

World Journal of *Stem Cells*

World J Stem Cells 2020 March 26; 12(3): 168-240



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The *WJSC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, and BIOSIS Previews. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJSC* as 3.534 (5-year impact factor: N/A), ranking *WJSC* as 16 among 26 journals in Cell and Tissue Engineering (quartile in category Q3), and 94 among 193 journals in Cell Biology (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Tong Cao, Shengwen Calvin Li, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

March 26, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Gut commensal bacteria, Paneth cells and their relations to radiation enteropathy

Yan-Li Gao, Li-Hong Shao, Li-Hua Dong, Peng-Yu Chang

ORCID number: Yan-Li Gao (0000-0003-2204-1324); Li-Hong Shao (0000-0002-5411-0016); Li-Hua Dong (0000-0002-5148-2949); Peng-Yu Chang (0000-0001-9047-7942).

Author contributions: Gao YL and Shao LH jointly prepare the figures and tables; Chang PY conceives and writes this review article; Dong LH is responsible for the concept of this review.

Supported by National Natural Science Foundation of China, No. 81874254 and No. 81773353.

Conflict-of-interest statement: All authors claim no conflicts of interest.

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Manuscript source: Invited Manuscript

Received: November 4, 2019

Peer-review started: November 4, 2019

First decision: December 6, 2019

Revised: December 12, 2019

Accepted: February 17, 2020

Yan-Li Gao, Department of Pediatric Ultrasound, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Li-Hong Shao, Li-Hua Dong, Peng-Yu Chang, Department of Radiation Oncology and Therapy, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Li-Hong Shao, Li-Hua Dong, Peng-Yu Chang, Jilin Provincial Key Laboratory of Radiation Oncology and Therapy, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Peng-Yu Chang, Key Laboratory of Organ Regeneration and Transplantation of the Ministry of Education, The First Hospital of Jilin University, Changchun 130061, Jilin Province, China

Corresponding author: Peng-Yu Chang, MD, PhD, Doctor, Department of Radiation Oncology and Therapy, The First Hospital of Jilin University, Xinmin Street, No. 71, Changchun 130021, Jilin Province, China. changpengyu@jlu.edu.cn

Abstract

In steady state, the intestinal epithelium forms an important part of the gut barrier to defend against luminal bacterial attack. However, the intestinal epithelium is compromised by ionizing irradiation due to its inherent self-renewing capacity. In this process, small intestinal bacterial overgrowth is a critical event that reciprocally alters the immune milieu. In other words, intestinal bacterial dysbiosis induces inflammation in response to intestinal injuries, thus influencing the repair process of irradiated lesions. In fact, it is accepted that commensal bacteria can generally enhance the host radiation sensitivity. To address the determination of radiation sensitivity, we hypothesize that Paneth cells press a critical "button" because these cells are central to intestinal health and disease by using their peptides, which are responsible for controlling stem cell development in the small intestine and luminal bacterial diversity. Herein, the most important question is whether Paneth cells alter their secretion profiles in the situation of ionizing irradiation. On this basis, the tolerance of Paneth cells to ionizing radiation and related mechanisms by which radiation affects Paneth cell survival and death will be discussed in this review. We hope that the relevant results will be helpful in developing new approaches against radiation enteropathy.

Key words: Gut commensal bacteria; Paneth cell; Radiation enteropathy; Epithelial homeostasis; Gut immunity; Intestinal defense

Article in press: February 17, 2020
Published online: March 26, 2020

P-Reviewer: Gassler N, Miloso M, Tanabe S

S-Editor: Gong ZM

L-Editor: A

E-Editor: Xing YX



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Core tip: In healthy individuals, Paneth cells restrict the overgrowth of commensal bacteria in the gut while killing luminal pathogenic bacteria by secreting antimicrobial peptides. Such a property protects crypt intestinal stem cells against bacterial infection, thus ensuring epithelial homeostasis in steady state. Among the active pool of intestinal stem cells, apoptosis commonly occurs as a result of ionizing irradiation. Nevertheless, the intestinal epithelium will recover its integrity after sublethal irradiation. On this basis, the mechanism by which Paneth cells provide growth signals for intestinal stem cells to facilitate epithelial regeneration is easy to understand, whereas the automatic recovery of irradiated intestine from sublethal irradiation is perplexing. Being challenged with luminal bacteria, the degranulation of Paneth cells can be stimulated in a cholinergic- or inflammatory-substance-dependent manner. Then, Paneth cells can perform an antibacterial function that influences the inflammatory milieu in irradiated intestine. Therefore, radiation-induced intestinal bacterial dysbiosis can be managed.

Citation: Gao YL, Shao LH, Dong LH, Chang PY. Gut commensal bacteria, Paneth cells and their relations to radiation enteropathy. *World J Stem Cells* 2020; 12(3): 188-202

URL: <https://www.wjgnet.com/1948-0210/full/v12/i3/188.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v12.i3.188>

INTRODUCTION

Ionizing irradiation is indeed a useful tool for treating malignant tumors. In current guidelines, radiation therapy is highly recommended for local rectal cancers with indications after preoperative or postoperative evaluations^[1]. However, the standard target volume includes the iliac lymph drainage area, thus enabling a portion of the small intestine and colon to be irradiated unavoidably^[2]. Clinically, the gut is regarded as an early responding organ to ionizing irradiation, and acute enteritis commonly occurs during treatment^[3]. Although acute injuries can be self-limited, more severe lesions, such as intestinal obstruction, bleeding or perforation, potentially increase their morbidities in the postirradiation period among some patients, thus poorly affecting their quality of life^[3].

