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The origin and fate of $\gamma\delta$ T cell subsets

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Recent experiments indicate that in contrast to $\alpha\beta$ T cells, $\gamma\delta$ T cell effector functions are largely preprogrammed in the thymus during fetal life. However the thymus also exports juvenile $\gamma\delta$ T cells that can mature and be polarized in the periphery. How these developmental pathways are regulated and how much they contribute to the $\gamma\delta$ T cell effector pool is unclear. Here we discuss recent advances in the understanding of $\gamma\delta$ T cell subset development, with particular focus on IL-17-producing $\gamma\delta$ T cells and their beneficial and pathogenic roles in immunity.

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Introduction

$\alpha\beta$ T cells leave the thymus after birth and migrate to the periphery as mature, naive cells. In an immune response, CD4⁺ cells further differentiate into various helper subsets characterized by distinct cytokine profiles. $\gamma\delta$ T cells can leave the thymus either as mature cells or as juvenile cells that finish maturation in the periphery. Furthermore, certain $\gamma\delta$ T cell subsets acquire effector functions already in the embryonic thymus, providing the first line of immune defense in newborns. Fetal $\gamma\delta$ T cells exit the thymus in waves and seed mainly epithelial surfaces. The first wave of cells generates IFN γ -producing V γ 5⁺ (nomenclature according to [1]) dendritic epidermal T cells (DETC) that perform crucial functions in the epidermis and in the development of specialized medullary thymic epithelial cells [2^{••}]. The next wave comprises IL-17-producing ($\gamma\delta$ T17) V γ 6⁺ T cells that seed epithelial linings of the lung, tongue and the genital tract, as well as the liver and peritoneal cavity. IL-4 and INF γ producing V γ 1⁺V δ 6⁺Thy-1^{dull} $\gamma\delta$ T cells ($\gamma\delta$ NKT) are also primarily generated in the fetal thymus and localize in tissues similarly to iNKTs [3,4].

Finally, starting just before birth and continuing throughout life, V γ 1⁺ and V γ 4⁺ cells migrate to the tissues and the

peripheral lymphoid organs, while V γ 7⁺ cells take their way to the intestines. These $\gamma\delta$ T cells subsets can produce different combinations of cytokines depending on the tissue and infection studied [5–7,8^{••}]. However, V γ 1⁺ and V γ 7⁺ cells usually produce IFN γ , while V γ 4⁺ cells frequently secrete IL-17. Expression of the surface molecules SCART2 and CD27 has been associated with the production of IL-17 and IFN γ , respectively. These markers may help to track the developmental pathways of different subsets, as they are found on thymocytes and peripheral T cells [9,10]. How and where V γ 1⁺, V γ 4⁺ and V γ 7⁺ $\gamma\delta$ T cells acquire their functional properties is poorly understood. In this review, we discuss the proposed pathways (Figure 1) and molecules involved (Figure 2), with a particular focus on IL-17 producing $\gamma\delta$ T cells.

