



# Novel Insight Into the Molecular and Metabolic Mechanisms Orchestrating IL-17 Production in $\gamma\delta$ T Cells

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Increasing evidence has demonstrated that IL-17-producing  $\gamma\delta$  T cells ( $\gamma\delta$  T17) play a tumor-promoting role in a series of cancers via various mechanisms in mice and human cancers, though the relationship between  $\gamma\delta$  T17 and human tumors has yet to be extensively characterized and established. Molecular signals such as intrinsic cascade, environmental cues and cellular metabolic pathways including nutrient uptake and utilization in  $\gamma\delta$  T17 cells are significantly important for their activation, differentiation, and function. Understanding the molecular mechanisms and metabolic pathways of  $\gamma\delta$  T17 cells in both the physiological setting and tumor environment would contribute to the development of therapeutic approaches or drugs targeting  $\gamma\delta$  T17 for immunotherapy in cancers.

**Keywords:** innate immune cells,  $\gamma\delta$  T17 cells, transcriptional regulation, metabolic reprogramming, cancer immunotherapy

Innate  $\gamma\delta$  T cells are a complex cohort of cells with diverse functionality in both physiological and disease conditions. While  $\gamma\delta$  T cells can be subdivided into multiple different subsets based on expression profile, they can largely be classified into two main functional groups- IFN- $\gamma$  producing ( $\gamma\delta$  T1) and IL-17-producing ( $\gamma\delta$  T17)  $\gamma\delta$  T cells (1). While both direct and indirect antitumor effects of  $\gamma\delta$  T cells have been reported, the emerging consensus within the field suggests that the  $\gamma\delta$ T17 subset possess pro-tumorigenic characteristics mainly mediated by IL-17A production. Specifically, IL-17A from  $\gamma\delta$  T cells has been shown to induce angiogenesis within the tumor microenvironment (TME), and increase recruitment of immunosuppressive cell types like myeloid-derived suppressor cells (MDSCs), neutrophils, and tumor associated macrophages (2). Therefore, given the prominent role of IL-17 in tumorigenesis, it is important to better understand the mechanisms responsible for regulating IL-17 secretion in cancer and at baseline in normal physiological conditions. Here, we review the mechanistic drivers and metabolic pathways controlling IL-17 production in  $\gamma\delta$  T cells in hopes to provide new approaches to cancer treatment by targeting  $\gamma\delta$  T17.

## $\gamma\delta$ T17 IN PHYSIOLOGICAL CONDITIONS AND TUMOR ENVIRONMENT

$\gamma\delta$  T cells are a unique subset of cells that combine conventional T cell adaptive immune features with rapid innate-like responses. Given this specific functionality,  $\gamma\delta$  T cells, particularly  $\gamma\delta$  T17,

are often found in barrier and mucosal sites like the skin, oral mucosa, gut lamina propria, and lung in both mice and humans (3–7). Murine  $\gamma\delta$  T17 have been shown to play important roles in tissue homeostasis, anti-infectious pathogen clearance and body temperature maintenance despite an overall low abundance in the body (3, 4, 8). Furthermore, in mice,  $\gamma\delta$  T17 cells contain  $V\gamma 4^+$ ,  $V\gamma 6^+$  and minor  $V\gamma 1^+$  subsets, and characteristically express ROR $\gamma$ t, c-Maf, and CCR6 (5–7, 9, 10). While both  $V\gamma 4^+$  and  $V\gamma 6^+$  subsets have been shown to produce IL-17,  $V\gamma 6^+$  cells produce IL-17 exclusively, and augment production in the context of cancer or inflammation whereas  $V\gamma 4^+$  are more heterogeneous and can produce IFN- $\gamma$  or IL-17 depending upon environmental context. The difference in cytokine profile is likely a result of differential development and peripheral regulation. It has been shown that development of  $V\gamma 6^+$  is restricted to a functional embryonic wave that is dependent on the fetal thymus whereas  $V\gamma 4^+$  are more complex and are heavily reliant on bone marrow progenitors (5). Further studies revealed differential homing patterns in the dermis and lung, and to a less extent in the lymph nodes (LN) and spleen, between the two subsets with  $V\gamma 6^+$  often outcompeting  $V\gamma 4^+$ . However, in spontaneous and transplantable cancer models, both subsets have been identified as prominent IL-17 producers (2, 11, 12). While the protumoral characteristics of  $\gamma\delta$ T17 cells are not the topic of this review it should be noted that other prominent tumor promoting roles include functioning like regulatory T(Treg)/T helper2 (Th2) like cells, interfering with dendritic cell effector functioning, and inhibiting T cell effector functioning via the programmed death-1 (PD-1)-programmed death ligand-1 (PD-L1) pathway (2, 13, 14).

