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Review

Radiation Impacts Microbiota Compositions That Activate Transforming Growth Factor-Beta Expression in the Small Intestine

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Abstract: The composition of the gut microbiota represents an early indicator of chronic post-radiation outcomes in elderly bone and gastrointestinal homeostasis. Fecal microbiota analyses revealed that the relative abundances of *Bacteroides massiliensis*, *Muribaculum* sp., or *Prevotella denticola* were different between conventional microbiota (CM) and anti-inflammatory restricted microbiota (RM). The murine RM was found conditional on mucosa-associated dysbiosis under both, disturbances of interleukin (IL)-17 signaling and exposure to radiation alone. This review discusses the hypothesis that intestinal microbiota induced alterations in DNA repair and expressed transforming growth factor (TGF)-β in the small intestine, thereby impacting bone microstructure and osteoblast dysfunction in silicon ion (1.5 Gy ^{28}Si ions of 850 MeV/u) irradiated mice. Bacterial microbiota compositions influenced therapeutic approaches, correlated with clinical outcomes in radiotherapy and were associated with alterations of the immune response to severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infections during the last global pandemics. In the absence of TGF-β, functional metagenomics, cytokine profiles, bacterial community analyses in human and murine mucosa cells, and inflammatory markers in rat intestines were analyzed. This research finally showed radiation-induced osteolytic damage to correlated with specific features of intestinal bacterial composition, and these relationships were expatiated together with radiation effects on normal tissue cell proliferation.

Keywords: TGF-beta; radiation; small intestine; enteropathy; antitumor immunity

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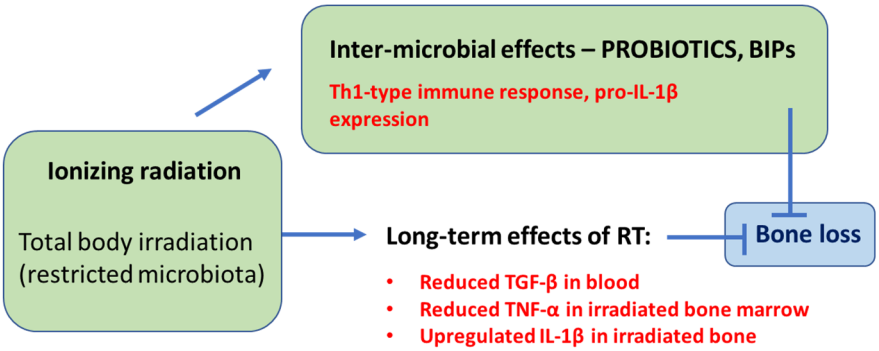
1. Introduction

Bacterial indicator phylotypes (BIPs), which were associated with double-stranded DNA breaks in peripheral blood, were depleted in CM mucosa cells and increased in irradiated CM mice after exposure to sub-lethal dose of high-linear energy transfer (LET) radiation [1]. Contrarily, two of the bacteria which we identified in RM were enhanced by particle-beam radiation, namely *Muribaculum intestinale* and an unidentified Gram-negative bacterium. An unidentified *Bacteroidetes* was directly correlated with trabecular thickness (Tb.Th) in anti-IL-17 neutralized and radiation-exposed mice, but inversely decreased with body weight in anti-IL-17 treated sham mice [2,3], thus reflecting tibiae bone microarchitecture and cell immunity in a longitudinal study (Scheme 1). Moreover, microbiota restriction reduced inflammatory tumor necrosis factor (TNF) in bone marrow, and chemokine (C-C motif) ligand 20 (CCL20) in marrow compared to small intestine upon anti-IL-17 treatment. Double-stranded DNA breaks in blood lymphocytes were associated with the anti-inflammatory intestinal microbiota in both, wild-type RM mice and aged RM mice deficient of ataxia-telangiectasia-mutated [2], in which kynurenic acid (a tryptophan metabolite) was found elevated in feces [4]. Treatment with anti-IL-17 antibodies revealed

TGF-β in their bone marrow, but not in irradiated RM mice, indicating reprogrammed immune suppression by activated regulatory T cells (Tregs) in RM. These findings indicated a key role of intestinal microbiota in bearing autoantigens that are inductive for rheumatoid arthritis [5,6], bone loss [7], and osteoporosis [8].



Scheme 1. Microbiota Restriction Improved Bone Micro-architecture.