Development of $\gamma\delta$ T cell subsets

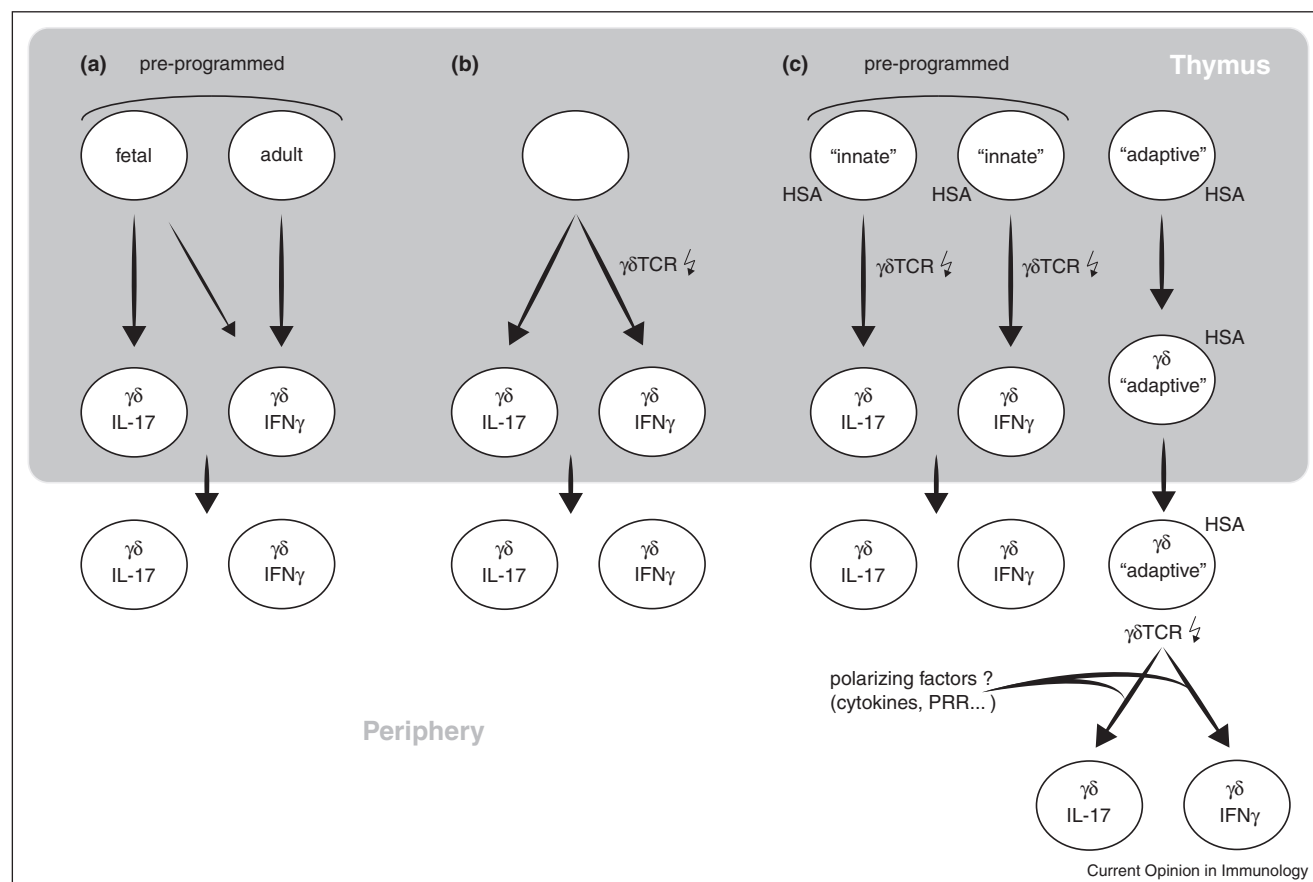
Fetal versus postnatal origin of IL-17-producing $\gamma\delta$ T cells

It was recently suggested that all $\gamma\delta$ T17 cells are of fetal origin (Figure 1a) [8^{••},11^{••}]. This was based on experiments showing that dermal and systemic $\gamma\delta$ T17 cells could not be efficiently reconstituted in irradiated mice by bone marrow transplantation, nor in adult RAG-deficient mice by *de novo* RAG induction [8^{••}]. Indeed, only fetal thymocytes were able to reconstitute peripheral lymph node and dermal $\gamma\delta$ T17 cells in adult WT mice [11^{••}]. Interestingly, $\gamma\delta$ T17 cell development from adult precursors has been observed in mixed bone marrow chimeras containing $\alpha\beta$ T cells with a disrupted IL-17 gene, suggesting that IL-17 produced by $\alpha\beta$ T cells suppresses development of $\gamma\delta$ T17 cells in adult mice [8^{••}]. Furthermore, evidence for postnatal development of IL-17-producing $\gamma\delta$ T cells can be found in the collagen-induced arthritis (CIA) mouse model [7]. $\gamma\delta$ T17 cells present in the joints express TCRs with coding sequences carrying substantial N-nucleotide additions, which indicate a postnatal origin because terminal deoxynucleotidyl transferase is not expressed in the fetus [12]. This $\gamma\delta$ T17 population also showed a biased TCR sequence, suggesting antigen-driven expansion. Thus, their IL-17-production could have resulted from cytokine-mediated polarization during activation (Figure 1c).

