Immune Netw. 2020 Feb;20(1):e5
https://doi.org/10.4110/in.2020.20.e5
pISSN 1598-2629·eISSN 2092-6685

IMMUNE NETWORK

Review Article

Check for updates

Heterogeneity of Human γδ T Cells and Their Role in Cancer Immunity

Hye Won Lee [1], **Yun Shin Chung** [2], **Tae Jin Kim** [2,*]

[1]Department of Hospital Medicine, Yonsei University College of Medicine, Seoul 03722, Korea
[2]Department of Immunology, Sungkyunkwan University School of Medicine, Suwon 16419, Korea

OPEN ACCESS

Received: Dec 25, 2019
Revised: Feb 4, 2020
Accepted: Feb 8, 2020

***Correspondence to**
Tae Jin Kim
Department of Immunology, Sungkyunkwan University School of Medicine, 2066 Seobu-ro, Jangan-gu, Suwon 16419, Korea.
E-mail: tjkim@skku.edu

ORCID iDs
Hye Won Lee
https://orcid.org/0000-0002-0303-4658
Yun Shin Chung
https://orcid.org/0000-0002-4971-486X
Tae Jin Kim
https://orcid.org/0000-0001-9802-0568

Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
BTN3A, butyrophilin 3A; DETC, dendritic epidermal T cell; KIR, killer inhibitory receptor; NCR, natural cytotoxicity receptor; NKG2D, NK group 2 member D; Tfh, follicular Th; TME, tumor microenvironment; ULBP, UL16-binding protein

ABSTRACT

The γδ T cells are unconventional lymphocytes that function in both innate and adaptive immune responses against various intracellular and infectious stresses. The γδ T cells can be exploited as cancer-killing effector cells since γδ TCRs recognize MHC-like molecules and growth factor receptors that are upregulated in cancer cells, and γδ T cells can differentiate into cytotoxic effector cells. However, γδ T cells may also promote tumor progression by secreting IL-17 or other cytokines. Therefore, it is essential to understand how the differentiation and homeostasis of γδ T cells are regulated and whether distinct γδ T cell subsets have different functions. Human γδ T cells are classified into Vδ2 and non-Vδ2 γδ T cells. The majority of Vδ2 γδ T cells are Vγ9δ2 T cells that recognize pyrophosphorylated isoprenoids generated by the dysregulated mevalonate pathway. In contrast, Vδ1 T cells expand from initially diverse TCR repertoire in patients with infectious diseases and cancers. The ligands of Vδ1 T cells are diverse and include the growth factor receptors such as endothelial protein C receptor. Both Vδ1 and Vδ2 γδ T cells are implicated to have immunotherapeutic potentials for cancers, but the detailed elucidation of the distinct characteristics of 2 populations will be required to enhance the immunotherapeutic potential of γδ T cells. Here, we summarize recent progress regarding cancer immunology of human γδ T cells, including their development, heterogeneity, and plasticity, the putative mechanisms underlying ligand recognition and activation, and their dual effects on tumor progression in the tumor microenvironment.

Keywords: T-lymphocyte subsets; γδ T cell; T Cell Receptors, gamma delta; Tumor microenvironment

INTRODUCTION

Among 3 main lineages of lymphocytes—αβ T cells, γδ T cells, and B cells, γδ T cells are the most enigmatic lymphocytes that express TCRs rearranged from TCR γ and δ genes (1-3). The γδ T cells are one of the innate immune cells that have a pivotal role in cancer immunosurveillance as the deficiency of γδ T cells increased the susceptibility to cancers (4-7). They can mediate potent direct cytotoxicity by recognizing transformed target cells via the γδ TCRs, but they may also detect cancer cells via activating NK cell receptors such as NK

IMMUNE NETWORK

Author Contributions

Conceptualization: Lee HW, Chung YS, Kim TJ; Funding acquisition: Kim TJ, Chung YS; Project administration: Kim TJ; Validation: Kim TJ; Writing - original draft: Lee HW, Kim TJ; Writing - review & editing: Lee HW, Chung YS, Kim TJ.

group 2 member D (NKG2D) or natural cytotoxicity receptors (NCRs) (8,9). The application of γδ T cells, mostly Vγ9Vδ2 T cells, for cancer immunotherapy has been explored against various tumors of hematological and epithelial origin (10-16). Many clinical trials have shown that those treatments are feasible and safe, but with some obvious limitations (4,12,17). Therefore, a better understanding of γδ T cell subset-specific responses during tumor immunity is vital to rationally develop optimal strategies for maximizing the anti-tumor activity of γδ T cells and inhibiting their pro-tumor activity. Here, we summarize the recent progress regarding the immunobiology of human γδ T cells, including the heterogeneity and plasticity, the putative mechanisms of ligand recognition and activation, their positive and negative effects on the cancer progression, and the future perspective of immunotherapy using γδ T cells.

ORIGIN AND DEVELOPMENT OF THE HUMAN γδ T CELLS

The γδ T cells develop earlier than αβ T cells in the thymus and are exported to different peripheral tissues according to the chronological order of the thymic development (18,19). In the mouse, the first γδ T cells at the embryonic day of 14, $V\gamma5^+V\delta1^+$ T cells are selected by selection and upkeep of intraepithelial T cells protein 1 presented on thymic epithelial cells and become dendritic epidermal T cells (DETCs) responsible for body-barrier surveillance (20,21). A later process of thymic T cell development generates $V\gamma6^+V\delta1^+$ T cells that are destined for the female genital tract, peritoneal cavity and tongue, and other γδ T cells with diverse VDJ clonotypes containing Vγ1, 2, 4, and 7 segments (18,22). Whereas the early developing γδ T cells have invariant TCRs, the γδ T cells appearing during the later period of the development are diverse in TCR repertoire (22-24).

Human γδ T cells are also present in the thymus as well as the periphery, suggesting the thymic development of human γδ T cells (25). Although adult blood γδ T cells are predominated by Vγ9Vδ2 cells, neonatal cord blood γδ T cells express a diversity of Vγ and Vδ chains paired in various combinations, and the majority of neonatal γδ T cells are $V\gamma9^-V\delta1^+$ cells (26,27). Therefore, the adult blood Vγ9Vδ2 cells appear to represent the post-natal expansion of Vγ9Vδ2 cells expressing canonical CDR3s in response to microbial phosphoantigens that are described below (28-30). Human Vγ9Vδ2 cells have been shown to expand rapidly after birth within 1 year of life (31). In the adult, Vδ1 and Vδ2 γδ T cells are localized in the barrier tissues and the peripheral blood, respectively (32).

HETEROGENEITY OF THE HUMAN γδ T CELLS

Although γδ T cells are cousins of αβ T cells, γδ T cells directly recognize Ags via their γδ TCRs without the need of MHC molecules similarly to B cells (1,33,34). The γδ T cells are sometimes referred to as innate lymphocytes since they can recognize microbial or stress-induced patterns and respond rapidly without previous exposure to the Ags (1,24). However, some γδ T cells exhibit highly adaptive features such as clonal expansion and differentiation from naïve cells to effector cells (35). The overall characteristics of γδ T cells may be positioned between NK cells and $CD8^+$ T cells (36). The γδ T cells are heterogeneous concerning functional features depending on the usage of TCR γ and δ chains and the tissue localization. The γδ T cell population consists of tissue-resident and peripheral blood γδ T cells (1). Human γδ T cells account for 0.5%–5% of all peripheral blood T cells (2,7).

https://doi.org/10.4110/in.2020.20.e5

In humans, several functional Vγ gene segments (including Vγ2, Vγ3, Vγ4, Vγ5, Vγ8, Vγ9, and Vγ11) rearrange into 5 Jγ segments and 2 Cγ segments on chromosome 7 to generate TCRγ chains, whereas TCRδ chains are generated by the rearrangement of at least 7 Vδ, 3 Dδ, 3 Jδ, and 1 Cδ segments on chromosome 14 (2,3,7,37). Whereas Vδ1, Vδ2, and Vδ3 segments are used only in the rearrangement of the TCR δ chains, Vδ4–Vδ7 segments are also used in the rearrangement of the TCR α chains and have alternative gene names belonging to TCR Vα gene segments (37). The functional features of γδ T cells are closely correlated with the usage of the TCRδ chains (24). Among 7 Vδ segments, Vδ1 and Vδ2 segment-using γδ TCRs are the most common human γδ TCRs (2).

