

## Intestinal inflammation and the microbiota: Beyond diversity

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### Abstract

The recent manuscript entitled "Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis" reported a difference in the intestinal microbiota of patients with ulcerative colitis according to the severity of the colitis. The influence of the intestinal microbiota on the development and progress of gastrointestinal disorders is well established. Besides the diversity in the microbiome, the presence of virulence factors and toxins by commensal bacteria may affect an extensive variety of cellular processes, contributing to the induction of a proinflammatory environment.

**Key Words:** Inflammation; Microbiota; Toxins; Intestinal; Ulcerative; Colitis; Cancer

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**Core Tip:** The manuscript entitled “Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis” and previous investigations have identified alterations in the intestinal microbiome of patients with inflammatory bowel disease, ulcerative colitis, and colorectal cancer. The microbiota composition impacts the development of inflammatory disorders. Nevertheless, investigations should focus on identifying alterations not only on the diversity of the microbiota but the presence of the toxin-producing bacteria. Further investigations should investigate alterations in the microbiota composition and the production of toxins by commensal bacteria such as *Escherichia coli*, *Clostridium perfringens*, and *Bacteroides fragilis*.

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## TO THE EDITOR

We read with great interest the manuscript entitled “Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis” published by He *et al*[1] in the *World Journal Gastroenterology*. He *et al*[1] performed an investigation on the microbiota composition on the fecal and mucosa samples from patients with ulcerative colitis. Their work reinforces the importance of the microbiota on the inflammatory process and gastrointestinal disorders. Importantly, the manuscript provided information on the composition of the gastrointestinal microbiota of patients with ulcerative colitis of various severity and patients without ulcerative colitis[1]. We would like to raise a few considerations regarding the microbiota and gastrointestinal inflammatory disorders.

The microbiota is an ecosystem in constant regulation, influenced by the diet, antibiotics, sanitary conditions, environmental stimulus, and the host’s immune system[2]. The gastrointestinal tract is the largest reservoir of bacteria in the human body and shapes both the local and systemic immune responses[3-5]. The microbiome influences the maturation and development of the host’s immune system[6], regulating the development of food tolerance, response to inflammation, infections, vaccination, and metabolism[7,8]. Importantly, the microbiota directly influences the development of the inflammatory process independent of dietary intake[9], and abrupt alterations in the microbiota composition can result in an inflammatory insult[10]. He *et al*[1] identified an increase in *Escherichia* and *Shigella* in patients with ulcerative colitis in comparison to patients without ulcerative colitis[1]. *Escherichia* and *Shigella* has been implicated in a reduction in the response to anticoagulation therapy and could impact the treatment of patients with gastrointestinal disorders and under anticoagulation therapy such as coronavirus disease 2019 patients[11-14].

Shiga toxin-producing *Shigella* species and *Escherichia coli* are considered pathogenic, associated with diarrhea and colitis[15]. These toxins can induce the activation of the NOD-like receptor protein 3 inflammasome, inducing the production of interleukin (IL)-1 $\beta$  and IL-18 and cellular death by pyroptosis[16]. The virulence of Shiga-toxin-producing *Escherichia coli* can lead to diarrheal sicknesses and death[17,18]. Shiga-toxins can be encapsulated within microvesicles and influence the inflammatory response in other organs, such as the kidneys[19]. Shiga toxin-producing *Escherichia coli* (O26:H11 strain 97-3250 and O145:H28 strain 4865/96) induces a greater production of chemokines and cytokines, such as IL-8 and IL-1 $\beta$ , in comparison to *Escherichia coli* (O9:H4 strain HS)[20].

The complex symbiotic interaction between the microbiota and the host is mediated by an equilibrium in the tolerance and inflammatory response to microbial products in the gut[6]. He *et al*[1] did not identify an increase in other strains in patients with ulcerative colitis. Nevertheless, in addition to the microbiota composition, certain commensal bacteria, such as *Clostridium perfringens* and *Bacteroides fragilis*, can express a wide range of toxins and metabolic compounds to induce inflammation [21-23]. *Clostridium perfringens* is a gram-positive anaerobic bacteria, commonly in the environment and is part of the resident microbiota but can become virulent by the expression of toxin genes[24,25]. *Clostridium perfringens* can produce over 20 toxins including alpha ( $\alpha$ ), beta ( $\beta$ ), epsilon ( $\epsilon$ ), enterotoxins, and hydrolytic enzymes[26-29]. These toxins can damage and kill intestinal cells, disturb the epithelial barrier, and induce proinflammatory and pro-pathogenic milieu[26,30,31].

