The microbiota: an underestimated actor in radiation-induced lesions?

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The co-evolution of humans and microbes that colonise the GI tract is shaped by environmental factors and evolved to promote health.[1] Microbial derangements (termed dysbiosis) have been observed for a variety of intestinal and extraintestinal diseases.[1] Metabolic, autoimmune, liver and intestinal disorders have been linked to microbial dysbiosis which promotes susceptibility to inflammatory disease in some cases as largely assessed in animal models.[2] Intestinal dysbiosis has also been implicated in colorectal cancer[3] and microbes may determine treatment response for non-intestinal malignancies.[4]

For more than 10 years, intestinal microbial alterations have been associated with localised radiation in humans and mouse models.[5–8] Importantly, mice that lack colonisation of microbes (ie, raised germ free) were resistant to lethal radiation enteritis, indicating that the microbiota controls intestinal disease processes consequent to radiation-induced damage.[9] In this context, however, the functional role of radiation-induced microbial alterations remained yet to be determined.

In this issue, Gerassy-Vainberg *et al*[10] demonstrated that radiation-induced dysbiosis promoted susceptibility to radiation-induced injury and intestinal inflammation. In this study, the authors took advantage of a mouse model of radiation that allowed localised injury to the rectum which mimics human radiation proctitis. The most significant shift in microbial composition was specifically noted in the inflamed colon 6 weeks after irradiation, with reduced *Firmicutes* abundance and increased abundance of *Proteobacteria* and of six genera including *Akkermansia* spp and *Bacteroides*. Transmission of the radiation-altered microbiota into germ-free wild-type mice rendered them susceptible to dextran sodium sulfate-induced colitis and radiation injury. Incubating colonic epithelial cells with faecal suspensions from irradiated mice increased tumour necrosis factor-α and interleukin (IL)-1β secretion when compared with suspensions derived from non-irradiated mice. Anakinra, an IL-1 receptor antagonist in clinical use, ameliorated radiation-induced injury and inflammation.

The data presented by Gerassy-Vainberg *et al*[10] are reminiscent of what is observed in IBD in which the dysbiotic microbiota is a strongly suspected actor in disease evolution. Indeed, the radiation-induced dysbiosis described is reminiscent to IBD and to colitis models in mice with notably a decreased abundance in *Firmicutes* and an increased abundance in *Proteobacteria*. Moreover, the driving forces leading to this specific dysbiosis might be, at least partially, common to these two conditions. We suggest that specific cell types with antimicrobial capacity (eg, neutrophils or intestinal epithelial cells) alter microbial composition in the injured intestine. For example, massive production of reactive oxygen species (ROS) is a shared feature of intestinal inflammation in IBD and radiation-induced injury. ROS are mainly produced by neutrophils and intestinal epithelial cells in IBD, whereas they are the direct product of water radiolysis following ionising radiation. Oxidative stress is actively inducing the expansion of *Proteobacteria*[11 12] and possibly being detrimental to the numerous oxygen-sensitive *Firmicutes* members in the intestinal microbiota. Consequent to dysbiosis, intestinal inflammation in both disease entities (ie, radiation-induced enteritis and IBD) may be partly driven by IL-1 receptor signalling.[10 13] Thus, the results presented by Gerassy-Vainberg *et al*[10] suggest that common mechanism(s) are engaged in intestinal inflammation of different origin which culminate in dysbiosis and consecutive derangements in the host–microbiota crosstalk.

These findings indicate that the microbiota emerges as a critical driver of radiation-induced intestinal disease processes in part by modulation of IL-1β signalling.[9 10] The results by Gerassy-Vainberg *et al*[10] pose several questions. (1) Is microbial composition or diversity a reliable predictive marker of radiation-induced lesions? (2) What is the impact of radiation-induced injury on viruses and fungi and what is their role for intestinal disease processes? (3) Do specific bacterial species determine the inflammatory tone and how do they modulate inflammatory responses? (4) Is it possible to prevent or treat radiation-induced lesions by targeting the gut microbiota? In this regard, a recent study in mice demonstrated that microbiota composition is associated with susceptibility to radiosensitivity and that faecal microbiota transplantation alleviated consequences of irradiation.[14] Whether these findings may be translated into a therapeutic approach for human radiation-induced disease deserves further attention.

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REFERENCES

1 Kåhrström CT, Pariente N, Weiss U. Intestinal microbiota in health and disease. *Nature* 2016;535:7:47.

2 Marchesi JR, Adams DH, Fava F, *et al*. The gut microbiota and host health: a new clinical frontier. *Gut* 2016;65:330–9.
3 O'Keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. *Nat Rev Gastroenterol Hepatol* 2016;13:691–706.
4 Vétizou M, Pitt JM, Daillère R, *et al*. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015;350:1079–84.
5 Manichanh C, Varela E, Martinez C, *et al*. The gut microbiota predispose to the pathophysiology of acute postradiotherapy diarrhea. *Am J Gastroenterol* 2008;103:1754–61.
6 Wang A, Ling Z, Yang Z, *et al*. Gut microbial dysbiosis may predict diarrhea and fatigue in patients undergoing pelvic cancer radiotherapy: a pilot study. *PLoS One* 2015;10:e0126312.
7 Johnson LB, Riaz AA, Adawi D, *et al*. Radiation enteropathy and leucocyte-endothelial cell reactions in a refined small bowel model. *BMC Surg* 2004;4:10.
8 Kim YS, Kim J, Park SJ. High-throughput 16S rRNA gene sequencing reveals alterations of mouse intestinal microbiota after radiotherapy. *Anaerobe* 2015;33:1–7.
9 Crawford PA, Gordon JI. Microbial regulation of intestinal radiosensitivity. *Proc Natl Acad Sci U S A* 2005;102:13254–9.
10 Gerassy-Vainberg S, Blatt A, Danin-Poleg Y, *et al*. Radiation induces proinflammatory dysbiosis: transmission of inflammatory susceptibility by host cytokine induction. *Gut* 2018;67:97–107.
11 Winter SE, Winter MG, Xavier MN, *et al*. Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. *Science* 2013;339:708–11.
12 Morgan XC, Tickle TL, Sokol H, *et al*. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012;13:R79.
13 Shouval DS, Biswas A, Kang YH, *et al*. Interleukin 1β mediates intestinal inflammation in mice and patients with interleukin 10 receptor deficiency. *Gastroenterology* 2016;151:1100–4.
14 Cui M, Xiao H, Li Y, *et al*. Faecal microbiota transplantation protects against radiation-induced toxicity. *EMBO Mol Med* 2017;9:448–61.