As the most abundant human γδ T cells are Vγ9Vδ2 T cells that recognize unique phosphoantigens and Vδ1 T cells have adaptive features distinct from Vγ9Vδ2 T cells, γδ T cells are commonly classified into Vδ2 and non-Vδ2 γδ T cells (2,35,38). The Vγ9Vδ2 T cells are the most well-known human γδ T cells and have been exploited for anti-cancer immunotherapy (10,11). The characteristics and the adaptive features of non-Vδ2 γδ T cells, especially Vδ1 γδ T cells, are recently recognized, and these Vδ1 γδ T cells are also thought to be a candidate for anti-cancer immunotherapy (35).

THE γδ TCR STRUCTURE AND ACTIVATION OF THE HUMAN γδ T CELLS

Although γδ T cells share TCR rearrangement mechanism and memory functions with αβ T cells, they differ in the immune response kinetics and mechanisms of target cell recognition (39). The γδ T cells do not recognize MHC molecules, but many γδ T cells respond to non-peptide Ags or MHC-like molecules, such as MHC class I-related chain A (MICA), MICB, or UL16-binding protein (ULBP), that are upregulated in cells under stressed conditions such as infection or cancer transformation in MHC-unrestricted manner (2,3). Similarly to αβ TCRs, γδ TCRs are also associated with CD3 molecules, but differently from murine αβ TCRs, murine γδ TCRs contain only CD3γε dimers, not CD3δε dimers (40). Notably, murine γδ TCR cells can develop in the absence of CD3ε or CD3δ (41,42), but the expression of CD3γ is indispensable for the murine γδ T cell development (43). Furthermore, CD3ζ chain is not necessary for the γδ T cell development and FcεRIγ chain, a CD3ζ chain family member that can dimerize with CD3ζ, is expressed upon activation and then included in the γδ TCR complexes (44). On the other hand, human γδ TCR complex contains CD3δ chain and shows a TCRγδCD3ε_2δγζ_2 stoichiometry similarly to human αβ TCR complex, whereas mouse γδ TCR complex has a TCRγδCD3$\varepsilon_2\gamma_2\zeta_2$ stoichiometry (45). Human γδ TCR signaling is less dependent on CD3γ chain than CD3δ chain as human patient lacking CD3γ have abundant peripheral blood γδ T cells expressing high levels of γδ TCR (46). Interestingly, forced expression of human, but not murine, CD3δ transgene rescue the γδ T cell development in mice deficient in both CD3δ and CD3γ genes, suggesting the unique role of human CD3δ in the TCR signaling (45).

The γδ TCR signaling is qualitatively different from the αβ TCR signaling (44). The γδ TCRs self-oligomerize and cause constitutive signaling in the absence of ligands (47). These γδ TCR signaling characteristics are similar to those of pre-αβ TCR signaling responsible for the β selection during thymic T cell development (48). During the thymic γδ T cell development, γδ T cells that encounter strong agonistic ligands obtain the capability of secreting IFN-γ. In contrast, γδ T cells that do not encounter strong agonists adopt IL-17-default position (1,47).

https://doi.org/10.4110/in.2020.20.e5

In the periphery, the stimulation of γδ T cells via γδ TCR and costimulatory receptors or NK cell receptors triggers γδ T cells to undergo clonal expansion and differentiation into effector cells and to produce large quantities of pro-inflammatory cytokines such as IFN-γ or IL-17. Upon activation, γδ T cells can also exert a potent cytotoxic activity without the obligatory delay associated with clonal expansion and differentiation (49).

Although γδ TCR is regarded as an activating receptor, γδ TCR may act as an inhibitory receptor in certain contexts. The consequence of the constitutive γδ TCR signaling can be inhibition of γδ T cell activation when the ligands on target cells are constitutively presented (50). In NK cells, the constitutive inhibitory signaling through killer inhibitory receptor (KIR) sets up a threshold that NK cells are not easily activated, and a full activation of NK cell requires very high concentrations of activating ligands for NK cell-activating receptors and/or downregulation of inhibitory ligand, MHC class I on the target cells (51). The Vγ5δ1 TCRs in mouse DETCs form constitutive immunological synapses with keratinocytes in the steady state and are argued to have a role similar to KIR on NK cells (20).

Since γδ T cells have a lot of NK cell-activating receptors such as NCRs and NKG2D (8,9), the functional roles of γδ TCR should be carefully investigated in heterogeneous subpopulations of γδ T cells since the NK receptors, not γδ TCR, could be main receptors for γδ T cell activation. The NK cell-activating receptors can be considered as costimulatory receptors if γδ TCR and NK cell receptors induce synergistic signaling for γδ T cell responses (52). The list of costimulatory receptors for αβ T cells has been expanded and includes a prototype costimulatory molecule CD28 (53). The relevance of costimulatory molecules for αβ T cells in γδ T cells remains debatable. About 40%–60% of γδ T cells express CD28, and the expression of CD28 is decreased upon the activation of γδ T cells (54,55). Since anti-CD28 agonistic Abs enhance human γδ T cell proliferation, the role of CD28 as a costimulatory molecule is valid in a subpopulation of human γδ T cells. Considering the phenotypes of memory and effector $CD8^+$ αβ T cells (56), it may be hypothesized that the expression of CD28 is lost upon the prolonged activation of a subpopulation of γδ T cells. It is noteworthy that a higher proportion of Vδ1 γδ T cells do not express CD28 than that of Vδ2 γδ T cells, but the most of Vδ2 γδ T cells express CD28 similarly to naïve αβ T cells (35,57).

THE γδ T CELLS IN THE TUMOR MICROENVIRONMENT (TME)

Recruitment of human γδ T cells into the TME

Cancer is characterized not only by transformed cancer cells but also by non-cancer cells, such as immune cells, fibroblasts, and endothelial cells, and the extracellular matrix that establishes the TME. Initially, the cellular stresses experienced by transformed cancer cells trigger the upregulation of ligands for NK cell receptors (58). Although initially recruited NK cells can kill cancer cells, the cytotoxic activity of NK cells is not sustained but exhausted when cancer cells outnumber NK cells in the advanced stage of cancer (59). The persistent chronic inflammation associated with cancer recruits many kinds of immune cells, including Treg cells and myeloid-derived suppressor cells into the TME. It is a common consensus that the TME inhibits the anti-tumor immune responses in most clinical situations (60-62).

The γδ T cells also infiltrate into a variety of the tumors in the early and late stages of cancer development, where they are known to modulate the anti-tumor response through pro- or

anti-inflammatory cytokines and their interactions with different types of innate and adaptive immune cells in the TME (7,49,63,64). The γδ T cells migrate into the TME in response to CC chemokines such as MCP-1, regulated on activation normal T cell expressed and secreted, MIP-1α and MIP-1β (11,35,65).

