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$\gamma\delta$ T Cells: Unexpected Regulators of Cancer Development and Progression

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Abstract

Accumulating evidence suggests a role for $\gamma\delta$ T cells as unexpected drivers of tumor development and progression. These protumoral $\gamma\delta$ T cells are abundant in the tumor microenvironment in both mouse and human. They promote tumor progression by 1) inducing an immunosuppressive tumor microenvironment and angiogenesis via cytokine production; by 2) functioning as Treg/Th2-like cells; by 3) interfering with dendritic cell effector function; and by 4) inhibiting antitumor adaptive T cell immunity via the PD-1/PD-L1 pathway. Understanding how these cells are regulated and what their specific role in cancer is will provide insight for developing approaches that specifically target these cells and can thus improve the efficacy of cancer immunotherapies.

Keywords

$\gamma\delta$ T cells; tumor microenvironment; protumoral; PD-1 regulation

Gammadelta ($\gamma\delta$) T Cells in Cancer

The complexity of $\gamma\delta$ T cells continues to grow in terms of subsets and functional variations from suppressive to inflammatory depending on development and peripheral regulation (1,2). While certain subsets of $\gamma\delta$ T cells have been selected as potential agents for immunotherapy, other subsets with newly emerging tumorigenic effector functions will be the focus of this review. In particular, it is becoming more evident that certain subsets of $\gamma\delta$ T cells possess a large regulatory capacity, particularly within the context of cancer. Therefore, it is important to further investigate $\gamma\delta$ T cell regulation in the tumor microenvironment and under the pathophysiology of development and progression of tumors due to the highly dynamic and complex nature of infiltrating $\gamma\delta$ T cells.

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The majority of known subsets of $\gamma\delta$ T cells, named by the Heiling system in this review, can be found within the tumor microenvironment. In mice, these populations consist of V γ 6, V γ 4 and V γ 1 (3,4). V γ 6 cells are the major inflammatory T cells in the tumor, and predominantly produce IL-17 along with other inflammatory cytokines including IL-22, GM-CSF and IL-8 (5–8). V γ 4 cells have a substantiated role in both inflammation and tumor surveillance, and are capable of producing IL-17 and IFN- γ (4,8). V γ 1 cells show a suppressive phenotype through the production of TGF- β and IL-10 (4,9,10). In humans, V γ 9V δ 2 and V δ 1⁺ cells are both present, but depending on the tumor type, one subset can be predominant over the other (7,11,12). *In vivo*, V γ 9V δ 2 cells appear to be more involved in tumor immunosurveillance and regulation, however, *in vitro*, they have tremendous plasticity allowing differentiation into many pro-tumorigenic phenotypes including Treg-like and Th2-like (13,14). V δ 1⁺ cells, particularly within breast and colonic epithelial tissues, can be either potent inflammatory cells through the production of IL-17 and other related cytokines, or suppressive cells capable of drastically reducing the immune system's ability to kill and fight off cancer (7,11).

$\gamma\delta$ T cells in general are regulated either through cell-to-cell contact or by soluble factors such as cytokines (15,16). In humans, the adaptive response of TCR and NKG2D engagement with ligands, isopentenyl pyrophosphate (IPP) and MHC class I-chain-related molecules A/B (MICA/B), respectively, is important to their ability to lyse target cells. Whether similar TCR signaling is important for pro-tumor effector functions is still debatable (17,18). Immediate innate $\gamma\delta$ T cell responses appear to be more regulated through cytokine stimulation, recognition of various molecular patterns such as pattern associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs), and metabolic regulation (19–23).

Therefore further investigation into the regulatory mechanisms and downstream effector functions of the different protumoral $\gamma\delta$ T cell populations could prove to be paramount in developing new more targeted cancer interventions. Particularly, developing a more intricate understanding of the regulatory role these $\gamma\delta$ subsets play within the tumor microenvironment could result in more precise drug design and better utilization of combinational therapies that ultimately lead to more efficacious outcomes for cancer patients.