The alpha toxin produced by *Clostridium perfringens* is a zinc-dependent metalloenzyme, is able to rupture the plasma membrane of the host’s cells[25,32], induces an immature profile in the host’s innate immune response (neutrophils), and is involved in the formation of myonecrosis in animals, including humans[33,34]. The  $\beta$  toxin is a pore-forming toxin associated with hemorrhagic diarrhea[35]. *Clostridium perfringens* with the expression of  $\alpha$  and  $\beta$  toxins is associated with necrotic enteritis in animals and humans[36-38]. The  $\epsilon$  toxin is also pore-forming and is involved in intestinal and neurological diseases in humans[39-43].

In addition, *Clostridium perfringens* is able to produce several other toxins such as enterotoxins[44-46], NetB[47,48], and TpeL[49,50], which can induce inflammatory responses, biofilm formation, and chronically disrupt the intestinal epithelium[44,47,50]. *Bacteroides fragilis*, another resident bacteria, can produce a zinc-dependent metalloprotease called fragilisyn[51]. Fragilisyn-producing *Bacteroides fragilis* are named *Enterotoxigenic Bacteroides Fragilis* (ETBF)[52]. ETBF toxin is coded by the *bft* gene and is highly correlated with diarrhea in humans[53,54]. ETBF can cleave E-cadherin in the epithelial cells, allowing bacterial translocation[55,56]. ETBF induces an IL-17-mediated immune response with the infiltration of lymphocytes and neutrophils and damages the DNA *via* the formation of microadenoma [4,53,54]. In addition, the inflammatory process may be mediated by several bacteria. For example, in the “driver-passenger” model, the colonization by one bacteria may facilitate the expansion and proinflammatory action of another microorganism[55].

A recent manuscript by Avril and DePaolo[56], identified that the co-colonization of ETBF and *Escherichia coli* strains, harboring the pks island, promotes the development of intestinal cancer. ETBF promotes the degradation of the intestinal mucus and induction of IL-17-mediated inflammation by the host’s immune cells. This process enables the adherence of *Escherichia coli* to the intestinal wall, releases colibactin, and promotes cancer development[56]. Therefore, quantitative analyses are important to characterize the composition of the microbiota in several diseases and aid in the design of possible interventions to modulate the immune response of the host in microbiota-mediated inflammatory disorders[1]. Nevertheless, due to the potential pathobiont role of several resident bacteria, investigations on toxin-producing bacteria are crucial for an overall interpretation of the role of the microbiota on gastrointestinal disorders.

## FOOTNOTES

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## REFERENCES

- 1 He XX, Li YH, Yan PG, Meng XC, Chen CY, Li KM, Li JN. Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis. *World J Gastroenterol* 2021; **27**: 4722-4737 [PMID: 34366632 DOI: 10.3748/wjg.v27.i28.4722]
- 2 Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. *Front Microbiol* 2014; **5**: 494 [PMID: 25295033 DOI: 10.3389/fmicb.2014.00494]
- 3 Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol* 2015; **21**: 8787-8803 [PMID: 26269668 DOI: 10.3748/wjg.v21.i29.8787]
- 4 Lucas C, Barnich N, Nguyen HTT. Microbiota, Inflammation and Colorectal Cancer. *Int J Mol Sci* 2017; **18** [PMID: 28632155 DOI: 10.3390/ijms18061310]
- 5 Chiu CY, Chan YL, Tsai MH, Wang CJ, Chiang MH, Chiu CC. Gut microbial dysbiosis is associated with allergen-specific IgE responses in young children with airway allergies. *World Allergy Organ J* 2019; **12**: 100021 [PMID: 30937143 DOI: 10.1016/j.waojou.2019.100021]
- 6 Pandiyan P, Bhaskaran N, Zou M, Schneider E, Jayaraman S, Huehn J. Microbiome Dependent Regulation of T<sub>regs</sub> and Th17 Cells in Mucosa. *Front Immunol* 2019; **10**: 426 [PMID: 30906299 DOI: 10.3389/fimmu.2019.00426]
- 7 Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; **9**: 313-323 [PMID: 19343057 DOI: 10.1038/nri2515]
- 8 Fonseca DM, Hand TW, Han SJ, Gerner MY, Glatman Zaretsky A, Byrd AL, Harrison OJ, Ortiz AM, Quinones M, Trinchieri G, Brenchley JM, Brodsky IE, Germain RN, Randolph GJ, Belkaid Y. Microbiota-Dependent Sequelae of Acute

