

Nature products of traditional Chinese medicine provide new ideas in $\gamma\delta$ T cells for tumor immunotherapy

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Abstract

Due to the unique features of innate immune cells, the role of $\gamma\delta$ T cells in tumor immunity has gradually attracted more and more attention. Previous studies have found that $\gamma\delta$ T cells play a dual role in tumor immunology: tumor-promoting and tumor-controlling. The anti-tumor therapy of $\gamma\delta$ T cells has made remarkable success in clinical application. Especially in recent years, researchers have provided some novel effective ways such as $\gamma\delta$ T cells exosomes and adoptive chimeric antigen receptor- $\gamma\delta$ T cells immunotherapy. However, some problems remain to be solved, such as low expansion rate, poor targeting, and tumor microenvironment limiting the effectiveness of $\gamma\delta$ T immunotherapy. Traditional Chinese medicine is expected to play a positive role in the body immune-enhancing function, promoting the proliferation and activation of $\gamma\delta$ T cells, and inducing the differentiation of $\gamma\delta$ T cells. In this review, we summarize the recent research progress and urgent problems of $\gamma\delta$ T cells in anti-tumor immunotherapy. Moreover, some new strategies of $\gamma\delta$ T cells for tumor immunotherapy were proposed.

Keywords: $\gamma\delta$ T cells, Traditional Chinese medicine, Tumor immunotherapy

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Introduction

Malignant tumor is one of the major diseases that threaten human health, and the mortality rate is second only to cardiovascular and cerebrovascular diseases. Tumor immunotherapy is the most potential malignant tumor treatment method emerging after surgical resection, radiotherapy, and chemotherapy, and brings new hope for tumor treatment. Tumor immunotherapy can be roughly divided into immune checkpoint inhibitors, cancer vaccines, cellular immunotherapy and small molecule inhibitors. Cellular immunotherapy works by expanding and cultivating immune cells *in vitro* which are adopted by patients with malignant tumors later on, thereby activating the immune response *in vivo* or activating immune effector cells, inhibiting the occurrence and development of tumors, and the quality of life of

patients with malignant tumors could be effectively improved as a result. $\gamma\delta$ T cells activation is not restricted by the major histocompatibility complex (MHC), and has a positive antitumor effect on a variety of tumors^[1]. As a strong candidate for tumor immunotherapy strategies, $\gamma\delta$ T cells has more potential safe therapeutic effects. This paper summarizes the research progress and urgent problems of $\gamma\delta$ T in tumor immunotherapy, and proposes Nature products of traditional Chinese medicine (TCM) to provide new ideas for $\gamma\delta$ T cells tumor immunotherapy.

Characteristics, classification, and distribution of $\gamma\delta$ T cells

Different from $\alpha\beta$ T cells, the TCR of $\gamma\delta$ T cells is a heterodimer composed of γ chains and δ chains (TCR- $\gamma\delta$). In the mucosa such as the tract, it can account for 50% of CD3⁺T cells, but in peripheral blood, it only accounts for 1% to 10% of CD3⁺T cells^[2]. According to the structural differences of the δ chain, $\gamma\delta$ T cells are mainly divided into three subgroups, namely V δ 1, V δ 2, and V δ 3 cells^[3] (Table 1). According to the function of $\gamma\delta$ T cells, it can be further divided into regulatory $\gamma\delta$ T cells ($\gamma\delta$ Treg), $\gamma\delta$ T cells that secrete interleukin 17 ($\gamma\delta$ T-17 cells), $\gamma\delta$ T cells that secrete interferon γ (IFN- γ $\gamma\delta$ T cells), and $\gamma\delta$ T cells with other functions^[4]. As a special innate immune cell, $\gamma\delta$ T cells activation is not restricted by MHC, and can enter the activated state within minutes after antigen stimulation^[5]. Activated $\gamma\delta$ T cells directly kill tumor cells through cytotoxicity, produce cytokines, and regulate antigen presentation functions to affect other immune cells and play an anti-tumor effect^[6]. $\gamma\delta$ T cells can show positive anti-tumor function against hematological tumors such as leukemia, lymphoma, and various solid tumors such as melanoma, breast cancer, and colon cancer.

