Arch Gastroenterol Res. 2022;3(1):18-22.

Archives of Gastroenterology Research | Short Communication

New Trends in Interrelation of Infectious Colorectal Cancer with Intestinal Microbiota

Vishnu P. Tripathi[1], Daniel Goo[2], Bokyo N Maidya[3], M K Aneebuddin[4]

[1]Department of Biotechnology, V.B.S. Purvanchal University, Jaunpur, India

[2]Department of Biomedical Engineering, University of Memphis, USA

[3]Department of Gastroenterology, Uzhhorod National University, Ukraine

[4]Department of Pharmaceutics, Shadan College of Pharmacy, Telangana State, India

[*]Correspondence should be addressed to Vishnu P. Tripathi, tripatipvishnu@gmail.com

Received date: January 13, 2022, **Accepted date:** January 21, 2022

Citation: Tripathi VP, Goo D, Maidya BN, Aneebuddin MK. New Trends in Interrelation of Infectious Colorectal Cancer with Intestinal Microbiota. Arch Gastroenterol Res. 2022;3(1):18-22.

Abstract

The Colon has a complicated microbial community, which is indispensable for retaining homeostasis and regulation of metabolic functions, assisting the intestinal barrier, and controlling immune responses. Preceding research has supported a connection between colorectal cancers (CRC) and intestinal microbiota. In light of these findings, the existing assessment analyzed the several interactions that appear between microbiota and CRC, beginning from the position of intestinal microbiota in colonic homeostasis. In addition, fundamental metabolic elements such as bile acids and short-chain fatty acids (SCFAs) are covered in CRC pathogenesis. Different pathogenic pathways have been announced amongst distinct CRC areas (proximal or distal). Differences in the microbial populations are advised among the CRC from these colonic areas, perchance reflecting the bacterial dysbiosis and biofilm distribution. Regarding the therapeutic approach in CRC, the intestinal microbiota is similarly concerned with the modulation of the host response to chemotherapeutic drugs (5-fluorouracil and irinotecan) through the involvement with drug efficacy and by related toxicity and adverse effects. Moreover, the latest study on CRC immunotherapy exhibits an essential interaction between the immune system and intestinal microbiota, which incorporates the opportunity of focusing on microbiota for the improvement of anticancer treatment. Additional research will further make clear the interplay between CRC and microbiota, ensuing in the expansion of possible therapeutic techniques via manipulating microbiota composition.

Keywords: Immunotherapy, Intestinal Microbiota, Pathogenesis, Chemotherapy

Introduction

The intestinal microbiota creates a bodily barrier for invading pathogen by using aggressive exclusion. Pathogens and immune cells can interact directly and dynamically with symbiotic bacteria, determining the pathophysiology and outcome of an infection. They can defend the host through a variety of processes, including attachment site occupancy, nutrition intake, metabolite competition, and the synthesis of antimicrobial compounds including bacteriocins that influence pathogen survival (a process referred to as colonization resistance). The intestinal microbiota is capable to modulate potential pathogen survival and virulence by inducing intestinal epithelial cells to produce and excrete peptides with antimicrobial properties and other molecules, or by stimulating enteric dendritic cells and recruiting other innate immune cells both systemically and locally to advance anti-pathogen responses of effector T and B cells. Nevertheless, this immune system stimulation requires particular rules as it can cause autoimmune illnesses and inflammation under certain circumstances of uncontrolled induction [1-4]. Likewise, the microbiota's capability for efficient infection suppression is linked to its unique ability to enhance both innate and adaptive immune responses [5]. The complicated and dynamic processes of intestinal microbes involve a huge number of possible ligands and metabolites in a dynamic equilibrium. Members of the intestinal microbiota and its metabolites are increasingly being recognized as having