- Infection Compromise Tissue-Specific Immunity. *Cell* 2015; **163**: 354-366 [PMID: 26451485 DOI: 10.1016/j.cell.2015.08.030]
- 9 **Battson ML**, Lee DM, Li Puma LC, Ecton KE, Thomas KN, Febvre HP, Chicco AJ, Weir TL, Gentile CL. Gut microbiota regulates cardiac ischemic tolerance and aortic stiffness in obesity. *Am J Physiol Heart Circ Physiol* 2019; **317**: H1210-H1220 [PMID: 31559829 DOI: 10.1152/ajpheart.00346.2019]
  - 10 **Saltzman ET**, Palacios T, Thomsen M, Vitetta L. Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. *Front Microbiol* 2018; **9**: 61 [PMID: 29441049 DOI: 10.3389/fmicb.2018.00061]
  - 11 **Wang L**, Liu L, Liu X, Xiang M, Zhou L, Huang C, Shen Z, Miao L. The gut microbes, Enterococcus and Escherichia-Shigella, affect the responses of heart valve replacement patients to the anticoagulant warfarin. *Pharmacol Res* 2020; **159**: 104979 [PMID: 32505835 DOI: 10.1016/j.phrs.2020.104979]
  - 12 **Gu S**, Chen Y, Wu Z, Gao H, Lv L, Guo F, Zhang X, Luo R, Huang C, Lu H, Zheng B, Zhang J, Yan R, Zhang H, Jiang H, Xu Q, Guo J, Gong Y, Tang L, Li L. Alterations of the Gut Microbiota in Patients With Coronavirus Disease 2019 or H1N1 Influenza. *Clin Infect Dis* 2020; **71**: 2669-2678 [PMID: 32497191 DOI: 10.1093/cid/ciaa709]
  - 13 **Alberca GGF**, Solis-Castro RL, Solis-Castro ME, Alberca RW. Coronavirus disease-2019 and the intestinal tract: An overview. *World J Gastroenterol* 2021; **27**: 1255-1266 [PMID: 33833480 DOI: 10.3748/wjg.v27.i13.1255]
  - 14 **Giannis D**, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020; **127**: 104362 [PMID: 32305883 DOI: 10.1016/j.jcv.2020.104362]
  - 15 **Wang X**, Sun J, Wan L, Yang X, Lin H, Zhang Y, He X, Zhong H, Guan K, Min M, Sun Z, Wang B, Dong M, Wei C. The *Shigella* Type III Secretion Effector IpaH4.5 Targets NLRP3 to Activate Inflammasome Signaling. *Front Cell Infect Microbiol* 2020; **10**: 511798 [PMID: 33117724 DOI: 10.3389/fcimb.2020.511798]
  - 16 **Hauser JR**, Atitkar RR, Petro CD, Lindsey RL, Strockbine N, O'Brien AD, Melton-Celsa AR. The Virulence of *Escherichia coli* O157:H7 Isolates in Mice Depends on Shiga Toxin Type 2a (Stx2a)-Induction and High Levels of Stx2a in Stool. *Front Cell Infect Microbiol* 2020; **10**: 62 [PMID: 32175286 DOI: 10.3389/fcimb.2020.00062]
  - 17 **Harrison LM**, Lacher DW, Mammel MK, Leonard SR. Comparative Transcriptomics of Shiga Toxin-Producing and Commensal *Escherichia coli* and Cytokine Responses in Colonic Epithelial Cell Culture Infections. *Front Cell Infect Microbiol* 2020; **10**: 575630 [PMID: 33194815 DOI: 10.3389/fcimb.2020.575630]
  - 18 **Huycke MM**, Gaskins HR. Commensal bacteria, redox stress, and colorectal cancer: mechanisms and models. *Exp Biol Med (Maywood)* 2004; **229**: 586-597 [PMID: 15229352 DOI: 10.1177/153537020422900702]
  - 19 **Blacher E**, Levy M, Tatirovsky E, Elinav E. Microbiome-Modulated Metabolites at the Interface of Host Immunity. *J Immunol* 2017; **198**: 572-580 [PMID: 28069752 DOI: 10.4049/jimmunol.1601247]
  - 20 **Louis P**, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014; **12**: 661-672 [PMID: 25198138 DOI: 10.1038/nrmicro3344]
  - 21 **Uzal FA**, Vidal JE, McClane BA, Gurjar AA. *Clostridium Perfringens* Toxins Involved in Mammalian Veterinary Diseases. *Open Toxicology J* 2010; **2**: 24-42 [PMID: 24511335]