Emerging Immunosuppressive $\gamma\delta$ T Cell Subtypes in Humans and Mice

In the past fifteen years, translational $\gamma\delta$ T cell research has been hampered by the belief that murine and human $\gamma\delta$ T cells are quite different from each other. However, recent studies of cancer patients showed that there are in fact similarities between the two species' $\gamma\delta$ T cells (7,24). A recent elegant study showed that human and mouse epithelia can use organ-specific butyrophilin-like (Btl) genes to induce selective extrathymic maturation and proliferation of mouse V γ 7⁺ and human V γ 4⁺ T cells, suggesting a conserved mechanism for the development and maturation of mouse and human $\gamma\delta$ T cells (25). In particular, it is becoming more evident that $\gamma\delta$ T cells within the tumor microenvironment in mice and humans share similar characteristics and functionalities. Thus far, a tumor-infiltrating immunosuppressive $\gamma\delta$ T cell population has been identified in a variety of human cancers

and murine tumor models (Tables 1 and 2). Close examination of the different cancer models in both species revealed that the major cytokine responsible for driving this immunosuppressive phenotype is IL-17.

In addition to classification as mainly $\gamma\delta$ T17 cells, most of these pro-tumor $\gamma\delta$ T cell subsets also display an effector memory phenotype, characterized by CD27⁻, CCR6⁺, and CD45RA⁻ surface markers. Another marker that commonly appeared was ROR γ t, a transcription factor that plays an important role in Th17 differentiation (26). Collectively, these pro-tumor $\gamma\delta$ T cells can be characterized overall as IL-17 capable (ROR γ t⁺), effector memory (CD27⁻ CCR6⁺ CD45RA⁻) cells. This phenotype is markedly different than a sizable portion of V γ 4⁺ or V γ 1⁺ $\gamma\delta$ T cells in mice or V γ 9⁺V δ 2⁺ $\gamma\delta$ T cells in humans found under homeostatic conditions which express a “naïve-like” phenotype being either CD44⁻CD62L⁺ or CD45RA⁺CD27⁺, respectively (27). Furthermore, some of these pro-tumor $\gamma\delta$ T cells bear Treg-like or Th2-like phenotype which will be explored further in the next section (4,11).

The differences between human and mouse pro-tumor $\gamma\delta$ T cells lies in V γ TCR usage and the cytokines they produce. The main immunosuppressive subset in humans is V δ 1⁺ whereas in mice it can either be V γ 1⁺, V γ 6⁺, or to an extent V γ 4⁺. In mouse B16 melanoma models, V γ 4⁺ and V γ 1⁺ subsets play opposing roles within the tumor microenvironment (5). Interestingly, the IL-4 producing V γ 1⁺ subset suppressed the anti-tumor capabilities of the V γ 4⁺ subset and promoted tumor growth. However, other models, namely the hepatocellular carcinoma and the pancreatic ductal carcinoma (PDA) models, have found the V γ 4⁺ population to be the main secretor of IL-17 in the tumor microenvironment (8,28). This discrepancy is likely due to the heterogeneity of V γ 4 T cells and types of cancer.

Regulation of $\gamma\delta$ T Cells in the Tumor Microenvironment

With $\gamma\delta$ T cells straddling the line between the innate and adaptive immune systems, it is important to look at different mechanisms of regulation within tumors. Specifically, are these cells being regulated through antigen recognition in their TCR, cytokine stimulation, or both? This section will focus on the two main ways by which $\gamma\delta$ T cells are regulated in the tumor microenvironment.

Regulation via Secreted Cytokines

It was previously thought that a large fraction of mouse $\gamma\delta$ T cells are pre-programmed in the embryonic thymus, prior to birth, to either secrete IL-17 or IFN- γ (29–32). However, Bruno and Chien found that some cell populations of mouse $\gamma\delta$ T cells can be induced in the periphery (31,33,34). Using breast cancer models, Coffelt et al showed that treatment with IL-1 β neutralizing antibody decreases levels of IL-17 in the spleen, blood, LN, and lungs. His previous work confirmed that tumor-infiltrating $\gamma\delta$ T17 cells were the main producers of IL-17 within these tissues (6).