It has been well accepted that radiation-induced intestinal injury is an independent disease, which is termed as radiation enteropathy (RE). The pathogenesis of RE is indeed complicated, and several factors are involved in this process^[3]. First, radiation-induced DNA damage occurs at the initial stage of RE. As is known, the intestinal epithelium represents one tissue with fast self-renewing capability in humans, thus enabling the epithelium to be compromised by ionizing irradiation^[4]. However, the cells that form intestinal tissues differ in their radiation sensitivities. For example, smooth muscle cells are more resistant to ionizing irradiation than lymphocytes or endothelial cells partially due to their inactive cell cycle^[5]. Moreover, the large bowel is well tolerant to ionizing irradiation compared to the small bowel^[6,7]. Apart from the potential differences between the small and large bowels in their histological structures, several other factors also account for radiation sensitivity determination. Herein, commensal bacteria have emerged as critical candidates because they function in shaping host immunity along with strengthening intestinal epithelial homeostasis^[8,9]. In clinical practice, most colorectal cancer (CRC) patients undergoing radiation therapy bear tumor burdens. Critically, intestinal bacterial dysbiosis has been proven in gut carcinogenesis, as has its promotion of tumor progression^[10,11]. Moreover, radiation itself is able to potentiate intestinal bacterial dysbiosis as well^[8]. In this regard, although radiation therapy induces in-field tumor shrinkage, it should be argued whether radiation-induced intestinal bacterial dysbiosis further aggravates the immunological milieu, which potentially increases the risk of local or distant CRC relapse. If so, radiation-induced intestinal bacterial dysbiosis will enable radiation therapy to be contraindicated in CRC patients. In fact, it is well known that several types of cells in the gut can produce antimicrobial substances, such as secretory IgA (sIgA) by B cells or plasma cells and antimicrobial peptides by epithelial cells. Herein, Paneth cells are specialized epithelial cells of the small intestine, which provide a wider range of secretions than other epithelial cells in this process. In this regard, we hypothesize that Paneth cells are critical in regulating microbial ecology

postirradiation.

COMMENSAL BACTERIA AND GUT RADIATION SENSITIVITY

Experts in radiation-associated fields have long understood the importance of commensal bacteria in the pathogenesis of RE. To elaborate on this issue, some landmark studies should be mentioned here. Several decades ago, McLaughlin *et al.*^[12] reported that germfree mice were more resistant to whole-body irradiation (WBI) than conventional mice, thus confirming specific roles of commensal bacteria in determining host radiation sensitivity. Afterwards, Potten^[13] identified that the numbers of crypt apoptotic cells did not differ within six hours postirradiation when using doses from 1 Gy to 10 Gy. Likewise, Beck *et al.*^[14] found that either 6 Gy or 14 Gy could induce a significant reduction in the number of goblet cells at the third day postirradiation, suggesting no discrimination between these doses in damaging goblet cells. Nevertheless, it is widely observed that mice can recover from sublethal irradiation even though they lack foreign interventions. To support this view, basic research revealed that intestinal injuries could be repaired automatically if irradiated using doses from 6 Gy to 12 Gy, whereas greater than 15 Gy led to an irreversible breakdown of the epithelium^[15]. Moreover, although 0.01 Gy is enough to induce apoptosis in a portion of Lgr5-positive intestinal stem cells (ISCs)^[16], doses less than 6 Gy barely impair epithelial structures^[15]. In this case, what is the force in discriminating the biological effects between lethal and sublethal irradiation? In fact, a previous study reported that SCID mice could survive no more than two weeks if they were irradiated using doses larger than 5 Gy^[17], suggesting the participation of adaptive immunity in controlling the tolerance of hosts to radiation. In general, it has been determined that ionizing irradiation can affect host immunity. After extensive exploration, it is gradually deduced that radiation therapy affects host damage and repair processes by regulating the balance between effector T (Teff) cells and regulatory T (Treg) cells or by altering the numbers of other lineage-derived promoters or suppressors infiltrating into lesioned sites^[18]. According to this concept, several strategies should become potential candidates for RE treatment, such as regenerative medicine by using mesenchymal stem cells, which exhibit capacities for activating host repair responses^[19]. In contrast to immunomodulatory effects, the beneficial implications of stem cell therapy in intestinal bacterial dysbiosis are rarely reported. To resolve this imbalance, bacteria-supportive care (BSC) can be used for RE because several lines of evidence from clinical trials have indicated the therapeutic efficacies of probiotics, prebiotics and symbiotics^[8]. Therefore, commensal bacteria play critical roles in determining intestinal radiation sensitivity^[20].

COMMENSAL BACTERIA AND GUT Th17/Treg BALANCE POSTIRRADIATION

As mentioned above, intestinal commensal bacteria shape the host immunity. Herein, small intestinal bacterial overgrowth occurs as a result of radiation^[21], thus enabling the immune milieu within irradiated sites to be altered reciprocally. In this process, Treg cells and their counterparts, Th17 cells, should be highlighted here because the mutual restriction between Treg and Th17 cells certainly impacts the prognosis in various diseases, especially in autoimmune diseases^[22]. In the gut, Treg and Th17 cells can be induced from CD4⁺ naïve T cells by luminal commensal bacteria. In steady state, the human colon contains higher frequencies of commensal bacteria than the small intestine^[23]. Herein, polysaccharide (PSA)-producing *Bacteroides fragilis* (*B. fragilis*) are mainly distributed in the colon, and these bacteria primarily exert the function of inducing Treg cell generation in colonic lamina propria (LP)^[24]. By contrast, Th17 cells show peak numbers in the LP of the small intestine both in humans and mice^[25]. Then, these cells are redistributed into other sites to defend against bacterial infection^[26]. In mice, the terminal ileum was reported to contain the highest numbers of segmented filamentous bacteria (SFB) and *Cytophaga-flavobacterium-bacteroidetes* (CFB), which specifically induced Th17 cell generation^[27,28]. In contrast to mice, although commensal bacteria accounting for Th17 induction in the human gut are still unclear so far, species including enterotoxigenic *B. fragilis* and *Bifidobacterium adolescentis* are able to induce Th17 cell generation from the gut of germfree mice^[25,29], while colonizing mice with feces from inflammatory bowel disease (IBD) patients also induces colonic accumulation of Th17 cells^[30]. Likewise, fecal microbiota

