Macedonian pharmaceutical bulletin, 69 (Suppl 1) 271 - 272 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.132
Short communication

The Impact of the Human Microbiome on Cancer Immunotherapy

Filip Djokoski*, Marija Hiljadnikova-Bajro

Institute of Applied Biochemistry, Faculty of Pharmacy, Ss. Cyril and Methodius University in Skopje, Majka Tereza 47, Skopje, Republic of North Macedonia

Introduction

It is now well known that the human microbiome significantly impacts the development and support of fundamental physiological elements such as metabolism and immunity, influencing even one's behavior. Dysbiotic microbiota is significantly involved in the etiopathogenesis of many diseases including neoplasia, affecting the processes of tumor initiation and progression, either by direct action on the tumor cells or indirect influence via the individual's immune system,

This paper addresses the current knowledge about the impact of the human microbiome on the efficacy of cancer immunotherapy (CI) based on immune checkpoint inhibitors-(ICI) and the possible application of the microbiota as a novel therapy for cancer.

Materials and methods

A comprehensive Pubmed-based literature survey of articles published within the last five years using the keywords: microbiome implications, checkpoint inhibitors, microbiota, and cancer immunotherapy responses was performed, with an aim to investigate the complex interplay between intestinal microbiota, host's immune system, and cancer therapy

Results and discussion

Numerous scientific studies are focused on elucidating the mechanism of microbiota interaction with the host and various xenobiotics. Some receptors, as constituents of innate immunity, are mainly expressed in immune cells, serving as a bridge between innate and adaptive immunity, and are associated with microbial homeostasis. The metabolites secreted by the intestinal microbiota can activate these receptors and stimulate the secretion of proinflammatory cytokine IL-18 by immune and nonimmune cells, which maintains the stability of the mucus and the expression of antimicrobial peptides. With the PD-1 from Th cells binding to PD-L1 on B cells, Th cells control the function of the gut microbiota through the secretion of IgA. This type of binding with other cells prevents T cells from killing cancer cells. Bifidobacteria (B. longum/breve/ pseudolongum/ bifidum) and Akkermansia muciniphila have been shown to enhance the PD-1 blockade, contrary to the microbial-derived short-chain fatty acids (SCFAs), Bacteroides (B.fragilis/ thetaiotaomicron/ caccae), Clostridium and Escherichia which enhance CTLA-4 blockade. At the same time Faecalibacterium prausnitzii, Enterococcus faecium, and Bacteroides are able to enhance both PD-1 and CTLA-4 blockades (Rezasoltani et al., 2020; Bae et al., 2022). A recent study (Liu et al., 2022) showed that Inosine produced by A. muciniphila and B. pseudolongum, exerts synergistic antitumor effects when combined with ICI therapy, increasing the immunogenicity of tumor cells by improving their ability to present tumor antigens, easily recognized and eliminated by the cytotoxic immune cells, furthermore, this nucleotide can also promote the immune cell activation. It's been demonstrated that SCFAs have the potential to inhibit the proliferation and induce apoptosis in cancer cells and some of them can also improve the antitumor effect of ICIs. SCFAs, provide an energy supply for the immune cells like B-, both memory and effector T-cells by glycolysis, the tricarboxylic acid cycle and β-

* Filip_Djokoski@hotmail.com

oxidation. Kiousi et al. (2023) demonstrate that peptidoglycan, flagellin, polysaccharide A, and outer membrane vesicles can promote anti-tumor immune responses by their stimulatory effects on myelopoiesis and cytokines production.

Widely studied bacterial wall lipid A and O-antigens aid in the activation of the immunological T cell-mediated response against several cancer cells. Similarly, the monophosphoryl lipid A that is secreted from Salmonella enterica has been used as an adjuvant to a vaccine-based treatment against cervical carcinoma. Also, an anti-tumor immune response and a direct cytotoxic effect on the tumor cells can be achieved with attenuated and/or genetically modified Salmonella typhimurium. It's known that Bacteria-derived-pyridoxine helps in the modulation of the host's antitumoral immunosurveillance, and Ferricrome metabolite secreted from Lactobacillus casei can induce apoptosis in tumor cells. Mycobacterium bovis has been successfully used to cure bladder tumors by host immune activation and immune cell recruitment, and oral administration of L. casei has shown cytotoxic properties and led to a decrement in superficial bladder cancer recurrence (Choudhry, 2021).

