REVIEW

Recent advances in understanding the development and function of $\gamma\delta$ T cells [version 1; peer review: 2 approved]

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Abstract

$\gamma\delta$ T cells are a subset of T cells with attributes of both the innate and adaptive arms of the immune system. These cells have long been an enigmatic and poorly understood component of the immune system and many have viewed them as having limited importance in host defense. This perspective persisted for some time both because of critical gaps in knowledge regarding how the development of $\gamma\delta$ T cells is regulated and because of the lack of effective and sophisticated approaches through which the function of $\gamma\delta$ T cells can be manipulated. Here, we discuss the recent advances in both of these areas, which have brought the importance of $\gamma\delta$ T cells in both productive and pathologic immune function more sharply into focus.

Keywords

$\gamma\delta$ T cells, development, function, immune response

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Introduction and context

The cloning of the T-cell receptor (TCR) γ chain in 1984 led to the discovery of the second major T-cell lineage, $\gamma\delta$ T cells¹⁻⁴. $\gamma\delta$ T cells use the $\gamma\delta$ TCR complex to recognize antigen and differ from $\alpha\beta$ T cells in numerous ways, including their phenotype, anatomic location, and contribution to host immunity^{5,6}. Since the discovery of the $\gamma\delta$ lineage, immunologists have sought to decipher how it is specified during development and gain a comprehensive understanding of how this enigmatic T-cell subset contributes to host defense. These efforts have led to substantial progress over the past 15 years. Indeed, $\gamma\delta$ lineage T cells have been shown to arise from the same progenitor pool as $\alpha\beta$ lineage T cells⁷, and TCR signal strength has been shown to be a key determiner of lineage identity^{8,9}. Moreover, unlike $\alpha\beta$ lineage T cells that exit the thymus as naïve T cells, many $\gamma\delta$ lineage T cells have been shown to acquire effector function in the thymus¹⁰⁻¹⁴, and the generation of interleukin-17 (IL-17)-producing $\gamma\delta$ cells has been shown to occur primarily during fetal life¹⁵. Finally, numerous $\gamma\delta$ TCR ligands have been identified, revealing that $\gamma\delta$ TCR ligands do not generally require processing or presentation by major histocompatibility complex (MHC) antigens¹⁶, and $\gamma\delta$ TCR recognition of ligand is more reminiscent of ligand binding by antibody than by the $\alpha\beta$ TCR^{17,18}. However, an exception to this general rule was recently reported, indicating that human $\gamma\delta$ T cells are capable of recognizing melanoma-associated antigenic peptides in an MHC-restricted manner¹⁹. $\gamma\delta$ TCR ligands include a diverse array of unprocessed molecules, such as non-classic MHC class Ib molecules, H2-T10 and H2-T22, lipids presented via CD1 family members, MHC-related protein 1 (MR1), which presents vitamin B derivatives, and annexin A2, a molecule expressed on the cell surface in response to oxidative stress²⁰⁻²³. Both the capacity of $\gamma\delta$ T cells to recognize ligands associated with infection, tissue stress, and transformation and their abundance at epithelial surfaces have direct implications for function, allowing $\gamma\delta$ T cells to contribute to host defense through recognizing stress- and tumor-associated molecules expressed by epithelial or tumor cells and promote a rapid stress surveillance response^{6,24}. Despite the impressive progress noted above, many important and contentious questions remain to be addressed. These include the role of ligand and TCR signaling in controlling $\gamma\delta$ T-cell development, the influence of TCR-independent pre-programming on effector fate, and the ultimate contribution of $\gamma\delta$ T cells to host defense. Here, we examine recent efforts to address these gaps in understanding.

