**Focused REVIEW**

**Gut Microbiome and the Response to Immunotherapy in Cancer**

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**ABSTRACT**

Recent studies indicate that the composition of gut bacteria can influence the effectiveness of certain cancer immunotherapy drugs and that modulating the gut microbiome may expand the pool of patients benefiting from cancer immunotherapies. Checkpoint blockade therapy has been effective on several types of malignancies (e.g. melanoma, lung cancer, kidney cancer). However, the number of patients that do not respond, or only partially respond, to cancer immunotherapy is high. Recently, several human and mouse studies have shown that gut microbiome may be a significant determinant of the response to cancer immunotherapy. This review focuses on the recent advances in our understanding of the interaction between human gut microbiome and response to immunotherapy in cancer. The gut microbiome may serve as a theranostic biomarker, by acting both as a useful prognostic biomarker and a target in cancer therapy.

**Keywords:** Cancer, immunotherapy, microbiome, response to therapy, PD-1, PD-L1.

**Abbreviations:** Programmed Cell Death Protein 1 (PD-1); Food and Drug Administration (FDA); cytotoxic T cell (CTL); cytotoxic T lymphocyte antigen 4 (CTLA-4); Microbial Ecosystem Therapeutics (MET-4); US National Institutes of Health (NIH).

**1. Introduction**

Immune checkpoint therapies have enabled a breakthrough in the therapy of the hematologic and solid metastatic malignancies. Administration of monoclonal antibodies unleashes a T lymphocyte-mediated immune response by inhibiting the interaction of T-cell suppressing receptors with their corresponding ligand on tumor cells. In particular, immune checkpoint inhibitors that target programmed cell death protein 1 (PD-1) and its ligand PD-L1, have to date been approved by the U.S. Food and Drug Administration (FDA) for the use in the treatment of patients with 10 distinct cancer types.

In anti-tumor therapy, specific CD8+ cytotoxic T lymphocytes (CTL) are generated, recognize specific tumor antigens and induce caspase-dependent cell death in tumor cells. However, tumor cells can utilize a wide range of immune escape strategies. An important escaping mechanism is the one exploiting the PD-1 - PD-L1 interaction, in which CTLs are inhibited through PD-1 receptor on their surface by the PD-L1 ligand, found on tumor or other cells. For example, it was shown that PD-L1 expressing cancer cells induce caspase-dependent cell death of co-cultured activated CTLs and an anti-human PD-L1 monoclonal antibody can block this interaction and its effects. Other studies replicated these results in mouse models.

Although most normal tissues do not express detectable PD-L1 levels on their cellular surface, PD-L1 is highly expressed in tumor cells and some
immune/non-immune cells in tumor environment\textsuperscript{11-19}. Moreover, certain cytokines, such as TNF-alpha, IL-4, IL-10 and IFN-gamma play an important role in increasing the expression of PD-L1\textsuperscript{6,20,22}. PD-1 interaction with its PD-L1 ligand leads to suppression of the effector T cells, by inducing T cell apoptosis, anergy and/or exhaustion\textsuperscript{6,20,23}. Moreover, the phagocytic activity of macrophages against tumor cells can also be suppressed by PD-1 - PD-L1 interaction\textsuperscript{6,24}. All these results and others not mentioned here led to a significant number of studies focusing on disrupting this interaction for cancer treatment\textsuperscript{6}.

Many clinical trials are now underway, testing monoclonal antibodies against PD-L1 or PD-1, as a cancer immunotherapy strategy for a variety of malignancies. These treatments may work both by disrupting the immunological-related pathways, but also by disrupting intracellular tumor signaling pathways\textsuperscript{25}. Currently, there are at least 5 monoclonal antibodies targeting PD-1 or PD-L1 approved by the FDA as cancer immunotherapy\textsuperscript{6}.

Responses to immunotherapy targeting PD-1 or PD-L1 are often heterogeneous and not durable. Primary resistance, observed in the majority of the cases, has been associated with low mutational burden, poor intrinsic antigenicity of tumor cells, defective antigen presentation during the priming phase, functional exhaustion of tumor-infiltrating lymphocytes and local immunosuppression by extracellular metabolites\textsuperscript{6,8,11,26,27}. Thus, different approaches to optimize the efficacy of cancer immunotherapy are in high demand.