Prior research confirmed antitumor innate immunity in RM mice and a phenotype which was indicative of hypoxia-inducible factor (HIF)-1 mediated effects [9], IL-12 activation, and macrophage polarization [10]. The naïve $CD4^+$ T cell subset was functionally distinguished in restricted flora mice from specified pathogen-free (SPF) mice by increased activation-induced cell death [11]. Gut microbiota restrictions (restricted flora was defined as RM in the immune-genotoxicity model [12] and compared with SPF) revealed similar memory $CD4^+$ and $CD8^+$ T cell levels, whereas IL-12-expressing $CD11c^{high}$ dendritic cells (DC) were 2.7-fold increased in RM versus SPF mice; attributable with certain commensal bacteria in RM in comparison to the immunity of SPF mice [12,13]. Fujiwara, D. and colleagues compared the effect of SPF versus RM on the systemic status of DC populations. Due to commensal bacteria, plasmacytoid DC (pDC) were selectively deficient in spleen and mesenteric lymph nodes (MLN), accompanied by an increased prevalence of myeloid DC (mDC) and T cells with a proinflammatory phenotype. These data provide evidence that, through direct action on newly differentiated mDC, RM stimulated mDC maturation and IL-12 production [13]. Memory, and also activated, $CD8^+$ T cells were expanded in restricted flora mice and suspected to induce depleted invariant natural killer T (iNKT) cells [14]. The pDC deficiency in restricted flora mice was reversed by depletion of $CD8^+$ T cells and in mice lacking perforin function [13,14]. Indeed, iNKT cell numbers were restored in restricted flora mice bearing the CD8α(−/−) genotype; or in adult wild-type mice bearing RM, acutely depleted with anti-CD8 antibodies [14]. However, anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)–induced activation of splenic effector $CD4^+$ T cells was significantly suppressed in mice reared under germ-free conditions. The same reduced activation of effector $CD4^+$ T cells was achieved when mice were treated with broad-spectrum antibiotics, compared with mice having conventional microflora, and a phenotype with reduced intratumoral accumulation of $CD3^+$ tumor-infiltrating lymphocytes (TIL), T-helper(h)1 cells, and CTLs. As a result, interventions with anti-CTLA-4 monoclonal antibodies (mAb) lost therapeutic efficacy against established sarcomas, melanomas, and colon cancers in mice with a change of intestinal microbiota [15]. Next, cytotoxic $CD8^+$ cells were experimentally blocked with antibodies, and the mucosal compartment in the murine colon then analyzed for higher abundance of certain species of *Bacteroides* and *Turicibacter*, and of *Barnesiella* in the small intestine [16]. A 'T cell receptor-like' activation of autoimmunity was stimulated via receptor activator of nuclear factor-κB ligand (RANKL) by subsequent activation of bone marrow osteoclasts [17]. Herein, we discuss approaches to radiation-induced microbiota changes which alter inter-microbial interactions, immune responses, and virus-bacterial secondary infections with side-effects on bone health.

2. Different Gut Microbiota Can Both Negatively and Positively Impact Radiation-Induced Bone Loss

Gut bacterium *Bacteroides massiliensis* correlated higher relative bone volume in tibiae in IL-17 suppressed RM mice [3]. Whereas *Bacteroidetes* was found directly correlated with trabecular thickness (Tb.Th) in anti-IL-17 neutralized and radiation-exposed mice, *Turicibacter* sp. was found directly correlated with trabecular spacing (Tb.Sp) in solely anti-IL-17 treated mice. Only *Lachnospiraceae* correlated systemic genotoxicity in female irradiated RM, whose increased activity was seen in cigarette smoke-exposed mice along with altered immune factors [18] but were not changed in abundance in CM due to ionizing radiation. Neutralizing anti-IL-17 antibodies revealed high levels of TGF-β in the bone marrow of RM mice that were reduced by heavy ion radiation, delivered as a single fraction of 1.5 Gy (^{28}Si ions, 850 MeV/u). Likewise, IL-17 in CM mice was reduced by irradiation in the small intestine. Anti-IL-17 treated adult mice showed hardly any micronuclei formation in normochromatic erythroblasts at six hours postirradiation (CM < RM) [2]. The expression of pro-osteoclastogenic TNF genes, however, was interrogated and reported to be enhanced by radiation-induced genotoxicity [19]. Yu M, et al. confirmed TNF being relevant for the bone catabolic activity of parathyroid hormone and demonstrated that low-calcium diet led to bone resorption, high bone turnover, and impaired bone trabecular microarchitecture in bones [8], such as the hard palate, mandible, vertebrae, femur, and proximal tibia [8,20]. Blocking IL-1 showed that IL-1β was a major driver of radiation bone sensitivity [3], as well as IL-1 was associated with tissue damage, and microbiota with enhanced expression of TNF-α [21] in irradiated bone marrow [2]. By contrast, particle radiation reduced TGF-β in the absence of peripheral IL-17 in RM mice, particularly in females—to prevent pro-osteoclastogenic IL-17 in chronic inflammation-associated cancer [22]. TGF-β controlled osteoblast-specific gene expression in cooperation of runt-related transcription factor 2 (Runx2) and mothers against decapentaplegic homolog 5 (Smad5) signaling with bone morphogenic protein 2 [23].

