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Review Article

Immune Regulatory Networks and Therapy of γδ T Cells in Liver Cancer: Recent Trends and Advancements

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Abstract

The roles of γδ T cells in liver cancer, especially in the potential function of immunotherapy due to their direct cytotoxic effects on tumor cells and secretion of important cytokines and chemokines, have aroused research interest. This review briefly describes the basic characteristics of γδ T cells, focusing on their diverse effects on liver cancer. In particular, different subtypes of γδ T cells have diverse or even opposite effects on liver cancer. We provide a detailed description of the immune regulatory network of γδ T cells in liver cancer from two aspects: immune components and nonimmune components. The interactions between various components in this immune regulatory network are dynamic and pluralistic, ultimately determining the biological effects of γδ T cells in liver cancer. We also integrate the current knowledge of γδ T-cell immunotherapy for liver cancer treatment, emphasizing the potential of these cells in liver cancer immunotherapy.

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Introduction

Liver cancer, as a globally notorious malignant tumor, causes hundreds of thousands of deaths and poses a serious socioeconomic burden.[1,2] The pathogenesis of liver cancer is unclear and is inseparable from its complex tumor microenvironment (TME).[3] The protumor/antitumor factors or cellular/noncellular components form a multicellular network in the TME, collectively determining the malignant biological behaviors of liver cancer cells.[4–7] Since patients with liver cancer are often diagnosed in the middle to late stages, most patients lose the opportunity for surgical radical resection and face a poor prognosis.[8] Notably, immunotherapy has significantly improved the treatment of liver cancer.[9–11] Cellular immunotherapy, involving natural killer cells (NKs),[12,13] chimeric antigen receptor T cells (CAR-T cells),[14,15] and γδ T cells, is emerging as a star in the field of immunotherapy, with its efficacy confirmed by various of mechanistic studies and clinical research.

γδ T cells belong to the innate but nonconventional lymphocyte family, constituting approximately 5% (on average) of total T cells in peripheral blood.[16–18] γδ T cells, comprising 15–25% of the total liver T cells, are 5–10 times more abundant in the liver than in other tissues and organs.[19] Moreover, hepatic γδ T cells are highly localized in the liver, exhibiting a more active and mature phenotype with high CD44 and low CD62 markers.[20] In the thymus, "double negative" (DN) thymocytes, the primary immature precursors of γδ T cells, undergo rearrangement after α-selection, β-selection, γ-selection and δ-selection. Following TCR γδ signal stimulation,[21] TCR γδ+ DN progenitors are directed into the γδ T-cell lineage and subsequently differentiate and mature into γδ T cells.[22,23] Additionally, the gene expression profile reveals that the gene signatures of γδ T cells are equivalent to those of a mixture of αβ T cells and NK cells, endowing γδ T cells with the characteristics of both cell types.[24] Compared with αβ T cells, γδ T cells typically exhibit different immune phenotypes. Besides the common expression of CD2, CD3, CD5, and CD7, γδ T cells are usually negative for CD4 and CD8, with occasional CD8 positivity.[25] Although they both express CD3, the expression level is higher in γδ T cells than in αβ T cells.[26] The most notable distinction from αβ T cells is that γδ T cells are not restricted by major histocompatibility complex (MHC) molecules,[27] enabling them to be activated within minutes to detect molecular signals stimulated by infection or cancer and subsequently produce a large number of proinflammatory cytokines and chemokines.[21,28]

Much research attention is promptly focused on understanding the relationship between γδ T cells and tumors, as well as the therapeutic prospects of γδ T cells in antitumor activities. Here, we summarize the functional plasticity of γδ T cells and their dual role in liver cancer. We also discuss the

Keywords: Liver cancer; γδ T cells; Immunotherapy; Tumor microenvironment.
Abbreviations: APCs, antigen-presenting cells; ADCC, antibody-dependent cell-mediated cytotoxicity; CAR-T cells, chimeric antigen receptor T cells; CCR, C-C chemokine receptor; CCL, C-C motif chemokine ligand; DCs, dendritic cells; HSCs, hepatic stellate cells; MDSCs, myeloid-derived suppressor cells; NKs, natural killer cells; NKRs, natural killer cell receptors; TME, tumor microenvironment; ZOL, zoledronate.

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immune regulatory networks of γδ T cells involved in the microenvironment of liver cancer, γδ T-cell-based immunotherapy in liver cancer and perspectives on its development and use in the future.

Subtypes of γδ T cells and pathophysiological roles

Classification of γδ T Cells

Human γδ T cells are usually divided into Vδ1+, Vδ2+, and Vδ3+γδ T cells according to the difference in the arrangement of the γ chain and δ chain.[29] Vδ1+γδ T cells are mainly distributed in the epithelium and mucosa, accounting for approximately 5–10% of γδ T cells.[30,31] Vδ2+γδ T cells are mainly present in peripheral blood, constituting the majority of the total number of γδ T cells. In particular, γδ T cells expressing the Vγ9Vδ2 TCR account for 50–95% of total γδ T cells and are also the main cells responsible for the antitumor effects.[32] Vδ3+ γδ T cells are mainly present in the liver and small intestine epithelium. There is relatively little research on the role of Vδ3+ γδ T cells in tumors, but there is still research potential.[33,34] Furthermore, Vδ1+ γδ T cells and Vδ2+ γδ T cells can be further classified by the expression of different CD molecules and the skewed expression patterns of the memory markers CD45RA and CD27. Vδ1+ γδ T cells from healthy individuals mainly represent a CD45RA+CD27+ phenotype,[35] with high expression of CD56.[36] However, Vδ1+γδ T cells in tumor tissue tend to exhibit a CD45RA-CD27- phenotype.[37,38] Vδ2+ γδ T cells mainly exhibit a CD45RA- CD27+ phenotype, with CCR5 and CD161 generally overexpressed, allowing them to quickly migrate to inflammatory tissue.[36] Accordingly, γδ T cells display subset-specific features that need to be emphasized, as these features increase the understanding of the true role of γδ T cells in different diseases, especially their role in cancer.