Recent studies suggest that modulation of the gut microbiota is a promising approach. Several human and mouse studies have shown that gut microbiome may be a significant determinant of the response to cancer immunotherapy\textsuperscript{6,15,17-19,28-35}. The number of studies investigating microbiome’s relation with the cancer immunotherapy is growing exponentially (Figure 1). Thus, we and others think that the gut microbiome may serve as a theranostic biomarker, by acting both as a useful prognostic biomarker and a target in cancer therapy.

![Figure 1. Exponential growth of the number of articles published between 2003-2018 related to the “cancer immunotherapy” and “microbioma”. This graph is based on the PubMed publications data. Data for 2018 is collected for January-September 2018.](image-url)
2. Role of microbiota in immune checkpoint therapy

Stem cell transplant can be considered one of the first immunotherapy strategies for cancer treatment (e.g. transplant for leukemia treatment). In recent years, an exponential number of studies\(^{30,35}\) initiated new immunotherapeutic approaches, which were initially demonstrated in mouse models with many of them (e.g. anti-PD-1 or anti-PD-L1 treatments) being validated in humans\(^{30,35}\).

Although not considered immunotherapy, the response to the standard chemotherapy treatment is at least in part based on the activation of the immune system. Over 10 years ago, Paulos et al. observed that antibiotics inhibited anti-cancer activity in melanoma, a murine model of adoptive cell therapy, while translocation of bacteria from the gut helped by initiating a TLR4-dependent immune response\(^{36}\). Subsequent studies confirmed these findings by using platinum and cyclophosphamide-based therapy\(^{34,37}\).

The role of gut microbiome as a response to the immune checkpoint blockade was similarly initiated in mouse models, showing that gut bacteria influences the response to cancer immunotherapy (targeting CTLA-4 and PD-1)\(^{30,35}\). Many of the patients do not respond to the treatment with immune checkpoint inhibitors. Interestingly, oral administration of certain types of Bacteroides (Bacteroides fragilis together with Burkholderia cepacia or Bacteroides thetaiotaomicron) stimulated anti-CTLA-4 immunotherapy\(^{35}\). Many other studies were subsequently published showing that gut bacteria is associated and/or modulates the resistance to immunotherapy, such as anti-PD-1 or anti-PD-L1 treatments\(^{6,15,17,19,28,34}\).

Of note, microbiota can be transplanted to other mice and the beneficial effects are transmitted to the new host. Supplementation with a probiotic orally administered containing Bifidobacterium re-sensitized the tumors to anti-PD-L1 therapy in mice, by promoting DC maturation and an increase in anti-tumor CD8+ CTL activity\(^{33}\).

In the past two years, a significant number of bacteria were determined to modulate anti-PD-1 or anti-PD-L1 therapy in a wide range of malignancies, such as melanoma, lung cancer, kidney cancer. A summary of the most important bacterial candidates is presented in Table 1. Notably, few of them (such as Bifidobacterium) were confirmed in multiple studies to be present in higher abundance in responders to immunotherapy and that mice that received the bacteria species Bifidobacterium have a marked increase in anti-tumor T cell responses\(^{30}\).

The mechanisms through which some bacteria enhance anti-tumor immunotherapy are not yet clearly defined. Recent studies suggest that tumor antigens are similar to those found on infectious pathogens\(^{38,39}\). Other studies suggest that the metabolic effects are involved or that the microbiota determines “the tosus of the immune response”\(^{39,40}\). Thus, further studies are required to elucidate these mechanistic aspects.

3. Microbial intervention as adjuvant therapy for immunotherapy in cancer

Considering the exponential increase of the scientific community’s interest and the exciting already published studies, the involvement and potential modulation of gut microbiota may represent an important adjuvant in cancer immunotherapy in the near future.

Although the exact molecular mechanisms of the microbiota interactions with cancer therapies are not completely understood, several clinical trials are already ongoing (Table 2). For example, at least 3 observational studies (NCT02960282, NCT03643289, NCT0368834) and one interventional (NCT03686202) are now recruiting patients (Table 2). In the first mentioned trial, the gut microbiome will be investigated in the fecal samples from patients with metastatic cancer undergoing chemotherapy and immunotherapy. In a second clinical trial, the gut microbiome diversity will be assessed with metagenome sequencing before and after immunotherapy, in order to predict the response to immunotherapy for melanoma. The third trial will investigate the nasal, oral and fecal microbiome, and correlate the data with treatment response and toxicities of immunotherapy, in lung cancer and other malignancies. The NCT03686202 interventional clinical trial (phase 1) will assess the safety, tolerability and engraftment of Microbial Ecosystem Therapeutics (MET-4) strains when given in combination with immunotherapy, in solid tumors. Other clinical trials aim investigating the dietary, other lifestyle or environmental factors in relation to cancer therapy, or the direct use of live genetically modified bacteria as an immunotherapy treatment (Table 2).