CM mice (females) showed higher expression of interferon (IFN)-γ in the small intestine and its lower level in blood [2]. Relative to basal thickness, our recent study measured differences in mean cortical thickness in irradiated CM mice (−15%) versus irradiated RM mice (−9.2%) by ex vivo micro-computed tomography [2,3]. Higher trabecular bone volume fraction and improved bone morphologies were assessed in anti-IL-17 treated RM mice compared with anti-IL-17 treated CM mice. We showed a direct impact of antibody intervention at the early timepoints within two days postirradiation; but the resulting feedback upregulation of IL-17 in non-irradiated control mice at the time of three weeks after anti-IL-17 treatment suspected significantly reduced TGF-β by irradiation in mice with intestinal microbiota restriction. Increased TGF-β was measured in peripheral blood in RM and higher gene expression of proinflammatory cytokines in the small intestine in irradiated RM mice [2], along the lines of protected small intestinal crypt stem cells [24–26] or matrilysin expression [27]. Studies explored gain-in-function mutations for structural interactions among proteins of the carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family and TGF-β signaling genes to promote colorectal adenocarcinomas. Feces from mice with defects in TGF-β signaling had increased abundance of *Clostridium septicum* and decreased abundance of beneficial bacteria, such as *B. vulgatus* and *Parabacteroides distasonis* [28]. Previously, *Mucispirillum* and *Clostridium* species were demonstrated being adaptively modified with the rather low radiation-induced genotoxicity in blood lymphocytes in CM males, or the downregulated TGF-β level in blood. Taken together, crucial roles of RM have been considered which made mice radiation susceptible, whereas higher trabecular numbers and bone volume parameters were detected in both non-radiated and irradiated mice [2,3]. Colonization of mice by a defined mix of *Clostridium* strains provided an environment rich in TGF-β and affected Foxp3^{+} Treg numbers and function in the colon [2,29]. Oral inoculation of *Clostridium* during the early life challenged conventionally reared mice and resulted in resistance to colitis and systemic immunoglobulin (Ig) E responses in adult mice [29].