Major tumor-infiltrating γδ T cell subsets: human Vδ1 and Vγ9Vδ2 T cells

In humans, Vδ1 and Vγ9Vδ2 T cells are 2 main populations of γδ T cells in the tissues and peripheral blood. In tumors, one subset can be predominant over the other depending on the types and origin of the tumors (7,11,49,64-67). Both Vδ1 and Vγ9Vδ2 T cells have the cytotoxic capability and can have anti-cancer activity (11,36). The 2 subsets of γδ T cells express distinct chemokine receptors and cell adhesion molecules, suggesting different homing mechanisms that can be selectively utilized for cancer immunotherapy (35,68,69). A diagram is displayed in **Fig. 1**, which shows their differential involvement in the anti-cancer immunity.

The human Vγ9Vδ2 T cells are the most predominant γδ T cells in the adult peripheral blood, but they are not a major γδ T cell population at the time of birth as the Vδ1 γδ T cells are predominant during fetal and early life (24,31). The Vγ9Vδ2 T cells expand postnatally in response to phoshoantigens by microbes. The canonical Vγ9Vδ2 T cells with Vγ9JγP sequences recognize phosphoantigens presented by butyrophilin 3A (BTN3A). Interestingly, prenyl pyrophosphates (phosphoantigens) bind to the intracellular B30.2 domain of BTN3A1,

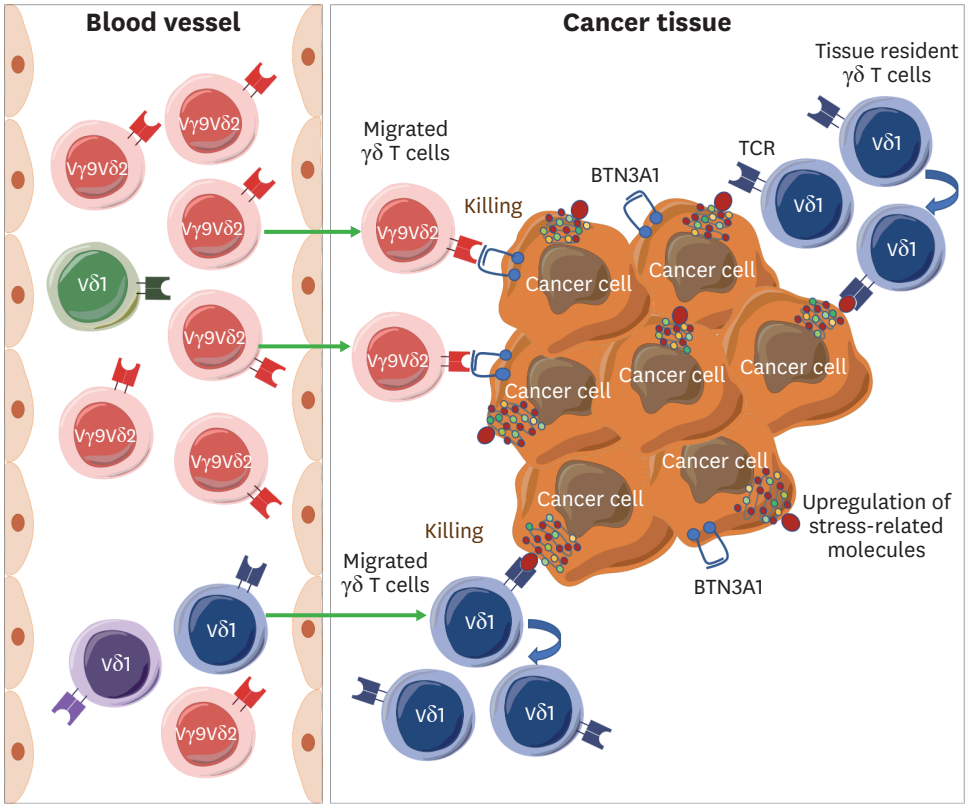

Figure 1. Differential recruitment of Vδ1 and Vγ9δ2 γδ T cells into the tumor tissue. In blood, Vγ9δ2 γδ T cells are predominant over Vδ2 γδ T cells in healthy individuals. Most of the Vγ9δ2 γδ T cells have canonical TCRs responding to prenyl pyrophosphates that are elevated in cancer cells and are recruited into the tumor via chemokine receptors. In contrast, some clonotypes of Vδ1 γδ T cells are selected from a diverse Vδ1 TCR repertoire. Specific Vδ1 γδ T cells migrate into the tumor tissues, expand, and kill cancer cells. The tissue-resident Vδ1 γδ T cells may respond to the tissue stress and proliferate to kill cancer cells.

https://doi.org/10.4110/in.2020.20.e5

suggesting that the Vγ9Vδ2 TCR senses the internal changes of mevalonate or non-mevalonate metabolic pathways within cancer or infected cells, respectively (70,71). Elevated cytoplasmic prenyl pyrophosphate levels as a result of a dysregulation of the mevalonate pathway triggers an inside-out signaling leading to a structural change of the extracellular domain of BTN3A1, which enhances the binding force between BTN3A1 and Vγ9Vδ2 TCR. It is noteworthy that the RhoB activation in cancer cells is another determinant for the relocalization of BTN3A1 and the activation of Vγ9Vδ2 γδ T cells (72). Therefore, the canonical Vγ9Vδ2 γδ T cells can be cancer-killing lymphocytes through the recognition of the altered metabolism of cancer cells and the mutation of RhoB. However, the functional role and Ags of non-canonical Vγ9Vδ2 γδ T cells are not well understood. The non-canonical Vγ9Vδ2 γδ T cells predominate over the canonical Vγ9Vδ2 γδ T cells in the fetal tissues, but the canonical Vγ9Vδ2 γδ T cells become predominant in the adult blood. Interestingly, glioblastoma-infiltrating γδ T cells have non-canonical TCR repertoire using Cγ2 segment (66). Regarding the ligands for Vγ9Vδ2 γδ TCR, it is needed to address the role of a novel ligand for Vγ9 TCR, BTN2A1, in the cancer immunity and whether BTN2A1 is upregulated in the cancer cells (73). The Vγ9Vδ2 T cells also recognize cancer cells through stress-related proteins that can be upregulated upon malignant transformation, including the F1-ATPase, MICA/B, heat shock protein 60, ULBP, human MutS homolog 2, and DNAX-associated molecule-1 through NK cell receptors (1,2,74,75).

Whereas most of the Vγ9Vδ2 T cells have restricted canonical TCRs, the Vδ1 T cells have diverse repertoires that use various kinds of Vγ chains (35). In most adults, a small number of specific clonotypes emerge from an initially unfocused neonatal Vδ1 TCR repertoire, undergo pronounced clonal expansion, and ultimately dominate the Vδ1 T cell compartment (69). The TCR-diverse $CD27^{high}$ and highly TCR focused $CD27^{low/-}$ populations represent naïve and effector Vδ1 T cell subsets, respectively. The transition from naïve to effector Vδ1 T cells is accompanied by a switch from lymphoid to peripheral homing receptors. Although ligands detected by Vδ1 TCRs remain largely uncharacterized, some peripheral circulating and tissue-resident Vδ1 T cells recognize CD1c, the lipid-presenting MHC-like molecule CD1d, or MHC-related protein 1 (2,76-78). In addition to the TCR, Vδ1 T cells also respond to a distinct set of cellular stress signals expressed by cancerous cells, such as MICA/B, ULBPs, B7-H6, and BAT3 via NKG2D or NCRs (1,77,79). In many tumors, Vδ1 γδ T cells are predominant over the Vγ9Vδ2 γδ T cells, which suggests that the Vδ1 γδ T cells expand responding to cancer Ags (80). The utilization of the Vδ1 γδ T cells is a promising option for cancer immunotherapy. Therefore, the relative importance of Vδ1 γδ T cells and Vγ9Vδ2 γδ T cells should be considered in the future immunotherapy using γδ T cells (4,10,12,14,16). Non-Vδ1 non-Vγ9Vδ2 γδ T cells should also be considered as the Vγ4Vδ5 γδ T cells are able to eliminate cancer cells by recognizing endothelial protein C receptor (81).