a function in immunological development and immune response [6,7]. Constant crosstalk between B lymphocytes, lamina propria, intestinal epithelial cells, and the microbiota is of indispensable significance for maintaining intestinal homeostasis [8]. The connections between host cells and microbiota and the host-pathogen interplays include the interaction between receptors and the number of immune cells, which affect immune homeostasis and inflammation. Microbiota performs an essential position in the functioning, instruction, and induction of the host's immune system and balances both systemic and local immune responses. The host-microbiota coevolution has allowed the immune system to conserve the symbiotic relationships of the host with the exceedingly dynamic and complicated group of microbes. If it is balanced, this immuno-microbial relationship permits each induction of protecting responses to pathogens and simultaneously the tolerance to innocuous antigens by means of different regulatory pathways. Therefore, a state of homeostatic equilibrium is sustained [9]. Both inflammatory and regulatory responses are continually integrated when homeostasis is well-maintained, resulting in the formation of a localized inflammation consistent with tissue immunity.

Assessing the Role of Microbiota in Colon Cancer

Symbiotic bacteria have an important function in the maturation of the immune system which in turn contributes to their restraint. Various research carried out with germ-free (GF) animals, disclose the capability of microbiota to chisel secondary and lymphoid shape development. Members of the microbiota, in addition to regulating the immune system, can help maintain and restore the integrity of the intestinal barrier through a variety of mechanisms, including inducing epithelial cell maturation, angiogenesis, and tight junction reinforcements [11]. A foremost method of the host to hold the homeostatic relationship with the microbiota in the colon is to reduce contact between microorganisms and the surface of epithelial cells, thereby minimizing microbial translocation and tissue inflammation. This method is executed by way of the combined action of immunological and structural elements such as epithelial cells, mucus layer, immune cells, IgA, and antimicrobial peptides (inclusively known as the "mucosal firewall") [12]. One of the primary modes of cross-talking among the host and the microbiota is mediated by means of the recognition of evolutionary conserved microbial associated molecular patterns (MAMPs) Innate pattern recognition receptors (PRRs) such as NOD-like receptors (NLRs) and Toll-like receptors (TLRs). These receptors apprehend damage- and pathogen-associated molecular patterns and spark off effector responses that promote each tolerance and activation of immune responses [13]. Toll-like receptors indicate on the surface and in the cytosol of phagocytic cells like neutrophils, dendritic cells (DCs), macrophages, and also in epithelial cells of the intestine [14]. Certain microbe-associate molecular patterns (MAMPs) that trigger the PRRs include different microbial factors such as flagella, lipoproteins, peptidoglycan, LPS, fungal cell wall β-glucans prokaryotic DNA, and foreign nucleic acids [15-19]. TLR signaling initiates immune defense mechanisms, which decorate barrier characteristics by zonula occludens and strengthening tight junctions. This eventually results in the obstruction of paracellular microbial invasion [20]. Cytidine-phosphate-guanosine (CpG) patterns of damaged human DNA or apoptotic particles (damage-associated molecular pattern - DAMP) may also trigger TLR9, an intracellular DNA sensor, and set off a self-destructive, chronic B-cell immune response. Chronic triggering of TLR9 May also accelerate the growth and spread of tumors in the GI tract [21-25]. Signaling through PRRs permits host immune sensing and reactivity regarding various stimuli. PRRs decode indicators from the microbiota and assist to structure the homeostatic host-microbiota interface. The improvement of deleterious outcomes to the host takes place when the immune response does not manage the microbiota modifications of commensal and symbiotic microbial communities [26-29]. The identifications of microbial MAMPs by PRRs result in triggering intracellular signaling cascades that in turn lead to activation of the NF-κB pathway, initiation of the immune response, and production of proinflammatory cytokines and chemokines [30]. Specifically, awareness of MAMPs through TLRs with subsequent activation of NF-κB and increase and recommends tumor cell proliferation and survival [31]. Negative rules of TLR with the aid of IL-1 (Interleukin-1), TOLLIP (Toll-interacting protein), IRAK-M (receptor-associated kinase-M), SIGIRR (single immunoglobulin interleukin-1-receptor-related molecule) stops an immoderate inflammatory response, which maintains intestinal homeostasis [32]. All of these activities have the potential to change the intestinal microbiota which can respond to TLR signaling increasing inflammation. Responses to microbial ligands like LPS, in the outer membrane of gram-negative bacterial walls the endotoxin observed, situation intestinal epithelial cells become hypo-responsive to subsequent TLR stimulation. Thus, the microbiota which is healthy causes a physiologic low-quality inflammatory reaction in the host mucosa managed by the innate immune system. Change in intestinal microbiota may additionally encourage inflammation through improved MAMP presentation to intestinal immune cells [33]. A fine regulation of PRR signaling in the intestine is significant in the balance between disease and health [34].

