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Review

Epigenetic and transcriptional regulation of γδ T cell differentiation: Programming cells for responses in time and space

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ABSTRACT

γδ T cells are major providers of the pro-inflammatory cytokines interferon-γ (IFNγ) and interleukin-17 (IL-17) in protective or pathogenic immune responses. Notably, murine γδ T cells commit to either IFNγ or IL-17 production during development in the thymus, before any subsequent activation in the periphery. Here we discuss the molecular networks that underlie thymic γδ T cell differentiation, as well as the mechanisms that sustain or modify their functional properties in the periphery. We concentrate on recent findings on lymphoid and tissue-resident γδ T cell subpopulations, with an emphasis on genome-wide studies and their added value to elucidate the regulation of γδ T cell differentiation at the transcriptional and epigenetic (chromatin) levels.

1. Introduction

The discovery of γδ cells began thirty years ago with the cloning of cDNAs and genes encoding the wholly unanticipated T cell receptor (TCR) γ chain gene [1,2]. γδ cells have been evolutionary conserved for more than 430 million years as one of only three cell types (together with B cells and αβ T cells) that generate antigen receptors through somatic V(D)J gene recombination. Provocatively, the jawless vertebrates that use an alternative, non-VDJ mechanism of adaptive immunity have also conserved three cell types with diverse antigen receptors [3,4], seemingly emphasizing the non-redundant roles of three types of lymphocyte.

A compare and contrast assessment of αβ and γδ T cells reveals striking similarities and clear distinctions. Thus, both develop in the thymus from common double negative stage 2 progenitors [5–7], but in all vertebrates in which it has been examined γδ T cells develop first during ontogeny, as early as embryonic days (E)15–18 in the mouse, when specific γδ T cell subsets emerge expressing (semi-)invariant TCRs, most notably, Vγ5$^+$Vδ1$^+$ dendritic epidermal γδ T cells (DETCs) that populate the murine epidermis. Likewise, whereas αβ and γδ T cells can both localize to the same peripheral sites, *e.g.* lymphoid nodes (LNs), their distribution within lymphoid organs is not the same, and many γδ T cells, as part of their development, home directly from the thymus to non-lymphoid organs, *e.g.* skin, uterus and gut, where they are sustained throughout life. Also, both T cell sub-types secrete a similar set of effector cytokines, but γδ T cells produce them with much faster kinetics and independently of clonal expansion, a property generally associated with cells of the innate immune system. In fact, while αβ T cells acquire effector functions following activation in the periphery, many γδ T cells are pre-committed in the thymus to either interferon-γ (IFNγ) or interleukin-17 (IL-17) production [8–12]. Consistent with this, whereas αβ and γδ T cells can participate in host defense against infectious agents, γδ T cells can, like myeloid cells, contribute profoundly to the early, afferent phase of the immune response, giving rise to the concept of "lymphoid stress surveillance" by "innate-like" or "unconventional" T cells [13].

Lymphoid stress surveillance is defined by the ability of lymphocytes – with γδ T cells as the prototype – to sense infections or non-microbial stress and subsequently respond rapidly without clonal expansion or *de novo* differentiation, in synchrony

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with innate responses [14]. Stress surveillance is initiated upon recognition of stress antigens by one of several T cell or natural killer receptors (TCR and NKR), and its action can not only rapidly limit the dissemination of infected or malignant cells but also regulate the nature of the subsequent adaptive immune response [13,15,16]. As a consequence, lymphoid stress surveillance is implicated in inflammation [17], autoimmunity [18] infectious diseases [19–21], and tumor immunology [22–26]. Importantly, γδ T cells can exert potent cytolytic functions against a variety of premalignant or malignant tumor cells, while able to promote the growth of normal cells: thus they are being manipulated for cancer immunotherapy [27–29].

All these characteristics make γδ T cells a fascinating and intriguing population of lymphocytes, as recently reviewed [30,31]. Here we will focus on the molecular mechanisms that underlie murine γδ T cell differentiation, namely the regulatory networks involved in the acquisition in the thymus and in the periphery of the signature effector capabilities of discrete γδ T cell subsets. The molecular characterization of murine γδ T cells is especially challenging as the cells comprise various heterogeneous subpopulations, many of very small size. Thus, we shall concentrate on recent key findings relating to thymic, peripheral and tissue-resident γδ T cells. The main emphasis will be on genome-wide studies and their added value to elucidate the regulation of γδ T cell differentiation at the transcriptional and epigenetic (chromatin) levels.