transplantation from irradiated conventional mice into germfree mice predisposes the recipients to colitis, demonstrating that such fecal bacteria are critical agents in increasing intestinal sensitivity to radiation^[31]. Nevertheless, an important question should be raised here, proposing whether intestinal bacterial dysbiosis occurrence relies on a threshold dose? To this end, it is known that intestinal bacterial dysbiosis occurs secondary to epithelial injuries because the intestinal epithelium exerts selection pressures on the gut composition of commensal bacteria by secreting antibacterial substances^[32]. As previously reported, genetic depletion of the IL-17 receptor (IL-17R) resulted in a dramatic loss of α -defensins, which specifically led to the overgrowth of *SFB*^[33]. Normally, IL-17R is widely expressed by intestinal epithelial cells^[34]. However, radiation-induced incomplete epithelium enables IL-17R protein levels to be reduced. On this basis, intestinal tissue will be attacked by excessive *SFB*, while the infiltrated Th17 cells will become pathogenic due to high levels of Th17-polarized cytokines, such as IL-1 β , IL-6 and IL-23 in lesioned sites^[31,35]. However, such cytokine milieu antagonizes the generation and immunosuppressive function of Treg cells^[35]. Moreover, *in vitro* studies showed that irradiation using 6 Gy potentiated TRAF6 reductions in pancreatic cancer cells^[36]. Originally, the expression of TRAF6 by intestinal dendritic cells (DCs) is critical for gut immune tolerance induction because intestinal DCs induce Treg cell generation by producing IL-2^[37]. Conversely, 10 Gy was reported to be able to induce a significant accumulation of Treg cells in irradiated intestine, whereas these cells were impotent in immunosuppression^[38]. In that way, the above results indicate that ionizing irradiation seems to establish a paradigm that favors Th17 cells rather than Treg cells. However, a previous study showed that high dose rate irradiation differed in its effect on TRAF6 expression by tumor cells compared to low dose rate irradiation^[39]. At least two approaches may have different impacts on Treg cell generation in the gut. In fact, several issues remain unknown in this process. For example, which kind of cell is mostly responsible for intestinal bacterial dysbiosis formation during RE pathogenesis? In this situation, will sublethal and lethal irradiation give rise to intestinal bacterial dysbiosis with similar characteristics or exert similar radioimmune responses alternatively? Last, how does a lethal dose cause irreversible injuries or even death among irradiated hosts? These questions should be explored in future work. Nevertheless, it is hopeful that the epithelium will become a therapeutic target^[40].

In steady state, DCs are potent in Th17 induction in gut of mice because the T-cell receptor (TCR) recognizes the *SFB* antigen presenting by DCs^[28]; Meanwhile, MHC class II molecule on DCs can provide all essential signals for Th17 polarization^[41]. Functionally, Th17 cells can stimulate synthesis of α -defensins by epithelial cells depending on IL-17/IL-17R interaction, thus protecting against *SFB* overgrowth in gut lumen^[33]. However, under the irradiated condition, epithelial injuries will augment the local concentrations of IL-1 β and IL-6^[31,35], which functionally upregulate expression of gene encoding IL-23^[35,42]. By binding with IL-23 receptor (IL-23R) on Th17 cells, IL-23 is able to stimulate Th17 cell expansion^[35]. Herein, both IL-23R/IL-22 loop and IL-23/IL-17 loop are able to increase Th17 cell-mediated immune response^[26,43], thus enabling the inflammation in irradiated gut to persist. In this regard, the Th17 cells are pathogenic (Figure 1). Besides, due to epithelial loss, low production of α -defensins will somewhat facilitate *SFB* overgrowth in gut lumen, thus facilitating Th17 induction as well. Collectively, Th17 cell induction will be robust in irradiated gut.

PANETH CELL AND EPITHELIAL HOMEOSTASIS

The gut possesses defensive functions in addition to nutrient absorption. Regarding the composition of the intestinal barrier, the epithelium is a critical portion^[40]. In healthy adults, the intestinal epithelium is rapidly renewed, and one turnover takes about 4 to 5 d^[44]. Such a capacity not only strengthens epithelial integrity but also establishes an optimal paradigm to avoid the accumulation of genetic mutations, thus protecting the gut against malformation^[45]. Herein, ISC accounts for epithelial homeostasis^[44], while in their niches, Paneth cells are specialized feeders due to high secretions of epidermal growth factor (EGF), Wnt3 and Dll1/4 (Notch ligands) to neighboring ISCs^[46]. Moreover, Paneth cells are derived from ISCs, and they are distributed in the basement of the crypts of Lieberkühn, tiny invaginations that line the mucosal surface all along the small intestine. The commitment of ISCs into functional Paneth cells is regulated by different signaling pathways, such as the Wnt/Sox9 and Notch/Krüppel-like factor 4 (Klf4) pathways^[47]. Herein, the former promotes Paneth cell development, which can be enhanced by high-mobility group A1 (HMGA1) chromatin remodeling proteins^[48]. In contrast, the retinoic acid receptor