Pathophysiological roles of γδ T cells

γδ T cells exert an extensive array of biological effects. Their main characteristics include cytotoxic activity against target cells and the secretion of different types of cytokines and chemokines. γδ T cells can also interact with other cells, such as αβ T cells, dendritic cells (DCs), B cells, NKs and macrophages. Through these functional activities, γδ T cells exhibit anti-infection and antitumor effects and play a role in immune regulation and damage repair.

Numerous studies have revealed that γδ T cells exert their antitumor effect mainly through the production of cytokines (such as interferon γ (IFN γ) and TNF-α), triggering γδ TCR recognition molecules, NK cell receptors (NKRs), and antibody-dependent cell-mediated cytotoxicity (ADCC). The recognition of γδ TCR depends on interactions with specific phosphoantigens,[39–41] such as butyrophilin 3 A1 (BTN3A1),[42] and subsequently activating Vγ9Vδ2 T cells. BTN2A1 is essential for BTN3A1-dependent Vg9Vd2 T-cell activation against cancer cells, regulating Vγ9Vδ2 T-cell binding to the TCR.[43] Representative molecules of the NK recognition mechanism include NKG2D,[44] NKp30,[45] and NKp44.[45] Various cytokines and chemokines assist γδ T cells in achieving cytotoxic functions while acting as regulators in the immune microenvironment. Some scientific evidence indicates that γδ T cells exhibit cytotoxic activity in liver cancer[46–48] and are under the regulation of cytokines such as IL-2 and IL-21.[49] Additionally, IL-17 and IL-2, the most common cytokines secreted by γδ T cells, have been identified as biomarkers of poor prognosis in malignant tumors, related to the maintenance and promotion of the inflammatory environment.[50,51] γδ T cells are the main providers of IFN γ in tumor immunity, and IFN γ plays an crucial role in controlling tumor development.[52,53] Currently, it is acknowledged that the chemokines produced by γδ T cells include C-C chemokine receptor (CCR)2,[54] CCR5,[55] CCR6,[56] CCR7,[57] and CCR9,[55] which play an auxiliary role in γδ T cell anti-infection and antitumor functions. The recruitment and activation of γδ T cells depend on the reactivity of different chemokine signals. Chemokines induce γδ T cells to accurately migrate to the desired site, and γδ T cells and other cells produce chemokines, achieving this goal together.

Elucidating the interactions between γδ T cells and other immune cells will increase the understanding of γδ T cells. γδ T cells have been confirmed to function as antigen-presenting cells (APCs), similar to DCs, effectively processing and presenting antigens to CD4+ T cells and CD8+ T cells to initiate immune responses.[58] Furthermore, γδ T cells provide strong stimulation signals for the differentiation and maturation of DCs through the Fas-Fas L pathway.[59,60] Another study found that γδ T cells and DCs mutually promote maturation, and the increase in DC-induced apoptosis induces the expression of γδ T-cell ligands, thereby activating γδ T cells.[59] The proliferation and differentiation of αβ T cells are still induced by γδ T cells,[61] but in the tumor microenvironment, γδ T cells show an inhibitory effect on the activation of αβ T cells and support the occurrence of pancreatic tumors.[62] It has been proven that Vδ2+ and Vδ3+γδ T cells affect the differentiation, antibody secretion, and cytokine production of B cells, starting from the moment that B cells are released from the bone marrow.[63,64] γδ T cells are associated with changes in the number of macrophages, and they also promote M2 macrophage polarization by secreting IL-17A, thus contributing to the clearance of infected cells.[65] Additionally, the number of peripheral γδ T cells is negatively correlated with the accumulation of neutrophils and M1 macrophages. Peripheral γδ T cells limit the expansion and recruitment of neutrophils to alleviate inflammation.[66,67] In a liver ischemia–reperfusion injury model, γδ TCR and IL-17a contribute to the increase in neutrophil numbers and exacerbate liver injury.[68] It is thus clear that the relationships between γδ T cells and other immune cells are extensive and far-reaching, shaping the body's vast immune regulatory network. The subtypes of γδ T cells and the pathophysiological roles of γδ T cells in tumors are summarized in Figure 1.

A dual role of γδ T cells in liver cancer

In the TME of liver cancer, the diversity of γδ T cell subpopulations in anti-tumor immune functions, such as the dynamic interactions between tumor promotion and inhibition, has received widespread attention, with special emphasis on the differences between Vδ 1+and Vδ2+ γδ T cells. The functional paradigm of γδ T cells and their secreted factors was defined in tumor immunity through an in-depth understanding of γδ T cell subpopulations, enabling these subpopulations to exert anti-tumor effects in the tumor microenvironment. However, the γδ T cell subpopulations and their corresponding tumor effects are still being refined. With the development of more experimental methods, the dual role and mechanism of γδ T cells in liver cancer will be elucidated in greater detail and accuracy, becoming the key to explaining immune tolerance in liver cancer. A dual role of γδ T cells in liver cancer is summarized in Figure 2.