In humans,  $\gamma\delta$  T cells mainly consist of tissue-resident  $V\delta 1^+$  and peripheral  $V\delta 2^+$  subsets. Tissue-resident  $V\delta 1^+$   $\gamma\delta$  T cells are often found in epithelial layers and play significant roles against infections and tissue integrity (15). The  $V\delta 2^+$  (mostly  $V\gamma 9^+$ ) population is more heterogeneous and can respond to a variety of pathogens (16). Both of these subsets can produce IFN- $\gamma$  upon activation, but the  $V\delta 1^+$  is reported to produce more IL-17 in some cancers like pancreatic ductal adenocarcinoma and colorectal carcinoma despite limited overall characterization studies (16, 17). Like their murine counterparts, human  $\gamma\delta$  T17 cells have been shown to promote tumor growth in a variety of human cancers including colorectal cancer, lung cancer, breast cancer and pancreatic ductal adenocarcinoma. (13, 16, 18, 19). However, a recent study revealed that breast-resident  $V\delta 1^+$  cells differentially produce IFN- $\gamma$ , not IL-17, and that breast-resident  $V\delta 1^+$  are associated with remission in triple-negative breast cancer (20), thus demonstrating the complexity of human  $\gamma\delta$  T17. There are some conserved protumor effectors mechanisms between murine and human  $\gamma\delta$  T17 cells including increased angiogenesis and inhibition of  $\alpha\beta$ T cells, but other distinct mechanisms have been identified in humans as shown in **Figure 1** (2). While further characterization of the role  $V\delta 1^+$  play within the human tumor microenvironment of different cancers is warranted, a limited collection of evidence suggests these cells convey an immunosuppressive pro-tumoral phenotype.

Overall,  $V\gamma 6^+$  and to an extent  $V\gamma 4^+$  cells in mice and  $V\delta 1^+$  cells in some human cancers like colorectal carcinoma

and pancreatic ductal adenocarcinoma are considered to be tumor progressing  $\gamma\delta$  T17. However, further studies are needed for exploring the human  $\gamma\delta$  T17 and its relationship with other cancer types. The molecular mechanisms governing IL-17 production are often specific to each particular cell type and will be covered individually in the next section. Therefore, understanding the molecular mechanisms and metabolic pathways orchestrating  $\gamma\delta$  T17 cells would help contribute to developing new immunotherapies in cancers.