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Diet may serve as an important tool for modulating the microbiome in relation to the anti-cancer immunotherapy. The main function of microbiota is to help in food digestion and producing valuable factors (e.g. vitamin K), that the host can’t produce itself\textsuperscript{41}. Dietary variation modifies the microbiome composition. Several proof-of-concept studies demonstrated how dietary modulation can be employed as a strategy to influence the gut microbiome and immune health\textsuperscript{29,30}. Dietary fibers have been previously established to have an important influence on the gut microbiome composition\textsuperscript{44}. The NCT02843425 (“BE GONE”) interventional clinical trial assesses the fiber supplementation-induced shift in bacterial populations, through the addition of a half cup of beans/day into the normal diets of cancer patients (colorectal cancer). Additional clinical trials investigating the role of dietary supplements and other factors on the microbiota/microbiome in the context of cancer are underway (NCT02079662, NCT03072641, NCT01895530, NCT03353402, NCT03358511)\textsuperscript{33}. Although, all these studies are just starting, they will provide critical information on how diet, lifestyle and environmental factors modulate the gut microbiome, provide new prognostic biomarkers and modulate the patient outcome.

### TABLE 1. Examples of bacteria as potential modulators of the anti-PD-1 immunotherapy in cancer (their modulatory mechanisms and effects have to be further investigated).

| Bacteria (Gut) | Effect | Ref. |
|----------------|--------|------|
| Ruminococaceae family | Higher abundance in responders to anti-PD-1 therapy (melanoma); also, higher diversity of bacteria observed | 33 |
| Faecalibacterium genus | Higher abundance in responders to anti-PD-1 therapy (melanoma); also, higher diversity of bacteria observed | 33 |
| Bifidobacterium longum and Bifidobacterium adolescentis | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29,30 |
| Collinsella aerofaciens | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Enterococcus faecium | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Klebsiela pneumoniae | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Veillonella parvula | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Parabacteroides merdae | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Lactobacillus sp. | Higher abundance in responders to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Akkermansia muciniphila | Higher abundance in responders to anti-PD-1 therapy (lung and kidney cancers); exposure to antibiotics decreases response; | 31 |
| Ruminococcus obeum | Higher abundance in **non-responders** to anti-PD-1 therapy (metastatic melanoma) | 29 |
| Roseburia intestinalis | Higher abundance in **non-responders** to anti-PD-1 therapy (metastatic melanoma) | 29 |

Ref. – Reference(s)
TABLE 2. Clinical trials evaluating microbial role/intervention as immunotherapy modulator in cancer (based on ClinicalTrials.gov, website maintained by the National Library of Medicine, at the US National Institutes of Health (NIH)).

| ClinicalTrials.gov Identifier | Name of the study                                                                 | Conditions                                                                 | Comments                                                                 | Status        |
|-------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------|
| NCT02960282                  | Gut Microbiome in Fecal Samples from Patients with Metastatic Cancer Undergoing Chemotherapy or Immunotherapy | Colorectal Cancer (stage 4)                                               | Observational study; Biospecimen Collection; Laboratory Biomarker Analysis | Recruiting    |
| NCT03643289                  | Predicting Response to Immunotherapy for Melanoma with Gut Microbiome & Metabolomics | Melanoma (stage 4)                                                        | Observational study; Assess the gut microbiome diversity with metagenome sequencing before and after immunotherapy. | Recruiting    |
| NCT03688347                  | Microbiome in Lung Cancer and other Malignancies                                  | Lung cancer, other cancers                                                | Observational study; Assess the nasal, oral and fecal microbiome, and correlate the data with treatment response and toxicities of immunotherapy | Recruiting    |
| NCT03686202                  | Feasibility Study of Microbial Ecosystem Therapeutics (MET-4) to Evaluate Effects of Fecal Microbiome in Patients on Immunotherapy | Solid tumors                                                              | Interventional (Phase 1); Assess the safety, tolerability and engraftment of Microbial Ecosystem Therapeutics (MET-4) strains when given in combination with immunotherapy | Recruiting    |
| NCT02592967                  | Safety & Immunogenicity of JNJ-64041757, Live-attenuated Double-deleted Listeria Immunotherapy, in Subjects with Non Small Cell Lung Cancer | Non-small cell lung cancer (NSCLC) (stages 3B and 4)                      | Interventional (Phase 1); Assess the JNJ-64041757, a live attenuated double deleted (LADD) Listeria monocytogenes as single immunotherapy | Active        |
| NCT02625857                  | Safety & Immunogenicity of JNJ-64041809, a Live Attenuated Double-deleted Listeria Immunotherapy, in Participants with Metastatic Castration-resistant Prostate Cancer | Prostate cancer, castration-resistant                                      | Interventional (Phase 1); Assess the JNJ-64041809, a live attenuated double deleted (LADD) Listeria monocytogenes as single immunotherapy | Completed     |
| NCT02843425                  | The Beans to Enrich the Gut Microbiome vs. Obesity's Negative Effects (BE GONE) Trial | Colorectal cancer Prevention                                              | Interventional; Assess the fiber supplementation - induced shift in bacterial populations, through the addition of a half cup of beans/day into the normal diets of cancer patients | Recruiting    |
4. Future directions

