

REVIEW

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Vitamin D, gut microbiota, and radiation-related resistance: a love-hate triangle



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Abstract

Radiation resistance is a serious issue in radiotherapy. Increasing evidence indicates that the human gut microbiome plays a role in the development of radiation resistance. Vitamin D is an important supplement for cancer patients treated with radiotherapy. Against this background, this paper reviewed research regarding the associations among vitamin D, microbiota dysbiosis, and radiation resistance. A hypothesis is developed to describe the relationships among vitamin D, the gut microbiota, and radiotherapy outcomes. Radiotherapy changes the composition of the gut microbiota, which in turn influence the serum level of vitamin D, and its distribution and metabolism in the body. Alteration of vitamin D level influences the patient response to radiotherapy, where the underlying mechanisms may be associated with the intestinal microenvironment, immune molecules in the intestines, gut microbiome metabolites, and signaling pathways associated with vitamin D receptors. Our understanding of the contribution of vitamin D and the gut microbiota to radiotherapy outcomes has been increasing gradually. A better understanding of the relationships among vitamin D, the gut microbiota, and radiotherapy outcomes will shed more light on radiation resistance, and also promote the development of new strategies for overcoming it, thus addressing an important challenge associated with the currently available radiotherapy modalities for cancer patients.

Keywords: Radiation resistance, Gut microbiota, Vitamin D

Background

In 2017, the global death population caused by cancer reached 9 million, which was nearly twice the number in 1990 [1]. In 2018, 18.1 million new cancer cases, and 9.6 million deaths from cancer, were reported worldwide [2]. Numerous treatments are available for non-melanoma skin cancer patients, with radiotherapy being an efficacious and tissue-preserving non-surgical option [3]. Radiotherapy is defined as the clinical use of ionizing radiation (IR), including α or γ rays, to induce DNA damage in all exposed cells to ultimately kill cancer cells or prevent cancer growth [4, 5]. It can be used to eradicate certain cancers or reduce their likelihood of recurrence, and as a palliative treatment [6]. Currently, approximately 60% of patients being treated for cancer in the United States have received radiotherapy. Despite the increasing clinical application of radiotherapy, the

resistance of tumor cells to IR remains a significant obstacle [7], potentially leading to relapse, a poor treatment response or poor prognosis [8–13]. Moreover, radiation resistance induces injury to tumor-adjacent tissues, resulting in disruption of normal physiological functions, as expressed in symptoms such as diarrhea and rectal bleeding [14], and significantly increasing the subsequent risk of a number of adverse events including cardiovascular disorders, micronutrient deficiencies, and even secondary tumors, all of which typically decrease patient quality of life. The phenomenon of radiation resistance presents two challenges to the advancement of radiotherapy: (1) development of a mechanistic understanding of the factors underlying radiation resistance and the heterogeneity thereof; and (2) development of effective treatments, based on clinical and experimental molecular methods, to decrease side effects and overcome radiation resistance in cancer patients. Currently, despite the rapid development of new technologies, our understanding of, and ability to treat, cancer is still limited by many factors, including radiation resistance [15]. The current perspective on resistance mechanisms, which is a complex process involving multiple genes, factors, and signaling pathways, points to an

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unmet need to examine novel factors, including the functional role of the gut microbiota. Additionally, utilizing a nutrient-focused approach in individual cancer patients may improve the likelihood of successful radiotherapy, a reduced rate of side effects, and long-lasting benefits. Against this background, this review discusses areas of mechanistic understanding that may benefit from a new perspective.

Radiation resistance-related mechanisms

Ionizing radiation deposits energy and generates reactive chemical species along “tracks”, resulting in cytotoxic and genotoxic injury to DNA, including DNA double-strand breaks, and posing a challenge to cancer cell survival by inhibiting the proliferation thereof [16]. Additionally, IR can induce cell cycle arrest, apoptosis, autophagy, and changes in the cellular microenvironment [12, 17], which can in turn lead to radiation resistance. Cancer cells may develop mechanisms to escape cell cycle arrest, resist DNA damage-induced cell apoptosis, or alter the cancer microenvironment through cytokines [18–20]. The radiation resistance associated with these changes benefits cancer cells and renders radiotherapy less effective. Several signaling pathways contribute to cellular resistance against IR (Fig. 1) [21]. Although radiation resistance-related molecular mechanisms have been intensively investigated, many questions remain unresolved. For example, does crosstalk exist between individual mechanisms, and are there genes and

proteins important in multiple mechanisms? For example, some reports have identified genes and proteins involved in both IR-induced cell cycle checkpoints and autophagy [22]. Are there other mechanisms that must be considered for a complete understanding of radiation resistance? Moreover, is there a single core regulator of multiple radiation resistance-related signaling pathways, active during all radiation resistance processes? [23, 24].