Taken together, $\gamma\delta$ T17 cells can develop in both fetal and adult thymi. The apparent embryonic origin of IL-17-producing $\gamma\delta$ T cells seems to result from lack of IL-17-mediated inhibition before birth, rather than from a truly programmed embryonic wave, as for example in the case of DETC development. Consistently, $\gamma\delta$ T17 [8^{••},13] and

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Figure 1



Models of functional specialization of $\gamma\delta$ T cells. **(a)** $\gamma\delta$ T17 cells originate exclusively during the embryonic development. **(b)** $\gamma\delta$ T17 cells develop if no agonistic TCR ligand is seen during thymic maturation. **(c)** The thymus contains different precursor pools, with preprogrammed ('innate') and unbiased ('adaptive') functional potential. 'Innate' precursors need agonistic TCR signals (depicted as $\gamma\delta$ TCR ligand) for functional maturation in the thymus, while 'adaptive' precursors leave the thymus as immature naive cells, mature in the periphery and polarize upon antigen recognition.

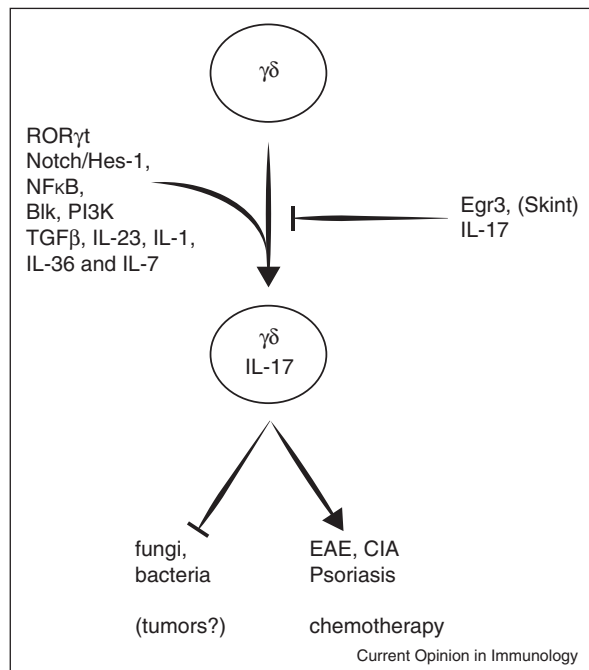
Th17 [13] cells were enriched in naive IL-17RA-deficient and IL-17AF-deficient mice.

Thymic and peripheral maturation of $\gamma\delta$ T cells

Analogous to $\alpha\beta$ T cell development, CD24 downregulation has been considered a sign of $\gamma\delta$ T cell maturation, although this has remained controversial because most $\gamma\delta$ recent thymic emigrants express CD24 [14–16]. In support, a detailed gene expression analysis indicated that loss of CD24 does indeed define the final step of $\gamma\delta$ T cells maturation [17^{••}]. The identified gene signatures of around 500 genes accompanying $\gamma\delta$ and $\alpha\beta$ thymocyte maturation showed 78% overlap. Only mature CD24[−]V γ 4⁺ thymocytes upregulated expression of $\gamma\delta$ T17 cell signature genes such as IL-17, IL-23R, IL-1R [18] and Blk [19[•]]. Similarly, V γ 1⁺ and V γ 7⁺ cells did not acquire full effector phenotype until the CD24[−] stage [17^{••}] and in adult mice only CD24[−] cells efficiently produced cytokines [8^{••},20] (and JK, unpublished results). Interestingly, while fetal V γ 5⁺ thymocytes

normally downregulate CD24 and produce IFN γ , they remain CD24^{hi} and produce IL-17 in mice lacking Skint-1 [21^{••},22], a novel butyrophilin-like surface molecule that mediates positive selection of DETCs [23].