## MOLECULAR SIGNALS ORCHESTRATING IL-17 PRODUCTION IN $\gamma\delta$ T CELLS

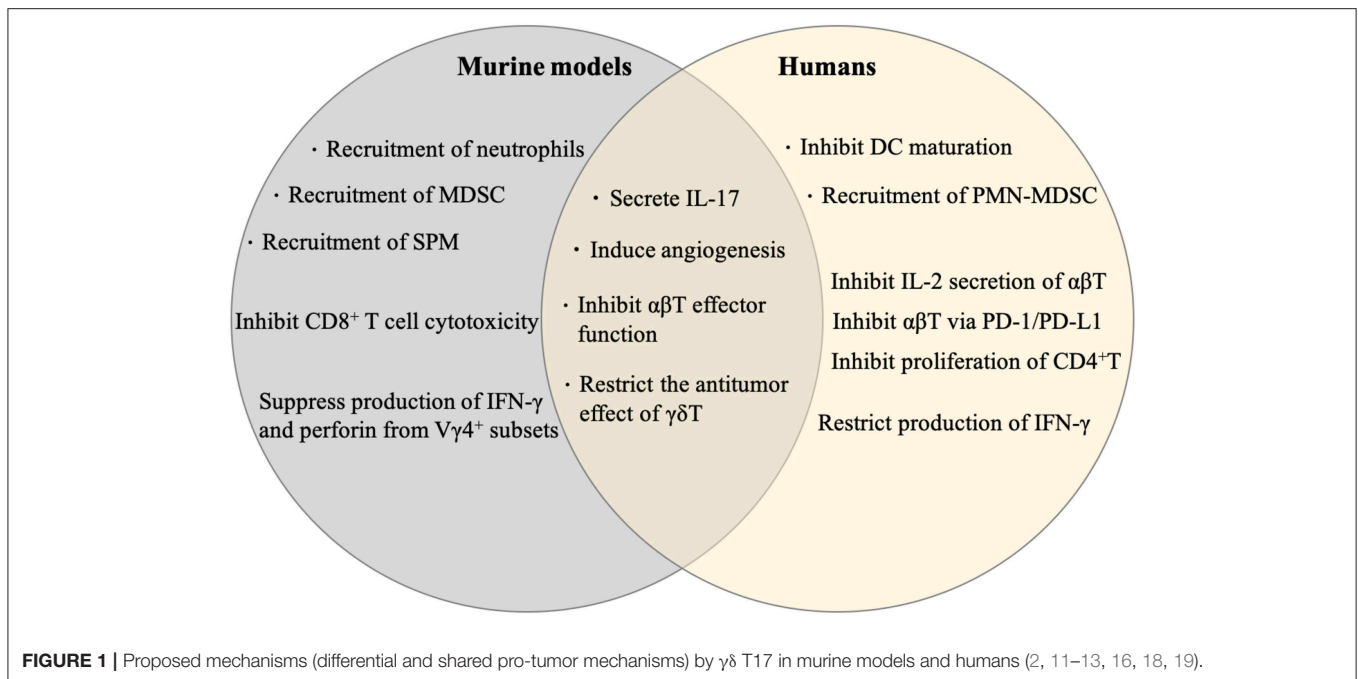
Cytokine production in  $\gamma\delta$  T cells can be preprogrammed in the embryonic thymus or induced in the periphery. Either way, cytokine production in  $\gamma\delta$  T cells requires complex networking. As shown in **Figure 2**, IL-17 production in murine  $\gamma\delta$  T cells is controlled by various transcriptional factors and also regulated by external stimulations. In this next section, we will identify specific transcription factors associated with IL-17 production in  $\gamma\delta$  T17.

### Transcription Factors (TFs)

One of the most prominent transcription factors associated with IL-17 production is ROR $\gamma$ t. It is known to control IL-17 production in Th17 cells and similarly has been found to be a core transcription factor for IL-17 production in murine CD27<sup>-</sup>  $\gamma\delta$  T cells (1, 21). However, unlike Th17 cells, ROR $\gamma$ t expression alone in  $\gamma\delta$  cells is enough to induce IL-17 whereas Th17 cells often need collaborative signals from TGF- $\beta$ , IL-6, or IL-21. Interestingly, ROR $\gamma$ t can maintain its own expression by binding at the *Rorc* CNS+10 (a conserved non-coding sequence located 10 kb from the *Rorc*(t) transcription start site) (10). ROR $\gamma$ t usually cooperates with other TFs such as STAT3, IRF4, and BATF in Th17 differentiation (22), but what specific factors regulate ROR $\gamma$ t in the context of  $\gamma\delta$  T17 cells remains largely unexplored.

One TF that has been identified to augment ROR $\gamma$ t driven IL-17 production in  $\gamma\delta$  T cells is c-Maf. The AP-1 TF c-Maf has been found to predominantly bind at *Rorc* CNS+10, thus stabilizing ROR $\gamma$ t expression (10). c-Maf also inhibits the binding of TCF1 (a negative regulator of ROR $\gamma$ t) to *Rorc* to further support the expression of ROR $\gamma$ t. Furthermore, c-Maf regulates chromatin accessibility thus increasing the probability of ROR $\gamma$ t binding. Interestingly, c-Maf can also promote  $\gamma\delta$  T17 through a ROR $\gamma$ t-independent mechanism via directly regulating *Blk* and *Tcf7* (encoding TCF1).