Antitumor immunosurveillance in liver cancer

Studies using γδ T cells, particularly Vγ9Vδ2 T cells, to treat liver cancer have shown positive results. A high proportion of Vγ9Vδ2 T cells is associated with longer HCC patient survival times.[69,70] NKRs expressed by γδT cells, especially the NK-

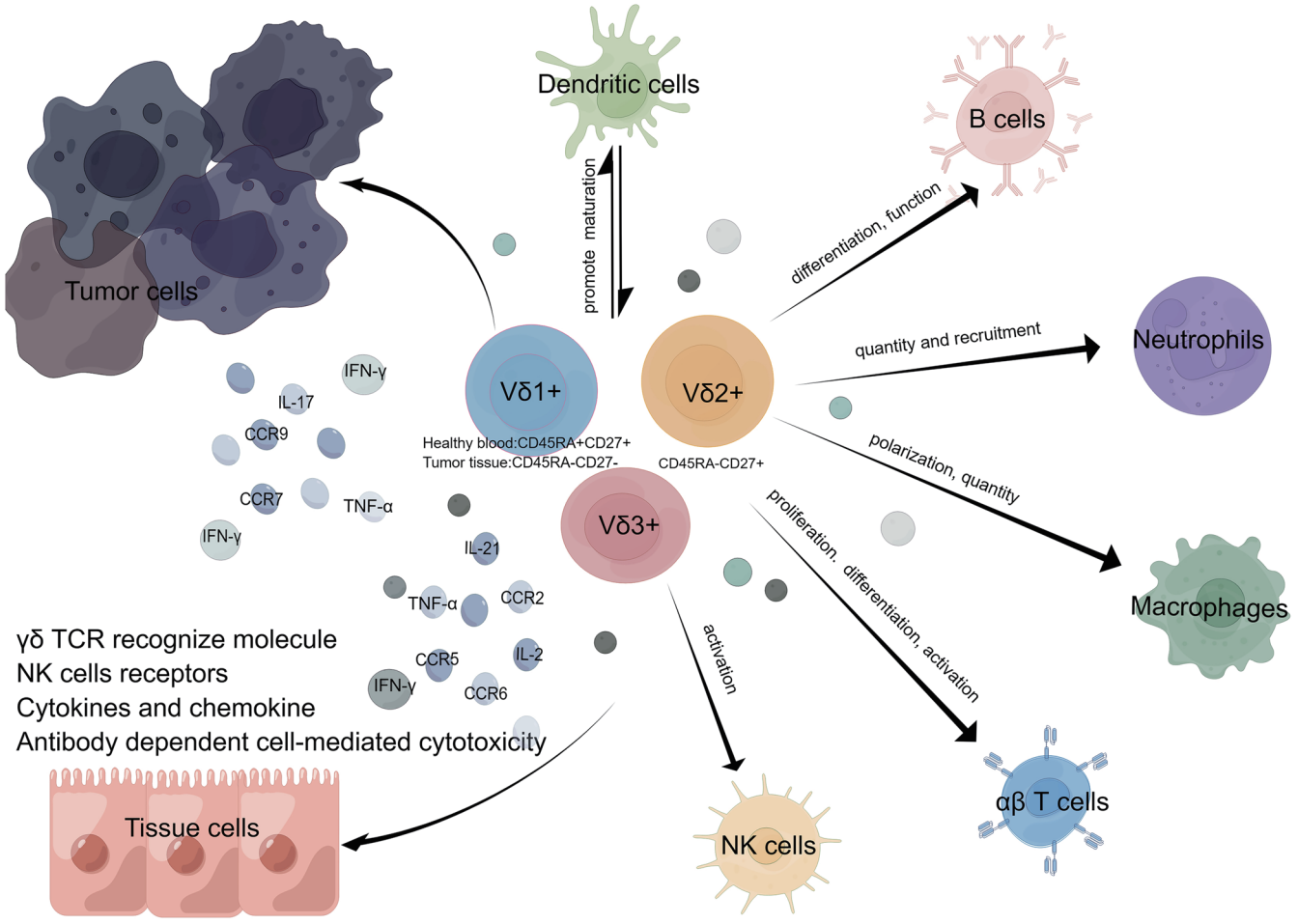

Fig. 1. The subtypes of γδ T cells and the pathophysiological roles of γδ T cells in tumors. Human γδ T cells are usually divided into Vδ1+, Vδ2+, and Vδ3+γδ T cells according to the arrangement of the γ chain and δ chain. Vδ1+ γδ T cells and Vδ2+ γδ T cells can be further classified by the expression of the memory markers CD45RA and CD27. The pathophysiological roles of γδ T cells include their cytotoxic activity against target cells, the secretion of different types of cytokines and chemokines and their interaction with other cells, such as αβ T cells, dendritic cells (DCs), B cells, natural killer cells (NKs), and macrophages. DCs, dendritic cells; NKs, natural killer cells. IFN-γ, interferon γ; CCR, C-C chemokine receptor; TNF-α, tumor necrosis factor-α; IL, interleukin; TCR, T cell receptor.