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Table 1
Types, tissue distribution, and main functions of $\gamma\delta$ T cells

Types	Common $v\gamma$ pairings	Tissue distribution	Mechanism	Function
V δ 1	γ 2, γ 3, γ 4, γ 5, γ 8	Skin, urinary tract, lung, small intestine and other mucosal epithelial tissues and thymus	Cytotoxicity, secretion of cytokines	maintain epithelial stability
V δ 2	γ 2, γ 3	peripheral blood	Secretion of perforin, granzyme, etc	the function of presenting antigen
V δ 3	γ 9	liver	Kill cells directly, secrete cytokines	regulate immune function

The role of $\gamma\delta$ T cells in tumor immunity

The anti-tumor mechanism of $\gamma\delta$ T cells in tumor immunity

Studies have confirmed that V δ 1 and V δ 2 subsets play an important role in the tumor immunity of $\gamma\delta$ T cells (Figure 1). V δ 1T cells recognize tumor cells mainly through natural killer cell receptors (NKG2D, NKp30, NKp44, NKp46, etc.)^[7]. After V δ 1T cells are activated, they can exert anti-tumor effects through direct contact and the secretion of cytokines. Wu D co-cultured V δ 1T cells isolated from human peripheral blood with colon cancer cells and found that V δ 1T cells had up-regulated expressions of CD69, CD107a, perforin, granzyme B, TRAIL, and CD57, which depended on cell-to-cell contact to kill colon cancer cells^[8]. Donnele's *in vivo* experiments showed that V δ 1T cells can secrete more cytokines such as TNF- α , IFN- γ , IL-10, and IL-13 after recognizing the activation of NKG2D ligand^[9], and play an anti-tumor effect. In addition, Silva-Santos's^[10] study found that under the continuous stimulation of TCR agonists and the induction of IL-2 or IL-15, V δ 1T cells can enhance the targeting of V δ 1T cells to tumor cells by recognizing NKp44, NKp30, NKp46, and other ligands: killing ability and ability to secrete IFN- γ ^[11]. V δ 2 of V δ 2T cells is mainly paired with γ 9 to form V γ 9V δ 2T cells, which mainly sense cell surface prenyl pyrophosphate (IPP) levels and stress signals (such as MICA/B,

ULBP4, and MSH2) through TCR to differentiate tumors cells and normal cells^[12]. After TCR-dependent activation, V γ 9V δ 2T cells can directly kill or induce tumor cell apoptosis, and can also exert anti-tumor effects by secreting cytokines or affecting other immune cells. Studies have shown that V γ 9V δ 2T cells can lyse tumor cells through perforin-granzyme and other pathways, and play a direct anti-tumor effect^[12]. V γ 9V δ 2T cells can also induce target cell apoptosis through Fas/FasL, TNF-related apoptosis-inducing ligand (TRAIL)/DR4/5, and other pathways^[13]. γ 9V δ 2T cells can also kill tumor cells by secreting cytokines such as IFN- γ and TNF- α ^[14]. HIMOUDI isolated V δ 2T cells from human peripheral blood and co-cultured them with lymphoma cells^[15]. The results show that V γ 9V δ 2T cells can secrete more IFN- γ and TNF- α cytokines after activation, thereby promoting the up regulation of dendritic cell (APC) CD86 and MHC-I molecules which enhances the antigen presentation of APC cells, thereby inhibiting the occurrence and development of tumors.

The tumor-promoting mechanism of $\gamma\delta$ T cells in tumor immunity

In recent years, more and more evidence has shown that $\gamma\delta$ T cells also have a tumor-promoting role. Infiltration of $\gamma\delta$ T-17 cells has been found in various tumors. Studies have found that infiltrating $\gamma\delta$ T-17 cells promote blood