2. Developmental pre-programming of innate-like γδ T cell functions

γδ T cells include IFNγ (γδIFNγ) and IL-17 (γδ17) producing capacities (revealed by short *in vitro* re-stimulation) without explicit induction of an immune response. These functionally committed γδ T cells can be found in peripheral tissues (*e.g.* LNs and spleen) and in barrier tissues of naïve mice (Fig. 1) [8–10]. Importantly, γδIFNγ and γδ17 cells are already found in the fetal thymus, as early as embryonic day 18 [8,10]. The acquisition of functional potential during thymic development originated the concept of "developmental pre-programming" of innate-like γδ T cells [13]. Nonetheless, it should be noted that a substantial fraction of γδ T cells leaves the thymus as functionally immature and only acquires cytokine production in response to antigen encounter [32]. This defines an "induced" or "adaptive" differentiation process (in the periphery) that resembles that of conventional αβ T cells, except for a lack of truly extensive clonal expansion upon activation [30,32]. The dissection of these processes has been greatly facilitated by the identification of cell surface markers that segregate two functional γδ T cell subsets: CD27, CD122 and NK1.1 mark γδIFNγ cells, whereas γδ17 cells are $CD27^{(-)}$ $CCR6^{+}$ [8,10,33].

Thymic development of γδ17 cells is restricted during ontogeny to the embryonic and perinatal periods [12,21,34,35]. Prinz and co-workers demonstrated that γδ17 cells are only generated in the fetal thymus, and that adult bone marrow cells cannot reconstitute IL-17 producing γδ T cells. The capacity to produce IL-17 is seemingly endowed before TCR engagement, suggesting the IL-17 program as a default in the absence of additional instructive signals [11,12]. Along these lines, the analysis of γδ thymocytes reactive to non-classical MHC molecules T10/T22 demonstrated that TCR ligation favored the development of γδIFNγ cells, whereas ligand-naïve cells differentiated into γδ17 cells [9]. Several other molecular cues were shown to differentially influence the developmental pre-programming of innate-like γδ T cells. For example, CD70–CD27 co-stimulation promoted the development of γδIFNγ cells [10,36], whereas TGF-β and IL-7 favored γδ17 cells [37,38].

Recently, Shibata and colleagues reported that distinct thymic progenitors can differentially give rise to either γδIFNγ and γδ17 cells. Whereas DN2 cells can develop into both functional subsets, DN3 can only generate γδIFNγ cells (Fig. 1) [39]. In this regard, we previously showed that early thymocyte precursors receive key differentiation signals from late αβ T cell progenitors – "transconditioning" of γδ T cell development – that may also skew cells toward discrete pathways of maturation [40,41].

3. Transconditioning of γδ T cell development by αβ T cell progenitors

In searching for genes that might provide important clues on γδ T cell lineage commitment and development, we identified an expression profile that distinguished γδ thymocytes from αβ thymocytes and that included transcription factors (TFs) such as ICER, Nor1, Nurr1, and Nurr77, together with regulators of G protein signaling (*e.g.* RGS1 and RGS2) [42]. While this gene expression profile was sustained in peripheral γδ T cells, including in the spleen and in the gut intra-epithelial lymphocyte (IEL) compartment, it was also shared with $TCR\alpha\beta^{+}$ $CD8\alpha\alpha^{+}$ IEL [42], which co-localize with γδ IEL in the gut and synergise to ensure protection at this body barrier. These results fostered the concept of "unconventional T cells" – both $TCR\alpha\beta^{+}$ and $TCR\gamma\delta^{+}$ – which commonly reside in epithelial tissues, are not restricted to MHC but recognize stress-associated molecules, and that have many features (including rapid response dynamics) typical of innate immunity; hence the alternative designation of innate-like lymphocytes.