G2D receptor, are the main cell type that combats cancer.[71] High expression of the NKG2D receptor is beneficial for enhancing the cytotoxicity of γδ T cells against HCC cell lines.[72] The ULBP family, which binds to NKRs and is expressed by tumors, is involved in the recognition of tumor antigens by Vγ9Vδ2 T cells, and its expression level determines the susceptibility of Vγ9Vδ2 T-cell lysis.[73,74] High ULBP1 expression is positively correlated with the degree of severity of HCC.[75] In patients with HCC, ULBP1 deficiency is an independent risk factor for early recurrence and poor prognosis.[72] After binding to NKG2D, the release of IFN-γ and TNF-α is induced to promote γδ T-cell cytolytic activity.[76] γδ T cells are important sources of IFN-γ and TNF-α, which are known to inhibit tumor growth by specifically inducing apoptosis and inhibiting angiogenesis.[77,78] γδ T cells expressing DNAX accessory molecule-1 (DNAM-1) and CD96 can more efficiently recognize Nectin-like-5 expressed on HCC cells and enhance the lysis of HCC cells, with a concomitant increase in IFN-γ production.[79] In addition, research has found that CD96+ γδ T cells are released from the liver and circulate in the bloodstream, having an inhibitory effect on the progression of other tumors.[80] Several reports have shown that the killing ability of γδ T cells against cancer cells is related to external factors. A co-culture system of zoledronate (ZOL),[81] alendronate (ALD),[82] or artesunate[83] with γδ T cells can effectively activate γδ T cells and increase tumor susceptibility. The antitumor properties of γδ T cells have great clinical application value. Further in-depth research is still needed to determine how γδ T cells can increase their own efficacy and enhance their recognition of HCC cells.

Tumor-promoting tolerance in liver cancer

Some studies have revealed the protumor effects of γδ T cells. HCC-infiltrating γδ T cells are mainly composed of IL-17-producing Vδ1 γδ T cells,[84] which play a role in promoting tumor proliferation,[85] angiogenesis,[86] metastasis[87] and immunotherapy resistance.[88] Vδ1 γδ T cells are considered tissue-resident cells that are significantly enriched in the liver.[69] Tissue residence produces a local immune tolerance effect that can be maintained for a long time, which is becoming a key feature of antitumor protection.[89] Further research has found that the Vδ1+ T-cell population, which highly expresses LAG3, negatively regulates the antitumor function of T cells through immune suppression.[90] In the HCC mouse model, IL-17A was secreted mainly by Vγ4 γδ T cells, so re-

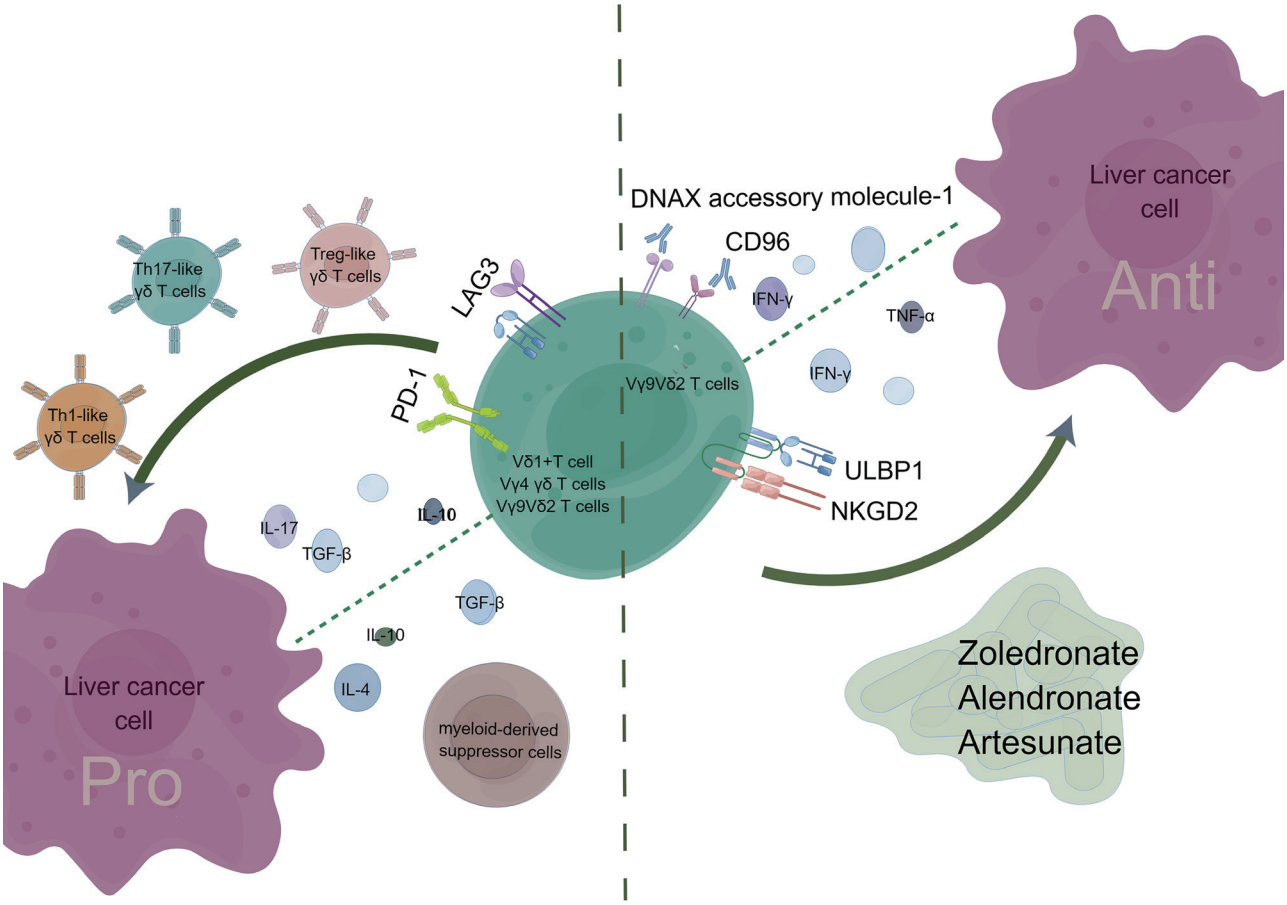

Fig. 2. A dual role of γδ T cells in liver cancer. Different subtypes of γδ T cells have diverse or even opposite effects on liver cancer. IFN-γ, interferon γ; TGF-β, tumor growth factor-β; TNF-α, tumor necrosis factor-α; IL, interleukin; LAG3, lymphocyte activation gene-3; PD-1, programmed death -1; CD96, cluster of differentiation-96; ULBP1, ul16-binding protein; NKGD2, natural killer group member D.