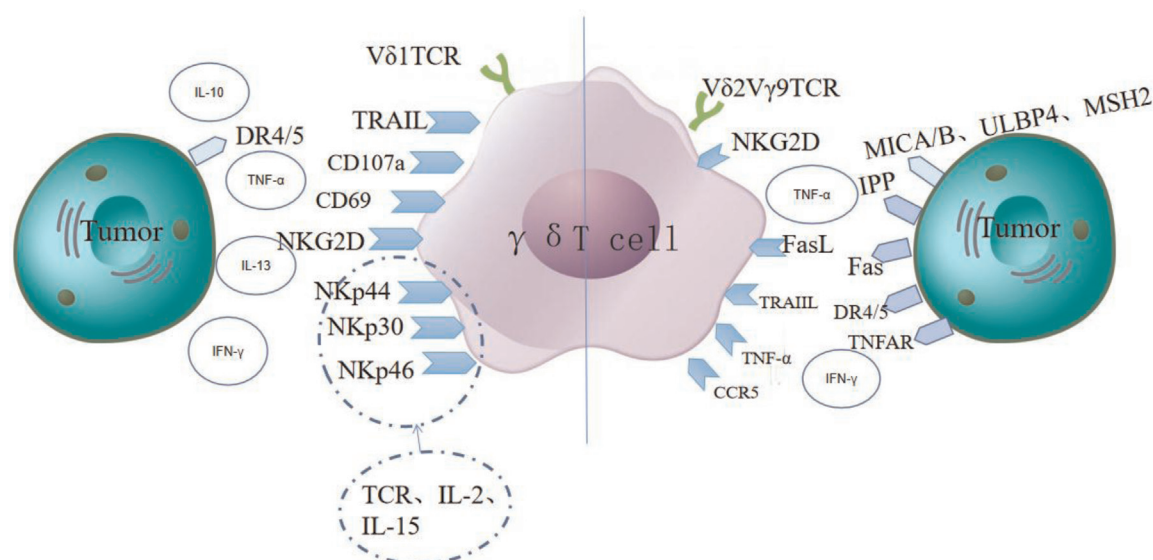


Figure 1. The mechanism of direct antitumor effect of $\gamma\delta$ T cells.

vessels in tumor tissues (such as non-small cell lung cancer, gastric cancer, gallbladder cancer, etc.) by secreting the pro-inflammatory cytokine IL-17, which in turn promotes tumor development^[16]. Dorien crossed K14-HPV16 mice (human papillomavirus transgenic mice) with TCR- $\gamma\delta^{-/-}$ gene-deficient mice, and analyzed the skin damage of hybrid mice and K14-HPV16 mice, and found local HPV oncoproteins in the epidermis. The expression of $\gamma\delta$ T-17 cells can induce more $\gamma\delta$ T-17 cells subsets, and tumor-infiltrating $\gamma\delta$ T-17 cells then secrete more IL-17A, which promotes the further development of tumors^[17]. In addition, infiltrating $\gamma\delta$ T-17 cells can also participate in the formation of the tumor microenvironment by recruiting myeloid-derived suppressor cells, thereby inhibiting the anti-tumor immune response of other immune cells, and ultimately promoting tumor development^[18].

$\gamma\delta$ T cells in the tumor microenvironment can differentiate into $\gamma\delta$ Treg cells in an immunosuppressive state under the influence of various cytokines and tumor cell metabolites secreted by tumor cells. $\gamma\delta$ Treg cells can inhibit the function of CD4⁺ and CD8⁺ T cells in TME by producing more adenosine, and promoting tumor development. Guoming Hu's team found that $\gamma\delta$ Treg cells in human colorectal cancer mainly express CD39⁺. Under the induction of TGF- β 1 secreted by tumor cells, the cells will produce more adenosine, which shows a strong direct immunosuppressive function on CD4⁺ T cells through the adenosine pathway and promotes tumor development^[19]. The team also found that $\gamma\delta$ Treg cells in human breast cancer mainly express CD73⁺, and $\gamma\delta$ Treg cells can produce more adenosine through the IL-6/STAT3 pathway under the action of IL-6 produced by tumor-associated fibroblasts (CAFs). The adenosine/A2BR/p38MAPK signaling pathway secretes more IL-6, thereby forming a positive IL-6/adenosine feedback loop, which exhibits a strong direct immunosuppressive function on CD4⁺ and CD8⁺ T cells and promotes tumor growth^[20].

Clinical study of $\gamma\delta$ T cells antitumor therapy

There are two main ways for V δ 2T cells to be used for tumor immunotherapy: one is to expand V δ 2T cells *in vivo* by aminobisphosphonates, and the other is to specifically expand V δ 2T cells *in vitro* by adoptive transfer^[21], including leukemia, lymphoma, melanoma, renal cell carcinoma, hormone-refractory prostate cancer, breast cancer, non-small cell lung cancer, colorectal cancer, multiple myeloma, gastrointestinal tumors, ovarian cancer, cervical cancer, and bone cancer^[22]. Wilhelm's team first proved through experiments that pamidronate and low-dose IL-2 were well tolerated in expanding V δ 2T cells *in vivo*, and there were no adverse reactions in the clinical treatment of patients with non-Hodgkin's lymphoma^[23]. Zoledronate and low-dose IL-2 *in vivo* expansion of V δ 2T cells have also been used to treat prostate cancer and advanced breast cancer. Clinically, 70% of patients were observed to have no further deterioration, and 30% of patients showed slight improvement^[24]. The ALNAGGAR team found that after using zoledronic acid to expand V δ 2T cells *in vitro*, adoptively infusing them into patients with stage IV gallbladder cancer, and found that the tumor volume of the patients was significantly reduced, the quality of life was improved, and there were no obvious side effects^[25].