It has been reported that IRF4, ROR $\alpha$  and BATF are not required in IL-17 production of  $\gamma\delta$  T cells (22, 23), but a recent study revealed that IRF4 played a significant role in IL-17 production of murine dermal  $\gamma\delta$  T cells including  $V\gamma 4^+$  and  $V\gamma 6^+$  subsets (24). Specifically IRF4 links IL-1R and IL-23R signaling pathways to IL-17 production. One of the main transcription factors upstream from IRF4 is STAT3 (24). STAT3 activation is crucial for ROR $\gamma$ t expression in Th17 cells and also significant for IL-17 production in  $\gamma\delta$  T, though some subsets



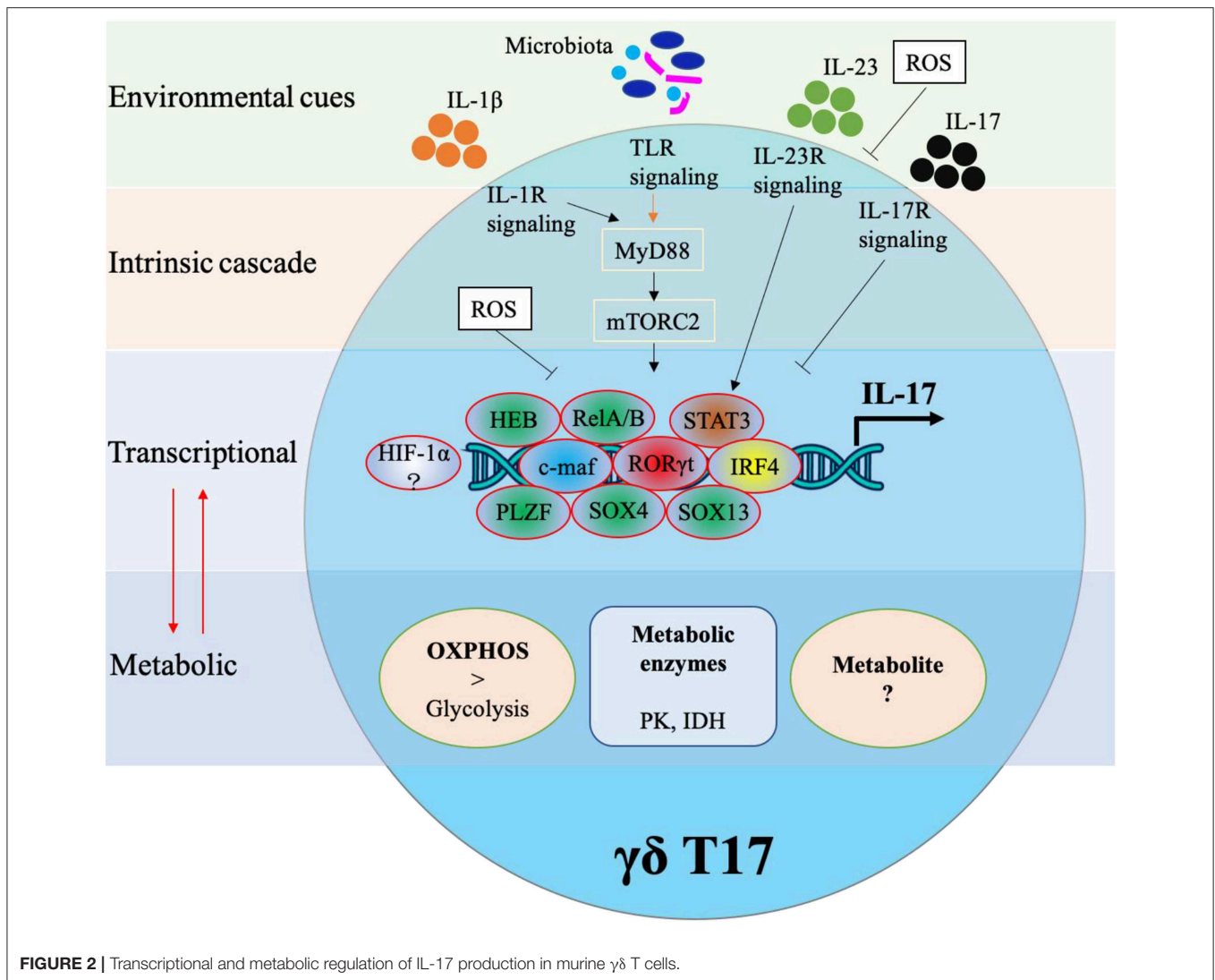
of  $\gamma$  $\delta$  T have been found to be independent of STAT3 (24–26). Specifically, IL-23-induced STAT3 signaling plays a pivotal role in the production of IL-17 in dermal V $\gamma$ 4<sup>+</sup> but not in V $\gamma$ 6<sup>+</sup> subsets (24). Similar to STAT3, some other TFs have been found to control IL-17 production in  $\gamma$  $\delta$  T subsets. The high-mobility group (HMG) TFs SOX4 and SOX13 were required for V $\gamma$ 4<sup>+</sup> subsets, and SOX4 was an essential regulator of *Rorc* whereas SOX13 regulated *Blk* expression (27). Moreover, their upstream TF HEB (HeLa E-box binding protein) regulated the expression of SOX4 and SOX13 by interacting with the regulatory region of DNA (~25 kb 5' of the *Sox4* transcriptional start site and predicted 32 kb 5' of the second start site of the *Sox13* locus) (28). The promyelocytic leukemia zinc finger (PLZF) TF was required for IL-17 secretion and maturation in V $\gamma$ 6<sup>+</sup> subsets, but the detailed molecular mechanism remains to be explored (29). Interestingly, a recent report found that PLZF<sup>+</sup>  $\gamma$  $\delta$  T cells promote a thermogenic response via directly producing cytokines such as IL-17 and TNF- $\alpha$  and indirectly maintaining catecholamine sensitivity (8). Collectively, apart from the core transcription factor ROR $\gamma$ t, universal transcription factors (c-Maf, IRF4), which play a role in all  $\gamma$  $\delta$  T17 subsets, and partial transcription factors (STAT3, HEB, SOX4, SOX13, and PLZF), which play a role in some  $\gamma$  $\delta$  T17 subsets, work in concert or independently for the controlling of IL-17 production in different  $\gamma$  $\delta$  T subsets.

