



Opinion

Intestinal microbiota and related metabolites are essential mediators for adoptive $\gamma\delta$ T cell antitumor immunotherapy

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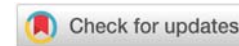
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Abstract

Intestinal microbiotas modulate multiple biochemical reactions and immune hemostasis of the host, numerous pieces of evidence have revealed that they are also tightly involved in the efficacy of antitumor immunotherapy. However, which way local intestinal microbiota influences the activity of distant organs is still unknown. In this review, we highlighted the importance of metabolites produced by intestinal microbiotas which disorder prompted cytotoxic capability of adoptive $\gamma\delta$ T cells. The microbiota-metabolites- $\gamma\delta$ T cell axis is dominant in the antitumor immune response of adoptive $\gamma\delta$ T cell immunotherapy.

$\gamma\delta$ T cells are characterized by γ and δ chains and MHC unrestricted antigen recognition, thus being activated rapidly by various non-peptide antigens. Therefore, $V\gamma9V\delta2$ cells expanded from human peripheral blood were applied for plenty of clinical research which focused on cancer therapy, for instance, CAR-T, TCR-T, and other genetic engineering T cells based on the advantage of $\gamma\delta$ T cell. Since adaptive immune cells are not always working well when encountering complex circumstances inside the human body, further improvements are required to enhance the cytotoxicity of those cells.

Microbiota, especially intestinal bacteria, which modulating various immune responses [1]. Studies have revealed that specific bacteria species that determine anti-PD-1 immunotherapy responses of melanoma patients, such as *Akkermansia muciniphila* and *Ruminococcaceae* substantially increased the immune response of patients against tumors by regulating the ratio of cytotoxic CD8⁺T and Treg cells [2,3], but how they communicate with tumor microenvironment where outside of intestinal area hasn't been elucidated. In recent studies, the importance of microbiota-related metabolites was highlighted in $\gamma\delta$ T cells' antitumor capability [4,5]. The

dysbiosis of intestinal microbiota induced by antibiotics ahead of adoptive $\gamma\delta$ T cell therapy enhanced cytotoxicity of $\gamma\delta$ T cell against HepG2 hepatocellular carcinoma cells, metabolites produced by microbiota are essential mediators to facilitate intestinal bacteria commune with $\gamma\delta$ T cell that infiltrated within the tumor microenvironment.

The diversity and abundance of bacteria determine the characteristics of the intestinal environment, including the concertation of various microbiota-related metabolites which influence the antitumor responses of transferred immune cells. Besides in vivo evidence that antibiotic-treated mice generated higher concertation of 3-into propionic acid (IPA) according to the analysis of metabolites from cecum content by gas chromatography/mass spectrometry, thus better responded with $\gamma\delta$ T cell therapy with more granzyme B, perforin production (Figure 1). Moreover, in vitro cytotoxicity assay of $\gamma\delta$ T cell in the presence of IPA also be significantly improved against various tumor cell lines without causing damage to the tumor cell itself. But it is still debatable which specific bacteria species are the main resource of IPA production in the gut. Since IPA are from tryptophan metabolism under the assistance of

Microbiota-metabolite-adoptive $\gamma\delta$ T cell axis

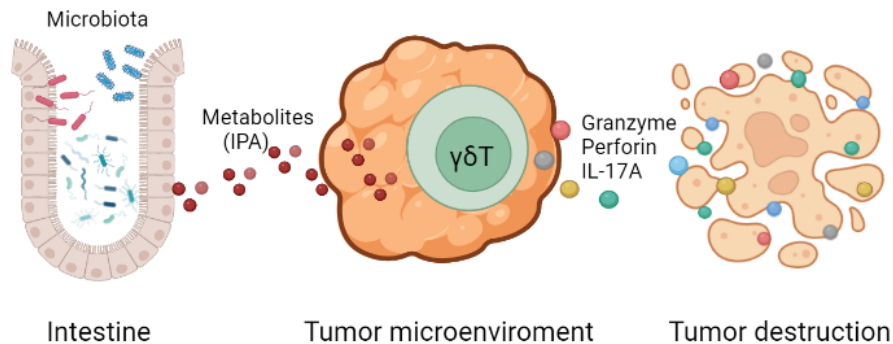


Figure 1: Microbiota-metabolite-adoptive $\gamma\delta$ T cell axis.

numerous bacteria, we conduct that there are many microbiotas that may involve in IPA production and eventually make this happen after antibiotics treatment. Additionally, it needs to be determined in which way IPA induces cytotoxicity molecules release of $\gamma\delta$ T cells, such as granzyme B and perforin. In sum, we tend to believe that metabolites are functional operators for intestinal microbiota to modulate the immune response in the distant tumor site. Therefore, it would be better to pay more attention to the alteration of specific metabolites instead of focusing on microbiotas only in future studies.

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