These findings are akin to those found by Carmi et al. in Lewis Lung Carcinoma metastatic models where they found IL-1 β to be critical for $\gamma\delta$ T17 cell responses (35). Similarly, *in*

vitro blockade of IL-6, TGF- β and IL-23 in tumor homogenate showed reduced numbers of $\gamma\delta$ T17 cells suggesting these factors could play a role in driving IL-17 production by $\gamma\delta$ T cells. IL-6 was also found to be a critical recruiter and regulator of $\gamma\delta$ T17 cells in spontaneous pancreatic Kras models (36). These and many other studies found that $\gamma\delta$ T17 cells within the tumor microenvironment participate in a positive feedback loop in which $\gamma\delta$ T17 cells mainly recruit cells capable of further propagating their own immunosuppressive responses. For example, in an ovarian cancer study, the inflammatory macrophages induced by $\gamma\delta$ T17 cells could in fact produce TGF- β , IL-6 and IL-1 β to increase further $\gamma\delta$ T17 cell responses by stimulating both proliferation of $\gamma\delta$ T17 cells as well as their IL-17 production (3). Another key example is the study performed by Ma et al. using hepatocellular carcinoma to show that $\gamma\delta$ T17 cells are induced by IL-1 β and IL-23 from IL-17 recruited MDSCs in a positive feedback mechanism (8).

Regulation by microbiota and PAMP engagement

Since many $\gamma\delta$ T cell populations locate at epithelial barriers, it is important to investigate how the microbiota influence $\gamma\delta$ T cell function. In a spontaneous lung cancer model, Cheng et al. found that antibiotic treatment reduced IL-6 and IL-23 responses thereby suppressing $\gamma\delta$ T17 cells capabilities to secrete IL-17 and hamper anti-tumor responses (37). Using tissue samples from colorectal cancer patients, we showed that inflammatory DCs stimulated by bacterial products from a leaky colon epithelial barrier could produce IL-23 thus driving V δ 1⁺ $\gamma\delta$ T17 responses with the production of IL-17, GM-CSF and IL-8 (7).

In an alternative mechanism that enhances the non-specific, innate like capabilities of $\gamma\delta$ cells, bacterial PAMP engagement can propagate a non-IL-17 dependent, $\gamma\delta$ T pro-tumor effector function (11,24). Specifically, it was found that bacteria-activated MDSCs induce $\gamma\delta$ T cells to produce galectin-1 through TLR5 (PAMP receptor for flagellin). Galectin-1 was shown to induce apoptosis on effector Th1 and CD8 T cells while enhancing the suppressive activity of Tregs. In the same study, Rutkowski et al. also found that increased expression of galectin-1 in $\gamma\delta$ T cells negatively correlates with 5-year survival rates within ovarian cancer patients without the TLR5 defective polymorphism (24).

More investigation on how microbiota regulate $\gamma\delta$ T cells in cancer is necessary to determine to what extent the development of pro-tumorigenic $\gamma\delta$ T cells is dependent on tumor infiltration of microbiota and other microbial interactions. Some bacterial products have already been shown to be important in promoting $\gamma\delta$ T17 responses in human colorectal and lung cancer (7,35,37). These studies are less surprising as it is well known that bacteria can induce the production of IL-1 β and IL-23 which are key modulators of $\gamma\delta$ T17 IL-17 responses. However, it has yet to be elucidated as to whether bacteria can modulate $\gamma\delta$ T17 responses by other means than cytokine secretion and PAMP engagement. Understanding how $\gamma\delta$ T cells are regulated in the tumor microenvironment and determining whether they can be “re-educated,” as is possible with other pro-tumorigenic immune populations such as Tregs, MDSC and TAMs, is critical for improving the success of future immunotherapies targeting tumors where these cells are abundant and potent inducers of tumor growth and progression.

Tumor Promotion by of $\gamma\delta$ T Cells

In this section, we discuss the downstream effector functions of tumor promoting $\gamma\delta$ T cells through four independent mechanisms namely, IL-17a production; $\gamma\delta$ Treg-like and $\gamma\delta$ Th-2-like activity; inhibition of dendritic cell effector function; and PD-1/PDL-1 immune checkpoint inhibition.

$\gamma\delta$ T cells promote tumor progression via IL-17-a-mediated immunosuppression