### Cell Surface Receptors and Cellular Intrinsic Cascade

Mouse  $\gamma$  $\delta$  T17 cells express a variety of innate receptors including TLR1, TLR2, and dectin-1, but not TLR4. Activation of TLRs and dectin-1 leads to increased IL-17 production in  $\gamma$  $\delta$  T cells (30), solidifying their role as non-histocompatibility complex

restricted lymphocytes. Moreover,  $\gamma$  $\delta$  T17 cells express IL-23R and IL-1R which, following IL-1 $\beta$  with IL-23 stimulation, enhances IL-17 gene expression and protein production (6, 31, 32), suggesting that both PAMP and cytokine receptors play significant roles in the IL-17 production in  $\gamma$  $\delta$  T cells. In fact, the indispensable roles of IL-1R and/or IL-23R in  $\gamma$  $\delta$  T17-mediated diseases such as experimental autoimmune encephalomyelitis (EAE) and psoriasis-like skin inflammation have been validated in murine models (6, 31, 32). By exploring the molecular mechanism underlying the IL-1 $\beta$ -IL-17 axis, IL-1R-MyD88-mTORC2 was found in both dermal V $\gamma$ 4<sup>+</sup> and V $\gamma$ 6<sup>+</sup> subsets, which primarily produced IL-17 (24). MyD88 is an adaptor protein which is required for most TLR signaling and therefore is necessary for TLR signaling-induced expansion and cytokine production of  $\gamma$  $\delta$  T17. However, the detailed cascade or mechanism of TLR signaling in IL-17 production of  $\gamma$  $\delta$  T remains to be understood. The cytokine IL-23 differentially enhanced IL-17 production via the IL-23R/STAT3/IRF4 pathway in dermal V $\gamma$ 4<sup>+</sup> and via the IL-23R/RelA/IRF4 pathway in dermal V $\gamma$ 6<sup>+</sup> (24). These results suggested that IL-1 $\beta$  and IL-23 synergistically induced IL-17 production albeit through distinct pathways. Unexpectedly and of note, IL-17 itself is a negative regulator of  $\gamma$  $\delta$  T17 as *Il-17r* knockout increased the IL-17 production of  $\gamma$  $\delta$  T from cervical LN and inguinal LN (5, 33). The mechanism behind this negative feedback loop have yet to be determined.