Major recent advances

$\gamma\delta$ TCR ligands and their effect on $\gamma\delta$ T-cell development and function

One of the primary impediments to a deeper understanding of how $\gamma\delta$ T-cell development and function are controlled is the paucity of known $\gamma\delta$ TCR ligands, particularly those implicated in development. In recent years, efforts to identify $\gamma\delta$ TCR ligands have been increasingly successful, revealing that $\gamma\delta$ TCR ligands generally do not require the processing events necessary to generate $\alpha\beta$ TCR ligands²⁵. The identity of many of these molecules, such as the non-classic MHC-I molecules

H-2T22, as specific ligands has been validated by measures of direct interaction, such as x-ray crystallography or surface plasmon resonance^{26,27}. However, the legitimacy of another set of putative ligands, the B7-like members of the butyrophilin (BTN) or butyrophilin-like (BTNL) family, was long questioned because of the absence of demonstrable physical interaction with the $\gamma\delta$ TCR^{10,28}. Indeed, murine BTNL family member, Skint-1, is critical for thymic selection of the V γ 5V δ 1⁺ subset of dendritic epidermal T cells (DETCs) and their homing to the skin^{29,30}. Likewise, human family member BTN3A1 is critical for phospho-antigen (p-Ag)-mediated activation of human V γ 9⁺V δ 2⁺ T cells³¹. Nevertheless, unequivocal evidence for direct binding of these putative ligands to the $\gamma\delta$ TCR was lacking²⁵.

Recent efforts have addressed this issue and provided unequivocal evidence supporting the legitimacy of BTNL proteins as $\gamma\delta$ TCR ligands and this represents a significant advance in the understanding of how $\gamma\delta$ T cells are able to contribute to immunity using both adaptive and innate-like modes of action. Indeed, the Hayday³² and Willcox³³ labs determined that the $\gamma\delta$ TCR employs two modes of ligand binding: (1) a traditional, clonally restricted mode of binding involving CDR3 sequences that are generated somatically by V(D)J recombination and (2) a CDR3-independent mode of recognition linked to germline-encoded sequences in the V region of the TCR γ chain (Figure 1). Melandri *et al.* employed a TCR downmodulation assay to demonstrate reactivity of the V γ 7 subunits of murine $\gamma\delta$ intraepithelial lymphocytes (IELs) with Btl1-Btl6 heterodimers and the reactivity of human V γ 4-containing $\gamma\delta$ TCR complexes with BTNL3-BTNL8 heterodimers and to show that this reactivity was dependent on germline-encoded sequences in framework region 3, also known as hypervariable region 4 (HV4)³². Moreover, this mode of ligand recognition, resembling that of superantigen binding by $\alpha\beta$ TCR complexes, did not preclude CDR3-mediated clonotypic reactivity with cognate ligand, indicating that individual $\gamma\delta$ TCR complexes are capable of both modes of ligand recognition³². Willcox *et al.* reported similar findings and were also able to provide unequivocal evidence for the direct physical interaction between human V γ 4 and BTNL3³³. Importantly, the ability of the human V γ 9V δ 2 $\gamma\delta$ TCR to mount BTN3A1-dependent responses to the p-Ag products of the mevalonate pathway was also dependent on the HV4 of V γ 9³³. An additional germline-encoded recognition structure in the V γ 9 subunit also appears to contribute to binding, since a recent report by Rigau *et al.* indicated that V γ 9V δ 2 recognition of p-Ags is also dependent on BTN2A1, which interacts with V γ 9 more through the ABED β -sheet of V γ 9 than through HV4³⁴. The basis by which p-Ag exposure triggers binding of BTN3A1 to the human V γ 9⁺V δ 2⁺ TCR has long been a controversial issue; however, recent studies have suggested that the role of BTN3A1 as sensor of p-Ag concentration is mediated through its intracellular B30.2 domain³⁵. In support of this, Yang *et al.* reported crystal structures of the intracellular domain of BTN3A1 protein in complex with the potent microbial p-Ag, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), revealing that dimerized intracellular

Figure 1. Distinct models of ligand recognition by the $\gamma\delta$ T-cell receptor (TCR). Relatively few $\gamma\delta$ TCR ligands have been identified. One of the major classes of ligands is the butyrophilin (BTN) or butyrophilin-like (BTNL) family. This class of ligands interacts with the $\gamma\delta$ TCR in a distinct, CDR3-independent manner that is dependent on framework residues encoded in the germline sequence of TCR-V γ chains. Consequently, unlike CDR3-mediated ligand recognition that activates only a particular clonotype of $\gamma\delta$ T cells, BTN or BTNL ligands are capable of a more innate mode of functioning as they are able to activate all $\gamma\delta$ T cells expressing the cognate V γ chain, irrespective of its TCR γ junctional sequences or its TCR δ subunit. Depicted is the human V γ 4 subunit that binds BTNL3.

domains cooperate in sensing HMBPP and providing insight into the “inside out” triggering of V γ 9V δ 2 T-cell activation³⁶.