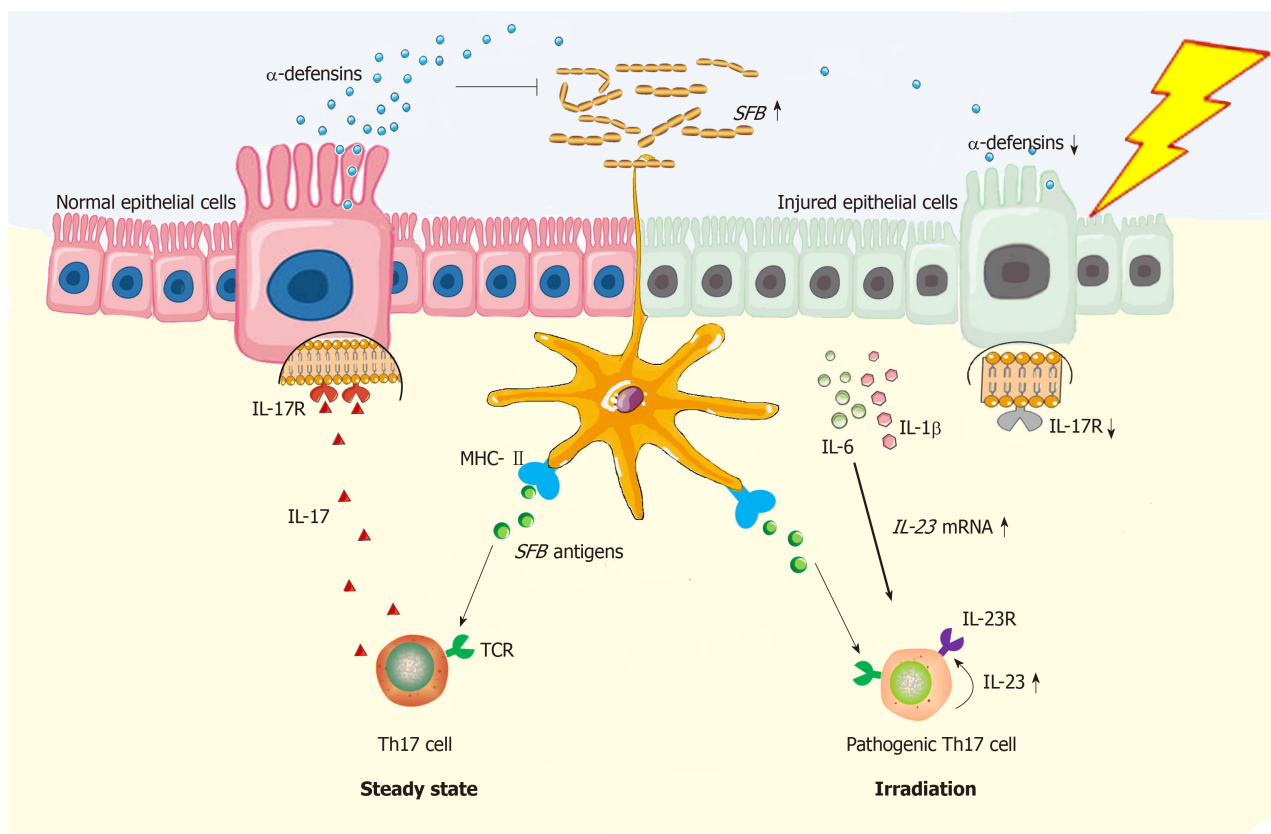


Figure 1 Schema of radiation exposure in pathogenic Th17 cell induction in gut. In steady state, dendritic cells (DCs) are potent in Th17 induction in gut of mice because the T cell receptor recognizes the *segmented filamentous bacteria* (SFB) antigen presenting by DCs^[28]; Meanwhile, MHC class II molecule on DCs can provide all essential signals for Th17 polarization^[41]. Functionally, Th17 cells can stimulate synthesis of α -defensins by epithelial cells depending on interleukin (IL)-17/IL-17R interaction, thus protecting against SFB overgrowth in gut lumen^[33]. However, under the irradiated condition, epithelial injuries will augment the local concentration of IL-1 β and IL-6^[31,35], which functionally upregulate expression of gene encoding IL-23^[35,42]. By binding with IL-23R on Th17 cells, IL-23 is able to stimulate Th17 expansion^[35]. Herein, both IL-23R/IL-22 loop and IL-23/IL-17 loop are able to increase Th17 cell-mediated immune response^[26,43], thus enabling the inflammation in irradiated gut to persist. In this regard, Th17 cells are pathogenic. Besides, due to epithelial loss, low production of α -defensins will somewhat facilitate SFB overgrowth in gut lumen, thus facilitating Th17 induction as well. Collectively, Th17 cell induction will be robust in irradiated gut. DCs: Dendritic cells; SFB: *Segmented filamentous bacteria*; MHC-II: Major histocompatibility complex class II; TCR: T cell receptor; Th17: T helper cell 17; IL-17: Interleukin-17; IL-17R: Interleukin-17 receptor; IL-1 β : Interleukin-1 β ; IL-6: Interleukin-6; IL-22: Interleukin-22; IL-23: Interleukin-23; IL-23R: Interleukin-23 receptor.

α (RAR α)/Klf4 pathway antagonizes this process, implying that retinoic acids or their precursor vitamin A serve as inhibitors during Paneth cell development^[49]. In fact, several other genes downstream of Wnt and Notch jointly control the equilibrium number of Paneth cells, such as the agonists of Math1 and Gfi1, along with the antagonists of Hes1 and Elf3^[47]. Through their actions, the number of Paneth cells in each crypt will be constantly maintained, thus profiting epithelial integrity and disease prevention.

PANETH CELL AND INTESTINAL DEFENSE

Paneth cells feature several characteristics. Unlike absorptive cells or other secretory lineage cells, Paneth cells are not swiftly replaced through epithelial turnover. In mice, the life span of Paneth cells is estimated as two months^[46]. Such a long-lived potential ensures the stability of the number of ISCs in each crypt, which relies on Paneth cell peptides in regulating ISC development as well as in defending against luminal microbial attack. Several important peptides with anti-infective functions are derived from Paneth cells, such as α -defensins, β -defensins, regenerating islet-derived protein III γ (RegIII γ), lysozyme, phospholipase A2 (PLA2) and matrix metalloproteinase 7 (MMP7)^[50] (Figure 2). These peptides form a defensive network together with other lineages of cells, such as M cells in Peyer's patches (PPs), goblet cells, absorptive cells, and LP innate or adaptive immune cells. For example, goblet cells enable Paneth-cell-derived antimicrobial peptides to be well preserved in the mucus layer^[51]. Moreover, α -defensins will acquire antibacterial function if processed by MMP7^[52]. In this regard, Paneth cells serve as gatekeepers in the gut.