Furthermore, both the classical and non-canonical NF- $\kappa$ B signaling pathways are important for  $\gamma$  $\delta$  T17. RelA or RelB conditional deficiency leads to reduction of  $\gamma$  $\delta$  T17 cells through reducing *Il-17* and *Rorc* expression at the transcriptional level, and p52, not p50 was also required for IL-17 production (34). NF- $\kappa$ B-inducing kinase (NIK), which is required for non-canonical NF- $\kappa$ B signaling, was essential for IL-17 production as NIK



depletion led to impaired *Rorc* and *Sox13* expression (35). Notch signaling and its downstream target *Hes1*, one of the basic helix-loop-helix (bHLH) proteins, were essential for the IL-17-producing function of mature  $\gamma\delta$  T cells in the periphery (36). It should be noted that the majority of mouse  $\gamma\delta$  T17 cells get functional preprogramming in the thymus, and factors like Notch signaling that have influence on the development of  $\gamma\delta$  T17 may affect the IL-17 production of  $\gamma\delta$  T cells.

It has been reported that TCR signaling is a major determinant of the functional differentiation of  $\gamma\delta$ T cells in the thymus. Strong TCR signaling determines the lineage fate of the earliest progenitor T cells toward the  $\gamma\delta$  subset (37, 38). However, little is known about how  $\gamma\delta$  TCR engagement drives IL-17 production in mature  $\gamma\delta$  T cells. A recent study identified the Syk/PI3K/Akt pathway as one means to control the development of  $\gamma\delta$  T17 (39). Additionally, c-Maf regulation of ROR $\gamma$ t which was noted above is dependent on  $\gamma\delta$  TCR ligation with too strong a signal limiting c-Maf expression (10). Overall, a variety of signaling pathways

including PAMPs, cytokines, Notch and  $\gamma\delta$  TCR ligation have been shown to orchestrate IL-17 production in murine  $\gamma\delta$  T cells.

It is important to keep in mind that human  $\gamma\delta$  T17 are different from murine  $\gamma\delta$  T17. Little is known about human  $\gamma\delta$  T17 in terms of origin, differentiation, and transcriptional regulation. While they express ROR $\gamma$ t, CCR6, IL-23R, and IL-1R like their murine counterparts (40), human  $\gamma\delta$ T17 cells may originate from naive precursors in the peripheral blood when activated with pathogen products and IL-23 stimulation (41). STAT3 deficiency in humans leads to a loss of IL-17 in  $\gamma\delta$  T cells though it does not affect the frequency of  $\gamma\delta$  T cells (42). ROR $\gamma$ t inhibition could selectively target IL-17-producing innate cells including  $\gamma\delta$  T17 in patients with spondyloarthritis, demonstrating that ROR $\gamma$ t antagonism could be a promising therapeutic approach (43). It has been reported that a cocktail of cytokines could maintain and differentiate human  $\gamma\delta$  T17 (44, 45), however a detailed mechanism has not been elucidated. Therefore, more information is needed for a better understanding

of the mechanism underlying the development and function of IL-17-producing  $\gamma\delta$  T cells in humans.

## CELLULAR METABOLISM AND METABOLIC REPROGRAMMING OF $\gamma\delta$ T17 CELLS

Cellular metabolism is coming to the forefront as an important indicator of cellular function. Specifically, cells often undergo metabolic reprogramming in the context of disease which ultimately affects the cells natural effector function. Naive T cells, for example, are quiescent with low metabolic demands and mainly rely on oxidative phosphorylation (OXPHOS) for ATP, while activated T cells dramatically upregulate glycolysis and downregulate mitochondria-dependent fatty acid oxidation (FAO) and pyruvate oxidation through the TCA cycle (46). This hypermetabolic reprogramming meets the demands for T cell activation in the context of infection or autoimmunity. Conversely in cancer, exhausted T cells are often found to be in a hypometabolic state which corresponds to their overall suppressed phenotype. The relationship between metabolism and T cell function has been summarized in detail elsewhere (47–49). However, how metabolism impacts the effector function and differentiation of  $\gamma\delta$  T cells has been largely unexplored. Here, we will review what is known about the factors orchestrating  $\gamma\delta$  T17 cell metabolism and how they may contribute to the understanding of  $\gamma\delta$  T cell metabolism for immunotherapy.