The role of ligand in regulating $\gamma\delta$ T-cell development remains a contentious issue. The finding that $\gamma\delta$ TCR complexes can recognize ligand in both a clonotypic, CDR3-dependent and a V γ -restricted, HV4-dependent manner at once provides clarification and raises additional questions about the role of ligand in $\gamma\delta$ T-cell development. The recognition of Btl family members, Skint1 and Btl1-Btl6, clearly plays an important role in selection of the V γ 5⁺ DETC and V γ 7⁺ IEL $\gamma\delta$ subsets, respectively^{29,30,37}. However, the contribution of clonotypic, CDR3-mediated recognition of ligand to $\gamma\delta$ T-cell development and the shaping of the repertoire, was more controversial¹⁴. Data from TCR transgenic models have provided clear support for the role of CDR3-mediated ligand recognition in the development of murine V γ 4⁺ $\gamma\delta$ T-cell progenitors reactive with the MHC class Ib ligand, H-2T22⁹. Moreover, a recent study indicated that the repertoire of CDR3 sequences (WEGYEL) of polyclonal T-22 reactive $\gamma\delta$ T cells that developed in the absence of T22 was markedly altered, suggesting that the CDR3-mediated clonotypic mode of ligand recognition played a positive role in shaping the repertoire of this subset of $\gamma\delta$ T cells²¹. Importantly, whereas this study did not reveal evidence of negative selection induced by CDR3-mediated ligand recognition, previous analysis using transgenic models has suggested that it may occur^{38,39}. Finally, the $\gamma\delta$ T-cell repertoire also appears to continue to be shaped post-thymically since the relatively diverse TCR δ CDR3 repertoire of $\gamma\delta$ T cells in human cord blood becomes markedly restricted in adults after viral infection or following reconstitution after hematopoietic stem cell transplantation^{40,41}. Despite these recent insights into the role of ligand in $\gamma\delta$ T-cell development, it remains unclear how extensively CDR3-mediated selection occurs, how CDR3-dependent versus CDR3-independent signals might differ, and the role that these two modes of ligand binding play in determining whether $\gamma\delta$ T cells act in an adaptive or more innate-like mode of action in presence of the selective ligand.

Addressing the relative contributions of CDR3-dependent and -independent modes of ligand binding to $\gamma\delta$ T-cell development and repertoire diversity must await the identification of other CDR3-mediated selection ligands and a determination of whether all V γ subunits have cognate BTNL family ligands.

Role of $\gamma\delta$ TCR signaling in specification of $\gamma\delta$ T-cell effector fate

In addition to commitment to the $\gamma\delta$ T-cell lineage, the effector fate of most $\gamma\delta$ T cells is determined in the thymus; however, the respective contributions of cellular context and TCR signaling to the specification of effector fate have long been debated. This is a particularly important issue, as $\gamma\delta$ T cells can contribute to either host defense or immune-mediated pathology, depending on their effector fate. Indeed, although IL-17-producing $\gamma\delta$ T cells are critical for combating infections, aberrant regulation of these cells can contribute to autoimmunity (multiple sclerosis, type 1 diabetes, and psoriasis) and promote tumor progression^{42–46}. Likewise, interferon gamma (IFN γ)-producing $\gamma\delta$ T cells play critical roles in host defense but can also contribute to pathology, such as in cerebral malaria^{47–49}.

There is clear evidence that TCR signals regulate effector fate. Numerous reports indicate that strong TCR signals, in some cases induced by ligand-engagement of the $\gamma\delta$ TCR, promote adoption of the IFN γ -producing effector fate but that the IL-17-producing effector fate depends on weaker $\gamma\delta$ TCR signals^{14,21,47,50}. The signals of differing intensity that lead to adoption of these effector fates have been linked to transcription factors (TFs) that are required for effector function. Indeed, IFN γ producers depend on Egr2, Egr3, Id3, and T-bet function whereas IL-17 producers depend on the action of ROR γ t, SOX13, and c-MAF^{10,12,47,51,52}. Nevertheless, accumulating evidence suggests that the paradigm of strong and weak TCR signals promoting the IFN γ and IL-17-producing effector fates, respectively, may be too simplistic. Specifically, the Hayday laboratory reported that, unlike the IL-17 producers that