The γδ T cells have both anti-tumor and pro-tumor activities

Upon migration to the TME, γδ T cells exert potent anti-tumor effects via multiple mechanisms (77,82). The γδ T cells can eliminate cancer cells via cytolytic receptor-ligand interactions including Fas ligand (83) and TNF-related apoptosis-inducing ligand (84) in addition to granzyme B and perforin and also have cytostatic anti-cancer activities by releasing IFN-γ or TNF-α (82,85). The γδ T cells are also able to kill Ab-coated cancer cells by Ab-dependent cellular cytotoxicity using cell surface CD16 (FcγRIII) similar to NK cells (86). Lastly, γδ T cells exhibit indirect anti-tumor responses by modulating different immune cell types including DCs, NK cells, neutrophils, αβ T cells and B cells in the TME (1,4,22,75,77,82,85).

In general, the extent of intratumoral γδ T cell infiltration is highly associated with the $CD8^+$ T cell signature and patients' prognosis, suggesting that γδ T cells largely perform anti-tumor

activity rather than pro-tumor activity (87,88). However, complex interactions between TME and intratumoral γδ T cells can result in the diversion of anti-tumor γδ T cells into pro-tumor cells. Therefore, the precise role of γδ T cells in each individual patient may depend on the specific γδ T cell subsets and their functional polarization in the TME (63,77,82,85). Regarding T cell polarization, it is generally stated that Th1 and follicular Th (Tfh) cells have anti-tumor activity, whereas Th17 and Treg cells have pro-tumor activity (89). As the γδ Tfh cell-driven GC response tends to induce autoreactive B cells instead of pathogen-specific B cells, the anti-tumor activity of Tfh cells is not well established (90), but the involvement of Tfh cells in cancer tissues indicates an organized anti-tumor immunity with tertiary lymphoid tissue (91). Effector γδ T cells can also be classified as γδ Th1, γδ Th2, γδ Th17, γδ Tfh, and γδ Treg cells based on their functional polarization (1,7,22,35,49,75,77,85,92). Interestingly, in response to different cytokines, γδ T cells can trans-differentiate from one phenotype to another (1,7,22,35,49,75,77,85,92). Both Vδ1 and Vγ9Vδ2 T cells can be polarized into γδ Th1 cells, γδ Tfh cells, γδ T17 cells, γδ Treg cells, and γδ Th2 cells with distinct cytokines. It is important to investigate further whether γδ T cells are a primary driver of T cell polarization or whether the immunotherapy targeting γδ T cells can change the overall polarization of αβ T cells within the TME.

The γδ T cells are also subjected to immune exhaustion similarly to cancer-reactive cytotoxic T cells and NK cells. Although the nature of the γδ T cell immune exhaustion is not well reported, prolonged stimulation of γδ T cells appears to trigger their immune exhaustion. Since the immune exhaustion is reviewed extensively elsewhere (93-95), it will not be discussed here. It would be important and interesting to address how easily and deeply γδ T cells are exhausted and whether exhausted γδ T cells can be easily reawakened by strong stimuli, including cytokines or Ags such as phosphoantigens.

FUTURE DIRECTIONS FOR OPTIMIZING ADOPTIVE γδ T CELL TRANSFER AS AN ALTERNATIVE CANCER IMMUNOTHERAPY

The ability of γδ T cells to recognize the cellular stress via an MHC-independent mechanism and to potentiate other innate and adaptive immune cells makes them attractive mediators of cancer immunotherapy with potent and broad anti-tumor cytotoxicity (4,7,11,64,65,68,77,82,85,89). Especially, given their potent MHC-unrestricted anti-tumor activities, γδ T cells also can be considered as universal allogeneic adoptive T cell transfer for cancer patients. Accordingly, recent applications of γδ T cells to solid tumors have yielded promising results with associated clinical benefits, but issues of limited efficacy still remain with an average response ratio of only 21% and low proportion of complete remissions (7,14-16,85,96,97). Unfortunately, the tumor cells are effectively protected from tumor cell-killing immune activities in the immune-suppressive TME, which may also block the infiltration of infused γδ T cells. Furthermore, the anti-tumor function of γδ T cells can be limited by the pleiotropic effects of a mixture of heterogeneous populations of immune cells in the TME (4,7,14,16,63,64,85,97).

Therefore, current efforts in favor of a durable anti-tumor benefit from γδ T cell immunotherapy lie in the quest to minimize activation-induced γδ T cell death, anergy, and the polarization to specific γδ T cells with immunosuppressive function (4,7,14,15,92,98-100). Additionally, several cytokines such as IL-15, IL-18, and IL-21 have been found to have the ability to promote the

expansion of γδ T cells with a higher proliferative capacity, a more pronounced Th1 polarization, and an increased cytotoxic capacity and secretion of immune-stimulating paracrine factors such as GM-CSF, IFN-γ, and TNF-α (101-103). In particular, disruption of the immunosuppressive TME could be a new strategy for improving the anti-tumor efficacy of γδ T cells. For example, IL-36γ acts synergistically with TCR signaling and is able to promote IFN-γ production by $CD8^+$ T cells, NK cells, and γδ T cells by transforming the TME in favor of cancer eradication (104).

Up to date, clinical trials have been based on the adoptive transfer of peripheral circulating Vγ9Vδ2 T cells after *ex vivo* expansion and activation (11,15,16,68,82,97,105). Given the accumulating pieces of evidence supporting the superior anti-tumor functionality of Vδ1 T cells compared with that of Vγ9Vδ2 T cells, at least in the context of certain tumors (14,67,77,98,99,106-110), Vδ1 T cells may be a potent tool for clinical manipulation in cancer immunotherapy, and efforts have been put forth to explore strategies for clinical-grade expansion. An interesting property of Vδ1 T cells for the adoptive transfer approach is their CCL2-mediated chemotaxis toward tumors (67,111,112). Vδ1 T cells are also less susceptible to activation-induced cell death and could persist in the circulation for many years, which is in favor of a durable anti-tumor immunity (98,99,110). Intriguingly, IL-4 promotes the proliferation of Vδ1 T cells and simultaneously inhibits Vδ2 T-cell growth (77,80,113), thus providing a novel basis to develop the preferential expansion approaches for Vδ1 T cells.

CONCLUDING REMARKS

Although γδ T cells are a small population of lymphocytes, they contribute significantly to rapid and sustained immune responses against cancer. In order to utilize the inherent activity of γδ T cells for cancer immunotherapy, it is critical to better characterize human γδ T cell subsets and the engaged mechanisms in various types of cancers. It is also necessary to understand the central paradigms that govern the tissue tropism, the stage of differentiation, the activation status, and the immune checkpoint receptor expression in γδ T cells so that γδ T cells can be durably activated with a potent anti-tumor phenotype. To maintain the anti-tumor activity of γδ T cells for a long period of time, the specific depletion of pro-tumor γδ T cells before the immunotherapy, the co-transfer of other immune cells that activate γδ T cells, and the modification of the cytokine balance in the TME should be considered in the immunotherapy using γδ T cells. In summary, as γδ T cells are heterogeneous, the pro-tumor or anti-tumor activities of different γδ T cell populations need to be thoroughly delineated and utilized to maximize the efficacy of the immunotherapy using γδ T cells.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. NRF-2019R1A2C2006717 and NRF-2017R1A6A3A11034402).