In addition, the researchers proved through experiments that compared with autologous V δ 2T cells adoptive transplantation, allogeneic V δ 2T cells adoptive transplantation can improve the immune function of cancer patients, such as increasing the number of CD4⁺T cells, CD8⁺T cells, and NK cells, which can relieve liver cancer patients' condition^[25]. Therefore, allogeneic V δ 2T cells are more promising for clinical tumor therapy than autologous V δ 2T cells adoptive immunotherapy.

In recent years, it has been found that V δ 1T cells show stronger anti-tumor activity, so the application of V δ 1T cells to achieve tumor immunotherapy has received more and more attention. The researchers are working on the *in vitro* expansion technology of V δ 1T cells to solve the problem of the serious shortage of peripheral blood sources of the cells. The study found that $\gamma\delta$ T cells isolated from human peripheral blood were stimulated specifically by TCR agonists and various cytokines (such as IL-4, IL-21, IFN- γ , and IL-1 β) within 3 weeks. The V δ 1T cells subset, which previously accounted for only 0.5%, can be increased to more than 70%. And studies have shown that the adoptive treatment of acute myeloid leukemia after specific culture and expansion of V δ 1T cells *in vitro* mainly relies on the specific recognition of tumor cells by NKp30, and has no killing effect on normal white blood cells, thereby relieving the disease and significantly prolonging the survival time of patients^[26].

Although the clinical application of $\gamma\delta$ T cells anti-tumor therapy has made encouraging progress, there are still problems such as unstable $\gamma\delta$ T cells expansion conditions, weak activity of $\gamma\delta$ T cells after expansion, and autoimmune status of tumor patients to kill $\gamma\delta$ T cells. The inhibitory effect of activity and other urgent problems have led to the failure of $\gamma\delta$ T cells tumor immunotherapy to achieve the expected effect.

New progress in anti-tumor therapy of $\gamma\delta$ T cells

Study on anti-tumor immunity of $\gamma\delta$ T cells exosomes

Exosomes are tiny vesicles with a double-membrane structure with a diameter of about 20 to 200nm, encapsulated with a large number of lipids, proteins, nucleic acids, and other substances. They are involved in information transmission and material exchange between cells^[27] and provided with high bioavailability, biostability, and biocompatibility. Tu Wenwei's team reported that human peripheral blood V δ 2T cells exosomes (V δ 2-T-Exos) showed good anti-tumor effects *in vitro* and *in vivo* experiments in animals, and the study found that V δ 2-T-Exos has anti-tumor effects similar to V δ 2V γ 9T cells: first, V δ 2-T-Exos carries FasL, TRAIL, and NKG2D, which can interact with Fas, DR5, and MICA/B of EBV-related tumor cells, respectively, thereby inducing tumor cell apoptosis; secondly, V δ 2-T-Exos can recognize MHC-II and CD86, promote the proliferation of CD4⁺ T cells, increase the secretion of IFN- γ , and inhibit the development of tumors^[28]. Experimental studies have also found that allogeneic V δ 2-T-Exos compared with autologous V δ 2-T-Exos, adoptive treatment of allogeneic V δ 2-T-Exos induces more CD4⁺ and CD8⁺ T cells to migrate to tumor tissue, and enhances the antitumor effects mediated by CD4⁺ and CD8⁺ T cells. Although adoptive exosome therapy has improved the problems of adoptive immune cells, such as exosomes can

be stored for a long time under freezing conditions and have strong activity, and improve the tumor immune microenvironment to avoid cytokine storm^[29]. It also provides a new idea for the treatment of other malignant tumors with allogeneic V δ 2-T-Exos, but the application of exosomes in the treatment of other malignant tumors and its mechanism of action need to be further studied.