The promotion of tumor progression by IL-17 is multi-faceted. In many types of tumors, including pancreatic adenocarcinoma; hepatocellular carcinoma; and non-small cell lung, colorectal, and breast cancers, increased levels of IL-17 are associated with metastasis and poor prognosis (38) (8) (7). The consensus among the literature points to two main mechanisms by which IL-17 can influence tumor progression and metastasis: recruitment of immunosuppressive cell types like MDSCs and tumor infiltrating neutrophils, and increased angiogenesis (39). Wu et al. show that IL-17 $\gamma\delta$ T cell infiltration is indicative of tumor progression and metastasis in human colorectal cancer patients (7). They found that inflammatory DCs stimulated by bacterial products produce IL-23 driving V δ 1⁺ $\gamma\delta$ T17 responses with the production of IL-17, GM-CSF and IL-8. This IL-17, GM-CSF and IL-8 production led to increased infiltration of PMN-MDSCs correlating with further cancer progression. He and colleagues showed that IL-17 is necessary for both the recruitment and development of immunosuppressive MDSCs as IL-17-deficient mice showed a decrease in the ability of MDSCs to suppress CD8⁺ T cell proliferation (40). More recently, Coffelt and colleagues identified tumor-infiltrating neutrophils within a breast cancer model that were regulated by IL-17 and capable of suppressing CD8⁺ T cell activation (41). IL-17 depletion in these mice showed a decreased number of circulating cKIT⁺ neutrophils and decreased metastatic tumor burden.

Another main way IL-17 has been shown to perpetuate tumor progression is via angiogenesis. In both a MCA induced fibrosarcoma model and ID8 ovarian tumor model, it has been shown that IL-17 markedly increases the transcription of pro-angiogenic factors, Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) within the tumor (3,39). Similarly, a deficiency in IL-17 resulted in decreased vascular density and arrest of tumor growth. The second mechanism of angiogenesis was proposed by Numasaki and colleagues who showed increased secretion of angiogenic CXC chemokines CXCL1, CXCL5, CXCL6, and CXCL8 in three different non-small cell lung carcinoma cell lines in the presence of IL-17a (42,43).

$\gamma\delta$ T cell suppression through mimicry of Treg and Th-2-like activity

Treg and Th2 cells have distinct immunoregulatory capabilities, mediated in particular by the characteristic cytokines these cell types secrete. $\gamma\delta$ T cells portray a Treg like phenotype by having the capability to produce more conventional suppressive cytokines including IL-10 and TGF- β in order to inhibit $\alpha\beta$ T cell immune responses (10,28,44–46). In mice, an accumulation of IL-10 and TGF- β producing $\gamma\delta$ T cells resulted in much lower adaptive and NK anti-tumor responses (46). Using rejection models, including the transplantation of tumors derived from one strain onto another background, it has been shown that the

suppressive capabilities of IL-10⁺ $\gamma\delta$ T cells can in fact inhibit rejection of the tumor by the adaptive and anti-tumor $\gamma\delta$ T cell immunosurveillance (45).

Similarly, through their ability to secrete IL-4, $\gamma\delta$ T cells have been shown to adopt a Th2-like phenotype. For example, within the context of a melanoma mouse model, Hao and colleagues found a V γ 1⁺ population capable of suppressing anti-tumor V γ 4⁺ $\gamma\delta$ T cells through production of IL-4 (4). This Th2-like phenotype was further confirmed by demonstrating that these particular cells expressed high levels of GATA-3, a transcription factor driving Th2 immunity known to be particularly powerful in promoting tumor progression and suppressing anti-tumor immune responses. In humans, elevated levels of IL-4 have been found in the microenvironment of a variety of different cancers including renal cell cancer, non-small cell lung cancer, prostate, colon, and breast cancers (44). Unsure of how this affects $\gamma\delta$ T cells, Mao and colleagues challenged human peripheral blood samples with IL-4. Interestingly, the results showed that IL-4 stimulation led to an increased absolute number and ratio of V δ 1⁺ to V δ 2⁺ cells. Furthermore, following IL-4 stimulation, the V δ 1⁺ cells increased their IL-10 secretion resulting in inhibited *in vitro* expansion of the V δ 2⁺ $\gamma\delta$ T cells, cells known for their potent anti-tumor killing capabilities (44).

Determining the downstream roles of pro-tumor $\gamma\delta$ T cells that are immunosuppressive is critical considering they can affect the use of immunotherapies. Traxlmayr et al. found during clinical trial studies that DC production of IL-12 and pyrophosphate activation can in fact induce regulatory $\gamma\delta$ T cell responses capable of hampering the proliferative capabilities of tumor-specific CD4 and CD8 T cells (47). A recent study demonstrated that tumor-infiltrating CD39⁺ $\gamma\delta$ T cells have potent immunosuppressive activity via secretion of adenosine in human colorectal cancer (48). More investigation is needed to better characterize which $\gamma\delta$ T cell populations are capable of becoming regulatory and how these suppressive populations operate *in situ*.