Association between radiotherapy and gut microbiota

The gut microbiota, i.e., the bacteria, archaea, viruses, and eukaryotic microbes residing primarily in the colon (but also in other organs including the lung and stomach) [25], accounts for approximately 1 kg of human body weight, and includes more unique genes than the human genome [26]. Over the past decade, rapid development of DNA and 16 s RNA sequencing technology has dramatically improved researchers’ ability to survey changes in gut microbiota in response to different stresses [27]. Increasingly, reports have indicated that the gut microbiota plays a major role in the maintenance not just of intestinal homeostasis, but of the overall health of the body [28]. In particular, the dysbiotic gut microbiome seen in cancer radiotherapy patients, with altered microbial diversity and richness relative to that of healthy individuals, has been associated with the outcomes of cancer therapy [29]. Recently, it has been shown that gut microbiota status is closely related to the

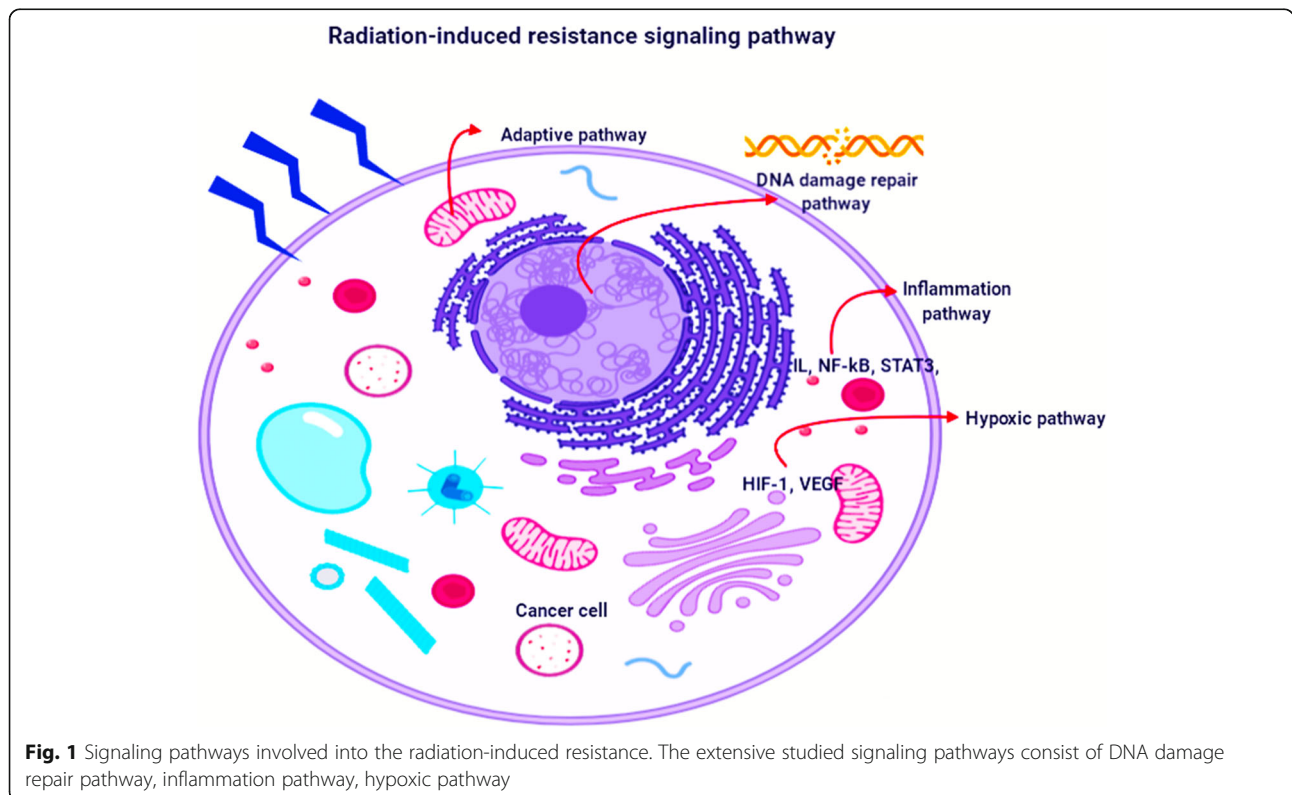


Fig. 1 Signaling pathways involved into the radiation-induced resistance. The extensive studied signaling pathways consist of DNA damage repair pathway, inflammation pathway, hypoxic pathway

response to radiotherapy. Many studies have discussed the effectiveness of radiotherapy for various types of cancer, and radiotherapy-related side effects, in the context of the gut microbiota. Tilg et al. recently reported a direct link between altered microbiota composition and the inflammatory status of patients with type 2 diabetes; decreased diversity of the intestinal microbiota may lead to a failure to maintain the intestinal barrier needed to prevent systemic dissemination of gut bacteria and associated chemical mediators [30]. Daily ultraviolet radiation of skin is a typical source of 25-hydroxyvitamin D₃ (25(OH)D₃) in the human body. Previous studies reported that ultraviolet radiation was associated with a significant change in the beta-diversity of feces. Specifically, members of the phylum Firmicutes family, including *Coprococcus*, were enriched, whereas members of the phylum Bacteroidetes family, such as Bacteroidales, were depleted [31].