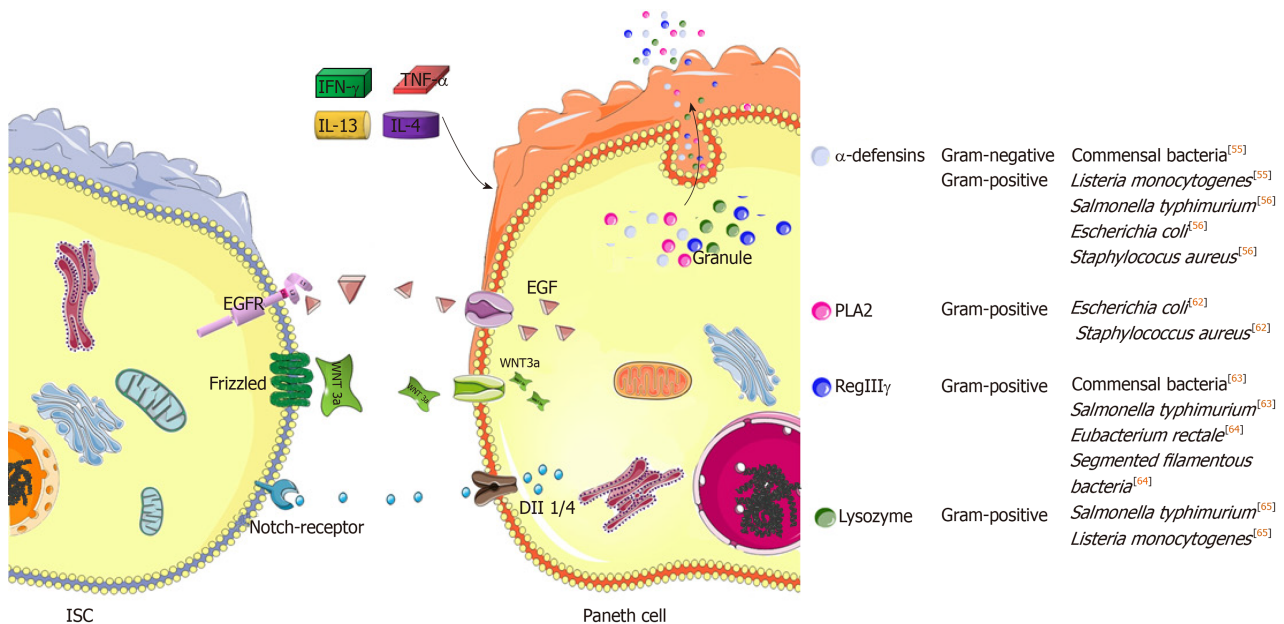


Figure 2 Specific roles of Paneth cells in maintaining epithelial homeostasis and defense. Paneth cells are critical feeders due to their high secretion of epithelial growth factor, Wnt3a or Notch ligands to neighboring intestinal stem cells (ISCs), thus driving ISC expansion^[44]. Moreover, several important peptides of antimicrobial functions are generated from Paneth cells^[50]. In this situation, several inflammatory cytokines, including interferon- γ , tumor necrosis factor- α , interleukin (IL)-13 and IL-4, will elicit the degranulation of Paneth cells to antagonize luminal bacterial overgrowth. growth factor receptor; DII1: Delta-like ligand 1; DII4: Delta-like ligand 4; IFN- γ : Interferon- γ ; TNF- α : Tumor necrosis factor- α ; IL-13: Interleukin-13; IL-4: Interleukin-4; PLA2: Phospholipase A2; RegIII γ : Regenerating islet-derived protein III γ .

In fact, the peptides mentioned above enable Paneth cells to possess a wide antimicrobial spectrum. Herein, the degranulation of Paneth cells is one of the most critical events in defending against luminal microbiota. In addition, degranulation can be stimulated by other factors, such as inflammatory cytokines and cholinergic substances^[53]. Afterwards, antimicrobial peptides achieve high concentrations on the surface of the epithelium. In general, defensins exert lethal effects on bacteria, fungi and viruses because most defensins can bind to microbes to perforate their membranes, thus leading to microbial death^[54] (Figure 2). To this end, Paneth cells mainly rely on α -defensins^[50]. In steady state, α -defensins potently restrict the overgrowth of commensal bacteria^[55]. In addition, pathogenic bacteria, including *Salmonella typhimurium* (*S. typhimurium*), *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*), are sensitive to α -defensins^[56]. Likewise, their antigens, including lipid A, lipopolysaccharide (LPS) and lipoteichoic acid (LTA), are able to induce the secretion of α -defensins by Paneth cells reciprocally^[56]. Herein, the secretion of α -defensins is stimulated by LPS in a concentration-dependent manner^[56]. Moreover, lipid A and LTA are the most common components of gram-negative and gram-positive bacteria, respectively^[57], indicating the wide antibacterial spectrum of Paneth cells by using α -defensins. In fact, among six isoforms, α -defensins 5 and 6 are the most important peptides. For example, human α -defensin 5 was tested to preferentially and powerfully defend against *S. typhimurium* infection in mice^[55]. In contrast to α -defensin 5, α -defensin 6 seldom exerts bactericidal function in a straightforward manner. Herein, a previous study found that nanonets of α -defensin 6 bound luminal *S. typhimurium* to prevent infection^[58]. However, unlike α -defensins, the antibacterial spectra of other peptides are relatively narrow; in particular, RegIII γ , lysozyme and PLA2 particularly antagonize gram-positive bacteria^[50]. Nevertheless, *in vivo* depletions of the α -defensins and RegIII γ could predispose the mice to spontaneous enteritis and colitis, respectively^[59,60]. In this regard, intestinal inflammation is largely attributed to intestinal bacterial dysbiosis occurring as a result of the loss of the bacterial selection pressures by these peptides^[55,56,61-65].

PANETH CELL, ANTIMICROBIAL PEPTIDES AND Treg/Th17 BALANCE IN GUT

Although epithelium-derived, Paneth cells serve as critical originators of intestinal inflammation^[66]. TNF- α , a prevalent cytokine regulating innate immune responses,

exists in the granules of Paneth cells^[67]. Herein, the specific roles of TNF- α in intestinal inflammation have been well documented in several aspects (reviewed in^[68]). For example, TNF- α is a pathogenic cytokine that facilitates the pathogenesis of Crohn's disease^[69]. In this process, the endoplasmic reticulum (ER) stress of Paneth cells occurs as a result of defects in the recognition of the autophagy-related 16-like1 (ATG16L1) gene, thus impairing cell autophagy^[70]. Normally, autophagy in Paneth cells is a central event against *S. typhimurium* infection^[71], which potentially increases the intestinal number of Paneth cells as well^[72]. In addition, ATG16L1 defects enable the granules of Paneth cells to be abnormal and hamper degranulation, proposing that ATG16L1 is essential for Paneth cell differentiation^[70,71]. In fact, ATG16L1 is required for Treg cell induction in the gut^[24]. Conversely, in response to *S. typhimurium* infection, the absence of ATG16L1 will increase the levels of IL-1 β and IL-6 in the terminal ileum and cecum^[71], the sites of which are inhabited by Th17 cells. In this regard, Paneth cells regulate Treg/Th17 balance by relying on ATG16L1 (Figure 3).