In the follow-up to these studies we demonstrated that the expression of the "γδ T cell-biased" expression profile is at least partially dependent on lymphotoxin and other signals provided by late αβ T cell progenitors, *i.e.*, $CD4^{+}CD8^{+}$ (so-called "double positive" (DP) thymocytes [40]. DP thymocytes express LTα, LTβ and LIGHT, while their counter-receptor, LTβR, is highly expressed on γδ T cells and DN2–DN3 thymocyte precursors (Fig. 1). This "transconditioning" of γδ T cell development by αβ thymocytes has important functional consequences, since it impacts upon the differentiation of γδIFNγ cells [40,42]. Thus, beginning from a global gene expression analysis, these studies led to the dissection of an unanticipated cellular cross-talk in the thymus involving molecular mediators previously only implicated in lymphoid organogenesis [40,41].

More recently, we identified an additional molecular pathway upstream of LTβR on γδ T cells; CD27. This TNF receptor superfamily member, known to co-stimulate $CD4^{+}$ and $CD8^{+}$ T cells upon engagement with CD70 [43], is highly expressed on γδ T cells [10] and particularly by a subpopulation of DN3 thymocytes [44]. We showed that CD27 was required for LTβR expression [10] and, consistent with the γδIFNγ commitment of DN3 thymocytes [39], CD27 expression distinguished γδIFNγ from γδ17 cells [10]. Importantly, CD70–CD27 signaling actively promoted γδIFNγ cell development *in vitro* and *in vivo* [10], providing the first functional role for CD27 co-stimulation in the thymus. It is noteworthy that the link between CD27 and LTβR came from a global gene expression (microarray) analysis, with LTβR being one of the most differentially expressed genes between WT and $CD27^{-/-}$ γδ T cells [10].

4. Innate-like programming of functional γδ T cell subsets

γδIFNγ and γδ17 cells segregate not only on the basis of CD27 expression [10], but also on specific Vγ and/or Vδ chain usage [9,45]. Thus, γδ17 cells primarily express Vγ4 or Vγ6 (although $V\gamma4^{+}$ T cells can produce IFNγ in certain experimental models) [10,46,47], whereas $V\gamma1^{+}$ T cells mostly produce IFNγ, with a