New Trends in Correlating Microbiota with Colon Cancer

Microbiota variations among distal colon and proximal in health and CR even though intestinal microbiota sincerely performs an imperative function in disease and human homeostasis, this ecosystem has imperfectly described and its variousness stays inefficiently decisive, both on its whole and its feasible variations between colonic regions. Eckburg et al. [35] used a comparative study of 16S rDNA sequences

in colonic mucosal tissue samples from healthy persons to look at the various variations of bacterial populations across people as well as a range of regions in the intestinal mucosa in order to define the aforementioned parameters. Phylogenetic analysis revealed that the majority of the inferred organisms belonged to the Firmicutes (the majority of Firmicutes sequences were from the Clostridia class) and Bacteroidetes phyla, with only a few sequences belonging to the Proteobacteria, Verrucomicrobia phyla, Actinobacteria, and Fusobacteria. These findings had been consistent with earlier research [36]. Using diversity coefficients and statistical analysis methods it was found that mucosal samples from various persons (inter-subject) had a greater range profile than those from distinct large intestine regions in each individual. However, when the right colon was excluded from this comparison, the inter-subject and intra-subject range profiles were not remarkably different [37]. Some research proposes that variety indices are extensively greater in the proximal colon than in the distal colon, showing that more species of intestinal microorganisms at the greater range are detected in the proximal colon [84], while some point out that for 97% of healthy samples, the microbiota of proximal colon and distal was not remarkably different in specific individuals [38]. The latest study finds out that microbiota variations between the distal colon and proximal in healthy individuals might also be due to the variations in oxygen distribution through colonic mucosa. The proximal colon typically hosts aerobic bacteria in its mucosae such as Facultative anaerobes and Pseudomonas like Actinomyces and Enterobacteriaceae because of their excessive oxygen concentrations. Adversely, the distal colon primarily harbors anaerobic species like *Porphyromonas*, *Anaerococcus*, *Peptoniphilus*, *Finegoldia* [39].

Effects of CRC Chemotherapy in Intestinal Microbiota

Chemotherapeutic drugs, such as irinotecan, 5-fluorouracil, and oxaliplatin are used to be as part of routine and standard CRC treatment. 5-fluorouracil with leucovorin in combination with oxaliplatin or irinotecan is used to treat advanced-stage CRC. As a result, it has been thought suitable to focus primarily on the effects of these chemotherapeutic drugs on the microbiota of the colon. Several researches have analyzed how these substances alter the microbiota and colon homeostasis. [40]. Irinotecan has been intensively explored in comparison to other drugs due to the key function of intestinal microbiota in its metabolic route. Irinotecan is a topoisomerase-I inhibitor that is used to treat a variety of solid cancers, including CRC. *In vivo* irinotecan converts to poisonous and active metabolite SN-38. SN-38 is in addition metabolized via glucuronidation, which converts SN-38 to the non-toxic metabolite SN-38 glucuronide (SN-38G) [41,42]. This molecule is discharged into the gastrointestinal system (through bile secretion), where it is subjected to bacterial enzyme processing. Intestinal microorganisms generate the enzyme β-glucuronidase, which can break the glucuronide molecule from irinotecan's less toxic metabolite, reactivating and making it toxic. This phenomenon was analyzed mainly in the cecum by *E. coli* (a bacterium that produces β-glucuronidase) [43].

