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HIGHLIGHT

Oral garlic-derived nanoparticles improve cancer immunotherapy

KEYWORDS

Oral administration;
Garlic-derived nanoparticle;
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Gamma-delta ($\gamma\delta$) T cells exhibit tissue tropism and possess antitumor activity that is independent of new antigen load and traditional MHC-dependent antigen presentation. These cells also present characteristics typical of both T cells and natural killer cells[1]. The gastrointestinal tract is the largest immune organ in the human body, containing approximately 70% of the body's immune cells, including a substantial population of $\gamma\delta$ T cells[2,3]. Therefore, developing gut-targeted $\gamma\delta$ T cell-based therapies holds significant potential for cancer treatment. Recently, a study by Chao Wang's group[4], published in *Nature Nanotechnology*, demonstrated that orally administered garlic-derived nanoparticles (GNPs) significantly promoted the activation and proliferation of intestinal $\gamma\delta$ T cells. When combined with anti-PD-L1 and paclitaxel, these GNPs exhibited promising therapeutic effects against extraintestinal subcutaneous tumors. These GNPs, derived from edible plants, provide a safe and potent approach to improve the efficacy of $\gamma\delta$ T cell-based immunotherapy.

The growing threat to human health of malignant tumors in cancer patients has become increasingly widespread, imposing a heavy burden on healthcare systems and generating substantial societal stress[5]. Immunotherapy, a therapeutic approach that leverages a patient's immune system to eliminate tumor cells, has achieved significant success in treating a variety of solid tumors[6,7]. Despite the considerable potential of $\gamma\delta$ T cells in tumor immunotherapy, their application in antitumor therapies has been limited because expansion is not only costly and time-consuming but also relies on highly specialized techniques.

Reflecting on the current state of $\gamma\delta$ T cell applications in cancer treatment, Jialu Xu and colleagues[4] obtained GNPs with long-term stability through differential centrifugation (Fig. 1A) and explored their effect on the activation of various innate immune cells in comparison with other plant-derived nanoparticles. Encouragingly, GNPs were more effective in activating a range of innate immune cells, particularly $\gamma\delta$ T cells, compared with other edible plant-sourced nanoparticles. To further elucidate the mechanism of GNPs' action on $\gamma\delta$ T cells, RNA sequencing was employed to analyze the gene expression profiles of $\gamma\delta$ T cells after incubation with GNPs. A significant upregulation of C-type lectin receptors (CLRs) on the surface of $\gamma\delta$ T cells following GNP treatment was seen (Fig. 1B), suggesting that GNPs might activate $\gamma\delta$ T cells through the CLR pathway. To further demonstrate how GNPs modulated $\gamma\delta$ T cell activity, $\gamma\delta$ T cells were co-incubated with β-glucan and GNPs. It was found that β-glucan could inhibit CLRs and weaken the activation of $\gamma\delta$ T cell by GNPs.

The gut is the largest immune organ in the body, and is endowed with a rich population of $\gamma\delta$ T cells that are crucial for maintaining the integrity of the intestinal epithelial barrier, regulating the microbial community, and protecting the intestines from invasion by pathogens[1]. In mice, $\gamma\delta$ T cells can be categorized based on their secreted cytokines into two types–those that produce IFN-γ and those that produce IL-17—and each type has a distinct role within the immune system. IFN-γ-producing $\gamma\delta$ T cells are primarily involved in antiviral and antitumor responses, while IL-17-producing $\gamma\delta$ T cells exert their effect on inflammatory modulation and barrier defense. To benchmark whether oral GNPs could activate intestinal $\gamma\delta$ T cells *in vivo* and to determine the type of activated $\gamma\delta$ T cells, Jialu Xu et al.[4] employed single-cell sequencing to track the source of IFN-γ in the intestine post-GNP ingestion. The study revealed that