Notably, the CD24[−] stage is reached after ligand recognition by the $\gamma\delta$ TCR [24,25], implicating that most immature (CD24^{hi}) cells did not receive TCR stimulation. Nevertheless, some of the CD24^{hi} cells already express signature transcription factors like Eomes, PLZF or ROR γ t [17^{••}]. Furthermore, principal component analysis of gene expression revealed that CD24^{hi} V γ 1⁺ and V γ 7⁺ cells are closely related and distant from the closely related CD24^{hi} V γ 4⁺ and V γ 6⁺ thymocytes [17^{••}]. Considering that the prevailing scheme of early T-cell development and lineage commitment is based on a pool of equivalent precursors that randomly rearrange TCR genes and undergo instructive TCR-mediated cell-fate decisions, it remains to be explained what determined differential gene expression in CD24^{hi} $\gamma\delta$ T cells that

Figure 2

A summary of factors influencing the development and function of $\gamma\delta$ T17 cells.

apparently did not receive any TCR signals. There are three mutually non-exclusive possibilities: some $CD24^{hi}$ $\gamma\delta$ T cells may have been positively selected by different TCR-ligands but have not yet downregulated CD24; expression of TCRs containing particular V segments may have triggered discrete signals without ligand engagement in a similar fashion to the preTCR [26]; finally, different $\gamma\delta$ T cell subsets may descend from distinct precursors.

Support for diversity among precursors before TCR-selection comes from several studies including a recent report showing temporal predisposition for $\alpha\beta$ and $\gamma\delta$ lineage fates among early $CD4^{-}CD8^{-}$ progenitors [27^{••}] and another report suggesting TCR-independent preprogramming of IL-17-production [8^{••}] (Figure 1a,c). In addition, the existence of discrete precursor pools for innate and adaptive T cells has been recently proposed to explain the presence of functional TCR γ chains in innate $\alpha\beta$ T cells [28]. Consistent with development from a common 'innate' precursor, $\gamma\delta$ NKT and $\alpha\beta$ NKT cells are remarkably similar in gene expression [17^{••}] (auto-) reactivity toward thymocytes [28], surface phenotype, cytokine production and tissue distribution [29[•]], although convergent development could also explain these features [30]. Interestingly, similarity in gene expression between $CD24^{hi}V\gamma4^{+}$ and DP thymocytes (especially $CD69^{+}$)

[17^{••}] could suggest their common origin from an 'adaptive' precursor pool.

Export of $CD24^{+}$ $\gamma\delta$ thymocytes indicates that many adult $\gamma\delta$ T cells complete maturation in the periphery, possibly upon ligand recognition (Figure 1c). However, as discussed below, the role of TCR-ligand interaction in the development of $\gamma\delta$ T17 cells is still unclear.

TCR signals

How TCR signals direct functional specialization of different $\gamma\delta$ T cell subsets is under intense investigation. It was proposed that TCR ligand recognition during maturation in the thymus induces the development of IFN γ -producing cells, while in the absence of the ligand the same $\gamma\delta$ T cells acquire the capacity to produce IL-17 (Figure 1b) [31]. In this manuscript, the phenotype of $\gamma\delta$ T cells reactive to the non-classical MHC class Ib molecule T22 was analyzed. Such cells were found in both WT and T22-deficient mice and according to the hypothesis should produce IFN γ and IL-17 respectively. Indeed, in WT mice T22-reactive $\gamma\delta$ T cells produced mainly IFN γ . Unfortunately, in T22-deficient mice their IFN γ and IL-17 production, was not sufficiently analyzed [31]. Furthermore, it is not clear if in T22-deficient mice, T22-reactive $\gamma\delta$ T cells develop in the true absence of a cognate ligand. Because T22-binding requires only a short motive in the TCR δ chain [32], calls carrying such TCR δ chains could potentially recognize also other ligands.

Stronger evidence for instructive $\gamma\delta$ T cell subset development comes from another study describing phenotypic changes in fetal $\gamma\delta$ T cells dependent on the presence or absence of Skint-1. In the presence of Skint-1, maturing $V\gamma5^{+}$ $\gamma\delta$ T cells induced an Egr3-mediated program and differentiated into IFN γ -producing DETCs. In the absence of Skint, $V\gamma5^{+}$ $\gamma\delta$ T cells expressed Sox13 together with ROR γ t and acquired IL-17-producing capacity [21^{••}]. However, in mice lacking Skint-1, $V\gamma5^{+}$ thymocytes showed increased apoptosis and accordingly the number of $V\gamma5^{+}$ thymocytes at E16 was decreased 2–3-fold [22]. Hence, a selection-based mechanism, whereby Skint-1 signals promote survival of Sox13⁺ROR γ t^{lo} precursors and other signals select Sox13⁺ROR γ t⁺ precursors, cannot be excluded. Complicating the issue is lack of evidence for Skint-1 being a TCR ligand. In an attempt to solve this problem, mice transgenic for TCRs (G8 and KN6) with known specificity (i.e. T22) were used. It was concluded that the skin-homing potential is intrinsically programmed in fetal precursors before selection, but TCR-mediated selection is required for the acquisition of receptors associated with skin homing (i.e. CCR10) [33[•]].