Anti-tumor immunity of chimeric antigen receptor (CAR)- $\gamma\delta$ T cells

CAR-modified T (CAR-T) cell immunotherapy is currently one of the effective ways for refractory acute and chronic leukemia, lymphoma, and other hematological tumors^[30], where problems that are easy to cause cytokine storm, weak targeting, poor effect on solid tumors and high recurrence rate^[31] yet still exists. Therefore, it is urgent to study other immune cells modified by CAR to improve the current problems in clinical treatment and improve the anti-tumor efficacy. There are two clinical trials involving CAR- $\gamma\delta$ T cells: one is CAR- $\gamma\delta$ T targeting CD19 in the treatment of lymphoma and leukemia. The DENIGER team established CAR- $\gamma\delta$ T cells targeting CD19. *In vitro* studies showed that CAR- $\gamma\delta$ T cells could secrete higher levels of pro-inflammatory cytokines such as IFN- γ , TNF- α , MIP-1 α , and MIP-1 β , and inhibit tumor cell proliferation. *In vivo* experiments in animals also showed a more obvious tumor-inhibiting effect^[32]. The second is CAR- $\gamma\delta$ T targeting ganglioside (GD2) for the treatment of relapsed or refractory solid tumors. The FISHER team constructed CAR-V γ 9V δ 2 $\gamma\delta$ T cells targeting ganglioside (GD2). *In vitro* experiments confirmed that the killing ability of tumor cells was significantly improved by increasing the proportion of IFN- γ CAR- $\gamma\delta$ T cells^[33]. Subsequent research by the CAPSOMIDIS team showed that compared with CAR-T cells, GD2-targeting CAR- $\gamma\delta$ T cells not only had more prominent tumor cell killing ability, but also exhibited better antigen presentation ability, without affecting the ability of tumor cells to be transmitted to the tumor^[34]. According to reports, the urgent problem to be solved by CAR- $\gamma\delta$ T in tumor immunotherapy is how to break through the troubles of the immunosuppressive microenvironment. The study found that CAR- $\gamma\delta$ T may not only be induced into $\gamma\delta$ T17 cells with pro-tumor effects by the immunosuppressive microenvironment, but also further inhibit the activity of $\alpha\beta$ T cells by secreting IL-17^[35].

Research on natural products of TCM and $\gamma\delta$ T cells anti-tumor

In recent years, more and more nature products of TCM have been widely used in the treatment of malignant tumors, and the relationship between nature products of TCM and $\gamma\delta$ T has been becoming more and more clear. Nature products of TCM can promote the proliferation of $\gamma\delta$ T cells, guiding their differentiation, and enhancing their antitumor effects^[36]. Our previous research results also showed that Glycyrrhiza polysaccharide can promote the differentiation of intestinal epithelial $\gamma\delta$ T cells into IFN- γ $\gamma\delta$ T cells in tumor-bearing mice, thereby exerting a tumor suppressive effect. Non-fermented mistletoe extract rapidly and directly (independent of accumulation of endogenous phosphorylated antigens) mediates anticancer V γ 9V δ 2T cells activation and

promotes V γ 9V δ 2T cell expansion while potentially inducing granzyme release, in the meanwhile promoting the production of cytokines IFN- γ and TNF- α , and then significantly improve the killing activity of V γ 9V δ 2T on tumor cells^[37]. Nature products of TCM can also enhance anti-tumor effects by promoting the secretion of various pro-inflammatory cytokines by $\gamma\delta$ T cells. For example, astragalus polysaccharide can promote the secretion of IL-12, IFN- γ , and TNF- α cytokines by $\gamma\delta$ T cells, and inhibit the proliferation of lung cancer A549 cells^[38]; Iwami saccharide can enhance the expression of perforin, granzyme B, CD107a, and NKG2D on the surface of $\gamma\delta$ T cells, promote the secretion of TNF- α and IFN- γ , and improve the killing effect on osteosarcoma cells^[39]. Nature products of TCM can also promote the killing and apoptosis induction of $\gamma\delta$ T cells. The study found that toosendanin can promote the release of cytochrome C from the mitochondria of $\gamma\delta$ T cells induced by colorectal cancer cells into the cytoplasm, and then combine with caspase activator 1 to form a complex activating caspase-9 and its downstream caspase-3, which ultimately kills colorectal cancer cells^[40]. Peng Qian's study found that treatment with artesunate can up-regulate the expression of Fas in HepG2 cells and enhance the apoptosis-inducing effect of $\gamma\delta$ T cells on HepG2 cells^[41]. The above studies suggest that nature products of TCM can enhance the anti-tumor effect of $\gamma\delta$ T cells by promoting the proliferation of $\gamma\delta$ T cells, affecting their differentiation, or increasing the secretion of pro-inflammatory cytokines. In addition, natural products of TCM can also indirectly enhance their anti-tumor effects by promoting the expression of certain proteins in tumor cells and improving the recognition of $\gamma\delta$ T cells to tumor cells. Therefore, nature products of TCM provide a new strategy for $\gamma\delta$ T cells tumor immunotherapy.