develop in response to weak signals in the absence of ligand, some IL-17-producing $\gamma\delta$ T cells are dependent on strong TCR signals, as evidenced by the impairment of their development by attenuation of TCR signaling¹¹. Although this report is seemingly at odds with several other studies indicating that the IL-17 fate is incompatible with strong TCR signals^{14,21,47,50}, two recent reports provide a potential explanation for this apparent discrepancy^{46,52}. The Ciofani laboratory determined that the TF, c-Maf, is required for development of IL-17-producing $\gamma\delta$ T cells and determined that c-Maf induction was inversely associated with $\gamma\delta$ TCR signal strength, as defined by CD5 induction⁵²; however, c-Maf is also robustly induced by ectopic expression of activated mutants of the signaling molecules, protein kinase C (PKC) and Ras⁵². Ectopic expression of these activated signaling molecules could not reasonably be described as generating weak signals but might rather be regarded as producing distinct signals compatible with c-Maf induction. Another study, from the Anderson laboratory, suggests that there are two distinct developmental pathways for IL-17-producing $\gamma\delta$ T cells and these pathways are distinguished by CD73 expression⁴⁶. CD73 expression, which is induced by $\gamma\delta$ TCR-ligand engagement and strong TCR signals, marks commitment of most $\gamma\delta$ precursors to the $\gamma\delta$ lineage^{46,53}; however, some IL-17-producing $\gamma\delta$ T cells do not pass through a CD73⁺ stage, consistent with their adoption of the IL-17-producing effector fate in response to weaker or distinct TCR signals⁴⁶. Taken together, these data clearly indicate that $\gamma\delta$ TCR signals play an important role in specification of $\gamma\delta$ T-cell effector fate but that role remains to be clarified for each effector subset.

There is also evidence in support of cellular context influencing effector fate potential in a TCR-independent manner¹⁵. It

has been previously proposed that the IL-17-producing effector fate is pre-determined, independent of any influence by TCR signals. Consistent with this perspective, IL-17-producing $\gamma\delta$ T cell development is restricted primarily to fetal life¹⁵. Moreover, the progenitors of IL-17 producing $\gamma\delta$ T cells express the regulatory network of TFs (Sox4, Sox13, Tcf1, and Lef1) that typify IL-17-producing cells at developmental stages that appear to be prior to receipt of TCR signals^{12,54}. The key experiment necessary to provide insight into the relative contributions of TCR signaling and cellular context to IL-17 effector fate specification was to perform lineage-tracing analysis with an IL-17 fate-defining reporter. Spidale *et al.* employed a Sox13 reporter to identify an early CD4⁺8⁺ double-negative thymic subset (DN1d) that had not yet expressed $\gamma\delta$ TCR, yet exhibited an expression signature linked to the IL-17-producing fate and was enriched in IL-17 progenitor activity⁵⁵. It should be noted that while the DN1e subpopulation was not marked by the Sox13 reporter, it possessed equivalent progenitor activity for IL-17-producing $\gamma\delta$ T cells⁵⁵. Importantly, development of IL-17-producing $\gamma\delta$ T cells from those marked progenitors required TCR signaling, indicating that although the potential to adopt the IL-17-producing effector fate could be established independent of $\gamma\delta$ TCR signaling, realization of that potential was dependent on $\gamma\delta$ TCR signaling (Figure 2)^{15,55}.

Assessing the functions of $\gamma\delta$ T cells

$\gamma\delta$ lineage T cells are less abundant in peripheral blood and lymphoid organs than $\alpha\beta$ lineage T cells, but $\gamma\delta$ T cells are increasingly understood to play a critical role in tissue homeostasis and host defense^{56–58}. Moreover, localization of $\gamma\delta$ T cells at epithelial barriers and their capacity to be rapidly