During the process of radiotherapy, gut microbiota including *Lactobacillus acidophilus*, *L.casei*, and *Bifidobacterium* spp. have been proven to reduce symptoms of radiation-induced gut toxicity, such as diarrhea [27]. However, Barker et al.(2015)reported that radiotherapy altered the composition of the gut microbiota, breaking the intestinal barrier and causing apoptosis in intestinal crypts [32], although other studies found no effect of radiation on the gut microbiota. For instance, Gosiewski et al. showed that therapeutic doses of radiation did not significantly affect *Lactobacillus* populations [33]. Dysbiotic gut microbiome may be due to factors other than irradiation, such as heterogeneity among patients, including with respect to their daily diets, alcohol intake, and medication use. This highlights the challenges faced by studies of the association of the gut microbiota with radiation resistance seeking to answer the following important questions. Which taxa/phyla play the most dominant role in the development of radiation resistance? How are gut microbiota-derived signaling molecules generated, and how do they increase or suppress radiation sensitivity? How do factors such as nutrients induce gut microbiota changes, and how is this linked to radiation resistance?

Vitamin D: role in biological processes

Vitamin D comprises a group of fat-soluble secosteroids responsible for the absorption of essential trace elements, such as calcium, magnesium, and phosphate, and having roles in multiple biological processes [34], including cell growth, as well as in immune function and inflammation (reduction thereof). Vitamin D supplements are provided to treat or prevent many diseases, including deficiency-induced rickets and osteomalacia [35, 36]. For example, clinically, the high incidence and poor prognosis of colorectal cancer has been found to be partly

attributed to insufficient vitamin D [37], and colorectal cancer patients with high levels of vitamin D have a lower risk of metastatic progression during neoadjuvant therapy before radical surgery [37]. A meta-analysis by Van den Blink et al. reported that vitamin supplementation reduced radiation-related bone fractures and the risk of avascular necrosis in patients undergoing pelvic radiotherapy [38]. Castro-Equiluz et al. recommended vitamin D as the most important nutrient for cancer patients treated with pelvic radiotherapy [14]. Typically, the natural form of cholecalciferol is produced in the skin from dehydrocholesterol, with pre-vitamin D₃ produced after ultraviolet irradiation. This process is essential for vitamin D biosynthesis in humans, although vitamin D can also be supplied via the diet. In the body, vitamin D is transported into the blood and metabolized in the liver, where it is then hydroxylated to produce the active form, 25-hydroxyvitamin D₃ (25(OH)D₃). Many cytochrome P-450 enzymes are involved in the conversion of vitamin D to 25(OH)D₃, including CYP2R1, CYP27A1, and CYP2D25 [39]. This active form of vitamin D has numerous biological effects, including inhibition of the epithelial-mesenchymal (EMT) transition in cancer cells; it also confers protection against cardiovascular disease and inflammatory bowel disease. 25(OH)D₃ prevents the EMT in human peritoneal mesothelial cells through regulation of the Wnt/ β -catenin signaling pathway [40]. Hou et al. observed that 1 α , 25(OH)2D₃ suppressed the migration of ovarian cancer cells by inhibiting the EMT, suggesting that 1 α , 25(OH)2D₃ might have potential as a therapeutic agent for ovarian cancer [41]. Furthermore, Findlay et al. showed that 1 α ,25(OH)2D₃ enhanced radiation sensitivity in colorectal cancer cells through regulating the EMT [42]. Higher plasma levels of 25(OH)D₃ are associated with a decreased risk of highly aggressive prostate cancer [43]. Mutation or deficiency of the genes and enzymes responsible for the transport or metabolism of 25(OH)D₃ may alter its levels and functions [43]. For instance, a mutation in CYP2R1, a key hydroxylase for 25(OH)D₃ production, resulted in deficiency thereof, as well as symptoms of vitamin D-dependent rickets [44]. In addition to its classic effects on calcium and bone homeostasis, vitamin D has other important roles in immune regulation and protection of the cardiovascular system [45]. As reported in the review article by Aranow, vitamin D receptors are expressed on immune cells, including B cells, T cells, and antigen-presenting cells; this indicates that active vitamin D metabolites are synthesized by these cells, suggesting that vitamin D can modulate innate and adaptive immune responses. In turn, this suggests that the beneficial effects of vitamin D supplementation in deficient individuals with autoimmune disease may extend beyond the effects on bone

and calcium homeostasis [45]. Similarly, vitamin D has a putative protective role in the cardiovascular system [46]. Growing evidence suggests that vitamin D levels are inversely associated with the risk of cardiovascular diseases, including ischemic heart disease, stroke, hypertension, blood lipids abnormalities, and obesity [47]. However, some studies, including randomized controlled trials (RCTs), did not report significant effects of vitamin D supplementation on cardiovascular outcomes [48], suggesting a need for further research. Current evidence indicates that vitamin D plays important roles in cardiovascular function, but more data are needed to establish causality. In this review, we focused on the underlying mechanisms of radiation resistance; thus, in the discussion below, we will address the following: (i) the association of vitamin D level with the risk of radiotherapy-induced side effects; (ii) the association of vitamin D level with radiation resistance; (iii) the effects of vitamin D on the integrity of the intestinal barrier, (iv) the effects of vitamin D on the gut microbiota; and (v) the effects of gut microbiota on vitamin D metabolism, distribution, and utilization.

