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Impact of Microbial Metabolites on the Efficacy of Cancer Immunotherapy

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ABSTRACT

Introduction: The gut microbiome and its metabolites have emerged as key determinants of antitumor immunity and response to cancer immunotherapy. Recent studies show that the composition of gut microbes and their metabolite profiles can influence the efficacy of immune checkpoint inhibitors (ICIs) by modulating host's immune pathways. Understanding these interactions may help overcome therapeutic resistance and improve patient outcomes.

Materials and Methods: This systematic review examined studies published between 2015 and 2024 that investigated the role of microbial metabolites—particularly short-chain fatty acids (SCFAs), tryptophan derivatives, and secondary bile acids—in the effectiveness of ICIs. Literature searches were conducted in PubMed, Scopus, and Web of Science, following PRISMA 2020 guidelines and focusing on clinical, preclinical, and mechanistic evidence linking microbial metabolites to immune regulation.

Results and Discussion: SCFAs, notably butyrate, enhance antitumor immunity via histone deacetylase inhibition, activation of the aryl hydrocarbon receptor, and modulation of the tumor microenvironment. Elevated levels of pro-inflammatory tryptophan metabolites, such as kynurenine, are associated with poorer responses to ICIs. Microbiome-targeted interventions including high-fiber diets, defined probiotics, and fecal microbiota transplantation, have shown promise in restoring sensitivity to treatment.

Conclusion: Microbial metabolites function as vital links between the gut microbiome to the efficacy of immune checkpoint therapy. Integrating metabolite-based biomarkers and microbiome-modulating interventions could enable personalized strategies to enhance immunotherapy outcomes. Further standardized and longitudinal clinical studies are warranted to validate these findings.

Keywords: Cancer immunotherapy, Gut microbiome, Microbial metabolites, Short-chain fatty acids, Therapy resistance

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