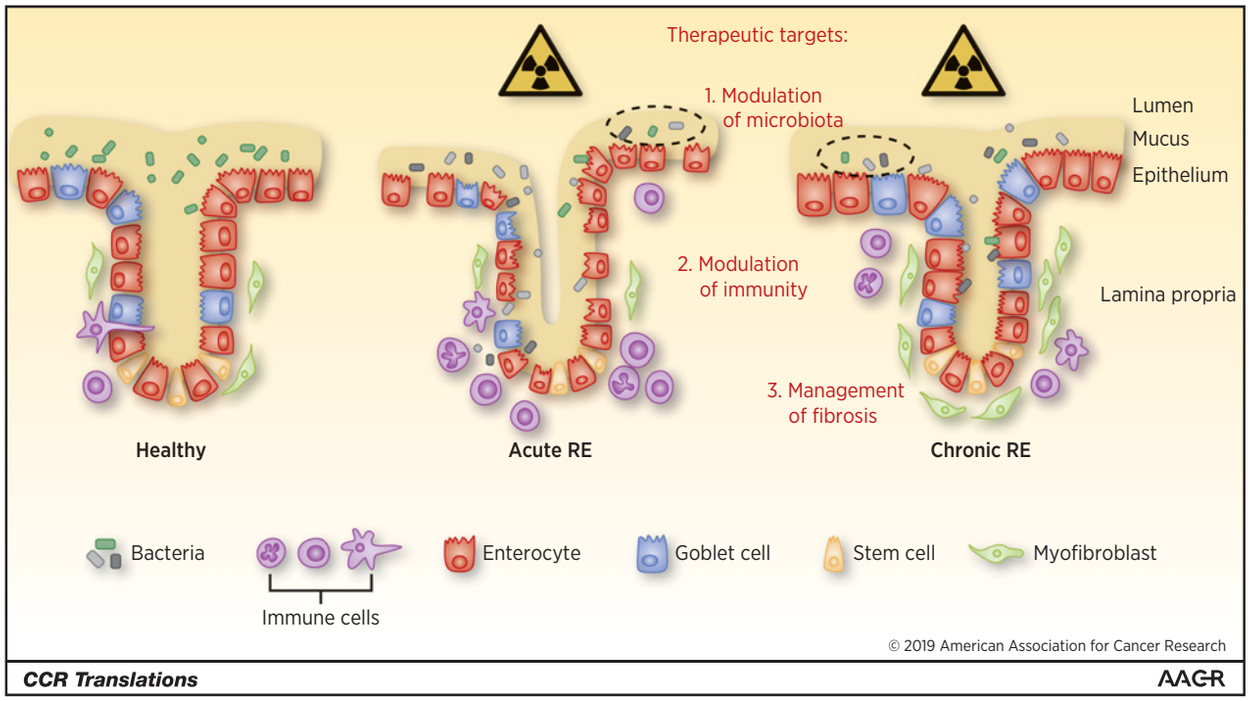

Figure 1.

The pathology of radiation enteropathy (RE) and its potential treatment options. The healthy epithelium sustains damage upon irradiation, which causes a decrease in barrier function and translocation of luminal bacteria. The composition of the bacterial flora is altered in patients with acute radiation enteropathy, which may contribute to an inflammatory response which can resolve the bacterial influx, but may also cause collateral damage through the production of reactive oxygen species and inflammatory cytokines. Reis Ferreira and colleagues (1) now show that while microbial balance may still exist in chronic radiation enteropathy to some extent, there is also an altered immunologic state, as evidenced by altered cytokine levels in mucosal biopsies from patients with ≥1 year of follow-up after radiotherapy. Treatment of radiation enteropathy may in future be aimed at modulating all aspects of radiation enteropathy, including the microbiota, its interaction with the immune system, and immune-mediated fibrotic responses.

a healthy microbiome. Thus, to what extent direct modulation of the microbiota in humans may contribute to prevention or treatment of radiation enteropathy remains to be seen.

It is conceivable that restoring the balance between host immunity and the microbiota is equally important for resolution of radiation enteropathy symptoms. Similar to IBD (10), Reis Ferreira and colleagues showed a clear relationship between microbial signatures and cytokine patterns, with a depletion of cytokines regulating intestinal homeostasis (IL7, IL12/IL23p40, IL15, and IL16) and an inverse correlation of IL15 with *Roseburia* and *Propionibacterium*. These structural and functional changes emphasize the complexity of radiation enteropathy, and demonstrate the existence of an immunity–microbiome axis in radiation enteropathy. In mice, IL1β secretion was found to be a major mediator in the sequelae of microbial-induced radiation damage, suggesting that treatment with IL1 inhibitors might be considered in clinical practice (6). Furthermore, the mortality of GI acute radiation syndrome mice treated with 7–9 Gy was shown to be associated with bacterial translocation, but could be controlled by modulation of macrophage polarization using CCL1 antisense oligodeoxynucleotide therapy (11). Hydrogen–water therapy similarly improved GI tract function and epithelial integrity, but its mechanisms of action was via the reduction of the innate immune cell bacterial sensor MyD88 in the small intestines (12). Altogether, these murine studies show that modulation of immunity may resolve microbial disbalance and alleviate radiation enteropathy symptoms. Importantly, inhibition of immune reactions has also been shown beneficial for prevention of immune-mediated fibrosis in patients with IBD, and may be speculated to also alleviate fibrosis during chronic radiation enteropathy. For patients with IBD, many immune modulators are now used in clinical practice. For instance, increased levels of IL12/IL23p40 and TNFα are seen in patients with IBD, and treatment with anti-p40 and anti-TNFα antibodies is now commonly prescribed. However, while a nonsignificant increase in TNFα levels in radiation enteropathy may indicate that some patients might benefit from anti-TNFα treatment, radiation enteropathy patients show reduced rather than increased mucosal levels of IL12/IL23p40 (1), making anti-p40 treatment obsolete. Thus, treatment strategies for radiation enteropathy based on immune modulation need to be carefully tailored.

The classic "target cell theory" with the epithelium as the only determinant of early pathology has currently been abandoned and replaced by the concept that epithelial injury, the microvasculature, the immune system, the enteric nervous system, the intestinal microbiota, and host factors are involved in pathogenesis of radiation enteropathy (2). It has also been underscored that acute and chronic radiation enteropathy are distinct features, and that delayed radiation-induced GI toxicity symptoms are not uncommon and often progressive in nature. Although the clinical implementation of bacterial microbes in toxicologic effects of radiotherapy is in its infancy, the findings thus far have been

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promising. Future work needs to combine clinical and laboratory efforts to establish optimal recognition and management strategies for patients with radiation enteropathy. A baseline screening tool to predict patient responses to cancer therapy and the risk for treatment-related toxicity would be beneficial for a more personalized treatment approach.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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