Vitamin D-mediated roles in radiation resistance

Recently, there has been increasing concern regarding the role of vitamin D in preventing radiotherapy-induced side effects. Surrounding tissues may be damaged during radiotherapy, leading to IR-induced symptom including diarrhea and rectal bleeding [14]. A study by Mukai et al. indicated that vitamin D supplementation was a significant factor in prolonged metastasis-free survival after preoperative chemoradiation therapy for patients with pancreatic ductal adenocarcinoma [49]. Radiation dermatitis occurs frequently during radiation therapy in cancer patients, and vitamin D ointment is helpful for its prevention [50]. In a case report, vitamin D supplementation prior to surgery and radiotherapy in a patient with recurrent breast cancer altered certain biological cancer markers, such as estrogen receptor, human epidermal growth factor receptor, and nuclear protein Ki67 [51]. Moreover, an increasing body of evidence suggests that gut epithelial vitamin D receptor signaling pathways play an essential role in maintaining the integrity of the intestinal mucosa. Vitamin D deficiency is associated with the severity of radiation-induced proctitis in cancer patients [52]. However, the mechanisms underlying the ability of vitamin D to decrease radiotherapy-induced side effects needs to be elucidated so that appropriate management guidelines and recommendations for cancer patients undergoing radiotherapy can be formulated. Sharma et al. found that 25(OH)D₃, the hormonally active form of vitamin D [53], promoted responses of non-small cell lung cancer to irradiation through induction of autophagy via the vitamin D

receptor/TP53/AMPK signaling pathway [54]. Another study asserted that vitamin D has the potential to improve genetic inhibition and increase sensitivity to radiation, by acting as a switch between cytoprotective and cytotoxic autophagy [55]. Elegant studies have indicated that loss of the DNA repair protein 53BP1 results in resistance of breast cancer cells to radiation. The active form of vitamin D, 1 α ,25(OH)₂D₃, stabilizes 53BP1 levels in tumor cells, restoring them as efficiently as cathepsin L inhibitors, and ultimately contributing to increased genomic instability in response to radiation and reduced proliferation of cancer cells [56].

Strikingly, 25(OH)D₃ is crucial for maintaining the intestinal barrier [57]. The physical intestinal barrier, comprised of a thick mucus layer and the epithelium, plays a critical role in the defense against microbes, harmful foreign antigens, endotoxins, and toxic metabolites of bacteria, in addition to other environmental hazards entering the body via the diet. The importance of 25(OH)D₃ in the gut has been demonstrated over the past decade. In brief, 25(OH)D₃ binds vitamin receptors on intestinal cells and regulates the transcription of target genes, promoting gut health by maintaining immune homeostasis and suppressing inflammation and fibrosis (Fig. 2). Furthermore, decreased intestinal epithelial vitamin D receptor expression alters gut microbial homeostasis, resulting in less butyrate production and, by extension, chemically induced colitis in mice [58]. In human studies, high-dose vitamin D₃ supplementation had a beneficial effect on the human gut microbiota, markedly reducing typical opportunistic pathogens and increasing phylotype richness [59]. Butyrate, a byproduct of carbohydrate breakdown by microbiota, has a well-established role in preventing mucosal inflammation. Sun et al. showed that decreased expression of intestinal epithelial vitamin D receptors led to lower butyrate production and intestinal barrier inflammation [60]. Vitamin D protects the intestinal barrier by regulating tight junction proteins and inhibiting intestinal apoptosis [61]. Furthermore, vitamin D enhances innate immunity by inducing antimicrobial peptides, and regulates adaptive immunity by promoting anti-inflammatory T cells and cytokines [61]. A review by Cantorna et al. suggested that vitamin D deficiency increases susceptibility to infection or injury of the gastrointestinal tract [62]. Vitamin D enhances the ability of innate lymphoid cells to produce IL-22, suppresses IFN- γ and IL-17 release from T cells, and induces regulation of T cells in the mucosal tissues, modulating microbial communities in the gut to maintain the integrity of the intestinal barrier. Mandle et al. showed that vitamin D₃ (1000 IU per day) significantly improved intestinal barrier function-related biomarkers, such as tight junction proteins claudin-1 (CLDN1), occludin (OCLD), and mucin-12 (MUC12), in