Figure 2. Contribution of cell context and TCR signaling to $\gamma\delta$ T-cell effector fate. The relative contribution of TCR signaling and TCR-independent pre-commitment processes to $\gamma\delta$ T-cell effector fate has long been debated, particularly regarding the origins of interleukin-17 (IL-17)-producing $\gamma\delta$ T cells. Recent lineage tracing studies using a Sox13 reporter revealed that, even before TCR is expressed, cells marked by the Sox13 reporter (stage DN1d) exhibit enriched progenitor activity for IL-17 production. However, that fate potential requires $\gamma\delta$ TCR signaling to be manifested and appears to be influenced by the nature of the TCR signal received, with IL-17 production associated with weak TCR signals, the interferon gamma (IFN γ)-producing effector fate being specified by stronger TCR signals, and the strongest TCR signals being required for development of PLZF expressing natural killer (NK) $\gamma\delta$ T cells. It should be noted some IL-17-producing subsets can also be induced by strong TCR signals.

activated make them particularly well suited to be the first line of defense against infections^{57,59}. $\gamma\delta$ T cells can produce large amounts of IFN γ , TNF- α , IL-17, and granzymes and can display pleiotropic immune effector functions⁶⁰. For instance, the DETC subset of $\gamma\delta$ T cells, which produce IFN γ and express high levels of granzymes, can also influence B cells through production of IL-13, regulate stromal cells through production of IGF1, and recruit other leukocytes to the skin by producing chemokines⁶. $\gamma\delta$ T cells have also been shown to be essential to prevent parasitic recurrence in malaria infections⁶¹. Surprisingly, $\gamma\delta$ T cells producing IL-17 in adipose tissue influence age-dependent regulatory T cell expansion and control core body temperature in response to environmental fluctuations⁶², whereas those in the meninges of neonatal mice play an essential role in synaptic plasticity and the development of short-term memory⁶³. $\gamma\delta$ T cells have emerged as important players in antitumor immunity, showing that many solid tumors and leukemia/lymphoma cells are susceptible to lysis by $\gamma\delta$ T cells⁶⁴. Finally, $\gamma\delta$ T cells are able to contribute to immune-mediated pathology, as IL-17-producing $\gamma\delta$ T cells have been implicated in the pathogenesis of both psoriasis and multiple sclerosis^{51,65,66}. Likewise, IFN γ -producing T cells have been implicated in the pathogenesis of cerebral malaria in mice^{47,48} and humans^{49,67}. Despite this large body of evidence suggesting that $\gamma\delta$ T cells contribute extensively to the health of the host, their role in immune responses and host defense remains poorly defined, at least in part because of the lack of effective, consistent strategies with which to acutely eliminate $\gamma\delta$ T cells or to selectively modulate their function.

Until recently, efforts to determine whether $\gamma\delta$ T cells play an important role in normal or pathologic immune processes have entailed either chronic elimination of $\gamma\delta$ T cells using TCR δ -deficiency (*Tcrd*^{-/-}) or acute elimination by antibody-mediated depletion. In some cases, these approaches have led to contradictory findings because of their inherent limitations^{68–70}. TCR δ -deficiency effectively eliminates all $\gamma\delta$ T-cell subsets but suffers from the limitation that long-term $\gamma\delta$ T-cell depletion enables other cell types to fill the vacated niches and to compensate for $\gamma\delta$ T-cell loss, thus leading to the failure to identify key functions. Efforts to acutely deplete $\gamma\delta$ T cells suffer from the problem that anti- $\gamma\delta$ TCR antibodies do not actually deplete $\gamma\delta$ T cells but only down-regulate their TCR complexes and make them invisible⁷¹. The limitations of both approaches have been circumvented through the development of an effective model of acute depletion of $\gamma\delta$ T cells, which involves transgenic expression of diphtheria toxin receptor (DTR) in $\gamma\delta$ T cells⁷². Using this model, the Prinz lab revealed that acute, diphtheria toxin-mediated depletion of IL-17-producing $\gamma\delta$ T cells attenuated the development of skin inflammation in a mouse model of psoriasis⁷². Importantly, the requirement for $\gamma\delta$ T cells in pathogenesis in this model was not evident if the mice were allowed to recover for 6 weeks after $\gamma\delta$ T-cell depletion; this is because the niches depleted of $\gamma\delta$ T cells were repopulated by innate lymphoid cells (ILCs) and IL-17-producing $\alpha\beta$ lineage T cells, which were capable of compensating for the loss of $\gamma\delta$ T cells and promoting skin inflammation⁷². The more general use of the DTR transgene to deplete $\gamma\delta$ T cells should

contribute to advancing our understanding of the role of $\gamma\delta$ T cells in normal and pathologic immune responses.