### Metabolic Pathway and Cellular Function in $\gamma\delta$ T Cells

Just like their cytokine profiles, the metabolic signatures of  $\gamma\delta$  T cells differ between the two main subsets.  $\gamma\delta$  T1 cells have a preference for glycolytic metabolism while  $\gamma\delta$  T17 rely more on OXPHOS (24). Classically, this fits with the pattern that pro-inflammatory cells rely more heavily on glycolysis while anti-inflammatory/pro-tumoral cells mainly utilize OXPHOS or fatty acid metabolism. Inhibition of glycolysis with 2-deoxy-D-glucose (2-DG) showed no impact on the IL-17 production of dermal  $\gamma\delta$  T, while inhibition of isocitrate dehydrogenase (IDH) or pyruvate kinase (PK) significantly reduced IL-17 production of dermal  $\gamma\delta$  T cells in a dose-dependent manner (24), suggesting that the citric acid cycle (TCA) and OXPHOS play a significant role in IL-17 production. One of the key regulatory enzymes that serves as a central mediator between extrinsic signals like cytokines and environmental cues to cell-intrinsic metabolism is mammalian/mechanistic target of rapamycin (mTOR) (24, 50–52). There are two distinct mTOR complexes, mTORC1 and mTORC2 which contain scaffold proteins Raptor or Rictor, respectively. In dermal  $\gamma\delta$  T cells, stimulation with IL-1 $\beta$  and/or IL-23 directly activates mTOR resulting in increased IL-17 production. However, conditional knockout (cKO) of Rictor leads to reduced IL-17 production in both V $\gamma$ 4<sup>+</sup> and V $\gamma$ 6<sup>+</sup> subsets while Raptor cKO has no influence on IL-17 production of dermal  $\gamma\delta$  T (24). Neither Raptor cKO nor Rictor cKO impacted 2NBDG uptake in T-cell indicating that mTOR signaling specifically impacts OXPHOS.

Overall, these results suggest differential roles of mTORC1 and mTORC2 in the regulation of  $\gamma\delta$  T17. Rictor cKO alone leads to more dysfunctional mitochondria and reactive oxygen species (ROS) production, which implies that functionally respiring mitochondria are essential to  $\gamma\delta$  IL-17 production. Additionally, ROS negatively feeds back to IL-17 production in  $\gamma\delta$  T cells since treatment with ROS inhibitor N-acetyl-L-cysteine (NAC) rescued the IL-17 production (24). A recent report found that murine V $\gamma$ 6<sup>+</sup>  $\gamma\delta$  T17 cells displayed low expression of ROS neutralizing antioxidant glutathione. Consequently, tumor-associated neutrophils were then able to inhibit the proliferation of murine V $\gamma$ 6<sup>+</sup>  $\gamma\delta$  T17 cells via induction of ROS, suggesting novel approach for targeting the neutrophil/ROS/ $\gamma\delta$  T17 axis in the tumor microenvironment (53).

While OXPHOS is most often mentioned in the context of metabolism and ATP generation, a secondary less recognized function is thermogenesis, or the generation of body heat. Uncoupling of OXPHOS from ATP synthesis via uncoupling protein 1 (UCP1) results in the potential energy of the electron transport chain being converted into thermal energy or heat. A recent study found that  $\gamma\delta$  T17 cells play an important role in regulating this process (8).  $\gamma\delta$  T cells and IL-17 have been linked to maintaining homeostasis through T regulatory cell (T<sub>reg</sub>) mediated thermogenesis. T<sub>regs</sub> dominate the CD4<sup>+</sup> compartment within adipose tissue and generate large amounts of IL-33, a cytokine critical for body temperature regulation. They found that V $\gamma$ 6<sup>+</sup> accumulate in adipose tissue over time and can directly influence non-shivering thermogenesis. Specifically, the CD27<sup>-</sup>  $\gamma\delta$  T cells through IL-17 mediate expansion of adipocyte resident T<sub>regs</sub> which secrete the IL-33 necessary to induce UCP1 thermogenic effector function. Mice deficient in V $\gamma$ 6<sup>+</sup> or global IL-17KOs were unable to successfully regain thermostatic equilibrium following cold challenge indicating the importance of  $\gamma\delta$  generated IL-17 in thermogenesis.