In addition to immunological participation, the antimicrobial peptides of Paneth cells also predispose the host to immune tolerance^[57]. Herein, a previous study confirmed that enteric α -defensins 5 and 6 could be detected in the medullary epithelial cells of the human thymus^[73]. In this situation, α -defensins 5 and 6 acted as self-reactive antigens, which could be specifically recognized by autoreactive CD4⁺ or CD8⁺ subpopulations^[73]. Normally, through the action of negative selection in the thymus, the leakage of such cells into the periphery can be radically prevented. However, defects in AIRE, a key autoimmune regulator that normally controls the thymic expression of a set of genes encoding tissue-specific antigens, including α -defensins 5 and 6^[74], will result in Th17 cell generation and spontaneous enteritis due to autoaggression targeting Paneth cells^[73]. In contrast, mice overexpressing genes encoding human α -defensin 5 significantly reduced their gut frequencies of *SFB* and the numbers of Th17 cells^[55]. These results further confirm the role of Paneth cells in restricting Th17 cell induction; moreover, the presence of AIRE is certainly required for Paneth cell survival. In fact, AIRE also exerts a negative impact on Paneth cell survival. For example, AIRE is required for the development of invariant natural killer T (iNKT) cells, which potentiate the degranulation of Paneth cells in an IFN- γ -dependent manner^[75,76]. Herein, Paneth cells will rapidly and completely lose their granules in response to IFN- γ , which impairs the survival of Paneth cells as well^[76]. In this regard, either the excessive activation or absence of AIRE seems to potentially reduce the number of Paneth cells.

Here, it is essential to mention Paneth cell degranulation in response to cytokines (Table 1). In line with IFN- γ , TNF- α , IL-13 and IL-4 cytokines induce Paneth cell degranulation as well^[77,78]. In contrast to agonists of toll-like receptor (TLR) 3 & 9, oral administrations of TLR4 & 5 ligands were tested to induce Paneth cell degranulation in a TNF- α -dependent manner, thus confirming the specific role of TNF- α in this process^[78]. Additionally, IL-13 receptor α 1 (IL-13R α 1) is profoundly expressed by Paneth cells. The IL-13/IL-13R α 1 interaction is able to activate STAT6 and PI3K/Akt, thus upregulating the expression of lysozymes and MMP7^[77]. Moreover, IL-4 is a member of the iNKT-secreted cytokines^[79], further enhancing the effect of iNKT cells on inducing Paneth cell degranulation. As is known, iNKT cells are positive for CD1d, an MHC class-I-like molecule responsible for foreign antigen presentation. In addition to this function, Paneth cell degranulation is CD1d-dependent. Herein, a previous study confirmed that both cholinergic stimulation by using pilocarpine and *E. coli* infection were not able to reduce the crypt lysozyme intensities under the CD1d-absent condition^[80]. Likewise, CD1d depletion also rendered the granules of Paneth cells abnormal in several aspects, mainly alterations in size, morphology and oligosaccharide content^[80]. Furthermore, *SFB* overgrowth occurred if CD1d was depleted^[80]. This result indicates that CD1d is required for the biosynthesis of functional α -defensins by Paneth cells because commensal *SFB* are sensitive to these peptides^[33]. Similarly, when being colonized with *E. coli* or *S. aureus*, CD1d-deficient mice exhibited increased gut frequencies of these bacteria along with their translocation into the periphery compared to wild-type mice^[80], further confirming the role of CD1d in mediating the protection against bacterial infections. In this process, CD1d is not a unique factor, and some other immune cells are able to assist Paneth cell degranulation or antimicrobial peptide secretion in addition to iNKT cells. Commonly, Th1 and group 1 innate lymphoid cells (ILC1s) are potent in producing IFN- γ , while IL-4 and IL-13 are typical cytokines produced by Th2 or ILC2^[81,82]. Moreover, IL-4 and IL-13 potentiate the secretion of retinoic acids by intestinal DCs^[83], thus potentially resulting in Paneth cell reduction by antagonizing the development process^[47]. In addition to this function, retinoic acids preferentially induce the commitment of naïve T cells into Treg cells rather than Th17 cells^[83]. Hereby, retinoic acids will synergize with α -defensin 5 in preventing the excessive generation of intestinal Th17 cells. Alternatively, in response to IL-23, intestinal TCRV γ 7⁺ γ δ