plenishing Vγ4 γδ T cells promoted tumor growth by recruiting myeloid-derived suppressor cells (MDSCs) in a CXCL5/CXCR2-dependent manner and further inhibiting CD8+ T cells to enhance immune suppression.[91] More recently, among HCC patients, the cytotoxicity of γδ T cells was significantly reduced, which is related to the expression of PD-1 in γδ T cells being significantly upregulated. Coincubation of γδ T cells leads to an increased proportion of PD-L1+ HCC cells, which is highly likely to enhance the immune escape of tumor cells.[49] Interestingly, Vγ9Vδ2 T cells, also representing immunosuppressive properties, deviate into Th1-, Th17-, or Treg-like phenotypes depending on the environment and secrete immunosuppressive factors (IL-4, IL-17 or IL-10 and TGF-β) to inhibit T-cell proliferation and indirectly suppress tumor immunity.[92,93] Thus, the tumor-promoting effect of γδ T cells on liver cancer is comprehensive. Weakening or inhibiting the antitumor effect of γδ T cells is both a challenge and an opportunity for liver cancer research.

Immune regulatory networks of γδ T cells involved in the microenvironment of liver cancer

Nonimmune component regulatory networks

The immune regulatory network of γδ T cells in liver cancer is extremely sophisticated and multivariant, of which nonimmune components are an important factor. Environmental factors, such as reactive oxygen species production,[94] oxygen tension,[95] and lipoprotein levels,[95] have been proven to impact the expression of IFN γ and/or NKR in γδ T cells. He *et al*. used single-cell sequencing to explain the metabolic changes of HCC-infiltrating γδ T cells which are significantly inhibited in oxygen metabolism, lipid metabolism, and amino acid synthesis, and tilt towards glutamine-rich metabolism, providing nutrients for tumor cell metabolism.[90] Combined with a genome-wide CRISPR screening of target cancer cells, another study found that the triggering of γδ T cells by BTN3A and BTN2A1 depended on AMP-activated protein kinase (AMPK), and demonstrated that γδ T cells are regulated by multiple layers of BTN3A, such as transcription, post-translational modifications, and membrane transport, further deepening our understanding of γδ T cell stress monitoring.[96] The homeostasis of IL-17A-producing γδ T cells retained in the liver is regulated by palmitic acid and CD1d, a necessary lipid antigen.[97] Moreover, apoptosis, ferroptosis, and pyroptosis significantly induce an immunosuppressive microenvironment in HCC, in which an imbalance in γδ T cells and an increase in the Vd1+/Vd2+ ratio are markers of poor prognosis in HCC patients.[98] Several reports have shown that the tumor-killing ability of γδ T cells is related to external factors. Artesunate enhances the antitumor function of γδ T cells by upregulating the expression of Fas on HepG2 cells while re-

ducing the secretion of TGF-β by HepG2 cells, thus reversing the immune escape of HepG2 cells.[83] The co-cultivation of zoledronate and HCC cell lines also resulted in an increase in the number and killing ability of γδ T cells.[99] Overexpression of miR-382 in normal liver cells increases the sensitivity of γδ T cells to HCC, thereby promoting HCC cell lysis.[100] Macrophage-stimulating protein (MSP) and peptide HP1 stimulate Vγ9Vδ2 T cells, which have high expression levels of IFN-γ and TNF-α, to exert a Th1-biased immune response for inhibiting HCC.[46] Other cellular components in the liver, such as hepatic stellate cells, activate TLR3 under the mediation of exosomes, thereby increasing γδ T cell-mediated production of IL-17A, which exacerbates liver fibrosis.[101] Evidently, the importance of γδT cell and cellular component interactions in elucidating the mechanism of liver cancer has begun to be recognized.[102]

Immune cellular regulatory networks

Crosstalk between γδ T cells and other immune cells, such as neutrophils, macrophages, T cells, and B cells, is widespread and has been identified in many malignant tumors. The immune balance in liver cancer is the result of γδ T cell self-regulation and their interactions with other immune cells. Tumor-infiltrating γδ T cells respond to signals from microorganisms and tumors, activate CD4+ and CD8+ T cells,[103] and regulate the number and function of CD4, CD8, and NK cells.[90] The activation of CD8+ T cells by γδ T cells may be achieved through the scavenger receptor CD36, resulting in tumor antigen-specific CD8+ T-cell responses.[104] The regulation between different immunocytes is often bidirectional, but the effect of CD4+, CD8+, and NK cells on γδ T cells has not yet been revealed. The elucidation of these effects will help clarify the mechanism of γδ T cells in liver cancer and even other diseases. IL-17A produced by HCC-infiltrating Vγ4 γδ T cells enhances the infiltration of MDSCs, leading to the inhibition of the CD8+ T-cell response and the promotion of tumor growth.[91] Additionally, MDSCs also harbor the capacity to modulate the generation of IFN-γ and the antitumor effect of Vδ2 γδ T cells in the tumor microenvironment.[105] Moreover, TEM results have shown that there is a negative correlation between the number of γδ T cells and the number of Treg cells in HCC, possibly because CD4+CD25+ regulatory T cells directly suppress the cytotoxic function and IFN-γ secretion of γδ T cells in a TGF-β- and IL-10-dependent manner.[106] On the other hand, γδ T cells can differentiate into γδ Treg cells and play an immunosuppressive role in cancer, as tumor-derived γδ Treg cells promote T cell and DC senescence through TLR8 signaling. This results in the inhibition of innate and adaptive immunity to maintain tumor suppression.[107,108] To date, there is limited research evidence for the interaction between γδ T cells and other immune cells in liver cancer, which can help elucidate the occurrence and development of the liver. The relationships between γδ T cells and other immune or nonimmune cells in liver cancer are worth further exploration.