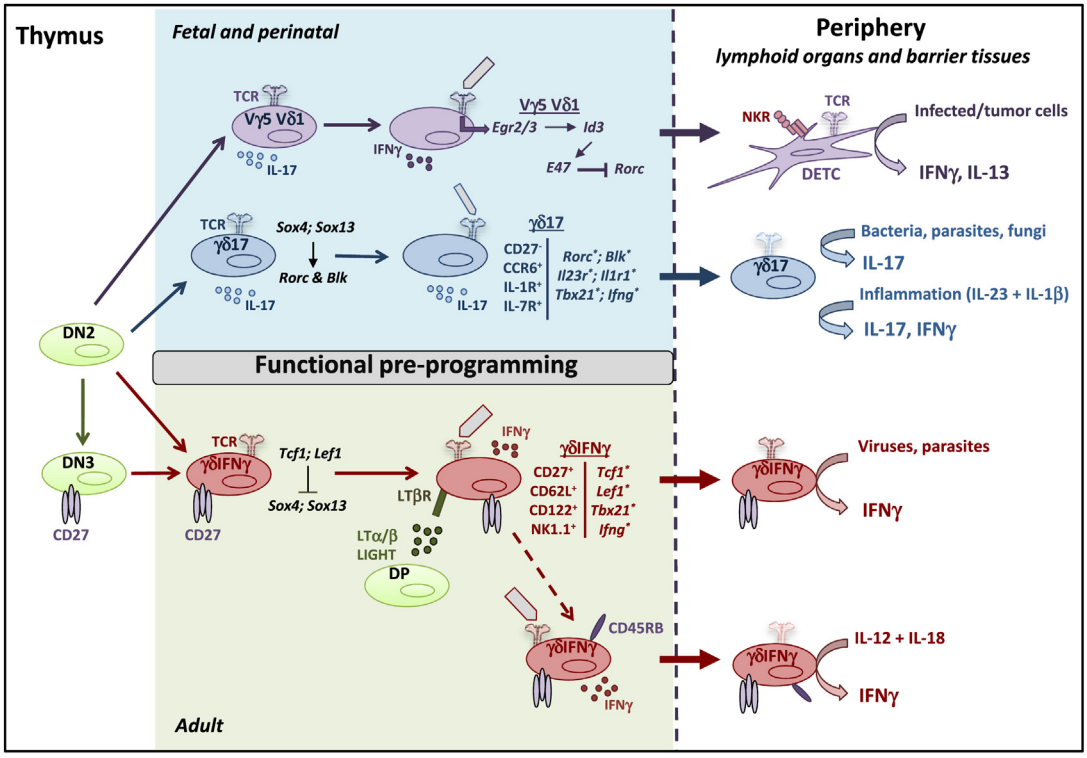

Fig. 1. Functional differentiation of murine γδ T cells. Molecular pathways associated with thymic pre-programming and peripheral activation of discrete cytokine-producing subsets of murine γδ T cells. Vγ5Vδ1 thymocytes (DETC precursors), as well as γδ17 T cells, develop exclusively in fetal and perinatal thymus, whereas γδIFNγ can arise from an adult thymus. Dashed arrow indicates hypothetical precursor–product relationship. Within known transcriptional pathways, key genes are indicated in italics, with an asterisk (*) noting open chromatin configuration. Gray bar next to the TCR represents (mostly unknown) putative ligands. Nonetheless, TCR signaling is required for the development of all subpopulations but its outcome may vary depending on the subset. The right panel shows physiological responses of the different subsets, with shadowed TCR indicating an incapacity to signal upon ligation.

particular Vγ1$^+$Vδ6$^+$ subset secreting both IFNγ and IL-4 upon stimulation [45]. This raised the possibility that each of these γδ T cell subsets harbored a distinct molecular network established early during thymic development. This was supported by a "big science" approach, in which the Immunological Genome Project (ImmGen; www.immgen.org) undertook in-depth transcriptional profiling of γδ thymocyte subsets, segregated according to Vγ and/or Vδ chain usage [48]. This revealed an early divergence in gene expression profiles and regulatory networks in γδ thymocyte subsets, identifying three transcriptional clusters associated respectively with Vγ4$^+$ and Vγ6$^+$ (IL-17 producers); Vγ1$^+$, Vγ1$^+$ Vδ6$^+$ and Vγ7$^+$ (IFNγ producers); and Vγ5$^+$ DETC progenitors [48] (see also below).

As follow-up to these resource data, Kang and colleagues concentrated on a specific gene network, consisting of four high-mobility group box TFs, Sox4, Sox13, TCF1 (also known as TCF7) and Lef1 (Fig. 1). Of note, TCF1 had been shown to be crucial for T cell commitment and differentiation [49], and Sox13 to contribute significantly to γδ *versus* αβ lineage commitment [50]. Sox4 and Sox13, whose expression precedes TCR signaling, positively regulated γδ17 cell development by inducing Rorc and Blk [51], two crucial mediators of the γδ17 program [52–54]. Furthermore, a spontaneous mutation in *Sox13* in a commonly used CD45.1$^+$ congenic C57BL/6 mouse sub-strain led to a selective deficiency in Vγ4$^+$ γδ17 cells, and this was associated with reduced skin lesions in a model of psoriasis-like dermatitis [55]. Conversely, TCF1 and Lef1 inhibited the differentiation of γδ17 cells by counteracting the effects of Sox4 and Sox13, and instead promoted γδIFNγ cell development [51]. Of note, the TCF1 and Lef1 loci (but not Sox4 or Sox13) displayed extensive positive histone marks (H3K4me2) in peripheral γδIFNγ cells, suggesting an epigenetic layer to ensure commitment to IFNγ production in innate-like CD27$^+$ γδ T cells in the periphery ([56]; see below).

Our genome-wide analysis of histone modifications highlighted the strong epigenetic patterning of Dickkopf 3 (DKK3), a modulator of the Wnt signaling cascade, in peripheral γδ T cell subsets. Moreover, Dkk3-deficient mice displayed abnormal γδ17 cell development [56]. Given that TCF1 and Lef1 are downstream of canonical Wnt signaling [57], these studies collectively emphasize the potential role of Wnt signaling in γδ T cell differentiation.