  - 22 **Kiu R**, Hall LJ. An update on the human and animal enteric pathogen *Clostridium perfringens*. *Emerg Microbes Infect* 2018; **7**: 141 [PMID: 30082713 DOI: 10.1038/s41426-018-0144-8]
  - 23 **Revitt-Mills SA**, Rood JI, Adams V. *Clostridium perfringens* extracellular toxins and enzymes: 20 and counting. *Microbiol Aust* 2015; **36** [DOI: 10.1071/MA15039]
  - 24 **Liu F**, Li J, Guan Y, Lou Y, Chen H, Xu M, Deng D, Chen J, Ni B, Zhao L, Li H, Sang H, Cai X. Dysbiosis of the Gut Microbiome is associated with Tumor Biomarkers in Lung Cancer. *Int J Biol Sci* 2019; **15**: 2381-2392 [PMID: 31595156 DOI: 10.7150/ijbs.35980]
  - 25 **Rood JI**, Adams V, Lacey J, Lyras D, McClane BA, Melville SB, Moore RJ, Popoff MR, Sarker MR, Songer JG, Uzal FA, Van Immerseel F. Expansion of the *Clostridium perfringens* toxin-based typing scheme. *Anaerobe* 2018; **53**: 5-10 [PMID: 29866424 DOI: 10.1016/j.anaerobe.2018.04.011]
  - 26 **Hotze EM**, Tweten RK. Membrane assembly of the cholesterol-dependent cytolysin pore complex. *Biochim Biophys Acta* 2012; **1818**: 1028-1038 [PMID: 21835159 DOI: 10.1016/j.bbamem.2011.07.036]
  - 27 **Schwabe RF**, Jobin C. The microbiome and cancer. *Nat Rev Cancer* 2013; **13**: 800-812 [PMID: 24132111 DOI: 10.1038/nrc3610]
  - 28 **Jewell SA**, Titball RW, Huyet J, Naylor CE, Basak AK, Gologan P, Winlove CP, Petrov PG. *Clostridium perfringens*  $\alpha$ -toxin interaction with red cells and model membranes. *Soft Matter* 2015; **11**: 7748-7761 [PMID: 26303814 DOI: 10.1039/c5sm00876j]
  - 29 **Junior CAO**, Silva ROS, Lobato FCF, Navarro MA, Uzal FA. Gas gangrene in mammals: a review. *J Vet Diagn Invest* 2020; **32**: 175-183 [PMID: 32081096 DOI: 10.1177/1040638720905830]
  - 30 **Takehara M**, Takagishi T, Seike S, Ohtani K, Kobayashi K, Miyamoto K, Shimizu T, Nagahama M. *Clostridium perfringens*  $\alpha$ -Toxin Impairs Innate Immunity via Inhibition of Neutrophil Differentiation. *Sci Rep* 2016; **6**: 28192 [PMID: 27306065 DOI: 10.1038/srep28192]
  - 31 **Hunter SE**, Brown JE, Oyston PC, Sakurai J, Titball RW. Molecular genetic analysis of beta-toxin of *Clostridium perfringens* reveals sequence homology with alpha-toxin, gamma-toxin, and leukocidin of *Staphylococcus aureus*. *Infect Immun* 1993; **61**: 3958-3965 [PMID: 8359918 DOI: 10.1128/iai.61.9.3958-3965.1993]
  - 32 **Matsuda T**, Okada Y, Inagi E, Tanabe Y, Shimizu Y, Nagashima K, Sakurai J, Nagahama M, Tanaka S. Enteritis necroticans 'pigbel' in a Japanese diabetic adult. *Pathol Int* 2007; **57**: 622-626 [PMID: 17685936 DOI: 10.1111/j.1440-1827.2007.02149.x]
  - 33 **Posthaus H**, Kittl S, Tarek B, Bruggisser J. *Clostridium perfringens* type C necrotic enteritis in pigs: diagnosis, pathogenesis, and prevention. *J Vet Diagn Invest* 2020; **32**: 203-212 [PMID: 31955664 DOI: 10.1177/1040638719900180]
  - 34 **Thiel A**, Mogel H, Bruggisser J, Baumann A, Wyder M, Stoffel MH, Summerfield A, Posthaus H. Effect of *Clostridium perfringens*  $\beta$ -Toxin on Platelets. *Toxins (Basel)* 2017; **9** [PMID: 29064418 DOI: 10.3390/toxins9100336]
  - 35 **Wagley S**, Bokori-Brown M, Morcrette H, Malaspina A, D'Arcy C, Gnanapavan S, Lewis N, Popoff MR, Raciborska D, Nicholas R, Turner B, Titball RW. Evidence of *Clostridium perfringens* epsilon toxin associated with multiple sclerosis.