3. Gut Microbiota Orchestrate Systemic Responses in Immune-Mediated Maladies

Secondly, gut microbiota appeared to play a new impacting role in rheumatoid arthritis [30,31] and other immune-mediated maladies [5]. Caspase-1 (cysteinyl-aspartate specific protease) is a protein involved in autophagy that is regulated by IL-1β, a pleiotropic cytokine [32], and an interesting target for deciphering the stimulator of interferon genes-(STING) in either mucosa cells, or osteoarthritis tissue as shown recently [33]. But both, DNA and RNA viruses trigger cell death and induced inflammatory cytokines such as IL-1β through activation of the inflammasome, where viral RNA seemed to activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome to generate mature IL-1β [34]. In our study, we measured a three-fold increase in the gene expression of IL-1β in irradiated RM bone compared with CM ($p < 0.05$) [3]. Apoptosis-transforming cytokines were involved in many antimicrobial activities, including induction of the acute response phase, promotion of proinflammatory cytokine cascades in inflammasomes [35,36], colitis [37], and differentiation of naïve T cells into IL-17-producing T-helper (Th17) cells [6]. Therefore, reduced cytokine-expression in antigen-stimulated RM mice (IFN-γ, TNF-α, and IL-4 by splenic iNKT cells [38]) was investigated for the reciprocal regulation of differentiation and pathogenicity of Th17 cells and Tregs [39], mediated by TGF-β [40] and IL-1β [41–43]. Differentiation of Th17 cells was reported to correlate with the presence of cytophaga-flavobacter-bacteroidetes (CFB) bacteria composition in the intestine and was independent of toll-like receptor, IL-21 or IL-23 signaling [40], but required TGF-β activation [40,44]. In correlation with the gain of body weight over four to six months, *Paramuribaculum intestinale* and *Muribaculum* spp. were found differentially enhanced in the mucosa of either microbiota group (CM and RM) due to lactobacillus treatment, looking at lamina propria bacteria composition in small intestine and mid-colon sections [2]. Longitudinal studies determined that *Faecalibaculum rodentium* and *Lactobacillus murinus* were more abundant in CM versus RM feces before and after irradiation [3]. In addition, female mice were lacking *Ureaplasma felinum* in mucosa-associated cells compared with males and *Helicobacter rodentium* and *Muribaculum intestinale* were more abundant in the colons of CM versus RM mice. *M. intestinale*, however, was increased in abundance in the small intestine of RM mice, implying they may deploy molecular countermeasures to persistent genotoxicity in bone marrow [2]. There was more than a 10-fold increase of *Muribaculum* spp. in the small intestine of irradiated female CM mice, and in all RM mice, when compared with CM mice. Taken together, this study showed how IL-17 neutralizing antibodies directly impacted osteolytic damage and immunogenicity of intestinal microbiota composition when, similarly to the approaches of combined radio- and immunotherapy, anti-IL-17 antibody was injected a day before, and at the early endpoint within two days postirradiation [1–3]. Reduced cytokine-expression in germ-free mice in bone (IL-6 and TNF-α [7]) could be indicative for a comparable mechanism to regulate the onset of osteoclastogenesis [8]. Independently of radiation-induced genotoxicity and cytokine expression in the gut, the intestinal microbiota composition was found a potential antagonist for the pathogenicity of Th17 cells and activation of Tregs. A single-cell RNA sequencing (scRNA-seq) survey of 40,186 ileal epithelial cells and proteomics analysis of ileal samples at six time points in the swine neonatal period investigated specific transcriptional factors, G protein-coupled receptors, TGF-β, bone morphogenetic protein signaling pathways, and gut mucosal microbiota in neonatal ileal development [45].

While our research associated *Muribaculum intestinale* with adopted radiation-resistance in murine colons concerning whole body irradiation with heavy ions [2], S. Kumar and coworkers described proliferation of gastrointestinal tissue which was accompanied by senescent cells and acquired senescence-associated secretory phenotype [46]. The latter demonstrated how low-dose ^{56}Fe radiation induced persistently delayed intestinal epithelial cell (IEC) migration that increased along with chronic heavy ions-induced alteration of sublethal cytoskeletal dynamics. In the small intestine, differentiated epithelial cells from the crypt-base stem cells migrated along the crypt–villus axis to replace apoptotic cells that shed into intestinal lumen [46,47]. Although IECs migration was higher after 60 days

relative to seven days postirradiation, it was significantly lower at both time points relative to control and γ-rays, indicating longer persistence of ^{56}Fe-induced effects relative to γ-rays up to a year. Higher dose (>1 Gy) demonstrated a modest increase in lethality with 50% survival at 30 days (LD50/30) for 5.8 Gy of ^{56}Fe ions compared to 7.25 Gy of γ-rays [48], and γ-irradiation induced function-impaired Tregs [49]. Low dose radiation is known from 0.5–4 Gy in several fractions as a tumor microenvironment modulating RT [50], and in cooperation with the modulating effects of TGF-β, was used as a trigger of immunotherapy in cancer [51]. Evidence is given that radiation relative biological effectiveness (RBE) is a function of radiation dose, tissue type, and LET [52], and a functional tool to predict intestinal crypt regeneration for new types of particle beams, including fast-neutrons, protons, carbon ions, and an epithermal neutron capture therapy (NCT) beam [53]. TGF-β also mediated the epithelial to mesenchymal transdifferentiation of cells via RhoA-dependent mechanism and could regulate metastasis at the point of immune control [54].

4. Microbiota Influence RT and Clinical Data

Microbiota have also been sequenced and explored as a biomarker for radiation, i.e., pelvic radiotherapy (RT) in humans [55–58]. Intestinal radiation tolerance after fractionated irradiation with protons [52] further plays a crucial role in activation of immunotherapy and prevention of secondary cancers [59]. In this course, microbial defense employed IL-12 to convert Foxp3$^+$ Tregs to IFN-γ-producing Foxp3$^+$ T cells due to microbial products in other than the murine intestinal organ, with a striking impact on inflammation, and to inhibit colitis [60]. The virus clearance promoting IL-12 release was found to protect mice from the lethal hematopoietic syndrome [61].