REFERENCES

1. Vantourout P, Hayday A. Six-of-the-best: unique contributions of γδ T cells to immunology. *Nat Rev Immunol* 2013;13:88-100.
PUBMED | CROSSREF

2. Adams EJ, Gu S, Luoma AM. Human gamma delta T cells: evolution and ligand recognition. *Cell Immunol* 2015;296:31-40.
PUBMED | CROSSREF
3. Chien YH, Meyer C, Bonneville M. γδ T cells: first line of defense and beyond. *Annu Rev Immunol* 2014;32:121-155.
PUBMED | CROSSREF
4. Stolk D, van der Vliet HJ, de Gruijl TD, van Kooyk Y, Exley MA. Positive & negative roles of innate effector cells in controlling cancer progression. *Front Immunol* 2018;9:1990.
PUBMED | CROSSREF
5. Girardi M, Oppenheim DE, Steele CR, Lewis JM, Glusac E, Filler R, Hobby P, Sutton B, Tigelaar RE, Hayday AC. Regulation of cutaneous malignancy by gammadelta T cells. *Science* 2001;294:605-609.
PUBMED | CROSSREF
6. Mishra R, Chen AT, Welsh RM, Szomolanyi-Tsuda E. NK cells and gammadelta T cells mediate resistance to polyomavirus-induced tumors. *PLoS Pathog* 2010;6:e1000924.
PUBMED | CROSSREF
7. Zhao Y, Niu C, Cui J. Gamma-delta (γδ) T cells: friend or foe in cancer development? *J Transl Med* 2018;16:3.
PUBMED | CROSSREF
8. Barrow AD, Martin CJ, Colonna M. The natural cytotoxicity receptors in health and disease. *Front Immunol* 2019;10:909.
PUBMED | CROSSREF
9. Wrobel P, Shojaei H, Schittek B, Gieseler F, Wollenberg B, Kalthoff H, Kabelitz D, Wesch D. Lysis of a broad range of epithelial tumour cells by human gamma delta T cells: involvement of NKG2D ligands and T-cell receptor- versus NKG2D-dependent recognition. *Scand J Immunol* 2007;66:320-328.
PUBMED | CROSSREF
10. Braza MS, Klein B. Anti-tumour immunotherapy with Vγ9Vδ2 T lymphocytes: from the bench to the bedside. *Br J Haematol* 2013;160:123-132.
PUBMED | CROSSREF
11. Hannani D, Ma Y, Yamazaki T, Déchanet-Merville J, Kroemer G, Zitvogel L. Harnessing γδ T cells in anticancer immunotherapy. *Trends Immunol* 2012;33:199-206.
PUBMED | CROSSREF
12. Kunzmann V, Smetak M, Kimmel B, Weigang-Koehler K, Goebeler M, Birkmann J, Becker J, Schmidt-Wolf IG, Einsele H, Wilhelm M. Tumor-promoting versus tumor-antagonizing roles of γδ T cells in cancer immunotherapy: results from a prospective phase I/II trial. *J Immunother* 2012;35:205-213.
PUBMED | CROSSREF
13. Nicol AJ, Tokuyama H, Mattarollo SR, Hagi T, Suzuki K, Yokokawa K, Nieda M. Clinical evaluation of autologous gamma delta T cell-based immunotherapy for metastatic solid tumours. *Br J Cancer* 2011;105:778-786.
PUBMED | CROSSREF
14. Rei M, Pennington DJ, Silva-Santos B. The emerging protumor role of γδ T lymphocytes: implications for cancer immunotherapy. *Cancer Res* 2015;75:798-802.
PUBMED | CROSSREF
15. Fournié JJ, Sicard H, Poupot M, Bezombes C, Blanc A, Romagné F, Ysebaert L, Laurent G. What lessons can be learned from γδ T cell-based cancer immunotherapy trials? *Cell Mol Immunol* 2013;10:35-41.
PUBMED | CROSSREF
16. Lo Presti E, Pizzolato G, Gulotta E, Cocorullo G, Gulotta G, Dieli F, Meraviglia S. Current advances in γδ T cell-based tumor immunotherapy. *Front Immunol* 2017;8:1401.
PUBMED | CROSSREF
17. Xiang Z, Tu W. Dual face of Vγ9Vδ2-T cells in tumor immunology: anti- versus pro-tumoral activities. *Front Immunol* 2017;8:1041.
PUBMED | CROSSREF
18. Turchinovich G, Pennington DJ. T cell receptor signalling in γδ cell development: strength isn't everything. *Trends Immunol* 2011;32:567-573.
PUBMED | CROSSREF
19. Baker JE, Cado D, Raulet DH. Developmentally programmed rearrangement of T cell receptor Vgamma genes is controlled by sequences immediately upstream of the Vgamma genes. *Immunity* 1998;9:159-168.
PUBMED | CROSSREF
20. Chodaczek G, Papanna V, Zal MA, Zal T. Body-barrier surveillance by epidermal γδ TCRs. *Nat Immunol* 2012;13:272-282.
PUBMED | CROSSREF

21. Boyden LM, Lewis JM, Barbee SD, Bas A, Girardi M, Hayday AC, Tigelaar RE, Lifton RP. Skint1, the prototype of a newly identified immunoglobulin superfamily gene cluster, positively selects epidermal gammadelta T cells. *Nat Genet* 2008;40:656-662.
PUBMED | CROSSREF

22. Bonneville M, O'Brien RL, Born WK. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. *Nat Rev Immunol* 2010;10:467-478.
PUBMED | CROSSREF

23. O'Brien RL, Born WK. Gammadelta T cell subsets: a link between TCR and function? *Semin Immunol* 2010;22:193-198.
PUBMED | CROSSREF

24. Vermijlen D, Prinz I. Ontogeny of innate T lymphocytes - some innate lymphocytes are more innate than others. *Front Immunol* 2014;5:486.
PUBMED | CROSSREF

25. Lanier LL, Weiss A. Presence of Ti (WT31) negative T lymphocytes in normal blood and thymus. *Nature* 1986;324:268-270.
PUBMED | CROSSREF

26. Morita CT, Parker CM, Brenner MB, Band H. TCR usage and functional capabilities of human gamma delta T cells at birth. *J Immunol* 1994;153:3979-3988.
PUBMED

27. Vermijlen D, Brouwer M, Donner C, Liesnard C, Tackoen M, Van Rysselberge M, Twité N, Goldman M, Marchant A, Willems F. Human cytomegalovirus elicits fetal gammadelta T cell responses in utero. *J Exp Med* 2010;207:807-821.
PUBMED | CROSSREF

28. Parker CM, Groh V, Band H, Porcelli SA, Morita C, Fabbi M, Glass D, Strominger JL, Brenner MB. Evidence for extrathymic changes in the T cell receptor gamma/delta repertoire. *J Exp Med* 1990;171:1597-1612.
PUBMED | CROSSREF

29. Cairo C, Mancino G, Cappelli G, Pauza CD, Galli E, Brunetti E, Colizzi V. Vdelta2 T-lymphocyte responses in cord blood samples from Italy and Côte d'Ivoire. *Immunology* 2008;124:380-387.
PUBMED | CROSSREF

30. Moens E, Brouwer M, Dimova T, Goldman M, Willems F, Vermijlen D. IL-23R and TCR signaling drives the generation of neonatal Vgamma9Vdelta2 T cells expressing high levels of cytotoxic mediators and producing IFN-gamma and IL-17. *J Leukoc Biol* 2011;89:743-752.
PUBMED | CROSSREF

31. De Rosa SC, Andrus JP, Perfetto SP, Mantovani JJ, Herzenberg LA, Herzenberg LA, Roederer M. Ontogeny of gamma delta T cells in humans. *J Immunol* 2004;172:1637-1645.
PUBMED | CROSSREF