Conclusion

To summarize, colonic microbiota performs an important role in cancer pathogenesis, but cancer also modifies colonic microbiota, which indicates a bidirectional relationship between them. All of the research mentioned above indicate a different mechanism by which the intestinal microbiota maintains colonic homeostasis and contributes to colorectal pathogenesis. They also show an important link between CRC therapy and microbiota changes, as well as disclose the dual function of microbiota by either improving or lowering the efficacy of CRC treatment. However, the data currently available is insufficient, and continuously new hypotheses are continuously being created. As a result, further research in humans and animal models is needed to decode and understand the mechanisms behind the connection between microbiota and CRC, in order to permit us to manipulate microbiota in favor of prevention and treatment of CRC.

References

1. Candela M, Guidotti M, Fabbri A, Brigidi P, Franceschi C, Fiorentini C. Human intestinal microbiota: cross-talk with the host and its potential role in colorectal cancer. Critical Reviews in Microbiology. 2011 Feb 1;37(1):1-4.

2. Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, et al. Microbial dysbiosis in colorectal cancer (CRC) patients. PloS One. 2011 Jan 27;6(1):e16393.

3. Watson AJ, Collins PD. Colon cancer: a civilization disorder. Digestive Diseases. 2011;29(2):222-8.

4. Ewing I, Hurley JJ, Josephides E, Millar A. The molecular genetics of colorectal cancer. Frontline gastroenterology. 2014 Jan 1;5(1):26-30.

5. Chung KY, Gore I, Fong L, Venook A, Beck SB, Dorazio P, et al. Phase II study of the anti-cytotoxic T-lymphocyte–associated antigen 4 monoclonal antibody, tremelimumab, in patients with refractory metastatic colorectal cancer. Journal of Clinical Oncology. 2010 Jul 20;28(21):3485-90.

6. Bogaert J, Prenen H. Molecular genetics of colorectal cancer. Annals of Gastroenterology. 2014;27(1):9.

7. Tomlinson IP, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23. 3. Nature Genetics. 2008 May;40(5):623-30.

8. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013 Jul 11;369:122-33.

9. Al-Tassan NA, Whiffin N, Hosking FJ, Palles C, Farrington SM, Dobbins SE, et al. A new GWAS and meta-analysis with 1000Genomes imputation identifies novel risk variants for colorectal cancer. Scientific Reports. 2015 May 20;5(1):1-1.

10. Dunlop MG, Dobbins SE, Farrington SM, Jones AM, Palles C, Whiffin N, et al. Common variation near CDKN1A, POLD3 and SHROOM2 influences colorectal cancer risk. Nature Genetics. 2012 Jul;44(7):770-6.

11. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014 Mar 27;157(1):121-41.

12. Sun J, Kato I. Gut microbiota, inflammation and colorectal cancer. Genes & Diseases. 2016 Jun 1;3(2):130-43.

13. Kamada N, Chen GY, Inohara N, Núñez G. Control of pathogens and pathobionts by the gut microbiota. Nature Immunology. 2013 Jul;14(7):685-90.

14. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nature Reviews Immunology. 2013 Nov;13(11):790-801.

15. Hammami R, Fernandez B, Lacroix C, Fliss I. Anti-infective properties of bacteriocins: an update. Cellular and Molecular Life Sciences. 2013 Aug;70(16):2947-67.

16. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proceedings of the National Academy of Sciences. 2010 Jul 6;107(27):12204-9.

17. Mason KL, Huffnagle GB, Noverr MC, Kao JY. Overview of gut immunology. GI microbiota and regulation of the immune system. 2008:1-4.

18. Grenham S, Clarke G, Cryan JF, Dinan TG. Brain–gut–microbe communication in health and disease. Frontiers in Physiology. 2011 Dec 7;2:94.

19. Manegold C, Van Zandwijk N, Szczesna A, Zatloukal P, Au JS, Blasinska-Morawiec M, et al. A phase III randomized study of gemcitabine and cisplatin with or without PF-3512676 (TLR9 agonist) as first-line treatment of advanced non-small-cell lung cancer. Annals of Oncology. 2012 Jan 1;23(1):72-7.