Mice deficient for TCF1 also showed impairment in IL-22 production by gut innate lymphoid cells (ILCs) [51]. This observation, together with others (see above) have collectively suggested that at least some innate-like T cell subsets (including some γδ T cells and invariant NKT cells) acquire "innate" properties before committing to the T cell lineage [58], with some possibly sharing a common progenitor with ILCs [51]. The analysis of progenitors should respect ontogenetic observations, with Vγ5$^+$, Vγ6$^+$, Vγ1$^+$Vδ6$^+$, and many Vγ4$^+$ cells requiring a fetal/neonatal thymic environment to develop, whereas Vγ1$^+$ (and a fraction of Vγ4$^+$) cells are generated in the adult thymus [12,34,59,60]. Likewise, it was recently reported that the fetal thymus is colonized by two distinct waves of progenitors: the first restricted to the embryonic thymus and giving rise exclusively to T cells (including Vγ5$^+$ DETCs); the second wave, just before birth, capable of differentiating into T, B and myeloid cells [61]. It remains to be seen how discrete innate-like properties of γδ T cells may segregate with these two waves of thymic progenitors, and how the somatically rearranged TCR then imposes its influence over γδ T cell development and functional differentiation, presumably steering γδ cells away from the arena of ILC that by definition lack antigen receptors.

5. Role for a TCR-induced network in γδ T cell differentiation

Conventional T cells go through strict selection processes mediated by the MHC-restricted TCRαβ. For MHC-independent γδ T cells, the paucity of known TCRγδ ligands or other thymic selecting determinants has significantly limited our understanding of the role played by TCRγδ in γδ T cell development [31,62]. Nonetheless, some key advances have been made from genome-wide studies focused on the development of DETC.

DETC sit in the mouse epidermis where they ensure skin integrity, at least in part by sensing NKG2D ligand expression [14,22]. DETC arise exclusively in the embryonic thymus, between E15 and E16, and carry an invariant TCR composed of a Vγ5 paired with a Vδ1 chain [63]. DETC fail to develop in FVB mice from the Taconic farm (FVB.Tac) [59], and genome-wide mapping (by comparison with reference FVB mice from Jackson laboratories; FVB.Jax) identified a unique premature termination mutation in *Skint1* [64]. This gene encodes an Ig-like molecule expressed on the surface of medullary thymic epithelial cells. Genetic complementation of FVB.Tac with *Skint1* rescued DETC development, thus showing that Skint1 is a thymic stromal determinant of (TCRγδ-dependent) DETC selection.

To dissect the transcriptional network involved in the selection of DETC progenitors, a microarray was performed comparing E15 and E16 Vγ5$^+$ thymocytes from FVB.Jax and FVB.Tac mice, respectively [11]. This revealed the upregulation of genes involved in DETC functions (*e.g.* Tbx21, Xcl1 and Ctsw) upon Skint1-mediated selection. Most importantly, Egr2 and Egr3 were found to be highly upregulated in *Skint1*-selected Vγ5$^+$ thymocytes, and their overexpression in FVB.Tac thymic organ cultures partially rescued DETC development. Egr3 is regarded as a marker of strong TCR signaling and has been associated with agonist-selected T cells, and with T cell anergy [65,66]. Moreover, Egr2 and Egr3 are transcriptional regulators of Id3, which inhibits the expression of E47, which in turn controls Rorc expression (Fig. 1) [48,67]. Consistent with this, Skint1-mediated selection downregulated Rorc and Sox13 expression in Vγ5$^+$ thymocytes [11]. Thus, Skint1-mediated selection of DETC progenitors inhibits the gene regulatory network that drives the IL-17 program [11]. As such, TCRγδ-mediated signals may be required to suppress the "default" (innate) IL-17 program in γδ thymocytes in order to commit to IFNγ production. This is also consistent with TCRγδ ligand (T10/T22) expression being necessary for the development of IFNγ-producing γδ T cells in so-called G8 transgenic mice that express a T10/T22-reactive γδ TCR [9].