32. Cruz MS, Diamond A, Russell A, Jameson JM. Human αβ and γδ T cells in skin immunity and disease. *Front Immunol* 2018;9:1304.
PUBMED | CROSSREF

33. Allison TJ, Winter CC, Fournié JJ, Bonneville M, Garboczi DN. Structure of a human gammadelta T-cell antigen receptor. *Nature* 2001;411:820-824.
PUBMED | CROSSREF

34. Legut M, Cole DK, Sewell AK. The promise of γδ T cells and the γδ T cell receptor for cancer immunotherapy. *Cell Mol Immunol* 2015;12:656-668.
PUBMED | CROSSREF

35. Davey MS, Willcox CR, Baker AT, Hunter S, Willcox BE. Recasting human Vδ1 lymphocytes in an adaptive role. *Trends Immunol* 2018;39:446-459.
PUBMED | CROSSREF

36. Pizzolato G, Kaminski H, Tosolini M, Franchini DM, Pont F, Martins F, Valle C, Labourdette D, Cadot S, Quillet-Mary A, et al. Single-cell RNA sequencing unveils the shared and the distinct cytotoxic hallmarks of human TCRVδ1 and TCRVδ2 γδ T lymphocytes. *Proc Natl Acad Sci U S A* 2019;116:11906-11915.
PUBMED | CROSSREF

37. Kazen AR, Adams EJ. Evolution of the V, D, and J gene segments used in the primate gammadelta T-cell receptor reveals a dichotomy of conservation and diversity. *Proc Natl Acad Sci U S A* 2011;108:E332-E340.
PUBMED | CROSSREF

38. Vavassori S, Kumar A, Wan GS, Ramanjaneyulu GS, Cavallari M, El Daker S, Beddoe T, Theodossis A, Williams NK, Gostick E, et al. Butyrophilin 3A1 binds phosphorylated antigens and stimulates human γδ T cells. *Nat Immunol* 2013;14:908-916.
PUBMED | CROSSREF

39. Simões AE, Di Lorenzo B, Silva-Santos B. Molecular determinants of target cell recognition by human γδ T cells. *Front Immunol* 2018;9:929.
PUBMED | CROSSREF

40. Hayes SM, Love PE. Stoichiometry of the murine gammadelta T cell receptor. *J Exp Med* 2006;203:47-52.
PUBMED | CROSSREF

41. Malissen M, Gillet A, Ardouin L, Bouvier G, Trucy J, Ferrier P, Vivier E, Malissen B. Altered T cell development in mice with a targeted mutation of the CD3-epsilon gene. *EMBO J* 1995;14:4641-4653.
PUBMED | CROSSREF

42. Dave VP, Cao Z, Browne C, Alarcon B, Fernandez-Miguel G, Lafaille J, de la Hera A, Tonegawa S, Kappes DJ. CD3 delta deficiency arrests development of the alpha beta but not the gamma delta T cell lineage. *EMBO J* 1997;16:1360-1370.
PUBMED | CROSSREF

43. Haks MC, Krimpenfort P, Borst J, Kruisbeek AM. The CD3gamma chain is essential for development of both the TCRalphabeta and TCRgammadelta lineages. *EMBO J* 1998;17:1871-1882.
PUBMED | CROSSREF

44. Hayes SM, Love PE. Distinct structure and signaling potential of the gamma delta TCR complex. *Immunity* 2002;16:827-838.
PUBMED | CROSSREF

45. Siegers GM, Swamy M, Fernández-Malavé E, Minguet S, Rathmann S, Guardo AC, Pérez-Flores V, Regueiro JR, Alarcón B, Fisch P, et al. Different composition of the human and the mouse gammadelta T cell receptor explains different phenotypes of CD3gamma and CD3delta immunodeficiencies. *J Exp Med* 2007;204:2537-2544.
PUBMED | CROSSREF

46. Recio MJ, Moreno-Pelayo MA, Kiliç SS, Guardo AC, Sanal O, Allende LM, Pérez-Flores V, Mencía A, Modamio-Høybjør S, Seoane E, et al. Differential biological role of CD3 chains revealed by human immunodeficiencies. *J Immunol* 2007;178:2556-2564.
PUBMED | CROSSREF

47. Jensen KD, Su X, Shin S, Li L, Youssef S, Yamasaki S, Steinman L, Saito T, Locksley RM, Davis MM, et al. Thymic selection determines gammadelta T cell effector fate: antigen-naive cells make interleukin-17 and antigen-experienced cells make interferon gamma. *Immunity* 2008;29:90-100.
PUBMED | CROSSREF

48. Taghon T, Yui MA, Pant R, Diamond RA, Rothenberg EV. Developmental and molecular characterization of emerging beta- and gammadelta-selected pre-T cells in the adult mouse thymus. *Immunity* 2006;24:53-64.
PUBMED | CROSSREF

49. Lafont V, Sanchez F, Laprevotte E, Michaud HA, Gros L, Eliaou JF, Bonnefoy N. Plasticity of γδ T cells: impact on the anti-tumor response. *Front Immunol* 2014;5:622.
PUBMED | CROSSREF

50. Hayday A, Tigelaar R. Casting new light on the TCR. *Nat Immunol* 2012;13:209-211.
PUBMED | CROSSREF

51. Parham P, Moffett A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. *Nat Rev Immunol* 2013;13:133-144.
PUBMED | CROSSREF

52. Wensveen FM, Jelenčić V, Polić B. NKG2D: a master regulator of immune cell responsiveness. *Front Immunol* 2018;9:441.
PUBMED | CROSSREF

53. Ribot JC, debarros A, Silva-Santos B. Searching for "signal 2": costimulation requirements of γδ T cells. *Cell Mol Life Sci* 2011;68:2345-2355.
PUBMED | CROSSREF

54. Testi R, Lanier LL. Functional expression of CD28 on T cell antigen receptor gamma/delta-bearing T lymphocytes. *Eur J Immunol* 1989;19:185-188.
PUBMED | CROSSREF

55. Penninger JM, Timms E, Shahinian A, Jezo-Bremond A, Nishina H, Ionescu J, Hedrick SM, Mak TW. Alloreactive gamma delta thymocytes utilize distinct costimulatory signals from peripheral T cells. *J Immunol* 1995;155:3847-3855.
PUBMED

56. Hamann D, Baars PA, Rep MH, Hooibrink B, Kerkhof-Garde SR, Klein MR, van Lier RA. Phenotypic and functional separation of memory and effector human CD8+ T cells. *J Exp Med* 1997;186:1407-1418.
PUBMED | CROSSREF

57. De Rosa SC, Mitra DK, Watanabe N, Herzenberg LA, Herzenberg LA, Roederer M. Vdelta1 and Vdelta2 gammadelta T cells express distinct surface markers and might be developmentally distinct lineages. *J Leukoc Biol* 2001;70:518-526.
PUBMED

58. Seelige R, Searles S, Bui JD. Mechanisms regulating immune surveillance of cellular stress in cancer. *Cell Mol Life Sci* 2018;75:225-240.
PUBMED | CROSSREF

59. Bassani B, Baci D, Gallazzi M, Poggi A, Bruno A, Mortara L. Natural killer cells as key players of tumor progression and angiogenesis: old and novel tools to divert their pro-tumor activities into potent anti-tumor effects. *Cancers (Basel)* 2019;11:461.
PUBMED | CROSSREF

60. O'Donnell JS, Teng MW, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat Rev Clin Oncol* 2019;16:151-167.
PUBMED | CROSSREF

61. Runa F, Hamalian S, Meade K, Shisgal P, Gray PC, Kelber JA. Tumor microenvironment heterogeneity: challenges and opportunities. *Curr Mol Biol Rep* 2017;3:218-229.
PUBMED | CROSSREF