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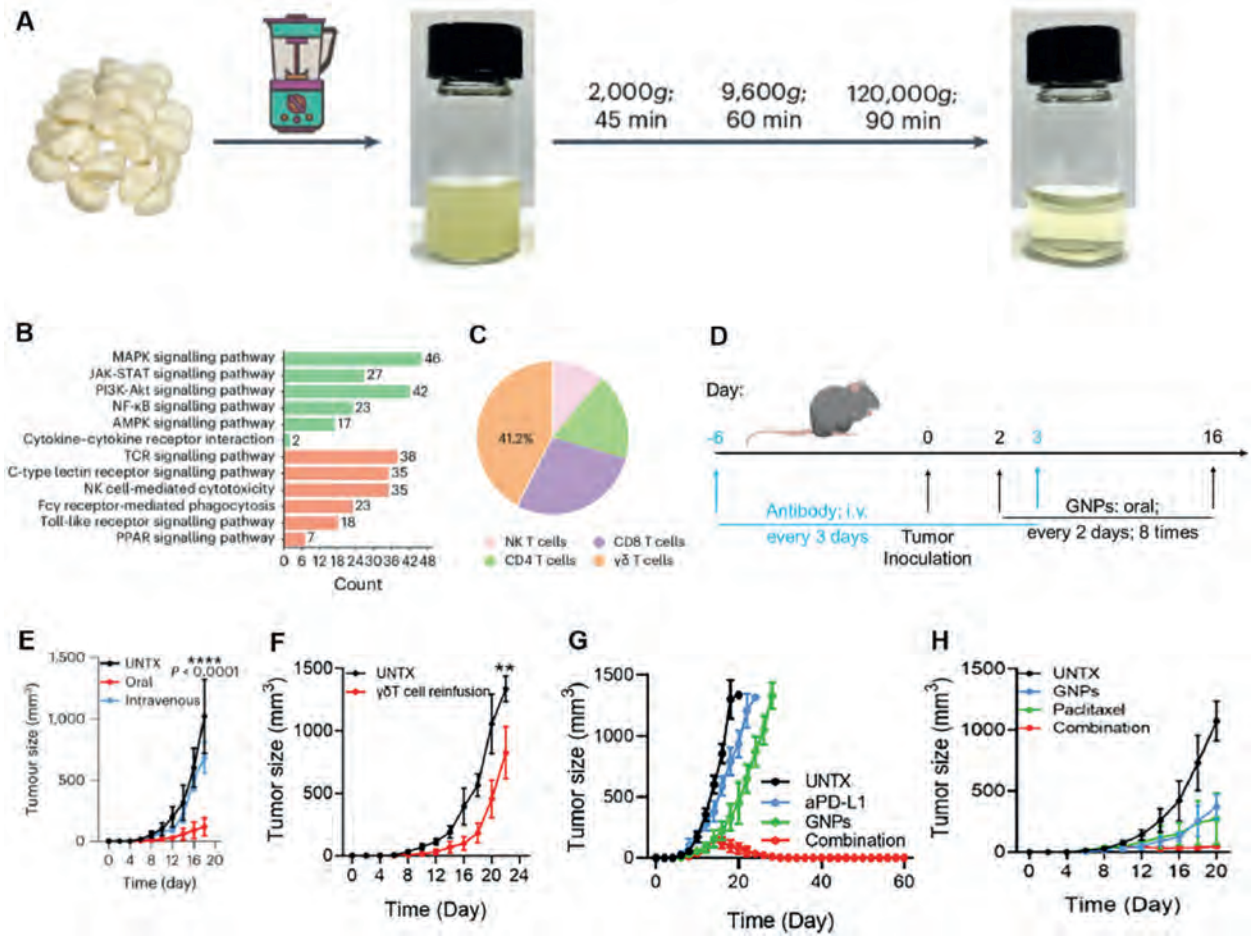

Figure 1 (A) Schematic illustration of the production of GNPs. (B) KEGG pathway analysis of γδ T cells. (C) Relative IFN-γ secretion levels by different T cells in the intestine. (D) Diagram showing the elimination of corresponding antibodies *in vivo* and oral administration of GNPs for treatment of subcutaneous tumors. (E) Mean tumor growth curves for the UNTX, oral, and i.v. groups (five mice in each group of 20). (F) Infusion of intestinal γδ T cell for tumor therapy. (G) Mean tumor growth curve after oral administration of GNPs combined with aPD-L1. (H) Mean tumor growth curve after oral administration of GNPs combined with paclitaxel. Reprinted with the permission from Ref. 4. Copyright ©2024 Springer Nature Limited.

approximately half of the IFN-γ in the gut originated from γδ T cells (Fig. 1C). As the duration of oral GNP administration increased, the relative levels of serum IFN-γ significantly increased, suggesting that the increased serum IFN-γ level was associated with IFN-γ production in the gut.

CXCR3 is a G-protein-coupled receptor expressed on the surface of a variety of immune cells, including T cells, natural killer cells, and certain macrophages. CXCL10 is one of the primary ligands for CXCR3, capable of attracting CXCR3-expressing cells to the site of inflammation and tumor immune microenvironment (TIME)[8]. Jialu Xu and co-workers[4] found that in mice bearing subcutaneous tumors, oral administration of GNPs could drive intestinal γδ T cells to distant subcutaneous tumors *via* the CXCR3-CXCL10 axis, thereby reshaping the TIME and prolonging survival of the tumor-bearing mice. By comparing different inoculation methods (depletion of γδ T cells or IFN-γ,intravenous versus oral administration) and adoptive transfer of intestinal γδ T cells, they further demonstrated the inhibitory effect of intestinal γδ T cells on distant subcutaneous tumors (Fig. 1D to F). Inspired by these results, the research team combined oral GNPs with drugs like anti-PD-L1 and paclitaxel. The results reveal that the combination with oral GNPs greatly increased the antitumor effect of anti-PD-L1 and paclitaxel (Fig. 1G and H).

This discovery not only highlights the promising application potential of oral GNPs in tumor immunotherapy but also provides crucial insights for developing novel and robust immunomodulatory strategies based on nanoparticles derived from edible plants.

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Author contributions

Kun Yang: Writing – original draft. Jinming Zhang: Writing – review & editing. Bo Xiao: Conceptualization, Funding acquisition, Writing – review & editing.

Conflicts of interest

The authors have no conflicts of interest to declare.

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