Immune molecular regulatory networks

Immune molecules are both executors and regulators of γδ T cell function. Relying on various immune molecules, γδ T cells successfully interact with other cells to construct a meticulous and efficient regulatory network in the liver cancer microenvironment. The high expression of CCR1/CCR5 makes γδ T cells recruited by C-C motif chemokine ligand 4 (CCL4)/CCL5 into HCC tissue, exerting protective effects on CD8+ T cells and strengthening the body's antitumor ability.[109] Another study pointed out that the high expression of CCR5 is a selective feature of Vδ2/Vγ9 γδ T cells, which is consistent with the shift in antitumor ability.[110] Blockade of the CCL2/CCR2 axis has been considered a novel protective factor during the recruitment of Vδ1 T cells to HCC lesions.[54,111] Furthermore, mutual crosstalk between chemokines and cytokines should be emphasized, which serves as a feedback mechanism that determines the final performance of γδ T cells in liver cancer.[112,113] The binding of CCR6 and CCL20 significantly aggregates IL-17- and IL-22-expressing γδ T cells in damaged liver cells, which promotes the apoptosis of hepatic stellate cells (HSCs) involving Fas ligands, preventing the liver from entering an inflammatory and fibrotic state.[114]

For the interleukin family, TNF-α and INF-γ are both produced by and act upon γδ T cells. For example, the decrease in the cytotoxicity of γδ T cells in the blood circulation of HCC patients may be explained by the fact that the levels of some pro-inflammatory cytokines (IL-2 and IL-21) are reduced and PD-1 is upregulated.[49] Moreover, tumor-infiltrating Vγ1 γδ T cells produce IL-4, which significantly reduces the expression levels of NKG2D, perforin-1, and IFN-γ in Vγ4 γδ T cells, diminishing cytotoxicity and reducing antitumor function.[115] IL-35, an immunosuppressive cytokine, is produced by Treg cells in the hepatic microenvironment, and its overexpression promotes the depletion of γδ T cells and impairs their antitumor function in HCC.[116] However, the influence of PD-1 expression on γδ T cells is not well defined. In hematological tumors, the blockade of PD-1 does not directly affect the cell-dependent lysis ability of γδ T cells, but PD-1+ γδ T cells produce more IFN-γ to enhance their own lethality.[117] Similarly, IL-17A production from γδ T cells can be inhibited by high expression of PD-1 while reducing organ inflammation damage and immune resistance.[88,118] Other studies contradict the above viewpoints, suggesting that high numbers of PD-1+ γδ T cells are correlated with a poor prognosis for patients with acute leukemia.[119] In HCC cell lines, the cytotoxicity of PD-1+ γδ T cells is weakened.[49] Deeper exploration of the relationship between γδ T cells and PD-1 expression will lead to a more comprehensive understanding of immunotherapy. Thus, the immunoregulatory balance of γδ T cells involved in liver cancer is not yet completely understood, but the joint forces of multiple cytokines, chemokines, and immunocytes determine the overall performance of γδ T cells in liver cancer. Brief summary of immune regulatory networks of γδ T cells involved in the microenvironment of liver cancer is summarized in Figure 3.

γδ T-cell-based immunotherapy in liver cancer

γδ T-cell-based immunotherapy in liver cancer is being vigorously developed and has achieved surprising results. According to current research results, there are three mainstream directions for γδ T-cell-based immunotherapy, namely, synergistic effects of other antibodies, chimeric antigen receptor-based γδ T cells, and γδ T-cell transplantation. The practical application of γδ T cell-centered immunotherapy in liver cancer is both promising and challenging with tremendous room for exploration. Studies of potential γδ T-cell-based immunotherapy in liver cancer is summarized in Table 1.[70,120–127]

Synergistic effects of other antibodies

The cytotoxicity of γδ T cells in human liver sinuses depends on the signaling of phosphoantigens, NK receptors, and immune checkpoint molecules. Nitrogen-containing bisphosphonates have been widely used in tumor treatment, with outstanding therapeutic achievements.[128–132]

