

Modulatory Target for Tumor Immunotherapy: Gut Microbiota

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Abstract

Tumor immunotherapy has been the novel frontier of cancer therapy after surgical treatment, chemotherapy and radiotherapy. With the advancements of genomics and metabolomics, researchers are beginning to realize the roles of gut microbiota in cancer progression and treatment. Currently, several lines of evidence from preclinical to clinical research have established that microbiota was considered as a modulatory target for tumor immunotherapy and affect the efficacy of cancer immunotherapies, especially Immune Checkpoint Inhibitors (ICIs) [1]. Interpretation of the underlying mechanisms reveals that the gut microbiota reprograms Tumor Microenvironment (TME) immunity through regulating immune cells [2]. Thus, mechanistic exploration provides novel insights for developing microbiota-based therapeutic strategies by manipulating gut microorganisms.

Keywords: Cancer; Treatment; Chemotherapy; Immunotherapy.

Short report

Gut microbiota and antitumor immunotherapy: Directly or Derived metabolites?

The interaction between the gut microbiota and the host immune system raises the possibility that the TME interacts with the microbial immune network, supporting that the gut microbiota is emerging as an important regulator of TME. Current research has proved that gut microbiota could modulate antitumor immune responses by regulating immune system in the TME. Several studies have confirmed that specific gut microbiota induce CD8⁺ T cells in the systemic circulation or the TME [3]. Supplementation with *A. muciniphila* in FMT nonresponsive mice recovered anti-PD-1 responses by triggering CCR9⁺ CXCR3⁺ CD4⁺ T lymphocyte recruitment [4]. In addition, *Lactobacillus plantarum* effectively increased NCR protein expression and accelerated NK cell activation to trigger innate immunity [5]. Thus, the gut microbiota directly modulates innate and adaptive immunity and influence antitumor immune responses in the TME.

Notably, another major way in which the gut microbiota modulate antitumor immunity is through metabolites. The

gut microbiota can synthesize or transform many metabolites, which spread from their original locations in the gut to influence local and systemic antitumor immune responses. In these small molecules, SCFAs can directly promote the antitumor cytotoxicity of CD8⁺ T cells in vivo and in vitro and provide energy for immune cells. Butyrate derived by *Faecalibacterium prausnitzii*, has the ability to trigger the antitumor cytotoxicity of CD8⁺ T cells by inhibiting ID2-dependent IL-12 signaling. Inosine produced by intestinal *B. pseudolongum* promoted Th1 cell differentiation and enhanced the therapeutic response of anti-CTLA-4 and anti-PD-L1 therapy [6]. In addition, administering secondary bile acids bacteria *Clostridium scindens* attenuated NKT cell-mediated liver-selective tumor inhibition. However, *Bacteroides* and *Ruminococcaceae* can participate in the occurrence of HCC by aggravating hepatocyte inflammation, contributing to liver steatosis and accumulation of toxic substances [7].

Therefore, deeply understanding the interaction mechanism between gut microbiota and its metabolites with the host immune system in reshaping TME is profound for cancer immunotherapy.

Declarations

Competing interests: The authors have declared that no competing interest exists.

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