Effective combinatorial clinical strategies in RT should be inducing proliferation on normal cells, while reducing the differentiation of (tumor invasive) macrophages at activated DNA break sensing pathways [62,63]. Until today, the impact of ionizing radiation on intestinal microbiota has been studied in mice [1,21] and rats [64], especially the up- and downregulation of certain BIPs like *Turicibacter* spp. [3], *Fusobacterium*, or *Firmicutes* [64], respectively. Differences in microbiota between prostate cancer patients receiving radiotherapy were analyzed with and without acute or late radiation enteropathy [57,65], and higher counts of *Clostridium IV*, *Roseburia*, and *Phascolarctobacterium* significantly associated with those prostate cancer patients with radiation enteropathy [65]. Long-term side-effects of abdominal and pelvic RT in female patients with gynecologic malignancies were also decreased bone mineral density (BMD), major micro-architectural changes and osteoblast dysfunction [66,67]. These traits underlying clinical symptoms, such as bone loss, osteoporotic fractures [66–68], and for high-dose radiation treatment, pelvic pain [67], were deeply analyzed up to a year post-RT [68]. Patients suffered from rectal bleeding and fecal continence as a post-treatment side-effect to prostate cancer therapy [69] and reduced BMD following their cervical cancer radiation treatment, often depending on their age and age-related menopausal status [68]. Bone loss was further determined for RT plus androgen deprivation therapy in case of locally advanced prostate cancer [70]. Overall, a reduction in BMD of vertebrae in female cervical cancer patients has been reported to be systemic and to occur in the radiation-exposed part of the lumbar spine as well as in upper parts (thoracic vertebrae 9–12 and lumbar vertebrae 2–4), which were not irradiated [68]. In terms of pathogenic attacks on bone health, *Chlamydia pneumoniae*-infected mice had decreased ($p < 0.05$) total and subcortical BMD at the distal femur and proximal tibia compared with controls, but no body-weight gain differences at 16 days after infection [71].

The regulation of early and delayed radiation responses was explored in the small intestine, however, showing the stimulation of capsaicin-sensitive nerves [72] or expression of fibrogenic cytokines [73,74]. The abundance of *Roseburia* and *Propionibacterium* which are short-chain fatty acid (SCFA) producers, and *Streptococcus*, an acetate producer, therefore inversely correlated with IL-15 upon prostate and pelvic RT [65]. Sodium butyrate alleviated the symptoms of pre-eclampsia in pregnant rats, thus significantly decreased the levels of blood pressure, 24-h protein urine and inflammatory factors (IL-1β, IL-6 and TGF-β).

It increased the weights of the fetus and placenta and intestinal barrier markers (ZO-1, claudin-5 and occludin) [75]. TGF-β associated with chronic injury in both consequential and primary radiation enteropathy (Table 1) [76,77]; but the protein was also found a detected marker in human smooth muscle cells [78], and therefore recombinant TGF-β2 receptor has been in vivo tested for mitigating radiation enteropathy [79]. Among cervical cancer patients who received chemoradiotherapy, gastrointestinal toxicity resulted in generally decreased microbial diversity up to five weeks postirradiation [57]. Although cytokine levels in rectal mucosa and mucosa cells were mostly reduced after high-dose and highly fractionated RT [65], radiation dose-volume effects in radiation-induced rectal injury have been examined the most lethal side-effect for prostate cancer patients and were clinically evaluated [80–82]. The wildly used Lyman-Kutcher-Burman (LKB) normal tissue complication probability model in projecting the hazards of rectal complication with high-dose RT, i.e., rectal bleeding and late radiation toxicity, was based on three-dimensional conformal RT dose-escalation studies of early-stage prostate cancer [82]. The role of RT in the cancer-immunity cycle is increasingly being investigated (with a focus on conventional fractionation and hypofractionation with various outcomes) [50,65], and may involve different optimized regimen and specifications when the goal is immune-stimulation, as opposed to direct ablation of tumor cells [83].

Table 1. Overview of Radiation-injury and Microbiota-associated TGF-β Expression.