Interface between $\gamma\delta$ T cells and DC results in Senescence

Dating back to 1989, Patel et al. were the first to describe a suppressive effector function for $\gamma\delta$ T cells *in vitro* (49). Since then much work has focused on studying the duality of immunoregulatory versus pro-inflammatory $\gamma\delta$ T cells. In 2007, Peng et al. were first to find an immunoregulatory V δ 1⁺ $\gamma\delta$ T cell population in human breast cancer (50). Co-culture of BTIL31 $\gamma\delta$ T cells with DCs resulted in their decreased expression of maturation markers like CD86, CD80, and CD83. Additionally, co-cultured DCs were incapable of stimulating naïve CD4⁺ T cells following LPS stimulation. In a later paper, Peng and colleagues expanded upon this finding by showing $\gamma\delta$ T cell induced senescence in DCs as measured by increased SA- β -galactosidase (senescence associated β -galactosidase) expression (51). These DCs again showed decreased markers of maturation, decreased cytokine secretion capabilities, and decreased antigen presentation capacity. Additionally, CD4⁺ and CD8⁺ T cells co-cultured with tumor derived $\gamma\delta$ T cells also showed upregulation of SA- β -galactosidase expression as well as increased negative regulatory functioning as measured by IL-10/TGF- β secretion and inhibition of responding CD4⁺ cells. These findings suggest that tumor-programmed $\gamma\delta$ T cells use senescence as one mechanism to control anti-tumor immune responses within the tumor microenvironment.

Emerging Regulatory Role of $\gamma\delta$ T cells via Modulation of PD-1/PDL-1

The immune checkpoint molecules, PD-1 and its ligand PDL-1/2, are one of the main regulatory mechanisms of pro-tumor immunity with the ability to inhibit the effector function of T cells and to perpetuate the development of Tregs. Since the response rate for PD-1/PDL-1 therapy still hovers around 40% with a large proportion of partial responders, further investigation into the mechanisms modulating the PD-1/PDL-1 axis is warranted (52,53). Recent studies using both a breast and colorectal cancer model have shown that a saturated IL-17a tumor microenvironment can cause upregulation of PDL-1 expression on the tumor cells themselves and tumor infiltrating inflammatory DCs (54) (7). However, little is known about the expression profile of PDL-1/PD-1 on tumor-associated $\gamma\delta$ T17 cells and whether these cells themselves can increase expression of immune checkpoint molecules thereby directly modulating the tumor microenvironment.

Daley et al began to probe for an answer to this question using a murine model of PDA and human PDA tissues (28). PDA proves to be a useful model for studying tumor associated effects of $\gamma\delta$ T cells because up to 75% of all CD3⁺ cells within human PDA tissue are $\gamma\delta$ T cells. Further phenotyping of these cells demonstrated a unique T effector memory profile expressing higher FasL, NK1.1, CD39, CD44, JAML, OX40 and V γ 4⁺ as compared to the spleen control tissue. Depletion of these cells resulted in decreased ductal dysplasia and fibrosis along with a massive influx of CD4⁺ and CD8⁺ cells with restored functionality as assessed by increased TNF- α and IFN- γ production. *In vitro* studies suggested that tumor-infiltrating $\gamma\delta$ T cells inhibited $\alpha\beta$ T cell activation via PD-1/PD-L1 ligation. Addition of α -PD-L1 antibody to the WT model system restored CD4⁺ and CD8⁺ T cell functionality in a manner similar to $\gamma\delta$ T cell ablation. However, PD-L1 blockade failed to induce tumor protection in TCR δ -deficient mice with no enhanced CD4⁺ and CD8⁺ T cell infiltration. Therefore, via cell-to-cell contact by PD-L1, tumor infiltrating $\gamma\delta$ T cells are capable of restraining $\alpha\beta$ T cell activation thus promoting tumor progression.

Conclusion Remarks

It has been shown that within the tumor microenvironment, $\gamma\delta$ T cells are functionally multifaceted and compositionally heterogeneous. These pro-tumoral $\gamma\delta$ T cells are regulated and exhibit their tumor-prompting activity via multiple mechanisms (Figure 1). Much of what we know about $\gamma\delta$ T cell polarization and plasticity exist from *in vitro* manipulation studies which provide little insight into how $\gamma\delta$ T cells are regulated in the exceedingly complex tumor microenvironment.