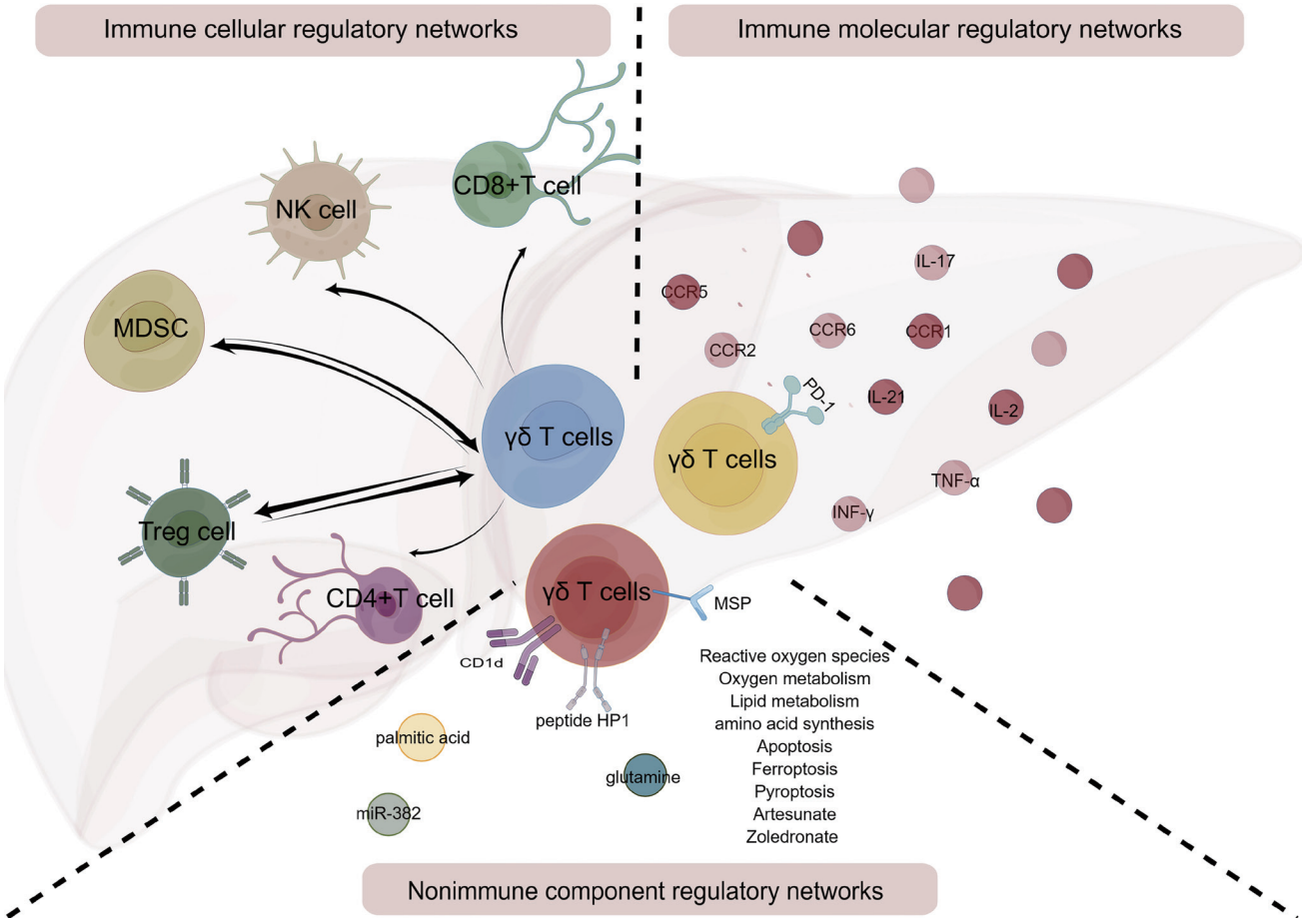

Fig. 3. Brief summary of immune regulatory networks of γδ T cells involved in the microenvironment of liver cancer. The immune regulatory network of γδ T cells in liver cancer is extremely sophisticated and multivariant. Immune regulatory networks of γδ T cells are involved in the immune microenvironment of liver cancer through immune molecules, immune cells and nonimmune components. CD, cluster of differentiation; NK cell, natural-killer cell; MDSC, Myeloid-derived suppressor cell; Treg cell, T regulatory cell; CCR, C-C chemokine receptor; IL, interleukin; IFN-γ, interferon γ; TNF-α, tumor necrosis factor-α.

Similarly, in HCC, the addition of zoledronate markedly optimizes γδ T-cell-mediated immunotherapy and directly inhibits tumor proliferation.[120,133] Moreover, the addition of EpCAM-specific monoclonal antibodies can prominently enhance the lysis effect of γδ T cells on hepatoblastoma.[121] Another study also revealed a thought-provoking phenomenon in which chemotherapy accelerates the immune senescence and dysfunction of Vδ2 γδ T cells in patients with metastatic liver cancer.[122] Therefore, the combination of γδ T cells and other drugs or antibodies is a double-edged sword that requires more clinical practice to provide more favorable evidence.

Chimeric antigen receptor (CAR) T-cell immunotherapy

CAR-T-cell immunotherapy is a precise and efficient tumor treatment method, while CAR-γδ T cells possess the advantages of both treatments, pushing tumor immunotherapy to a new level. This strategy has been applied in clinical practice in hematological tumors and has great potential in solid tumors.[123,134–137] Vδ1 γδ T cells engineered with glypican-3-specific CAR and soluble IL-15 efficiently and robustly control tumor growth in HCC and exhibit strong tumor tissue aggregation.[124] Although promising, some technical problems related to CAR-γδ T cells still need to be addressed, such as antigen recognition and design, gene delivery technology, and cell proliferation.

γδ T-cell transplantation.