Some $\gamma\delta$ T cells seem to require strong agonistic TCR signals for maturation [25,34], but whether low-affinity

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TCR-ligand interactions play a role is not clear. Studying TCR signaling in $\gamma\delta$ T cells is greatly hampered by the limited number of known $\gamma\delta$ TCR ligands and the fact that the few well-described $\gamma\delta$ TCR-ligand interactions are of rather high-affinity [32]. Therefore, definition of new $\gamma\delta$ TCR-ligands is badly needed. An excellent recent study identified the endothelial protein C receptor (EPCR) as a novel low-affinity ligand for a human $\gamma\delta$ TCR, which mediated the recognition of CMV-infected endothelial cells and epithelial tumors [35^{••}]. EPCR was bound in an antibody-like fashion, similarly to other known $\gamma\delta$ TCR-ligands, but costimulation was required for $\gamma\delta$ T cell activation. Thus EPCR could provide a model self-antigen for studying positive selection of $\gamma\delta$ T cells by low affinity interactions and shed light on the requirement for TCR signals for generation of IL-17-producing $\gamma\delta$ T cells.

Interestingly, while microbial compounds can activate $\gamma\delta$ T17 cells through pattern recognition receptors [36,37[•],38], it was recently shown that they can also be recognized by the $\gamma\delta$ TCR [39^{••}]. Immunization of mice with red algae derived phycoerythrine (PE) triggered rapid IL-17 production from $\gamma\delta$ T cells, which bound PE with high affinity. PE-specific cells expressed an array of genes characteristic for $\gamma\delta$ T17, but whether they were programmed for IL-17 production in the thymus or polarized during activation was not determined [39^{••}].

Cytokines required for $\gamma\delta$ T17 development

$\alpha\beta$ Th17 cell differentiation requires TGF β , IL-6, IL-1 and IL-23 [40]. $\gamma\delta$ T17 cell development in the thymus is also controlled by TGF β [41[•]]. $\gamma\delta$ T cells expressed the highest levels of TGF β R among thymocytes and mice deficient for TGF β or TGF β -signaling adaptor molecule Smad3 showed defective $\gamma\delta$ T17 development [39^{••}]. Interestingly, also maintenance of $\gamma\delta$ T17 cells in peripheral lymph nodes seems to be promoted by $\alpha\beta$ Th17 cells in a TGF β -dependent manner [42].

A role of IL-6 in the generation of $\gamma\delta$ T17 cells is controversial. IL-6-deficient mice with decreased [43[•]] or unaltered IL-17 production in $\gamma\delta$ T cells were reported [41[•],44]. Furthermore, in contrast to IL-23, IL-6 (together with TGF β) failed to induce IL-17 in peritoneal V γ 6⁺V δ 1⁺ $\gamma\delta$ T cells [45]. Altogether, IL-6 seems to have limited influence on the development of preprogrammed $\gamma\delta$ T17 cells, but its role in polarizing naive peripheral $\gamma\delta$ T cells needs to be further investigated.

Even though $\gamma\delta$ T17 cells constitutively express IL-23R and IL-23 triggers their expansion [18,46], IL-23 is dispensable for $\gamma\delta$ T17 development and maintenance in peripheral organs [43[•]]. Also in humans, IL-23R and TCR signaling drive the expansion of $\gamma\delta$ T17 cells. Interestingly, it can do so only in neonatal and not

in adult $\gamma\delta$ T cells [47[•]], underlining a role of $\gamma\delta$ T17 cells in newborns.