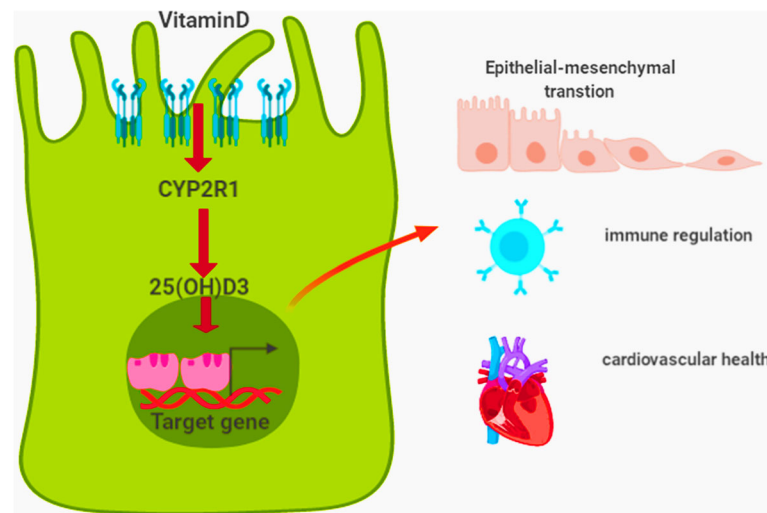


Fig. 2 The molecular mechanism of Vitamin D's role in the biological functions. 25(OH)D3, the major metabolite of vitamin D, binds vitamin receptors on intestinal cells and regulates the transcription of target genes, promoting gut health by maintaining immune homeostasis and suppressing inflammation and fibrosis

patients with recurrent colorectal adenoma [63]. Disruption of intestinal epithelial barrier homeostasis typically occurs due to altered composition of the gut microbiota [64], and the interaction between vitamin D and the gut microbiota serves as a primary defense against radiation resistance.

Radiotherapy influences vitamin D levels. A recent gene expression study showed that mice exposed to IR exhibited lower expression levels of the CYP genes *Cyp4f18* and *Cyp4v3* [65]. CYP4 proteins have been reported to metabolize vitamin D and play an essential role in the defense against environmental stressors, including radiation exposure [66]. The involvement of vitamin D metabolism in radiation injury has been documented in several gene expression studies [67]. The vitamin D metabolite calcitric acid increased in mice after high dose rate (HDR) cesium-137 (137Cs) and strontium-90 (90Sr) (1.1 Gy/min to) [67], whereas a low dose rate (LDR) (3.0 mGy/min) had no effect on this metabolite; this suggested that the effects on vitamin D metabolism differ by exposure level. However, studies in this area are limited, particularly those examining how radiotherapy influences the mechanisms of vitamin D metabolism.

Effects of vitamin D-on the gut microbiota

In addition to protecting the intestinal barrier, vitamin D may favorably alter the gut microbiota [60], with evidence also emerging of its role in reducing the resistance of cancer cells to radiation. In some human studies, high-dose vitamin D3 supplementation had a beneficial effect on human gut microbiota, markedly reducing typical opportunistic pathogen species including *Pseudomonas*, *Escherichia*, and *Shigella*, and increasing phylotype

richness [59]. An association between vitamin D and radiation resistance has also been posited, via alteration of the gut microbiota. Ferrer-Mayorga et al. showed that the vitamin D metabolite 1 α ,25-dihydroxyvitamin D3 inhibits colorectal cancer cell proliferation and promotes epithelial differentiation of colon cancer cell lines, thereby improving radiation sensitivity through altering the composition of intestinal microbiota communities [68]. Some studies reported that vitamin D influenced the gut microbiome through activation of enteric bacteria vitamin D receptor signaling [69, 70]. Commensal and pathogenic bacteria directly regulate colonic epithelial vitamin D receptor expression, which in turn negatively regulates bacteria-induced intestinal nuclear factor- κ B activation [71, 72]. Accordingly, vitamin D receptor gene mutations in humans should influence the intestinal microbiota. In vitamin D receptor knockout mice, *Parabacteroides* abundance was altered significantly [73], *Lactobacillus* was depleted, and *Clostridium* and *Bacteroides* showed enrichment [74]. Furthermore, vitamin D deficiency induces notable changes in the gut microbiota, including increased *Helicobacter hepaticus* and decreased *Akkermansiamuciniphila* population sizes [75]. *Lactobacillus sakei* is known to have a radioprotective effect for the enteritis compared to conventional chemical agents with inherent toxicities [76]. Intaking synbiotic powder containing *Lactobacillus reuteri* (108 CFU) reduce proctitis symptoms and improve quality of life by preventing rectal inflammation during radiotherapy for prostate cancer [77]. Moreover, *Bacteroides* increased in radiation-exposed conventional microbiota, and *H. hepaticus* is known to induce colon cancer [78]. *A. muciniphila* is also known to improve barrier function

and metabolic health [79]. These data indicate that one mechanism via which vitamin D protects against radiation resistance is through targeting the gut microbiota via the vitamin D receptor. Moreover, alterations of gut microbiota can be caused by vitamin D intake and other dietary components, rendering gut microbiota regulation by vitamin D complex. Further study is needed to uncover and confirm the mechanisms underlying the effects of vitamin D on the gut microbiota.