It's been demonstrated that transferring the gut microbiota of patients with colorectal cancer to germ-free mice can cause dysplasia, polyp formation, and tumorigenesis, and the existence of certain "unfavorable" bacteria in the gut can also negatively affect the efficacy of CI. In this context, bacteriophages could be used as targeted therapy for eradicating bacteria that promote tumor growth or reduce the effectiveness of ICIs due to their strong selectivity for particular bacterial species (Li et al., 2019). A proof of concept on the efficacy of fecal microbiota transplantation (FMT) combined with the reintroduction of anti-PD-1 in patients with immunotherapy-resistant cancer are two independent phase 1/2 trials reviewed in the study of Bullman et al. (2021). The FDA suggests that probiotics should be regulated as drugs, due to their effect on ICIs. Some of them, such as Bifidobacterium and Burkholderiales, could be used as "Anti-Cancer Probiotics" because combined with prebiotics, can aid the growth of intestinal bacteria which boosts anti-tumor immunity and can restore anticancer adaptive T-cell response (Szczyrek et al., 2021). According to 107 articles using data from 123 different cohorts, the antibiotic's lack of specificity results in dysbiosis, which in turn is linked to lower survival in cancer patients taking ICIs (Crespin et al., 2023).

Conclusion

The impact of the microbiome on CI efficacy is already established. But, the great discrepancy in the published data, and the differences among ongoing studies enrolling subjects from distinct geographic locations, with specific genetic and nutritional patterns, and different tumor types, pose a problem for validation of the data already obtained. It can be anticipated that rapid technological and informatic progress supported by the implementation of humanized GF mouse models and organ-on-a-chip models, will enable timely and efficient integration of this data into medical practice, production of novel medications, and elucidation of the functioning of the entire human holobiont soon. Future research holds great promise for development of novel therapeutics based on bacteriophages, locally administered intratumor injections of heat-inactivated bacterial strains, or combined therapies utilizing pre/probiotics, bacterial metabolites, and FMT as an adjuvant to ICIs.

References

Bae, J., Park, K., & Kim, Y. M., 2022. Commensal Microbiota and Cancer Immunotherapy: Harnessing Commensal Bacteria for Cancer Therapy. Immune network, 22(1), e3. doi.org/10.4110/in.2022.22.e3

Bullman, S., Eggermont, A., Johnston, C. D., & Zitvogel, L., 2021. Harnessing the microbiome to restore immunotherapy response. Nature cancer, 2(12), 1301–1304. doi.org/10.1038/s43018-021-00300-x

Choudhry H., 2021. The Microbiome and Its Implications in Cancer Immunotherapy. Molecules (Basel, Switzerland), 26(1), 206. doi.org/10.3390/molecules26010206

Crespin, A., Le Bescop, C., de Gunzburg, J., Vitry, F., Zalcman, G., Cervesi, J., & Bandinelli, P. A., 2023. A systematic review and meta-analysis evaluating the impact of antibiotic use on the clinical outcomes of cancer patients treated with immune checkpoint inhibitors. Frontiers in oncology, 13, 1075593. doi.org/10.3389/fonc.2023.1075593

Kiousi, D. E., Kouroutzidou, A. Z., Neanidis, K., Karavanis, E., Matthaios, D., Pappa, A., & Galanis, A., 2023. The Role of the Gut Microbiome in Cancer Immunotherapy: Current Knowledge and Future Directions. Cancers, 15(7), 2101. https://doi.org/10.3390/cancers15072101

Li, W., Deng, Y., Chu, Q., & Zhang, P., 2019. Gut microbiome and cancer immunotherapy. Cancer letters, 447, 41–47. doi.org/10.1016/j.canlet.2019.01.015

Lu, Y., Yuan, X., Wang, M., He, Z., Li, H., Wang, J., & Li, Q., 2022. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. Journal of hematology & oncology, 15(1), 47. doi.org/10.1186/s13045-022-01273-9

Rezasoltani, S., Yadegar, A., Asadzadeh Aghdaei, H., & Reza Zali, M., 2021. Modulatory effects of gut microbiome in cancer immunotherapy: A novel paradigm for blockade of immune checkpoint inhibitors. Cancer medicine, 10(3), 1141–1154. doi.org/10.1002/cam4.3694

Szczyrek, M., Bitkowska, P., Chunowski, P., Czuchryta, P., Krawczyk, P., & Milanowski, J., 2021. Diet, Microbiome, and Cancer Immunotherapy-A Comprehensive Review. Nutrients, 13(7), 2217. doi.org/10.3390/nu13072217