62. Nakamura K, Smyth MJ. Targeting cancer-related inflammation in the era of immunotherapy. *Immunol Cell Biol* 2017;95:325-332.
PUBMED | CROSSREF

63. Lo Presti E, Di Mitri R, Pizzolato G, Mocciaro F, Dieli F, Meraviglia S. γδ cells and tumor microenvironment: a helpful or a dangerous liason? *J Leukoc Biol* 2018;103:485-492.
PUBMED | CROSSREF

64. Paul S, Lal G. Regulatory and effector functions of gamma-delta (γδ) T cells and their therapeutic potential in adoptive cellular therapy for cancer. *Int J Cancer* 2016;139:976-985.
PUBMED | CROSSREF

65. Silva-Santos B, Serre K, Norell H. γδ T cells in cancer. *Nat Rev Immunol* 2015;15:683-691.
PUBMED | CROSSREF

66. Lee M, Park C, Woo J, Kim J, Kho I, Nam DH, Park WY, Kim YS, Kong DS, Lee HW, et al. Preferential infiltration of unique Vγ9Jγ2-Vδ2 T cells into glioblastoma multiforme. *Front Immunol* 2019;10:555.
PUBMED | CROSSREF

67. Cordova A, Toia F, La Mendola C, Orlando V, Meraviglia S, Rinaldi G, Todaro M, Cicero G, Zichichi L, Donni PL, et al. Characterization of human γδ T lymphocytes infiltrating primary malignant melanomas. *PLoS One* 2012;7:e49878.
PUBMED | CROSSREF

68. Deniger DC, Moyes JS, Cooper LJ. Clinical applications of gamma delta T cells with multivalent immunity. *Front Immunol* 2014;5:636.
PUBMED | CROSSREF

69. Davey MS, Willcox CR, Joyce SP, Ladell K, Kasatskaya SA, McLaren JE, Hunter S, Salim M, Mohammed F, Price DA, et al. Clonal selection in the human Vδ1 T cell repertoire indicates γδ TCR-dependent adaptive immune surveillance. *Nat Commun* 2017;8:14760.
PUBMED | CROSSREF

70. Sandstrom A, Peigné CM, Léger A, Crooks JE, Konczak F, Gesnel MC, Breathnach R, Bonneville M, Scotet E, Adams EJ. The intracellular B30.2 domain of butyrophilin 3A1 binds phosphoantigens to mediate activation of human Vγ9Vδ2 T cells. *Immunity* 2014;40:490-500.
PUBMED | CROSSREF

71. Yang Y, Li L, Yuan L, Zhou X, Duan J, Xiao H, Cai N, Han S, Ma X, Liu W, et al. A structural change in butyrophilin upon phosphoantigen binding underlies phosphoantigen-mediated Vγ9Vδ2 T cell activation. *Immunity* 2019;50:1043-1053.e5.
PUBMED | CROSSREF

72. Sebestyen Z, Scheper W, Vyborova A, Gu S, Rychnavska Z, Schiffler M, Cleven A, Chéneau C, van Noorden M, Peigné CM, et al. RhoB mediates phosphoantigen recognition by Vγ9Vδ2 T cell receptor. *Cell Reports* 2016;15:1973-1985.
PUBMED | CROSSREF

73. Rigau M, Ostrouska S, Fulford TS, Johnson DN, Woods K, Ruan Z, McWilliam HE, Hudson C, Tutuka C, Wheatley AK, et al. Butyrophilin 2A1 is essential for phosphoantigen reactivity by γδ T cells. *Science* 2020;367:eaay5516.
PUBMED | CROSSREF

74. Dai Y, Chen H, Mo C, Cui L, He W. Ectopically expressed human tumor biomarker MutS homologue 2 is a novel endogenous ligand that is recognized by human γδ T cells to induce innate anti-tumor/virus immunity. *J Biol Chem* 2012;287:16812-16819.
PUBMED | CROSSREF

75. Tyler CJ, Doherty DG, Moser B, Eberl M. Human Vγ9/Vδ2 T cells: innate adaptors of the immune system. *Cell Immunol* 2015;296:10-21.
PUBMED | CROSSREF

76. Uldrich AP, Le Nours J, Pellicci DG, Gherardin NA, McPherson KG, Lim RT, Patel O, Beddoe T, Gras S, Rossjohn J, et al. CD1d-lipid antigen recognition by the γδ TCR. *Nat Immunol* 2013;14:1137-1145.
PUBMED | CROSSREF

77. Wu D, Wu P, Qiu F, Wei Q, Huang J. Human γδT-cell subsets and their involvement in tumor immunity. *Cell Mol Immunol* 2017;14:245-253.
PUBMED | CROSSREF

78. Le Nours J, Gherardin NA, Ramarathinam SH, Awad W, Wiede F, Gully BS, Khandokar Y, Praveena T, Wubben JM, Sandow JJ, et al. A class of γδ T cell receptors recognize the underside of the antigen-presenting molecule MR1. *Science* 2019;366:1522-1527.
PUBMED | CROSSREF

79. Hudspeth K, Silva-Santos B, Mavilio D. Natural cytotoxicity receptors: broader expression patterns and functions in innate and adaptive immune cells. *Front Immunol* 2013;4:69.
PUBMED | CROSSREF

80. Almeida AR, Correia DV, Fernandes-Platzgummer A, da Silva CL, da Silva MG, Anjos DR, Silva-Santos B. Delta one t cells for immunotherapy of chronic lymphocytic leukemia: clinical-grade expansion/differentiation and preclinical proof of concept. *Clin Cancer Res* 2016;22:5795-5804.
PUBMED | CROSSREF

81. Willcox CR, Pitard V, Netzer S, Couzi L, Salim M, Silberzahn T, Moreau JF, Hayday AC, Willcox BE, Déchanet-Merville J. Cytomegalovirus and tumor stress surveillance by binding of a human γδ T cell antigen receptor to endothelial protein C receptor. *Nat Immunol* 2012;13:872-879.
PUBMED | CROSSREF

82. Deniger DC, Maiti SN, Mi T, Switzer KC, Ramachandran V, Hurton LV, Ang S, Olivares S, Rabinovich BA, Huls MH, et al. Activating and propagating polyclonal gamma delta T cells with broad specificity for malignancies. *Clin Cancer Res* 2014;20:5708-5719.
PUBMED | CROSSREF

83. Li Z, Xu Q, Peng H, Cheng R, Sun Z, Ye Z. IFN-γ enhances HOS and U2OS cell lines susceptibility to γδ T cell-mediated killing through the Fas/Fas ligand pathway. *Int Immunopharmacol* 2011;11:496-503.
PUBMED | CROSSREF

84. Tawfik D, Groth C, Gundlach JP, Peipp M, Kabelitz D, Becker T, Oberg HH, Trauzold A, Wesch D. TRAIL-receptor 4 modulates γδ T cell-cytotoxicity toward cancer cells. *Front Immunol* 2019;10:2044.
PUBMED | CROSSREF

85. Pauza CD, Liou ML, Lahusen T, Xiao L, Lapidus RG, Cairo C, Li H. Gamma delta T cell therapy for cancer: it is good to be local. *Front Immunol* 2018;9:1305.
PUBMED | CROSSREF

86. Angelini DF, Borsellino G, Poupot M, Diamantini A, Poupot R, Bernardi G, Poccia F, Fournié JJ, Battistini L. FcgammaRIII discriminates between 2 subsets of Vgamma9Vdelta2 effector cells with different responses and activation pathways. *Blood* 2004;104:1801-1807.
PUBMED | CROSSREF

87. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, Nair VS, Xu Y, Khuong A, Hoang CD, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nat Med* 2015;21:938-945.
PUBMED | CROSSREF