Another limitation that slows progress in understanding $\gamma\delta$ T-cell development and function is the paucity of approaches through which $\gamma\delta$ T-cell subsets or their functions can be selectively altered. Conditional ablation of key molecular effectors using Cre-recombinase is a standard approach to investigate the function of a particular gene in a cell lineage. For T-cell development, Cre expressed under the control of the proximal Lck promoter-driven Cre (*pLckCre*) has commonly been used to generate T cell-specific conditional knockout mice; however, Fiala *et al.*⁷³ determined that *pLckCre* does not reliably ablate gene targets in all $\gamma\delta$ T-cell subsets at all stages of gestation⁷⁴. In contrast, *Ptcr*-Cre has been found to reliably ablate gene targets in $\gamma\delta$ T cells⁷⁵. An alternative, which enables temporal control of conditional ablation of target alleles in $\gamma\delta$ T cells, is the *Tcrd-CreER* that is expressed in $\gamma\delta$ T-cell progenitors and inducible by tamoxifen treatment⁷⁶. The use of these newly developed tools, and others in progress, to selectively eliminate particular $\gamma\delta$ T-cell subsets or alter their effector fates will markedly accelerate progress toward a more comprehensive and unified view of the role of $\gamma\delta$ T cells in host health and immunopathology.

Potential for $\gamma\delta$ T cells in human cancer

$\gamma\delta$ T cells exhibit many attributes that make them perfectly suited to be anti-cancer effectors⁶⁰. They are able to infiltrate human tumors and recognize tumor antigens, secrete cytotoxic molecules such as granzyme and perforin, mount rapid cytokine responses without undergoing clonal expansion, and activate adaptive immune responses, all of which make them promising candidates for the development of $\gamma\delta$ T cell-based immunotherapies for cancer^{77,78}. For example, murine $\gamma\delta$ T cells have been reported to be effective against cutaneous malignancies⁷⁹. A recent report revealed that the ability of $\gamma\delta$ T cells to resist carcinogenesis in a chemically induced skin cancer model involved regulating the IgE response by B lymphoid cells⁸⁰. This mode of action may have human relevance since the expression level of the Fc receptor for IgE was linked to outcomes in patients with human squamous cell carcinoma⁸⁰. Human $\gamma\delta$ T cells are able to recognize and kill a broad range of tumor cells, including prostate cancer, melanoma, metastatic renal carcinoma, breast and ovarian cancer, colon carcinoma, hepatocellular carcinoma, lung cancer, and myeloma^{81,82}. It is likely that particular $\gamma\delta$ T-cell subsets exhibit specificity for distinct tumor types. In support of this, the V δ 1 $\gamma\delta$ T-cell subset exhibits cytotoxicity against hematopoietic malignancies, melanoma, neuroblastoma, and some other epithelial tumor cells⁸¹. The anti-cancer potential of $\gamma\delta$ T cells has prompted analysis of their prognostic value in human cancers. Indeed, informatic deconvolution of transcriptomic signatures from a large number (~18,000) of patients with solid tumors revealed that, among immune infiltrates, a $\gamma\delta$ T-cell infiltrate is the most favorable prognostic indicator⁸³. More recently, it was reported that the abundance of V δ 1⁺ $\gamma\delta$ T cells, but not total $\gamma\delta$ T cells, was associated with remission in patients with triple-negative breast cancer (TNBC)⁸⁴. These infiltrating V δ 1⁺ cells were enriched for cytotoxic and

IFN γ -producing ability and appeared to be functioning in an innate manner, since they were responsive to the NKG2D ligand MICA as well as cytokines IL-12 and IL-18⁸⁴.