As HCC progresses, the function of γδ T cells is lost, and the Vδ2 γδ T-cell population is heavily consumed.[90] At the same time, the expression of immunosuppressive receptors in the Vδ1 γδ T-cell population is upregulated, and the antitumor ability of Vδ2 γδ T cells is enhanced.[138] Therefore, allogeneic Vδ2 γδ T cells serve as a promising supplement in the treatment of liver cancer. In a study of Vγ9Vδ2 T-cell adoptive therapy, expanded cells also displayed robust antitumor efficacy against HCC and improved immune efficacy functions, including antitumor ability, proliferation, and differentiation.[70] In corresponding clinical trials, the prolonged survival time of patients confirmed the safety and effectiveness of allogeneic Vγ9Vδ2 T-cell immunotherapy.[70,125,128] Four clinical trials related to liver cancer have been registered so far (https://www.clinicaltrials.gov/ ID: NCT02425735, NCT03183219, NCT04518774, NCT05628545). In this clinical trial of advanced liver cancer (NCT03183219), of the 8 liver cancer patients, 7 survived for more than 10 months, and 3 survived for more than 30 months.[70] Moreover, local regional therapy combined with allogeneic γδ T-cell adoptive transplantation is also very safe and effective in the treatment of advanced

Table 1. Studies of potential γδ T-cell-based immunotherapy in liver cancer

Treatment	Tumor type	Effector cells	Mechanism	Outcomes	Reference
Zoledronic acid	SK-HEP-1 and H22 cells	–	ZOL optimizes γδ T-cell-mediated immunotherapy and inhibits growth of HCC cells	Inhibited tumor proliferation	120
Zoledronate	Hepatocellular carcinoma and colorectal carcinoma with hepatic metastases	Vγ9Vδ2 T cells	The cytotoxic level of Vγ9Vδ2 T cells against freshly autologous tumor cells isolated from patients could be significantly increased by pretreating the tumor cells with zoledronate	Improved cytotoxicity	123
Zoledronate and IL-2	Hepatocellular carcinoma	γδ T cells	Zoledronate with IL-2 may efficiently expand γδ T cells sourced from the peripheral blood of patients with HCC	Increased the quantity of the γδ T cells	127
EpCAM-specific monoclonal antibodies	Hepatoblastoma	γδ T cells	Tumor cell lysis by γδ T cells can be dramatically augmented	Improved cytotoxicity	121
Chemotherapy	Metastatic liver cancer	Vδ2+ T cells	Vδ2+ T cells are coupled with impairments in quantity, cytotoxicity and production of TNF-α and IFN-γ	Decreased cytotoxicity	122
Glypican-3 (GPC-3)-specific chimeric antigen receptor (CAR) and soluble IL-15	Hepatocellular carcinoma	CAR Vδ1 T cells	GPC-3.CAR/sIL-15 Vδ1 T cells displayed robust in vitro and vivo proliferation, cytokine production, cytotoxic activity and suppression of tumor growth	Delayed tumour growth	124
The expanded γδ T cells from healthy donors	Late-stage liver cancer	Vγ9Vδ2 T cells	The expanded γδ T cells possessed significantly improved immune effector functions, including proliferation, differentiation, and cancer cell killing, both in vitro and in the humanized mouse model, with the safety and efficacy in clinical trial	Improved antitumor efficacy and prolonged survival time of patients	70
The expanded γδ T cells from healthy donors	Cholangiocarcinoma	Vγ9Vδ2 T cell	Allogenic γδ T cell treatments positively regulated peripheral immune functions of the patient, depleted tumor activity, improved quality of life, and prolonged his life span	Improved antitumor efficacy	125
Locoregional Therapy Combined with Adoptive Transfer of Allogeneic γδ T Cells	Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma	γδ T cells	The novel combination of locoregional ablation with adoptive transfer of allogeneic γδ T cells was safe, and patients with HCC in the combined treatment group had a longer OS.	Prolonged survival time of patients	126

HCC and intrahepatic cholangiocarcinoma.[126]

For liver cancer patients, the optimization of γδ T-cell immunotherapy emphasizes individualization. The quality of γδ T-cell amplification is related to clinical and pathological characteristics such as tumor size, quantity, and serum AFP levels.[127] During γδ T cell immunotherapy, the physiological and biochemical indicators of patients should be dynamically monitored to maximize the advantages of γδ T cell immunotherapy.[127]

Conclusions and future perspectives

An increasing number of studies have confirmed the unique properties of γδ T cells and their plasticity in the field of cancer research. Different subtypes of γδ T cells and their secreted cytokines have different protumor or antitumor effects. The enormous immune regulatory network formed around γδ T cells, including immune and nonimmune components in the microenvironment of liver cancer, regulates the differentiation and performance of γδ T cells and determines the ultimate occurrence and development of liver cancer. γδ T-cell-based immunotherapy has gradually become a highly promising treatment protocol for liver cancer, accompanied by opportunities and challenges. However, the exploration of γδ T cells in liver cancer is still incomplete, and more systematic and accurate explorations are still needed in many aspects. First, the heterogeneity of γδ T cells needs to be emphasized during research, as the functions of different subpopulations are completely different. Second, breakthroughs and innovations in technology and methods, such as the application of high-throughput technologies and the development of stable transfer models of γδ T cells, can broaden the horizons of γδ T cell research. Third, research on how to thoroughly induce the activation of γδ T cells in clinical applications and develop specific engineered γδ T cells targeting tumor antigens still requires in-depth explorations of tumor-related mechanisms. Fourth, combination strategies with other forms of treatment, such as surgery and targeted therapy, should also be

the focus of future clinical investigation. Although research on γδ T cells is still in its infancy due to some technological limitations, γδ T cells, as attractive antitumor candidates, undoubtedly increase the understanding of liver cancer, and the application of γδ T cells in the field of liver cancer has great potential and a promising future.

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Conflict of interest

RL has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication

Author contributions

Study concept and design (KLY, KJC, DF, RL), drafting of the manuscript (KJC, ML, YXD, YXY, MQK), critical revision of the manuscript for important intellectual content (KJC, ML, YXD, YXY, MQK), administrative or material support (KJC, DF, RL), and study supervision (KLY, KJC, DF, RL), critical funding (DF, RL). All authors have made a significant contribution to this study and have approved the final manuscript.

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