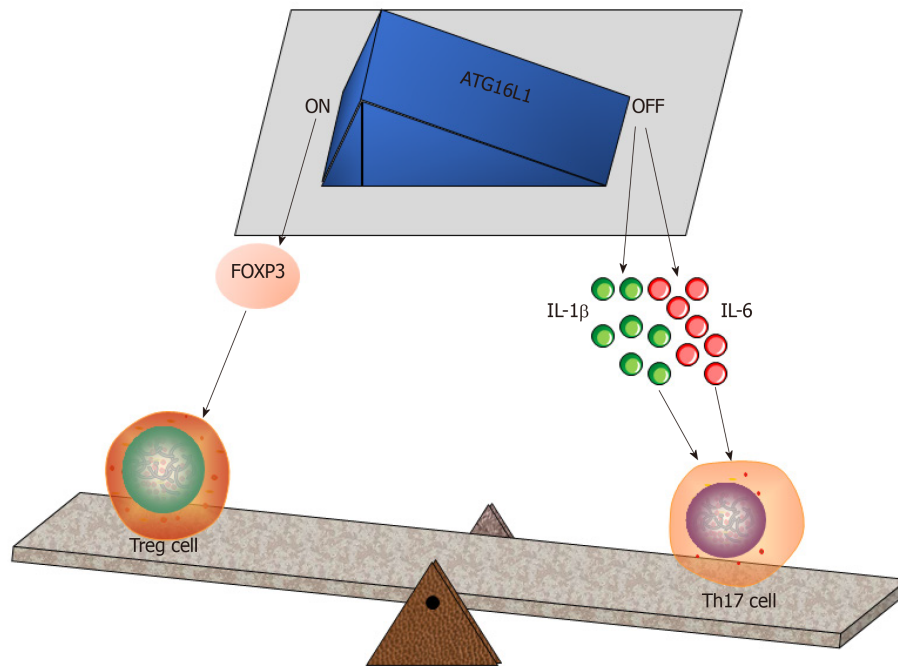


Figure 3 Autophagy-related protein 16 like protein 1 regulates the intestinal balance between Treg and Th17 cells. The autophagy-related protein 16 like protein 1 (ATG16L1)-FOXP3 axis plays a vital role in Treg cell induction^[24]. Conversely, a deficiency of ATG16L1 enables Paneth cell differentiation to be hampered, while this situation will increase interleukin (IL)-1 β and IL-6 in the gut^[71], thus promoting Th17 commitment. Treg: Regulatory T cell; Th17: T helper cell 17; IL-1 β : Interleukin-1 β ; IL-6: Interleukin-6; ATG16L1: Autophagy-related protein 16 like protein 1.

intraepithelial lymphocytes (IELs) can produce IL-22, which is able to induce angiogenin 4 secretion by Paneth cells to clear *S. typhimurium* infection^[84]. Herein, IL-23 and IL-22 are also classified as Th17-type cytokines^[85]. In this regard, Th17 cells potentially improve the anti-infective function of Paneth cells.

BACTERIAL DYSBIOSIS AND GUT CARCINOGENESIS

Although Paneth cells ensure the security of ISCs in steady state, the antimicrobial dysfunction of Paneth cells potentially enables ISCs to be attacked by luminal invaders. To address the importance of the gut microbiota in this process, it is documented that germfree mice with double depletions of genes encoding Rag2 and TGF- β exhibit no sporadic intestinal tumors, in contrast to conventional mice with the same phenotype^[86]. This finding suggests that intestinal commensal bacteria independently induce gut carcinogenesis even though they lack adaptive immunity. Recently, several studies revealed that carcinogenesis in the human gut occurred as a result of intestinal bacterial dysbiosis^[10,11]. In this situation, the feces could be used for human CRC screening^[87,88]. Actually, it is well accepted that infection-associated chronic inflammation will drive the genomic instability of cells^[61,89]. Herein, ISCs serve as major sources orchestrating gut malformation. In the process of phenotype conversion from ISCs to CRC stem cells, mutations or epigenetic alterations will accumulate in the genome^[90]. In the gut, several commensal bacteria are capable of eliciting carcinogenesis. For example, the genotoxic island of polyketide synthase (pks) from the pathogenic strains of *E. coli* is required for CRC induction^[91]. Instead of exerting genomic toxicity, the nonpathogenic *E. coli* K-12 strain potentiates the oncogenicity of colon epithelial cells by improving the activities of NF- κ B and β -catenin^[92]. Moreover, albeit indirectly, *Enterococcus faecalis* (*E. faecalis*) confers colon epithelial cells with oncogenicity by using their polarized macrophages, which induce cellular transformation along with gene mutation^[93]. In addition to tumor induction, some other bacteria promote CRC progression. Herein, *Fusobacterium nucleatum* (*F. nucleatum*) improves the proliferative and invasive capacities of CRC cells by upregulating their miRNA-21 expression^[94]. In addition, the Fab2 protein released by *F. nucleatum* will bind to TIGIT (T cell immunoglobulin and ITIM domain) on human T or NK cells, thus reducing their anticancer effects^[95]. Similarly, enterotoxins from *B. fragilis* will increase the expression of c-Myc, an important oncogene driving CRC progression^[96]. Moreover, enterotoxigenic *B. fragilis* induces Th17 cell generation^[29].

Table 1 Summary of the factors regulating Paneth cell degranulation

Sort	Object	Pathway	Effect
Cytokines	IFN- γ	IFN- γ -dependent manner ^[75]	Impairment of the survival of Paneth cells ^[76]
	TNF- α	TNF- α -dependent manner	Paneth cell degranulation ^[78]
	IL-13	STAT6 and PI3K/Akt	Upregulation of the expressions of lysozyme and MMP7 ^[77]
	IL-4	Antagonizing the development process ^[47]	Enhancing the effect of iNKT cells ^[79]
TLR	TLR3 / 9	TLR9 and TLR3 dependent manner	Paneth cell degranulation ^[78]
	TLR4 / 5	TNF- α -dependent manner	Paneth cell degranulation ^[78]
CD1d	iNKT cells	CD1d-dependent	Reducing the crypt lysozyme ^[80] Mediating the protection against bacterial infections ^[80]
Cholinergic	Pilocarpine and <i>E. coli</i>	CD1d-dependent	Crypt lysozyme intensities ^[80]

IFN- γ : Interferon- γ ; TNF- α : Tumor necrosis factor- α ; IL-13: Interleukin-13; STAT6: Signal transducers and activators of transcription 6; PI3K/Akt: Phosphatidylinositol 3 kinase/protein kinase B; MMP7: Matrix metalloproteinase 7; IL-4: Interleukin-4; iNKT: Invariant nature killer T cell; TLR: Toll-like receptor; *E. coli*: *Escherichia coli*.

However, the infiltration of massive Th17 cells in tumors predicts a poor prognosis in CRC patients^[97]. To a certain extent, Th17 cells direct CRC progression by producing IL-22, which potentially activates STAT3 to increase the “stemness” of tumor cells^[98]. Moreover, IL-22 elicits transient ER stress in intestinal epithelial cells^[99]. In concert with ATG16L1 defects, IL-22-induced epithelial necrosis will be aggravated due to robust activation of STING-dependent type I interferon (IFN-I) signaling, thus inducing excessive TNF- α production^[99]. As a result, intestinal bacterial dysbiosis will be further enhanced due to the augmented defects in the epithelial barrier.