Logically, altered gut microbiota should influence the vitamin D distribution and metabolism in the body. However, studies on the contribution of altered gut microbiota to these parameters are scarce. Bora et al. showed that germ-free mice infected with the pathogen *C. rodentium* exhibited decreased vitamin D and 25D absorption post infection [80]. They also measured serum 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D, and 1,25-dihydroxyvitamin D levels before and 2 weeks after broad-spectrum antibiotic treatment; the levels of all three compounds were increased, which was attributed to the microbiota or antibiotic treatment [81]. A recent study examined the effect of the gut microbiota on vitamin D metabolism [80], and found that it inhibited fibroblast growth factor 23 and induced increased serum 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D, and 1,25-dihydroxyvitamin D levels. Some researchers have suggested that different gut microbiota signatures and alterations in vitamin D3 levels may be useful markers of disease in clinical practice, and that fecal vitamin D3 and gut microbiota composition could serve as biomarkers for diagnosis and follow-up [82]. However, for effective interventions targeting the gut microbiome composition and vitamin D levels, further investigation is required, to determine the mechanisms underlying vitamin D regulation by the microbiota. Future studies should address the following questions. (i) What are the underlying mechanisms by which vitamin D regulates radiation resistance?; (ii) Are vitamin D levels regulated predominantly by one bacterial species, or by multiple, interacting species?; (iii) Environmental factors, including ultraviolet radiation, and lifestyle factors including reduced physical activity and insufficient consumption of vitamin D-rich foods, are involved in the alteration of gut microbiota and the etiology of vitamin D deficiency, and may also be important in radiotherapy outcomes; do these factors affect radiation resistance, and if so, how?

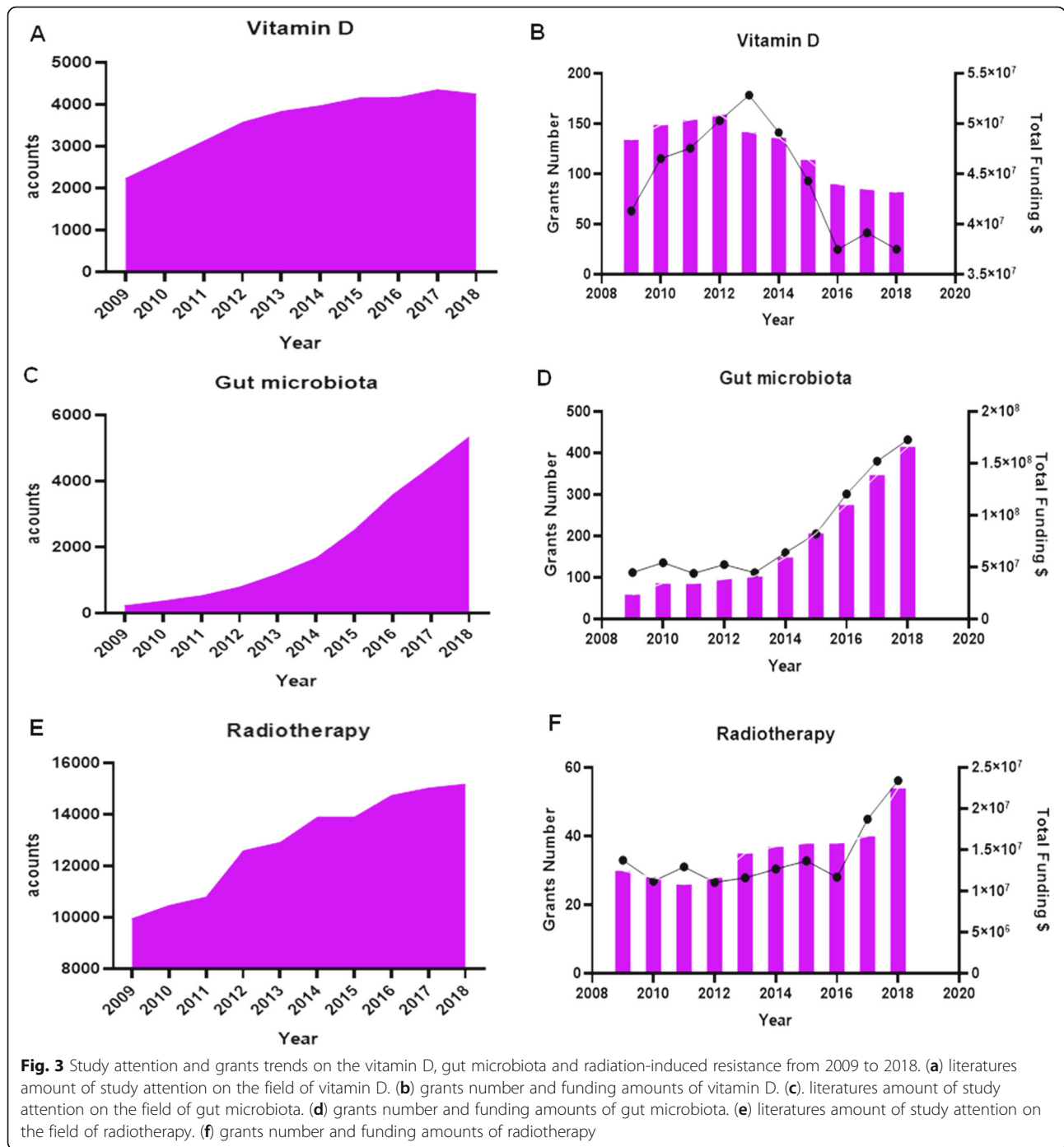
There is a pressing need for further investigation of the relationships among environmental factors, lifestyle factors, vitamin D levels, gut microbiota, and radiation resistance, to promote the development of vitamin D-based clinical interventions targeting the microbiota for addressing radiation resistance.