TGF-β Expression	Detection	Correlations	Impacts	Microbiota	Ref.
Bone marrow	Gene expression	Reduced by IR (single fraction of 1.5 Gy heavy ions)	Improved bone volume, trabecular number in tibiae reduced by IR	Restricted anti-inflammatory microbiota	[2]
Blood	Protein	Associated with IL-17	Improved bone volume	Conventional microbiota	[2,3]
Colon	Mouse model TGF-β-defective in gene expression	Protein interactions	Colorectal adenocarcinomas	Increased *Clostridium septicum*; Decreased *B. vulgatus* and *Parabacteroides distasonis*	[29]
Small intestine	Gene expression	Low genotoxicity	High IFN-γ IL-17 reduced by IR	*Mucispirillum*, *Clostridium* sp.	[2]
Small intestine	Respective mouse model for defined TGF-β expression	IFN-γ and IL-17	Differentiation of Th17 cells	Cytophaga-flavobacter-bacteroidetes (CFB) bacteria	[40]
Marker in mammalian ileal mucosa samples	Proteomics analysis	Undifferentiated cells, unique enterocyte differentiation, and time dependent reduction in secretory cells	Neonatal development	Not defined.	[45]

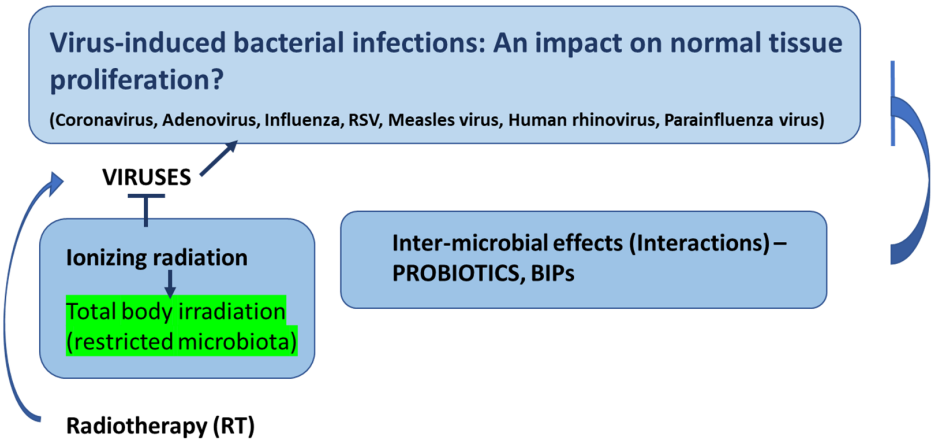
Table 1. *Cont.*

TGF-β Expression	Detection	Correlations	Impacts	Microbiota	Ref.
Intestine (rat)	Mast cell deficient rats	Collagen I accumulation and TGF-β immunoreactivity	Less chronic intestinal radiation fibrosis upon ablation of sensory neurons in the gut	Not defined.	[72]
Intestine (rat)	Immunohistochemistry after fractionated IR (9 daily fractions of 5.2 Gy [73,76]; 18 daily fractions of 2.8 Gy, or 9 fractions of 5.6 Gy [77]).	Increased expression of IL-1α, PDGF-AA [73], TGF-β [73,74], TM, PAR-1, neutrophils, collagen I and III measurements [74]; Vascular sclerosis [76]	Fibrosis and inflammatory cell infiltrates in irradiated intestine [74]; dose-dependent radiation injury; chronic intestinal wall fibrosis [77]	n.a.	[73,74,76,77]
Human smooth muscle cells	TGF-β is applied to muscle cells from normal or radiation enteritis biopsies	Radiation-induced fibrogenic differentiation	Nuclear accumulation of Smad as well as their DNA-binding activity were higher in N-SMC	n.a.	[78]
Mice	TGF-beta1 messenger RNA	TGFbetaR-II:Fc fusion protein treatment	Less radiation enteropathy	n.a.	[79]

IR = Irradiation; PDGF-AA = Platelet derived growth factor-AA; TM = Thrombomodulin; PAR-1 = Protease-activated receptor-1.

Long-term RT can increase the risk of secondary infections by suppressing cytokines, while in case of viral infections, patients became predisposed to secondary bacterial infections, which often have a more severe clinical course [84]. The mechanisms underlying post-viral bacterial infections are based on multifactorial processes mediated by interactions between viruses, bacteria, and the host immune system [85–87], and may be summarized as the disruption of commensal microbiota homeostasis [88]. Since the effects of probiotics inoculation have never been sufficiently reported, its stimulatory impact on cytokine release should be mentioned at this point [89] (Scheme 2). Dysbiosis in the respiratory and gastrointestinal tract, which in turn may alter subsequent immune function against secondary bacterial and fungal infection, were focused on the beneficial changes in the microbial compositions in this review [84,90–92]. Not just recently, clinical trials have investigated the potential applications of probiotics to minimize viral infections due to influenza virus, rhinovirus, respiratory syncytial virus, or rhinopharyngitis. Other current clinical trials explored the effectiveness of *Lactobacillus plantarum* and *L. coryniformis* as dietary supplements, or *Lactococcus lactis* via nasal irrigation in the context of COVID-19 [92]. Besides the release of IFN-α [93], IFN-γ, IL-2, and IL-12 from lactic acid bacteria (LAB) [89,90], TNF-α upregulation through a wide range of Lactobacilli [92], reduced viral entry through *Bacillus subtilis* [94], the production of defensins due to *Lactobacillus casei* [92] and the inhibition of chemokine responses related to *Bifidobacterium animalis* were described [95]. Enhancing the proliferation of potentially pathogenic bacterial species was limited. Probiotic supplements reduced a "cytokine storm" and proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [91]. Nevertheless, the pathogenesis of viral infections of the respiratory tract included infections with *Staphylococcus pneumonia*, *Staphylococcus aureus*, *Hemophilus influenzae* [89,90], *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Urinary tract infection following secondary colonization with *Hemophilus* and *Pseudomonas aeruginosa* induced immune responses, such as CXCL8 (C-X-C motif chemokine ligand 8),