Nature products of TCM provide new ideas for $\gamma\delta$ T cells tumor immunotherapy

There is sufficient evidence to show that $\gamma\delta$ T cells have both inhibitory and promoting effects on the occurrence and development of malignant tumors. Therefore, it is extremely important to study the mechanism of $\gamma\delta$ T cells in tumor immunity and to clarify the regulatory mechanism that induces $\gamma\delta$ T cells to differentiate towards anti-tumor. In addition, $\gamma\delta$ T cells adoptive immunotherapy is also faced with bottlenecks: firstly, the expansion rate of $\gamma\delta$ T cells is insufficient and the activity of $\gamma\delta$ T cells after the expansion is not high; low immune function and tumor immunosuppressive microenvironment in patients with malignant tumor seriously affect the antitumor activity of $\gamma\delta$ T cells and reduce their therapeutic effect. In response to the above problems, the application of natural products of TCM in $\gamma\delta$ T cells tumor immunotherapy can provide new perspectives from the following directions: (1) Screen nature products of TCM that promote the proliferation or inhibit the apoptosis of $\gamma\delta$ T cells, and improve their anti-tumor activity, and deeply explore the mechanism of nature products of TCM to promote proliferation or anti-apoptosis and improve anti-tumor activity, to ensure the safety of natural products of TCM. Under the premise, it can be used to enhance the anti-tumor effect of $\gamma\delta$ T cells *in vivo*, and it can also be used to expand and enhance the activity of $\gamma\delta$ T cells *in vitro* to improve the clinical efficacy of $\gamma\delta$ T cells adoptive immunotherapy. (2) Select nature products of TCM that

can induce $\gamma\delta$ T cells to differentiate towards anti-tumor, and clarify the mechanism of inducing differentiation, which can be directly applied to enhance the anti-tumor therapeutic effect of $\gamma\delta$ T cells *in vivo* in the future. (3) Under the guidance of the theory of traditional Chinese medicine, select the candidate drugs that can significantly improve the immune function of the body and the tumor microenvironment from the natural products of TCM, and further clarify the mechanism of action *in vivo* and *in vitro*. Nature products of TCM that improve tumor immunosuppression can be directly applied to enhance the anti-tumor effect of $\gamma\delta$ T cells *in vivo*, and the rest can be used in synergy with $\gamma\delta$ T cells adoptive tumor immunotherapy to improve the immune function of patients with malignant tumors, thereby improving the clinical treatment effect. (4) Clarify the regulation mechanism of $\gamma\delta$ T cells exosome secretion, screen out nature products of TCM that promote $\gamma\delta$ T cell exosome secretion, expect nature products of TCM to promote $\gamma\delta$ T cell exosome secretion *in vivo* or *in vitro*, and realize exosome-based $\gamma\delta$ T cells indirect anti-tumor therapy that makes $\gamma\delta$ T cells immunotherapy better applied in the treatment of solid tumors.

Conclusions

In summary, as a bridge between innate immunity and acquired immunity, $\gamma\delta$ T cells have received more and more attention in tumor immunotherapy due to their advantages of non-MHC-restricted recognition of receptors, rapid activation, and diverse anti-tumor mechanisms. Exciting achievements have also been made in the clinical tumor immunotherapy of $\gamma\delta$ T cells applied to a variety of hematological tumors and solid tumors. Faced with the bottleneck restricting $\gamma\delta$ T cells tumor immunotherapy, the researchers proposed a new idea of $\gamma\delta$ T cells exosomes and adoptive CAR- $\gamma\delta$ T cells. Nature products of TCM, especially traditional Chinese medicine, are unique medical resources in my country. Thousands of years of clinical practice under the guidance of traditional Chinese medicine theory have confirmed the safety and effectiveness of natural products of TCM in the treatment of tumors. Synthesizing the existing experimental reports, we propose a feasible path of nature products of TCM intervening $\gamma\delta$ T cells tumor immunotherapy, expecting the “Chinese plan” of $\gamma\delta$ T cells tumor immunotherapy to be better applied in clinical practice.

Conflict of interest statement

Yuhong Bian is editorial board members of this journal and other authors declare no conflicts of interest.

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