The tumor microenvironment and how it can regulate $\gamma\delta$ T cells with differential and still unknown means is an important factor to consider for both their potential use in the future as an immunotherapy as well as their increasing abundance within the pool of tumor infiltrating lymphocytes. One question that needs addressing is whether $\gamma\delta$ T cells *in vivo* are able to switch effector phenotypes according to the changing inflammatory environment (see outstanding questions). This is an important issue when using this potent effector population as an immunotherapy against cancer. Expanded *in vitro*, $\gamma\delta$ T cells are characterized as cancer killing effector cells; however, once injected *in vivo* they are subjected to the dysfunctional and unpredictable tumor microenvironment. In the future, TCR repertoire

sequencing combined with *in vivo* imaging and flow cytometric analysis of biopsies can be used to determine how these cells behave once subjected to the tumor microenvironment.

Investigations into tumor promoting $\gamma\delta$ T cells have provided many potential new targets for the development of new drugs and immunotherapies against cancer. IL-1 β , IL-23, IL-17 and GM-CSF could be useful targets when addressing highly suppressive MDSC infiltration and angiogenesis since these are major players in tumor progression. For cancers where $\gamma\delta$ T17 cells are not the primary $\gamma\delta$ T cell subset then targeting molecules like PD-L1, galectin-1 and IL-4 might prove essential in helping the adaptive anti-tumor immune responses overcome immune evasion and escape by the cancer. Current studies also propose that protumoral $\gamma\delta$ T cells may be closely related to immuncheckpoint blockade resistance. Thus combining approaches targeting protumoral $\gamma\delta$ T cells with immuncheckpoint blockade therapy may significantly improve cancer patient response rate and long-term survival. It is also possible that protumor $\gamma\delta$ T cells can be used as a biomarker for patient selection and treatment response monitoring.

Microbiota-host interaction is another key factor that can be very important in the future of cancer research and oncology care. This is especially true for the many types of epithelial tumors located at the host-environment interface. We have already begun to see the effects that microbiota play on driving $\gamma\delta$ T-dependent tumor development and progression in both murine models and patients. The host-microbiota interaction and how this regulates $\gamma\delta$ T cells will provide much needed additional answers as to how $\gamma\delta$ T cells are regulated during health (55) to then better understand how to restore proper functioning in disease. Understanding $\gamma\delta$ T cell homeostatic regulation will provide information needed to prevent cancer development. $\gamma\delta$ T cells provide protection from carcinogenesis so we can use preventative care to support these processes. As we continue to deepen our understanding of who these cells are, how they are regulated and what their specific role is in driving cancer progression, novel approaches may be developed to specifically target these unexpected drivers of cancer development and progression.

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Trends Box

- An immunosuppressive tumor microenvironment (TME) poses a significant challenge for effective tumor immunotherapy.
- Innate $\gamma\delta$ T cells within the TME are critical drivers of tumor progression and metastasis.
- Protumoral $\gamma\delta$ T cells have distinct phenotype and unique regulatory pathways that promote tumor development.

Outstanding Questions

1. Are $\gamma\delta$ T cells plastic and able to switch their effector phenotypes *in vivo* according to the differential inflammatory environment?
2. How does the microbiota regulate $\gamma\delta$ T cells in cancer and to what extent are pro-tumorigenic $\gamma\delta$ T cells dependent on the microbiota interaction for their differentiation and effector function?
3. Can targeting of protumoral $\gamma\delta$ T cells augment efficacy of cancer immunotherapies?

Figure 1. $\gamma\delta$ T cells in cancer

$\gamma\delta$ T cells in cancer can be regulated through cytokines, microbiota, and PAMP engagement for expansion and differentiation within the tumor microenvironment. These pro-tumor $\gamma\delta$ T cells promote tumor progression and metastasis via induction of immunosuppression and angiogenesis by cytokine secretion, mimicking Treg/Th2-like activity, interfering with DC effector function, and directly inhibiting antitumor adaptive T cell immunity. MDSC, myeloid-derived suppressor cells; PAMP, pathogen-associated molecular patterns; PD-1, program death-1; PD-L1, program death ligand-1; TAM, tumor-associated macrophages; TGF- β , transforming growth factor β ; TLR, toll-like receptor; Treg, regulatory T cells.