CCL2 and interleukins (IL-6, IL-8, IL-10, IL-17A), granulocyte colony stimulating factor (G-CSF), mucus response, and epithelial cell death [84]. None of these signatures of the adaptive immune response was shown in the RM model.



Scheme 2. Radio-immunogenic Control of Secondary Bacterial Infections.

5. SARS-CoV-2 Infections Impact Radio-Immunogenic Responses of the Gastrointestinal Tract

Given the high risk of the worldwide coronavirus spread to reinforce COVID-19 disease, low-dose radiation which has been described for the determination of RBE on thoracic and intestinal radiation [52,96], was tested on thirty COVID-19 pneumonia patients as low-dose radiotherapy (LDRT, <0.5 Gy) [97] that induced anti-inflammatory effects [98,99]. Paraoxonase-1 (PON1)-related variables and cytokines were analyzed in serum samples and reported concerning their relationship with the clinical and radiological characteristics of patients with COVID-19 pneumonia. One week after LDRT, 83% of patients had lower PON1 and TGF-β1 concentrations compared with 24-h after LDRT, PON1 specific activity increased, lactate dehydrogenase, and C-reactive protein decreased, and $CD4^+$ and $CD8^+$ cells increased after one week, whereas respiratory function improved [97]. In Japanese cancer patients compared with health care workers, the seroprevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies did not differ between the cancer patients and health care worker groups; however, findings suggested that systemic therapies, including chemotherapy and immune checkpoint inhibitors, lowered N (nucleocapsid)-IgG or S (spike)-IgG levels against SARS-CoV-2 in cancer patients, with immune checkpoint inhibitor treatment showing less impact on the infection immune response [100]. Across 34 human cancers, interferon-stimulated genes and T cell-inflamed interferon signatures in tumor and normal tissues correlated with angiotensin-converting enzyme 2 (ACE2) [101], the cell receptor for SARS-CoV and SARS-CoV-2 [102], which itself was negatively correlated with angiogenesis and TGF-β [101]. For various types of cancers, including lung cancer [103], ACE2 expression increased with the potential risk of cancers to SARS-CoV-2 infection [104] and correlated bacterial microbiota, but were inconsistent in associations between ACE2 and type II transmembrane serine protease (TMPRSS2) in the presence of viruses (HPV, Epstein-Barr virus, and hepatitis B virus) or tissue microbiota [101]. Collectively, the SARS-CoV-2 infection was associated with human enterocytes pathology [105] as well as reduced bacterial diversity and virus-specific lower relative abundance of beneficial symbionts in gut microbiota [106]. Lately, for colon adenocarcinoma and stomach adenocarcinoma, 1093 commensal microbiotas were correlated; and these cancers assessed as the two tumor types with the strongest and most prevalent positive correlation of ACE2 and TMPRSS2 gene expression with abundance of specific bacteria taxa, respectively. Chlamydia was the top microbiota among 75 taxa that positively correlated with ACE2 in colon adenocarcinoma ($p = 0.81$, FDR-adjusted $p < 0.0001$), and also kidney cancers correlated with both, ACE2 and microbiota [101]. Taken together,