This notwithstanding, more recent studies also argue for a role of the TCRγδ signaling pathway (specifically downstream kinases) in γδ17 cell differentiation. In particular, γδ17 cells failed to develop in mice carrying a hypomorphic mutation of Zap70 and in Itk-deficient mice [51,68]. Interestingly, subsequent to the impact of TCR signaling on their development, both γδ17 cells and DETC acquire altered responsiveness to TCR stimulation. For γδ17 cells, this is characterized by an overt inability to rapidly flux calcium and to phosphorylate TCR-dependent kinases (e.g., ERK), but rather a propensity to die upon TCR/CD3 cross-linking [18,36,68]. Instead, peripheral γδ17 cells are very responsive to innate cytokines, notably IL-1β and IL-23 [18,36]. DETC reacquire some degree of responsiveness to TCR signaling in the periphery, but it is highly atypical by comparison with conventional T cell activation, possibly related to which the DETC TCR *in vivo* is constantly engaged by keratinocytes [68,69]. Future research should address further how TCR signaling impacts on the pre-programmed molecular network of γδ T cell subsets, and how this conditions their functional responsiveness in the periphery.

6. Epigenetic regulation of γδ T cell differentiation

Regardless of how transcriptional networks are established during the thymic development of innate-like γδ T cells, their maintenance in the periphery requires specific epigenetic mechanisms operating on the cells' chromatin. These mechanisms ensure the autonomous maintenance of lineage phenotype in differentiated cells, even through mitotic divisions [70]. Among such mechanisms, histone H3 (H3) methylation at lysines 4 (K4) or 27 (K27) control the access to genes of the transcriptional machinery [70,71]. Thus, H3K4 methylation (H3K4me2/me3) marks transcriptionally active loci, whereas H3K27 (H3K27me3) assigns inactive gene regions. We have recently performed a genome-wide (ChIP-seq) analysis of H3K4me2 and H3K27me3 "marks" in peripheral CD27$^+$ *versus* CD27$^{(-)}$ CCR6$^+$ γδ T cell subsets [56] that largely correspond to γδIFNγ and γδ17 cells, respectively. Active histone modifications for *Il17* and other genes implicated in the IL-17 program, such as *Rorc* and *Blk*, were exclusively found in CD27$^{(-)}$ CCR6$^+$ γδ T cells. By contrast, and surprisingly, *Ifng* and its transcriptional regulator *Tbx21* were epigenetically primed for expression in both γδ T cell subsets (Fig. 1). These data were validated at the transcriptional level by RT-qPCR analyses. Importantly, these epigenetic and transcriptional signatures of peripheral γδ T cell subsets were already established in their thymic counterparts [56]. Consistent with these data, immature Vγ4$^+$ but not Vγ4$^{(-)}$ thymocytes showed an active histone modification profile on *Rorc* and *Blk* loci [51]. These data fully enforce the concept of developmental programming of γδ T cell subsets in the thymus. However, they raised questions over the functional potentials of peripheral CD27$^{(-)}$ CCR6$^+$ γδ T cells that bear active histone marks in the *Ifng* locus, particularly since CD4$^+$ Th17 cells had been shown to acquire IFNγ expression upon remodeling of the *Ifng* locus through changes in H3K4 and H3K27 methylation patterns [72].

7. Functional stability *versus* plasticity of γδ T cell subsets

In acute infection scenarios posed by four types of microorganisms – virus (murid herpes virus 4), bacterium (*Mycobacterium avium*), fungus (*Candida albicans*) and parasite (*Plasmodium berghei*) – peripheral CD27$^+$ and CD27$^{(-)}$ CCR6$^+$ γδ T cell subsets sustained the mutually exclusive functional properties evident in naïve animals: CD27$^+$ γδ T cells produced IFNγ whereas CD27$^{(-)}$ CCR6$^+$ γδ T cells produced IL-17 [10,36,56]. However, in three other settings *in vivo*, a population of IL-17$^+$ IFNγ$^+$ "double producers" was observed within the CD27$^{(-)}$ CCR6$^+$ γδ T cell compartment, but not among CD27$^+$ γδ T cells: in gut-associated lymph nodes after oral infection with *Listeria monocytogenes* [73]; in the brain of mice suffering from experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis [74]; and in the peritoneal cavity of mice bearing ovarian cancer cells [56]. One common characteristic of these three models is strong local inflammation, by contrast with the four acute infection models. Consistent with this, we defined the *in vitro* requirements for differentiation of the IL-17$^+$ IFNγ$^+$ double producers as being the inflammatory cytokines IL-1β and IL-23 [56], previously shown to trigger the selective expansion of CD27$^{(-)}$ CCR6$^+$ γδ T cells [18,36]. Of note, IL-23 is also the critical cytokine to drive the differentiation to double-producing CD4$^+$ T cells [75–77].