The generation of IL-17 in  $\gamma\delta$  T cells is closely tied with mitochondria function and oxidative phosphorylation capacity. It has been shown that  $\gamma\delta$ T17 cells preferentially utilize OXPHOS over glycolysis and reduction in OXPHOS capacity correlates with decreased mitochondria function and concomitantly decreased IL-17 production. Furthermore, decreased IL-17 and V $\gamma$ 6<sup>+</sup> cells in adipose tissue results in decreased uncoupling of OXPHOS and overall inability to thermoregulate in response to environmental thermofluctuations. However, further investigation into how OXPHOS and TCA metabolism regulates IL-17 production is warranted. It remains unclear how pre-programming in the thymus affects metabolism, whether there are any differences in metabolic condition between activated  $\gamma\delta$  T17 and resting  $\gamma\delta$  T17, and how  $\gamma\delta$ T17 metabolism differs from Th17 cells. Previous studies have shown that TF Myc is critical for glycolysis and glutaminolysis in activated T-cells, and HIF-1 $\alpha$  is important for Th17 differentiation (50, 54). How these transcription factors impact  $\gamma\delta$ T17 development, particularly in the context of a hypoxic tumor microenvironment, has yet to be explored. In summary, limited information about the metabolism of  $\gamma\delta$  T17 has been reported. With the advance of new technologies such as systems metabolomics and single cell

sequencing, more details on the metabolism of  $\gamma\delta$  T17 could be revealed.

## CROSSTALK BETWEEN $\gamma\delta$ T17 AND OTHER CELLS AND MICROORGANISM IN TME

We are just beginning to acquire a better understanding of the molecular mechanisms and metabolic regulations governing  $\gamma\delta$  T17. However, the question becomes even more complex when taking into account the interaction between  $\gamma\delta$  T17, other cells, and microorganisms in the TME. A recent report characterizing the interaction between microbiota, immune cells and  $\gamma\delta$  T17 in lung adenocarcinoma microenvironment found that altered commensal microbiota promote lung cancer by activating  $\gamma\delta$  T17 through PMAP/MyD88-mediated production of IL-1 $\beta$  and IL-23 from myeloid cells. (18). These tumor-associated  $\gamma\delta$  T17 showed a distinct transcriptional profile from that of spleen indicating environmental context is important for dictating function. This report builds on the previous suggestion that intact commensal microbiota and  $\gamma\delta$ T17<sup>+</sup> in the lungs are necessary to mount sufficient immune responses against B16/F10 or LLC tumor challenge (55). Therefore, further investigation into the drivers behind altered lung commensal microbiota is warranted along with identification of pathologic species to help tease apart the role of  $\gamma\delta$  T17 in health and disease. Whether the tumor-associated  $\gamma\delta$  T17 display a different metabolic condition as compared to other  $\gamma\delta$  IL-17 producing subsets remains unknown. In murine models, oral microbiota drives  $\gamma\delta$ T17 proliferation and activation via CD103<sup>+</sup> DCs' cell-to-cell contact (33), while in the human colorectal cancer microenvironment,  $\gamma\delta$ T17 were polarized by microbiota-activated inflammatory DC-producing IL-23 and played a pivotal role in the cancer progression (16). A key tumor promoting phenotype of IL-17 is to recruit tumor-associated neutrophils or PMN-MDSCs to the

local microenvironment. However, tumor-associated neutrophils can inhibit  $\gamma\delta$ T17 via ROS production (53). With more emerging reports, the crosstalk between  $\gamma\delta$  T17, microbiota and other cells reveals a complicated, dynamic network. Focusing on the regulatory factors driving IL-17 transcription in  $\gamma\delta$  T cells can help elucidate their role in cancer and could be the key to targeting  $\gamma\delta$  T17-mediated tumor growth and progression.

## CONCLUDING REMARKS

$\gamma\delta$  T17 promote cancer progression through IL-17 via various mechanisms in murine models and some human cancers. Understanding the molecular and metabolic mechanisms orchestrating IL-17 production of  $\gamma\delta$  T cells provides us with a better understanding of how these cells are supposed to function in health and how disease alters these processes. Knowing the intricate mechanisms governing IL-17 production can help contribute to the development of new therapies targeting  $\gamma\delta$  T17-associated inflammation and tumor progression.

## AUTHOR CONTRIBUTIONS

XC and SM drafted the manuscript. JY and FC discussed and revised the manuscript. All authors read and approved the final manuscript for submission.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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