tumor type and various tissues are susceptible to SARS-CoV-2 [104] and immunotherapy may aggravate SARS-CoV-2 infection and comorbidity among cancer patients [100]. Another immune-related response SARS-CoV-2 with possible variation due to tumors, is antibody-dependent cellular cytotoxicity (ADCC) [107] addressing glycan targeting [108]. The activated subset of effector cells, mostly NK cells [109,110], was known for antitumor activity [111]. There is currently no data available if a combined effect between ADCC to virus-infected cells and radiation was achieved after conventional RT, or supported by low-dose RT and microbiota changes after SARS-CoV-2 infection [112–114]. Tissue TGF-β expression followed conventional RT and pulsed low-dose rate radiation [115]. Coupled complex photobiomodulation, applying low-level light therapy, and probiotic interventions controlled the microbiome [116,117], improved viral clearance [118], as well as the activity of the immune system, the release of chemokines, and thus saved the lives of people with immune imbalances. In general, the last COVID-19 pandemics urged for the development of innovative treatments to successfully interact with the microbiota and the human immune system in the coronavirus crisis [116]. In the sense of reducing the risk for secondary cancers after RT, most bacterial strains that were mentioned to function anti-inflammatory or to reduce infection cytokines and chemokine CXCL8, were tested positive for medical antiviral effects on one of the viruses infecting the respiratory tract [91,92]. Gut, lung and oral microbiota composition influenced and reflected the severity of COVID-19 [114,119–121]. The probiotics mixture VSL#3 dampened proinflammatory and chemokine production, but accelerated restitution in the absence of a functional mucus layer and regeneration. Gut permeability mediated by the SCFA acetate was remarkedly improved in the colons of these mice [122]. Consistently, SARS-CoV-2 impaired SCFA acetate and L-Isoleucine biosynthesis [123], whereas SARS-CoV-2-associated gut microbiota alteration promoted pathogenesis of colorectal cancer [124,125], predominantly through lower abundance of *Faecalibacterium*, *Clostridium*, and *Eubacterium* [125].

Taken together, it remains uncertain how intestinal homeostasis maintains physiological integrity or prevents gastrointestinal tumorigenesis: Reduced abundances of members of the bacterial taxa *Bacteroidales*, the commensal *M. intestinale*, and an expansion in *Lactobacilli* in the ileal microbiome were most notably investigated with the onset of Crohn's disease and inflammatory bowel disease [126], implying that these bacteria impart a proinflammatory protection of cellular metabolism and redox homeostasis to acquire reducing agents for DNA-biosynthesis [127]. TGF-β1 and glutamine were shown to promote secretory IgA independently from the method of B cell activation [128] and through intestinal microbiota [129], respectively. Moreover, genetically modified *Bacteroides* sp. from the human gut microbiota have been engineered to thrive on endogenous glycans by employing multispecific gene loci, which encode surface glycan-binding proteins [130], thus emphasizing mucosal healing and health, particularly in human intestinal gut microbiota [131].

6. Conclusions

Recently, known clinical effects of acute radiation exposure, such as mucositis and diarrhea, were shown to be affected by the gut microbiota in correlation with conditions of treatment and disease [132–134]; but little is known about the subsequently penetrating effects on functional metagenomics initiated by enteric microbial products and systemic metabolomics for the treatment of, for example, prostate cancer [135–137], which has been treated with conventional intensity-modulated radiation therapy [137] and intensity-modulated proton therapy [138]. Analyses between the gut microbiota and bone microstructure revealed that *Bacteroides massiliensis* and *Muribaculum* sp. were different in abundance between CM and RM under mucosa-associated dysbiosis. Specifically, *B. massiliensis* promoted prostate cancer [135] and homeostasis in intestinal microbiota (colon) when colonized with *Helicobacter rodentium* [2,3]. The intestinal microbiota composition was reviewed for its interplay with Th17 cells and activation of Tregs, mediated by TGF-β and IL-1β [2,21,41]. In general, conventional RT was found associated with an increase in lymphocyte death, limiting the immune response [50,139]. Studying total body irradi-

ation (TBI, 1.5 Gy high-energy ^{1}H and ^{28}Si) of mice was relevant for the development of countermeasures to galactic cosmic rays [1,2]. Furthermore, the resulting RM model was susceptible to a shift towards pathophysiological hypoxia and activation of antigen presenting cells which possibly allowed for hypoxia-reoxygenation by TGF-β immune-suppressive regulation, macrophages, and osteoclasts' differentiation. From this perspective, the research referenced here provided linkages between gut bacteria and radiation-induced bone loss, imparting the upregulation of BIPs in the irradiated intestinal microbiota to modulate bone health in prostate and colorectal cancer patients. Post-treatment care, long-term observations, and the cure of second cancer malignancies are addressed in cross-functional studies on particle-beam radiation adverse events or compositions of anti-inflammatory microbiota.

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