20. Molloy MJ, Bouladoux N, Belkaid Y. Intestinal microbiota: shaping local and systemic immune responses. InSeminars in Immunology 2012 Feb 1 (Vol. 24, No. 1, pp. 58-66). Academic Press.

21. Arpaia N, Campbell C, Fan X, Dikiy S, Van Der Veeken J, Deroos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013 Dec;504(7480):451-5.

22. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-y M, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013 Aug 2;341(6145):569-73.

23. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science. 2018 Jan 5;359(6371):97-103.

24. Shulzhenko N, Morgun A, Hsiao W, Battle M, Yao M, Gavrilova O, et al. Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut. Nature Medicine. 2011 Dec;17(12):1585-93.

25. Gagliani N, Hu B, Huber S, Elinav E, Flavell RA. The fire within: microbes inflame tumors. Cell. 2014 May 8;157(4):776-83.

26. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. Science. 2001 Feb 2;291(5505):881-4.

27. Tripathi VP, Dubey DD. A replication-time-controlling sequence element in Schizosaccharomyces pombe. Chromosoma. 2017 Aug;126(4):465-71.

28. Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proceedings of the National Academy of Sciences. 2002 Nov 26;99(24):15451-5.

29. Macpherson AJ, Slack E, Geuking MB, McCoy KD. The mucosal firewalls against commensal intestinal microbes. InSeminars in immunopathology 2009 Jul (Vol. 31, No. 2, pp. 145-149). Springer-Verlag.

30. Hooper LV. Epithelial cell contributions to intestinal immunity. Advances in Immunology. 2015 Jan 1;126:129-72.

31. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Hamilton J, et al. Gastrointestinal microflora and mucins may play a critical role in the development of 5-fluorouracil-induced gastrointestinal mucositis. Experimental Biology and Medicine. 2009 Apr;234(4):430-41.

32. Ramanan D, Cadwell K. Intrinsic defense mechanisms of the intestinal epithelium. Cell Host & Microbe. 2016 Apr 13;19(4):434-41.

33. Abreu MT. Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nature Reviews Immunology. 2010 Feb;10(2):131-44.

34. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006 Feb 24;124(4):783-801.

35. Carvalho FA, Aitken JD, Vijay-Kumar M, Gewirtz AT. Toll-like receptor–gut microbiota interactions: perturb at your own risk! Annual Review of Physiology. 2012 Mar 17;74:177-98.

36. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, et al. Intestinal permeability–a new target for disease prevention and therapy. BMC Gastroenterology. 2014 Dec;14(1):189.

37. Kauppila JH, Karttunen TJ, Saarnio J, Nyberg P, Salo T, Graves DE, et al. Short DNA sequences and bacterial DNA induce esophageal, gastric, and colorectal cancer cell invasion. Apmis. 2013 Jun;121(6):511-22.

38. Lin L, Zhang J. Role of intestinal microbiota and metabolites

on gut homeostasis and human diseases. BMC Immunology. 2017 Dec;18(1):1-25.

39. Wells JM, Rossi O, Meijerink M, van Baarlen P. Epithelial crosstalk at the microbiota–mucosal interface. Proceedings of the National Academy of sciences. 2011 Mar 15;108(Supplement 1):4607-14.

40. Sansonetti PJ, Di Santo JP. Debugging how bacteria manipulate the immune response. Immunity. 2007 Feb 23;26(2):149-61.

41. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. Nature Reviews Cancer. 2009 Jan;9(1):57-63.

42. Shibolet O, Podolsky DK. TLRs in the Gut. IV. Negative regulation of Toll-like receptors and intestinal homeostasis: addition by subtraction. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2007 Jun;292(6):G1469-73.

43. Hu B, Elinav E, Huber S, Strowig T, Hao L, Hafemann A, et al. Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. Proceedings of the National Academy of Sciences. 2013 Jun 11;110(24):9862-7.