- Mult Scler* 2019; **25**: 653-660 [PMID: 29681209 DOI: 10.1177/1352458518767327]
- 36 **Savva CG**, Clark AR, Naylor CE, Popoff MR, Moss DS, Basak AK, Titball RW, Bokori-Brown M. The pore structure of *Clostridium perfringens* epsilon toxin. *Nat Commun* 2019; **10**: 2641 [PMID: 31201325 DOI: 10.1038/s41467-019-10645-8]
- 37 **Popoff MR**. Epsilon toxin: a fascinating pore-forming toxin. *FEBS J* 2011; **278**: 4602-4615 [PMID: 21535407 DOI: 10.1111/j.1742-4658.2011.08145.x]
- 38 **Freedman JC**, McClane BA, Uzal FA. New insights into *Clostridium perfringens* epsilon toxin activation and action on the brain during enterotoxemia. *Anaerobe* 2016; **41**: 27-31 [PMID: 27321761 DOI: 10.1016/j.anaerobe.2016.06.006]
- 39 **Harkness JM**, Li J, McClane BA. Identification of a lambda toxin-negative *Clostridium perfringens* strain that processes and activates epsilon prototoxin intracellularly. *Anaerobe* 2012; **18**: 546-552 [PMID: 22982043 DOI: 10.1016/j.anaerobe.2012.09.001]
- 40 **Freedman JC**, Shrestha A, McClane BA. *Clostridium perfringens* Enterotoxin: Action, Genetics, and Translational Applications. *Toxins (Basel)* 2016; **8** [PMID: 26999202 DOI: 10.3390/toxins8030073]
- 41 **Grass JE**, Gould LH, Mahon BE. Epidemiology of foodborne disease outbreaks caused by *Clostridium perfringens*, United States, 1998-2010. *Foodborne Pathog Dis* 2013; **10**: 131-136 [PMID: 23379281 DOI: 10.1089/fpd.2012.1316]
- 42 **Li J**, Miyamoto K, Sayeed S, McClane BA. Organization of the cpe locus in CPE-positive *Clostridium perfringens* type C and D isolates. *PLoS One* 2010; **5**: e10932 [PMID: 20532170 DOI: 10.1371/journal.pone.0010932]
- 43 **Rood JI**, Keyburn AL, Moore RJ. NetB and necrotic enteritis: the hole movable story. *Avian Pathol* 2016; **45**: 295-301 [PMID: 27009522 DOI: 10.1080/03079457.2016.1158781]
- 44 **Keyburn AL**, Bannam TL, Moore RJ, Rood JI. NetB, a pore-forming toxin from necrotic enteritis strains of *Clostridium perfringens*. *Toxins (Basel)* 2010; **2**: 1913-1927 [PMID: 22069665 DOI: 10.3390/toxins2071913]
- 45 **Chen J**, McClane BA. Characterization of *Clostridium perfringens* TpeL toxin gene carriage, production, cytotoxic contributions, and trypsin sensitivity. *Infect Immun* 2015; **83**: 2369-2381 [PMID: 25824828 DOI: 10.1128/IAI.03136-14]
- 46 **Schorch B**, Heni H, Zahaf NI, Brummer T, Mione M, Schmidt G, Papatheodorou P, Aktories K. Targeting oncogenic Ras by the *Clostridium perfringens* toxin TpeL. *Oncotarget* 2018; **9**: 16489-16500 [PMID: 29662661 DOI: 10.18632/oncotarget.24740]