Despite these encouraging findings that $\gamma\delta$ T cells are linked to favorable outcomes in cancer, there are also examples of $\gamma\delta$ T cells promoting tumor progression⁶⁸. In human pancreatic ductal adenocarcinoma (PDAC), in which long-term survival is rare, $\gamma\delta$ T cells represent the dominant T-cell population infiltrating the pre-neoplastic pancreas, comprising up to 75% of all T lymphocytes⁸⁵. $\gamma\delta$ T cells appear to promote PDAC progression by inhibiting $\alpha\beta$ T-cell activation via expression of immune checkpoint ligand PD-L1⁸⁵. $\gamma\delta$ T cells have also been shown to promote cancer progression through production of IL-17. IL-17-producing $\gamma\delta$ T cells were shown to promote metastasis in a murine breast cancer model by expanding and polarizing neutrophils in the tumor microenvironment⁴². The activation of IL-17-producing $\gamma\delta$ T cells may result from the accumulation of IL-17-polarizing cytokines (IL-1 β , IL-6, IL-23, and transforming growth factor- β) in the tumor microenvironment of certain cancers^{24,42}. Alternatively, the microbiota may also contribute to the capacity of $\gamma\delta$ T cells to produce IL-17 and promote tumor progression and metastasis⁸⁶. In lung, local commensal bacteria have been shown to stimulate the production of IL-1 β and IL-23, which induced proliferation and activation of lung-resident V γ 6V δ 1 $\gamma\delta$ T cells that produce IL-17 and generate the inflammation associated with lung adenocarcinoma⁸⁷. These findings highlight the need for a better and more comprehensive understanding of how $\gamma\delta$ T cells adopt a specific effector fate, so that anti-tumor function can be favored and the full potential of $\gamma\delta$ T cells as anti-tumor effectors can be realized.

Conclusions

Because of their under-representation relative to $\alpha\beta$ lineage T cells in blood and lymphoid organs, $\gamma\delta$ T cells were long neglected and thought to play a minor role in host defense. Nevertheless, compelling evidence now suggests that $\gamma\delta$ T cells are integral to tissue homeostasis, particularly at epithelial barriers, and are essential to the resistance to infections resulting from barrier breaches. Moreover, they appear to have great potential in cancer both as prognostic indicators and as anti-cancer effectors. Our capacity to exploit the potential of

$\gamma\delta$ T cells as key contributors to immune responses in general, and in cancer therapy in particular, has lagged behind that of $\alpha\beta$ T cells in part because of the lack of appropriate tools to interrogate $\gamma\delta$ T-cell function, because of the mistaken impression that $\gamma\delta$ T cells are somehow less functionally diverse than $\alpha\beta$ lineage cells, and because of a bias that analysis of $\gamma\delta$ T cells in mice will not inform their roles in humans. Discoveries described here leave little doubt about the functional diversity of $\gamma\delta$ T cells. Moreover, it should be noted that while the particular TCR complexes employed by mouse and human $\gamma\delta$ T cells differ substantially, their functional capabilities are quite similar. Indeed, recent evidence strongly supports the existence of human equivalents of the major functional $\gamma\delta$ T-cell subsets in mouse (for example, PLZF⁺ innate $\gamma\delta$ T cells, IFN γ producers, and IL-17 producers)^{61,88,89}. Accordingly, future efforts to gain a more comprehensive and unified understanding of the role of $\gamma\delta$ T cells in human health and disease ultimately will depend on the development of strategies in model organisms to selectively and acutely eliminate particular $\gamma\delta$ T-cell subsets to gain insight into their roles. This must be linked to investigation of the molecular processes that control $\gamma\delta$ T-cell effector fate so that beneficial and detrimental effector functions can be enhanced and minimized, respectively.

Abbreviations

BTN, butyrophilin; BTNL, butyrophilin-like; CDR3, complementary determining region 3; DETC, dendritic epidermal T cell; DTR, diphtheria toxin receptor; HMBPP, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; HV4, hypervariable region 4; IEL, intraepithelial lymphocyte; IFN γ , interferon gamma; IGF1, insulin-like growth factor-1; IL-17, interleukin 17; ILC, innate lymphoid cell; MHC, major histocompatibility complex; NKG2D, natural killer group 2D; p-Ag, phospho-antigen; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; PKC, protein kinase C; pLckCre, proximal Lck promoter-driven Cre; PLZF, promyelocytic leukemia zinc finger protein; PtcrA-Cre, pre-T-cell antigen receptor alpha-Cre; ROR γ t, retinoic-acid-receptor-related orphan nuclear receptor gamma; Sox4, SRY-box transcription factor 4; Sox13, SRY-box transcription factor 13; TCR, T-cell receptor; Tcrd^{-/-}, T-cell receptor delta-deficient; TF, transcription factor; TNBC, triple-negative breast cancer; TNF- α , tumor necrosis factor-alpha.

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