Transcription factors involved in $\gamma\delta$ T17 cell differentiation

It has previously been shown that DP thymocytes influence thymic maturation of $\gamma\delta$ T cells by lymphotoxin (LT) signaling. $\gamma\delta$ T cells from TCR β - and LT β R-deficient mice showed altered gene expression including a reduced capacity to produce IFN γ upon anti-CD3 stimulation [48,49]. Recent data further extend these findings by implicating NF κ B family members RelA and RelB in the regulation of LT β -mediated signals needed for $\gamma\delta$ T17 development [50^{••}]. RelA controlled LT expression in accessory DP thymocytes, while RelB acted downstream of LT β R and promoted expression of ROR γ t [50^{••}]. Interestingly, PMA and ionomycin induced normal IFN γ response in $\gamma\delta$ T cells from RelA-deficient, RelB-deficient and LT β R-deficient mice. RelB deficient mice also displayed a defect in the maturation of DETCs [2]. Together, these results indicate important roles for lymphotoxin-triggered NF κ B-signaling and $\alpha\beta$ thymocytes in the development of $\gamma\delta$ T cells, but sorting out the details requires further efforts.

STAT3 and ROR γ t are crucial for the generation of $\alpha\beta$ Th17 cells [51–53]. Similarly, $\gamma\delta$ T17 cells also require ROR γ t for development, indicated by their absence in peripheral organs and a reduction in fetal and adult thymus of ROR γ t-deficient mice. In contrast, development of $\gamma\delta$ T17 cells was completely unaffected in the absence of STAT3, as shown in STAT3^{flox/flox}xTie2-Cre mice, further questioning a role of the STAT3 activator IL-6 [54[•]]. The same study also unraveled a critical role of the Notch/Hes1 signaling pathway in the generation of $\gamma\delta$ T17 cells. Expression of Hes1 correlated with IL-17-production and mice deficient in Hes1 had very few $\gamma\delta$ T17 cells [54[•]].

As we gain new insights into the transcriptional regulation of $\gamma\delta$ T cell development at a single cell resolution, we will soon be able to trace the precursor–progeny relations with a much greater precision.

Functional relevance of $\gamma\delta$ T17 cells

Beneficial roles of $\gamma\delta$ T17 in fungal and bacterial infections

Evidence for protective roles of $\gamma\delta$ T17 cells acting as a first line of host defense against microbial pathogens comes from studies using fungal and bacterial infections. V γ 6⁺V δ 1⁺ and/or V γ 4⁺ $\gamma\delta$ T cells mediate early control of *Escherichia coli* [45] and *Listeria monocytogenes* [55] in the peritoneal cavity and liver by IL-17-driven recruitment of neutrophils. Interestingly, the maintenance of enteric immune tolerance and unresponsiveness to commensal microbes require suppression of intestinal $\gamma\delta$ T17 cells by Treg cells [56^{••}].

Considerable evidence also links $\gamma\delta$ T cells with immunity to *Mycobacterium tuberculosis* [57^{••}]. An IL-17-producing $\gamma\delta$ T cell subset was recently described in the skin dermis and shown to mediate cutaneous immune-surveillance, help the expansion of *M. tuberculosis* specific $\alpha\beta$ T cells, and promote early neutrophil recruitment [10,11^{••},57^{••}]. Furthermore, mice lacking $\gamma\delta$ T cells presented sustained and exaggerated pyogenic type of granulomatous response and succumbed to infection late (days 50–100) after aerosol infection [58] and V γ 6⁺ and/or V γ 4⁺ cells were identified as the predominant IL-17-producers and promoters of lung granuloma formation upon BCG infection [59].

Human patients with inborn defects in the IL-17A/L17F pathway develop chronic mucocutaneous candidiasis (CMC) [60^{••}]. Consistently, mice lacking IL-17A or IL-17RA are highly susceptible to chronic candidiasis and $\gamma\delta$ T17 cells protect within the first 24 hours of lung infection by mediating recruitment of neutrophils [61]. However, in oropharyngeal candidiasis $\gamma\delta$ T17 cells seem to be less important [62]. The contribution of $\gamma\delta$ T17 cells to human CMC remains to be determined.