THE MISSION OF PANETH CELLS IN RADIATION ENTEROPATHY

In steady state, Paneth cells are critical in protecting against intestinal bacterial dysbiosis. Here, the mission of Paneth cells postirradiation should be discussed. Foremost, autophagy will occur in Paneth cells in response to 9.25 Gy γ -irradiation^[100]. Meanwhile, α -defensin 4 increases its production by Paneth cells^[101]. Concerning the radiation sensitivity of Paneth cells, two previous studies confirmed that the phenotype conversion from the reserve pool of ISCs (Bmi1-positive) to the active pool of ISCs (Lgr5-positive) was a manifestation upon automatic recovery of the intestinal epithelium from radiation-induced damage, probably due to the interchange of their niche signals^[102-104]. In this regard, it is reasonable to conceive that Paneth cells mediate this process, not only because they act as niche cells of ISCs but also because the numbers of Paneth cells are not significantly reduced in murine guts when doses are no more than 12 Gy^[102,103]. Conversely, if doses are larger than 15 Gy, Paneth cells will dramatically lose their numbers^[15]. Herein, it has been documented that ISCs are normally found in small intestine of mice albeit complete elimination of Paneth cells by genetic depletion of *Math1*^[105]. However, *Math1*-mutant miniguts halt their growth *in vitro*^[105]. This case can be translated into *Wnt3*-mutant miniguts as well, suggesting the essential role of Paneth cells in support of ISC expansion^[105]. Moreover, conditional depletion of the gene encoding Frizzled-5, the receptor of *Wnt3*, will inactivate the MMP7/defensin maturation programme in Paneth cells of adult mice, suggesting the role of *Wnt3* in eliciting antimicrobial function of Paneth cell^[106]. Therefore, radiation-induced lethal effect on Paneth cells potentially impairs ISC regeneration due to loss of Paneth cell-derived niche signals and antimicrobials. In fact, Paneth cells are more resistant to ionizing irradiation than ISCs. The long-lived potential of Paneth cells is certainly attributed to their high genetic stability, while the survival of Paneth cells after irradiation can be controlled by their capacity to repair DNA lesions through nonhomologous end-joining^[107]. A recent study found that mutation in Tyr4046 of DNA-dependent protein kinase, catalytic subunit with synchronous Trp53 depletion, significantly increased the sensitivity of mice to 8 Gy of WBI because such a genetic background hampered the survival of Paneth cells postirradiation^[107]. To this end, it is proposed that Paneth cells press the button of controlling RE pathogenesis. In this

process, intestinal bacterial dysbiosis occurs postirradiation, thus eliciting a pro-inflammatory milieu in lesioned gut^[21]. In this context, the production of antimicrobial peptides by Paneth cells can be increased to overcome intestinal bacterial dysbiosis^[101]. Hence, maintaining Paneth cell survival postirradiation appears to be critical for epithelial regeneration.

THE STRATEGY AGAINST RADIATION ENTEROPATHY

In terms of RE treatment, current clinical strategies are mainly selected according to the standard classification of intestinal toxicity reported by the Radiation Therapy Oncology Group (RTOG). Herein, the principle of treatment for Grade 1 or 2 toxicity occurring during radiation therapy mainly includes anti-inflammation; symptomatic care for nausea, vomiting or diarrhea; and nutritional support^[3]. Concerning Grade 3/4 toxicities or more severe complications, multidisciplinary diagnosis and treatment are highly recommended^[3], yet the relevant strategies seldom support the regeneration of lesioned intestine. In fact, it has been presented that the histological features of RE overlap with those of IBD^[3,8]. Herein, MSCs have been demonstrated to be effective in patients with Crohn's disease^[108]. However, at the time of this writing, clinical trials with the purpose of managing RE using MSCs have still not been carried out. Nevertheless, clinical cases of prostate cancer with complications related to radiation-induced rectal injury could be well managed by using MSCs^[109]. In this management, the efficacies of MSCs mainly include relieving pain, stanching bleeding or repairing fistula, indicating the perspective of such a stem cell therapy^[109]. Additionally, TNF- α monoclonal antibody (infliximab) achieves good therapeutic effects in IBD patients. Therefore, this drug should be effective in RE, but this deserves further investigation. In parallel, some other issues should be addressed, particularly prior to RE treatment in clinical settings. For example, antibiotics are recommended for RE treatment only if infection occurs. As is known, long-lasting use of antibiotics will induce intestinal bacterial dysbiosis, but it is still unclear whether short-term use of antibiotics improves radiation-induced intestinal bacterial dysbiosis. Nevertheless, antibiotics exhibited potential in delaying CRC progression in an animal model^[110]. This finding means that antibiotics serving as candidates for BSC therapy may be available in the defense against CRC-related intestinal bacterial dysbiosis. As mentioned above, BSC using prebiotics or probiotics is effective in relieving diarrhea^[9]. In fact, BSC has become the hotspot for various diseases. To overcome bacterial dysbiosis, the administration of defensins or omega-3 polyunsaturated fatty acids is also promising in clinical settings^[111,112]. Instead of BSC, the reduction in and/or the dysfunction of pathogenic cells will be available choices for RE treatment as well. Herein, RORyt antagonists against Th17 cell commitment were tested to be useful in the IBD model^[113]. In this process, RORyt inhibition will potentially improve Treg cell generation because RORyt functionally antagonizes the transcriptional activity of Foxp3^[114]. In particular, Th17 cells are pathogenic cells of RE and CRC as well, thus predicting the perspective of RORyt antagonists in these diseases. Collectively, targeting any critical event during RE pathogenesis should become a candidate option for RE treatment. For the development of novel treatment targets of RE, related mechanisms deserve further exploration in the future.

CONCLUSION

Pathogenesis of radiation enteropathy is highly associated with intestinal bacterial dysbiosis. Herein, Paneth cells probably control the process of bacterial dysbiosis by using their antimicrobial peptides.

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