Relationships among vitamin D, gut microbiota, and radiation resistance

To review the research on the relationships of vitamin D, gut microbiota, and radiotherapy outcomes as well as acknowledge the study trend regarding these three topics, we searched published literature by the Pubmed (www.pubmed.com) and grants funded by the US National Institutes of Health (NIH, <https://www.nih.gov/>) over the past decade. We selected both two websites since Pubmed includes almost the possible published studies as possible as it can across the world scientific community, while NIH provide the grants funded mainly from developed countries such as USA and other developing countries such as India and China. As shown in Fig. 3, between 2009 and 2018, the number of publications on vitamin D, gut microbiota, and radiotherapy gradually increased, although grants and funding for vitamin D research have been gradually decreasing; in each of the last 3 years, there were fewer than 100 grants (Fig. 3a,b). In contrast, grants and funding for gut microbiota and radiotherapy research have been increasing gradually each year, and peaked in 2018 (Fig. 3c,d). The total funding for gut microbiota research in 2018 was almost \$200,000,000, far greater than that for vitamin D (\$40,000,000) and radiotherapy (\$25,000,000) research (Fig. 3e,f). Overall, these data suggest that vitamin D, gut microbiota, and radiotherapy are receiving attention from both the scientific community and governments.

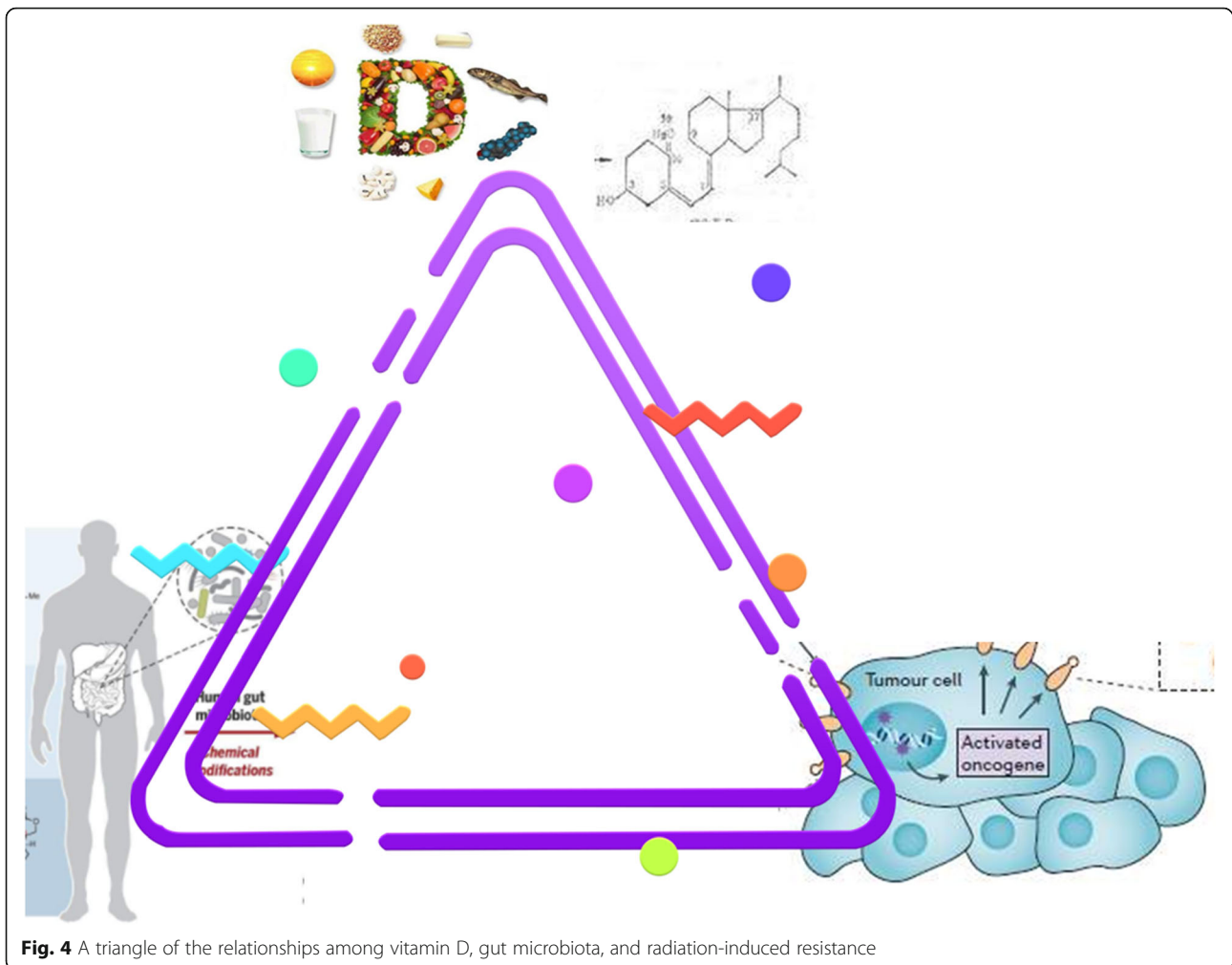
In summary, the relationships among vitamin D, gut microbiota, and radiotherapy outcomes can be described as a triangle, as illustrated in Fig. 4; the roles of the elements of this “love-hate triangle” differ according to the physiological/pathological status of the cell. Vitamin D plays a crucial role in protecting the intestinal barrier and preventing gastrointestinal mucosal inflammation. Vitamin D deficiency not only affects the integrity of the barrier, but also moderates the composition of the gut microbiome community in murine models. In humans, vitamin D deficiency, accompanied by vitamin D receptor gene mutations, also contributes to changes in the gut microbiome. Moreover, gut microbiota status influences vitamin D distribution and metabolism. Alterations of the gut microbiota have also been studied in relation to radiotherapy. Some species of gut microbiota are associated with radiation resistance, while radiation can in turn influence the gut microbiota composition, where marked changes are frequently seen in *Bifidobacterium*, *Clostridium*, and *Bacteroides spp.* Radiotherapy affects vitamin D metabolism and distribution in the body, which in turn affects radiotherapy outcomes; there are vitamin D receptor polymorphisms having differential sensitivity to radiation.

The interactions among vitamin D, the gut microbiota, and radiotherapy outcomes are important for understanding