Beneficial roles of $\gamma\delta$ T17 in stress-surveillance and tumor-surveillance

Another important function of $\gamma\delta$ T cells is stress-surveillance and tumor-surveillance [63,64]. Consistently, known $\gamma\delta$ TCR ligands represent stress-induced molecules including MHC-like proteins MICA, CD1c and EPCR [35^{••},65]. IL-17 was initially shown to support tumor growth by promoting angiogenesis [66], but later it became clear that it also promotes tumor-specific CD8⁺ T cell responses [67]. Recently, an interesting study demonstrated an important role of $\gamma\delta$ T17 in potentiating responses against tumors triggered by chemotherapy [68^{••}]. V γ 4⁺ and V γ 6⁺ $\gamma\delta$ T cells supported priming and IFN γ -production of tumor-specific T cells, while mice deficient for $\gamma\delta$ T cells, or IL-17, did not respond efficiently to chemotherapy. TGF β and IL-6 were not required, but IL-17 production by $\gamma\delta$ T cells needed DC-derived IL-1. Consistently, IL-1R-deficient $\gamma\delta$ T cells did not amplify the action of chemotherapy *in vivo* [68^{••}]. IL-23 was required for IL-22 production (not needed for efficient therapy), but not as much for IL-17 [68^{••}]. While the jury is still out on whether in absence of chemotherapy, $\gamma\delta$ T cells are tumor antagonizing or rather tumor promoting [69], recent results indicate that we can at least try to hijack $\gamma\delta$ T17 cells for efficient, immune-supported therapy.

Pathological role of $\gamma\delta$ T17 cells in autoimmune inflammatory diseases

On the flip side, $\gamma\delta$ T17 cells have been involved in several inflammatory diseases. In collagen-induced arthritis (CIA) [7], experimental allergic

encephalomyelitis (EAE) [18] or even upon CFA immunization only [70], $\gamma\delta$ T17 cells were shown to enhance Th17 functions and promote disease. In the EAE model, $\gamma\delta$ T17 cells prevent the induction of regulatory T cells and seem to render $\alpha\beta$ T cells refractory to their suppressive activity [43[•]]. The mechanism is still not well understood, but it is dependent on IL-23 and neither involves IL-6 nor IL-21. A pathogenic role for $\gamma\delta$ T17 cells was also suggested in human Ankylosing Spondylitis (AS) [71[•]].

Several recent reports demonstrate a key function of IL-23-dependent $\gamma\delta$ T17 cells in the development of psoriasisiform dermatitis in a mouse model [72[•],73[•],74[•]]. Interestingly, expansion of $\gamma\delta$ T17 cells and skin-disease were dependent on IL-36 but not IL-1 [74[•]]. This is in contrast to the key role of IL-1 in IL-23-driven IL-17 production by $\gamma\delta$ T cells shown *in vitro* [18,72[•]] and in bacterial infections [75] and tumor-chemotherapy [68^{••}]. Also IL-7, a crucial factor for the development of T cells and B cells, seems to be important for the expansion of skin $\gamma\delta$ T17 cells and the associated development of dermatitis [76].

Protection from psoriasis was also seen in both PI3K γ -deficient and PI3K δ -deficient mice due to impaired $\gamma\delta$ T17 and $\alpha\beta$ Th17 responses, implicating an important role of the PI3K kinase pathway in the generation of these cells. Notably, IL-23 was reduced only in PI3K γ -deficient mice [77[•]].

Concluding remarks

$\gamma\delta$ T17 cells contribute to protection of newborns and to the first line of defense against pathogens in adults. Beyond that, their important functions in stress-surveillance and tumor-surveillance are emerging. $\gamma\delta$ T17 cell fate is determined by the transcription factors ROR γ t, Notch/Hes-1 and NF κ B, the kinase Blk and by cytokines TGF β , IL-23 and IL-1, but not by STAT3 or IL-6. Additional factors that contribute to $\gamma\delta$ T17 cell function include IL-36, IL-7 and the PI3 kinase. Yet despite recent progress, thymic development and effector polarization of $\gamma\delta$ T cells remain poorly defined, in particular their requirements for TCR and costimulatory signals. Current data indicate that mature $\gamma\delta$ T cells can be separated into subsets with innate-like and adaptive-like functions. Whether these derive from unique or common precursors guided by instructive signals is not clear. Studying transcription factors in individual immature thymic and peripheral precursors and $\gamma\delta$ TCR interactions with novel ligands should help understanding these important issues.

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