In the very recent few years, we have gained significant insights into the role of gut microbiome in cancer therapy, with a special focus on immunotherapy. The number of published studies is growing exponentially, and the first clinical trials are now ongoing. However, the exact mechanisms, involved bacteria and utility in various types of malignancies remain to be further investigated and understood.

In order to efficiently tackle these objectives, one has to use the optimal methods available. For example, selection of the sequencing methods for the microbiome and reference databases is very important. Since reproducibility is often brought into question, it is important to properly set-up and execute these studies.

Further investigations should determine the bacterial combination pools needed to facilitate the response to cancer immunotherapy in different types of malignancies and how we can develop or induce the development of such combinations. The outcome should be carefully investigated in clinical trials. Moreover, the role of other influencers, such as medications (drug treatments for other conditions, antibiotics, probiotics etc.), diet, metabolic changes (e.g. exercise) and other internal conditions (e.g. mental health) and external factors have to be thoroughly investigated.

Taking advantage of the prognostic and modulatory role of the microbiome in cancer immunotherapy in particular, and cancer therapy in general, to enhance the anti-tumor immunity and immune surveillance, may be one of the dominant strategies in cancer therapy in the future.

Conflict of interests

The authors declare no conflicts of interest.

References

1. Robert C, Thomas L, Bondarenko I, O’Day S, Weber J, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26.
2. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, et al. Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. JAMA. 2016 Apr 19;315(15):1600-9.
3. Borghei H, Paz-Ares L, Horn L, Spigel DR, Steins M, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.
4. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443-54.
5. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017 Feb 9;168(4):707-723.
6. Wang Y, Ma R, Liu F, Lee SA, Zhang L. Modulation of Gut Microbiota: A Novel Paradigm of Enhancing the Efficacy of Programmed Death-1 and Programmed Death Ligand-1 Blockade Therapy. Front Immunol. 2018 Mar 5;9:374.
7. Engels B, Engelhard VH, Sidney J, Sette A, Binder DC, Liu RB et al. Relapse or eradication of cancer is predicted by peptide-major histocompatibility complex affinity. Cancer Cell. 2013 Apr 15;23(4):516-26.
8. Iwai Y1, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002 Sep 17;99(19):12293-7.
9. Blank C1, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, Gajewski TF. PD-L1/B7-H1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004 Feb 1;64(3):1140-5.
10. Hirano F1, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005 Feb 1;65(3):1089-96.
11. Johnson DB, Frampton GM, Rioth MJ, Yusko E, Xu Y, Guo X, et al. Targeted Next Generation Sequencing Identifies Markers of Response to PD-1 Blockade. Cancer Immunol Res. 2016 Nov;4(11):959-967.
12. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010 Mar 4;464(7285):59-65.
13. Taur Y, Jeng RR, Perales MA, Littmann ER, Morjaria S, Ling L et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood. 2014 Aug 14;124(7):1174-82.
14. Tran E1, Robbins PF1, Rosenberg SA1. ‘Final common pathway’ of human cancer immunotherapy:
15. Segre JA. MICROBIOME. Microbial growth dynamics and human disease. Science. 2015 Sep 4;349(6252):1058-9

16. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8

17. Muegge BD, Kuczynski J, Knights D, Clemente JC, González A, Fontana L, et al. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. Science. 2011 May 20;332(6032):970-4.

18. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012 Jun 13;486(7402):207-14.

19. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JL. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008 Apr 17;3(4):213-23

20. Dong H1, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med. 1999 Dec;5(12):1365-9.

21. Tamura H1, Dong H, Zhu G, Sica GL, Flies DB, Tamada K, Chen L. B7-H1 costimulation preferentially enhances CD28-independent T-helper cell function. Blood. 2001 Mar 15;97(6):1809-16.

22. Kondo A, Yamashita T, Tamura H, Zhao W, Tsuji T, Shimizu M, et al. Interferon-gamma and tumor necrosis factor-alpha induce an immunoinhibitory molecule, B7-H1, via nuclear factor-kappaB activation in blasts in myelodysplastic syndromes. Blood. 2010 Aug 19;116(7):1124-31.

23. Ghiotto M1, Gauthier L, Serriari N, Pastor S, Truneh A, Nunès JA, Olive D. PD-L1 and PD-L2 differ in their molecular mechanisms of interaction with PD-1. Int Immunol. 2010 Aug;22(8):651-60.

24. Gordon SR, Maute RL, Dulten BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature. 2017 May 25;545(7655):495-499.

25. Arasanz H, Gato-Cañas M, Zuazo M, Ibáñez-Vea M, Breckpot K, Kochan G, Escors D. PD1 signal transduction pathways in T cells. Oncotarget. 2017 Apr 19;8(31):51936-51945

26. Spranger S1, Bao R2, Gajewski TF3. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. Nature. 2015 Jul 9;523(7559):231-5. M. J. Smyth, S. F. Ngiow, A. Ribas, M. W. L. Teng, Nat. Rev. Clin. Oncol. 13, 143–158 (2016).

27. Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016 Feb 17;7:10501.

28. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science (New York, NY). 2018;359(6371):97-103.

29. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018 Jan 5;359(6371):104-108.

30. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science. 2015 Nov 27;350(6264):1084-9.

31. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018 Jan 5;359(6371):91-97.

32. Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog. 2017 Sep 21;13(9):e1006480.

33. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell. 2018 Apr 9;33(4):570-580.

34. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hänni D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science. 2013 Nov 22;342(6161):971-6.

35. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015 Nov 27;350(6264):1079-84.

36. Paulos CM, Wrzesinski C, Kaiser A, Hinrichs CS, Chiappa M, Cassard L. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. J Clin Invest. 2007 Aug;117(8):2197-204.

37. Goubet AG, Daillère R, Routy B, Derosa L, M Roberti P, Zitvogel L. The impact of the intestinal
microbiota in therapeutic responses against cancer. C R Biol. 2018 May - Jun;341(5):284-289.
38. Balachandran VP, Łuksza M, Zhao JN, Makarov V, Moral JA, Remark R. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017 Nov 23;551(7681):512-516.
39. Kroemer G, Zitvogel L. Cancer immunotherapy in 2017: The breakthrough of the microbiota. Nat Rev Immunol. 2018 Jan 30;18(2):87-88.
40. Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. Nat Rev Microbiol. 2017 Aug;15(8):465-478.
41. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005 Mar 25;307(5717):1915-20.
42. Ma N, Guo P, Zhang J, He T, Kim SW, Zhang G, Ma X. Nutrients Mediate Intestinal Bacteria-Mucosal Immune Crosstalk. Front Immunol. 2018 Jan 24; 9:5.
43. Shortt C, Hasselwander O, Meynier A, Nauta A, Fernández EN, Putz P, et al. Systematic review of the effects of the intestinal microbiota on selected nutrients and non-nutrients. Eur J Nutr. 2018 Feb;57(1):25-49.
44. Benus RF, van der Werf TS, Welling GW, Judd PA, Taylor MA, Harmsen HJ, Whelan K. Association between Faecalibacterium prausnitzii and dietary fibre in colonic fermentation in healthy human subjects. Br J Nutr. 2010 Sep;104(5):693-700.
45. Bucur O, Penrarun B, Stancu AL, Nadler M, Muraru MS, Bertomeu T, Khosravi-Far R. Poor antibody validation is a challenge in biomedical research: a case study for detection of c-FLIP. Apoptosis. 2013 Oct;18(10):1154-62.

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