- 47 **Pierce JV**, Bernstein HD. Genomic Diversity of Enterotoxigenic Strains of *Bacteroides fragilis*. *PLoS One* 2016; **11**: e0158171 [PMID: 27348220 DOI: 10.1371/journal.pone.0158171]
- 48 **Shah N**, Osmon D, Tande AJ, Steckelberg J, Sierra R, Walker R, Berbari EF. Clinical and Microbiological Characteristics of *Bacteroides* Prosthetic Joint Infections. *J Bone Jt Infect* 2017; **2**: 122-126 [PMID: 28540148 DOI: 10.7150/jbji.17129]
- 49 **Zhang G**, Svenungsson B, Kärnell A, Weintraub A. Prevalence of enterotoxigenic *Bacteroides fragilis* in adult patients with diarrhea and healthy controls. *Clin Infect Dis* 1999; **29**: 590-594 [PMID: 10530453 DOI: 10.1086/598639]
- 50 **Sears CL**. Enterotoxigenic *Bacteroides fragilis*: a rogue among symbiotes. *Clin Microbiol Rev* 2009; **22**: 349-369, Table of Contents [PMID: 19366918 DOI: 10.1128/CMR.00053-08]
- 51 **Wu S**, Rhee KJ, Zhang M, Franco A, Sears CL. *Bacteroides fragilis* toxin stimulates intestinal epithelial cell shedding and gamma-secretase-dependent E-cadherin cleavage. *J Cell Sci* 2007; **120**: 1944-1952 [PMID: 17504810 DOI: 10.1242/jcs.03455]
- 52 **Deng H**, Li Z, Tan Y, Guo Z, Liu Y, Wang Y, Yuan Y, Yang R, Bi Y, Bai Y, Zhi F. A novel strain of *Bacteroides fragilis* enhances phagocytosis and polarises M1 macrophages. *Sci Rep* 2016; **6**: 29401 [PMID: 27381366 DOI: 10.1038/srep29401]
- 53 **DeStefano Shields CE**, Van Meerbeke SW, Housseau F, Wang H, Huso DL, Casero RA Jr, O'Hagan HM, Sears CL. Reduction of Murine Colon Tumorigenesis Driven by Enterotoxigenic *Bacteroides fragilis* Using Cefoxitin Treatment. *J Infect Dis* 2016; **214**: 122-129 [PMID: 26908749 DOI: 10.1093/infdis/jiw069]
- 54 **Chung L**, Thiele Orberg E, Geis AL, Chan JL, Fu K, DeStefano Shields CE, Dejea CM, Fathi P, Chen J, Finard BB, Tam AJ, McAllister F, Fan H, Wu X, Ganguly S, Lebid A, Metz P, Van Meerbeke SW, Huso DL, Wick EC, Pardoll DM, Wan F, Wu S, Sears CL, Housseau F. *Bacteroides fragilis* Toxin Coordinates a Pro-carcinogenic Inflammatory Cascade via Targeting of Colonic Epithelial Cells. *Cell Host Microbe* 2018; **23**: 203-214.e5 [PMID: 29398651 DOI: 10.1016/j.chom.2018.01.007]
- 55 **Tjalsma H**, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. *Nat Rev Microbiol* 2012; **10**: 575-582 [PMID: 22728587 DOI: 10.1038/nrmicro2819]
- 56 **Avril M**, DePaolo RW. "Driver-passenger" bacteria and their metabolites in the pathogenesis of colorectal cancer. *Gut Microbes* 2021; **13**: 1941710 [PMID: 34225577 DOI: 10.1080/19490976.2021.1941710]



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