Table 1

Murine pro-tumor $\gamma\delta$ T cell subsets

Model	Cancer Type	$\gamma\delta$ TCR Expression	Cytokines	Surface/ Intracellular Markers	Pro-tumor Effector Function
Spontaneous	Breast Cancer	V γ 4 ⁺	IL-17, IFN- γ , G-CSF	CD27 ⁻ , ROR γ t ⁺ (intracellular), CCR6 ⁺	Induce G-CSF mediated recruitment of tumor infiltrating neutrophils (6)
Spontaneous	Pancreatic intraepithelial neoplasia (KRAS)	$\gamma\delta$ TCR ⁺	IL-17, IL-22 (36)		Proangiogenic survival (5)
Transplant (subcutaneous)	Subcutaneous heap 1-6 murine hepatocellular carcinoma	V γ 4 ⁺	IL-17	ROR γ t ⁺ , CD27 ⁻ , CCR6 ⁺	Mobilization of myeloid-derived suppressor cells by CXCR2 (8)
Transplant (subcutaneous)	B16-F10 melanoma	V γ 1 ⁺	IL-4	GATA-3 ⁺ (intracellular)	Th-2 like phenotype-reduce protective effect V γ 4 ⁺ , downregulation of IFN- γ , NKG2D, and perform (4)
Transplant (intravenous)	Lewis Lung carcinoma (3LL)	V γ 6 ⁺	IL-17		MDSC recruitment to tumor microenvironment(35)
Transplant (intraperitoneal)	ID8 ovarian cancer	V γ 6 ⁺	IL-17, IL-22	CD27 ⁻ , IL-7Ra ⁺	Mobilization of small peritoneal macrophages promoting proangiogenic factors (3)
Transplant (intraperitoneal)	MCA-induced CMS-G4 Fibrosarcoma	V γ 1 ⁺ ,	IL-17, IL-22	CD27 ⁻ , CCR6 ⁻ , NKG2D ⁺	Increased angiogenic related genes (<i>ang-2</i> and <i>Vegf</i>) (39)
Transplant (orthotopic)	Pancreatic Ductal Carcinoma	V γ 4 ⁺	IL-17, IL-10, TNF- α , IL-13	CD27 ⁺ , CCR6 ⁺ , PDL-1 ⁺	Inhibition of antitumor properties through suppression of $\alpha\beta$ T-cells (28)

Table 2Human pro-tumor $\gamma\delta$ T cell subsets

Cancer Type	$\gamma\delta$ Expression	Cytokines	Surface/intracellular Markers	Pro-tumor Effector Function
Colorectal Cancer	V δ 1 ⁺ , (<10% V δ 2)	IL-17A, IL-8, TNF- α , GM-CSF, IL-17F	CD27 ⁻ , CD45RO ⁺ , CD69 ⁺ , CD161 ⁺ , CCR6 ⁺ , CD45RA ⁻ , PD-1 ⁺ CD39 ⁺ (5, 48)	Chronic inflammation, recruitment of PMN-MDSCs and Treg-like suppressive function (7, 48, 56)
Melanoma	V δ 1 ⁺ (50%), V δ 2 ⁺ (42%)	IL-17, TNF- α , IFN- γ	CD45RA ⁻ , CD27 ⁻ (64.9%), CD45RA ⁺ , CD27 ⁻ (26.1%)	Higher frequencies of V δ 1 ⁺ cells are negatively associated with survival (57, 58)
Breast Cancer	V δ 1 ⁺	IL-17, IFN- γ , GM-CSF	CXCR3 ⁺ , NKG2D, CD56 ⁺ , CD8 $\alpha\alpha$ ⁺ , CD25 ⁻ , FoxP3 ^{low} ,	Treg functionality-inhibition of IL-2 and CD4/8 ⁺ effector function via TLR-8; impair maturation of DCs (12, 59–61)
Pancreatic Ductal Adenocarcinoma	$\gamma\delta$ TCR ⁺	IL-17, IL-22 (36)	ROR γ t ⁺ (36), CD27 ⁻ , CD45RA ⁻	Restriction of $\alpha\beta$ T-cell activation via enhanced expression of exhaustion ligands (28)
Rectal Cancer	V δ 1 ⁺			Inhibitory effect on proliferation rate of CD4 ⁺ T cells (62)
<i>In vitro</i> IL-4+ stimulation	V δ 1 ⁺ polarization	IL-10	CD124 ⁺	Inhibit <i>in vitro</i> expansion of V δ 2 ⁺ $\gamma\delta$ T cells which possess potent antitumor killing capabilities (44)