88. Meraviglia S, Lo Presti E, Tosolini M, La Mendola C, Orlando V, Todaro M, Catalano V, Stassi G, Cicero G, Vieni S, et al. Distinctive features of tumor-infiltrating γδ T lymphocytes in human colorectal cancer. *OncoImmunology* 2017;6:e1347742.
PUBMED | CROSSREF

89. Kim JS, Kim YG, Park EJ, Kim B, Lee HK, Hong JT, Kim Y, Han SB. Cell-based immunotherapy for colorectal cancer with cytokine-induced killer cells. *Immune Netw* 2016;16:99-108.
PUBMED | CROSSREF

90. Park C, Kim TJ. Expansion and sub-classification of T cell-dependent antibody responses to encompass the role of innate-like T cells in antibody responses. *Immune Netw* 2018;18:e34.
PUBMED | CROSSREF

91. Gu-Trantien C, Loi S, Garaud S, Equeter C, Libin M, de Wind A, Ravoet M, Le Buanec H, Sibille C, Manfouo-Foutsop G, et al. CD4+ follicular helper T cell infiltration predicts breast cancer survival. *J Clin Invest* 2013;123:2873-2892.
PUBMED | CROSSREF

92. Caccamo N, La Mendola C, Orlando V, Meraviglia S, Todaro M, Stassi G, Sireci G, Fournié JJ, Dieli F. Differentiation, phenotype, and function of interleukin-17-producing human Vγ9Vδ2 T cells. *Blood* 2011;118:129-138.
PUBMED | CROSSREF

93. Thommen DS, Schumacher TN. T cell dysfunction in cancer. *Cancer Cell* 2018;33:547-562.
PUBMED | CROSSREF

94. Xia A, Zhang Y, Xu J, Yin T, Lu XJ. T cell dysfunction in cancer immunity and immunotherapy. *Front Immunol* 2019;10:1719.
PUBMED | CROSSREF

95. Kim PS, Ahmed R. Features of responding T cells in cancer and chronic infection. *Curr Opin Immunol* 2010;22:223-230.
PUBMED | CROSSREF

96. Meraviglia S, Caccamo N, Guggino G, Tolomeo M, Siragusa S, Stassi G, Dieli F. Optimizing tumor-reactive γδ T cells for antibody-based cancer immunotherapy. *Curr Mol Med* 2010;10:719-726.
PUBMED | CROSSREF

97. Zou C, Zhao P, Xiao Z, Han X, Fu F, Fu L. γδ T cells in cancer immunotherapy. *Oncotarget* 2017;8:8900-8909.
PUBMED

98. Wu D, Wu P, Wu X, Ye J, Wang Z, Zhao S, Ni C, Hu G, Xu J, Han Y, et al. *Ex vivo* expanded human circulating Vδ1 γδT cells exhibit favorable therapeutic potential for colon cancer. *OncoImmunology* 2015;4:e992749.
PUBMED | CROSSREF

99. Siegers GM, Dhamko H, Wang XH, Mathieson AM, Kosaka Y, Felizardo TC, Medin JA, Tohda S, Schueler J, Fisch P, et al. Human Vδ1 γδ T cells expanded from peripheral blood exhibit specific cytotoxicity against B-cell chronic lymphocytic leukemia-derived cells. *Cytotherapy* 2011;13:753-764.
PUBMED | CROSSREF

100. Gonçalves-Sousa N, Ribot JC, deBarros A, Correia DV, Caramalho I, Silva-Santos B. Inhibition of murine gammadelta lymphocyte expansion and effector function by regulatory alphabeta T cells is cell-contact-dependent and sensitive to GITR modulation. *Eur J Immunol* 2010;40:61-70.
PUBMED | CROSSREF

101. Li W, Kubo S, Okuda A, Yamamoto H, Ueda H, Tanaka T, Nakamura H, Yamanishi H, Terada N, Okamura H. Effect of IL-18 on expansion of gammadelta T cells stimulated by zoledronate and IL-2. *J Immunother* 2010;33:287-296.
PUBMED | CROSSREF

102. Li W, Yamamoto H, Kubo S, Okamura H. Modulation of innate immunity by IL-18. *J Reprod Immunol* 2009;83:101-105.
PUBMED | CROSSREF

103. Van Acker HH, Anguille S, Willemen Y, Van den Bergh JM, Berneman ZN, Lion E, Smits EL, Van Tendeloo VF. Interleukin-15 enhances the proliferation, stimulatory phenotype, and antitumor effector functions of human gamma delta T cells. *J Hematol Oncol* 2016;9:101.
PUBMED | CROSSREF

104. Wang X, Zhao X, Feng C, Weinstein A, Xia R, Wen W, Lv Q, Zuo S, Tang P, Yang X, et al. IL-36γ transforms the tumor microenvironment and promotes type 1 lymphocyte-mediated antitumor immune responses. *Cancer Cell* 2015;28:296-306.
PUBMED | CROSSREF

105. Thedrez A, Harly C, Morice A, Salot S, Bonneville M, Scotet E. IL-21-mediated potentiation of antitumor cytolytic and proinflammatory responses of human V gamma 9V delta 2 T cells for adoptive immunotherapy. *J Immunol* 2009;182:3423-3431.
PUBMED | CROSSREF

106. Chen J, Niu H, He W, Ba D. Antitumor activity of expanded human tumor-infiltrating gammadelta T lymphocytes. *Int Arch Allergy Immunol* 2001;125:256-263.
PUBMED | CROSSREF

107. Choudhary A, Davodeau F, Moreau A, Peyrat MA, Bonneville M, Jotereau F. Selective lysis of autologous tumor cells by recurrent gamma delta tumor-infiltrating lymphocytes from renal carcinoma. *J Immunol* 1995;154:3932-3940.
PUBMED

108. Couzi L, Levaillant Y, Jamai A, Pitard V, Lassalle R, Martin K, Garrigue I, Hawchar O, Siberchicot F, Moore N, et al. Cytomegalovirus-induced gammadelta T cells associate with reduced cancer risk after kidney transplantation. *J Am Soc Nephrol* 2010;21:181-188.
PUBMED | CROSSREF

109. Knight A, Arnouk H, Britt W, Gillespie GY, Cloud GA, Harkins L, Su Y, Lowdell MW, Lamb LS. CMV-independent lysis of glioblastoma by *ex vivo* expanded/activated Vδ1+ γδ T cells. *PLoS One* 2013;8:e68729.
PUBMED | CROSSREF

110. Knight A, Mackinnon S, Lowdell MW. Human Vdelta1 gamma-delta T cells exert potent specific cytotoxicity against primary multiple myeloma cells. *Cytotherapy* 2012;14:1110-1118.
PUBMED | CROSSREF

111. Lança T, Costa MF, Gonçalves-Sousa N, Rei M, Grosso AR, Penido C, Silva-Santos B. Protective role of the inflammatory CCR2/CCL2 chemokine pathway through recruitment of type 1 cytotoxic γδ T lymphocytes to tumor beds. *J Immunol* 2013;190:6673-6680.
PUBMED | CROSSREF

112. Peng G, Wang HY, Peng W, Kiniwa Y, Seo KH, Wang RF. Tumor-infiltrating gammadelta T cells suppress T and dendritic cell function via mechanisms controlled by a unique toll-like receptor signaling pathway. *Immunity* 2007;27:334-348.
PUBMED | CROSSREF

113. Mao Y, Yin S, Zhang J, Hu Y, Huang B, Cui L, Kang N, He W. A new effect of IL-4 on human γδ T cells: promoting regulatory Vδ1 T cells via IL-10 production and inhibiting function of Vδ2 T cells. *Cell Mol Immunol* 2016;13:217-228.
PUBMED | CROSSREF