radiation resistance. Substantial progress has been made in our understanding of these interactions at the molecular level, which could help to guide strategies aimed at overcoming radiation resistance in radiotherapy patients. Nevertheless, many questions remain, as follows. (i) How and to what extent do distinct molecular pathways lead to a pathological imbalance in the “love-hate triangle”?; (ii) Does an unstable gut microbiome lead to progressive dysregulation of vitamin D metabolism beyond a critical threshold for radiotherapy-

induced radiation resistance?; (iii) What other dietary factors and microbiome metabolites are associated with host responses to radiotherapy, and through what molecular receptors and signaling pathways do they interact with vitamin D?; and (iv) Although gut microbiota transplantation has been documented in numerous studies, with encouraging outcomes, their clinical applications are limited. Could such transplantations serve as a novel intervention in radiation resistance?



These questions are of great importance, given the fundamental challenges that remain with respect to overcoming radiation resistance and improving the quality of life of cancer patients. Obtaining answers to these questions will allow us to better understand the interactions among vitamin D, the gut microbiota, and radiotherapy outcomes, and could guide the development of new interventions to restore homeostasis in both the intestinal barrier and the microbiome.

Conclusion

In conclusion, vitamin D and gut microbiota are key factors in shaping the radiation-induced resistance, and therefore, their impact on quality of patients' life and cancer recurrence. However, the challenge now is to fully decipher the molecular mechanisms that link the vitamin D, gut microbiota, radiation resistance in a network of communication that impacts radiotherapy outcomes, to eventually translate these findings to the clinical prevention and control of radiation-induced resistance. Additional studies including measuring novel

vitamin D metabolites by gut microbiota and utilizing randomized controlled trial to determine the impact of interaction of vitamin D and gut microbiota on benefit clinical radiotherapy outcomes in patients with cancer are warranted.

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Authors' contributions

PK Z conceived and designed the study; J X performed literature reviewing; RX H analyzed the data and performed the statistical analysis. RX H drafted the initial manuscript. PK Z critically reviewed and revised the manuscript. All authors read and approved the final Manuscript.

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Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

N/A

Consent for publication

N/A

Competing interests

The authors declare that they have no competing interests.

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