The responsiveness to IL-1β and IL-23 of CD27$^{(-)}$ CCR6$^+$ but not CD27$^+$ γδ T cells was predicted by the striking epigenetic and transcriptional polarization of *Il1r1* and *Il23r* (Fig. 1) [56]. Interestingly, this pattern was already established in γδ thymocyte subsets, indicating that the striking responsiveness to IL-1 plus IL-23 of CD27$^{(-)}$ CCR6$^+$ γδ T cells, and their potential for peripheral plasticity is also pre-programmed in the thymus. By contrast, CD27$^+$ γδ T cells produced exclusively IFNγ in all *in vitro* perturbation experiments,

including under Th17 polarizing conditions [56]. Moreover, a population of CD27^{hi}CD45RB^{+} peripheral γδ cells responded strongly to the innate combination of IL-12 plus IL-18, in the absence of TCR engagement, by making solely IFNγ (Fig. 1) [68]. The "hardwired" production of IFNγ by CD27^{+} γδ T cells is reminiscent of previous studies where the overexpression of GATA-3, the Th2 "master transcription factor", failed to down-regulate IFNγ in total γδ T cells [78]. Collectively, our data suggest that, among innate-like, thymic pre-programmed γδ T cells, the CD27^{+} subpopulation has a stable, lineage-like behavior, whereas the CD27$^{(-)}$ CCR6^{+} compartment is endowed with functional plasticity that deployed under strong inflammatory conditions in peripheral tissues.

It is unclear what conditions this would correspond to in human pathophysiology: specifically, whether IL-17-IFNγ co-production has a physiologic role or is a marker of pathologic immune dysregulation. Among CD4^{+} αβ T cells, Th1-like Th17 cells have been ascribed pathogenic roles in various autoimmunity models [77,79–81]. Likewise, IFNγ^{+} IL-17^{+} γδ T cells have been observed in the central nervous system of mice suffering from EAE, *versus* healthy controls [74]. However, in the *Listeria* infection model, Lefrançois and colleagues identified a protective function for the double-producing γδ T cells [73]. In fact, these cells displayed a "memory-like" phenotype and properties, enhancing protection against recall infection [73]. In humans, IL-17^{+} IFNγ^{+} double producing γδ T cells have also been identified under inflammatory conditions [82,83], and they may thus play unanticipated pathogenic *versus* protective roles in autoimmunity and cancer.

8. Concluding remarks

Genome-wide analyses have significantly contributed to the dissection of the molecular (epigenetic and transcriptional) mechanisms of γδ T cell differentiation. Even recently, an additional transcriptomic study by the ImmGen consortium implicated ETV5, an Ets family member, in γδ17 cell development. ETV5 was highly expressed in Vγ4^{+} thymocytes, and the analysis of T cell-specific ETV5-deficient mice revealed a specific loss of mature Vγ4^{+} thymocytes and γδ17 cells [84].

It seems now clear that whereas γδ T cells have the capacity to produce the same collection of cytokines as are made by CD4^{+} T cells, functional differentiation of cells within the two T cell lineages is regulated very differently (reviewed in [85]). For example, when we analyzed histone H3 modifications at the genome-wide level, only one third of the top 120 differentially marked loci in γδIFNγ and γδ17 cells were also differentially marked in CD4^{+} Th1 and Th17 cells [56]. Among "γδ-specific" differentiation factors are Egr-3 [11] for γδIFNγ cells; and Blk [54], Rel-b [86] and Hes-1 [87] for γδ17 cells. On the other hand, various crucial factors for CD4^{+} T cells are fully dispensable for γδ T cell differentiation; these include STAT3 [87], IRF4 [88] and BATF (J. Martins, K. Serre and B.S.-S., unpublished data).

Even among factors seemingly shared between γδ and CD4^{+} T cell subsets, the extent to which they impact on functional differentiation can be quite distinct. For example, in *Tbx21*-deficient mice, IFNγ^{+} CD4^{+} T cells are completely absent [89,90], but γδ T cells are still capable (albeit in reduced frequencies) of producing IFNγ [56,78,91].

The question naturally arises as to the value of distinct transcriptional networks being employed to control IFNγ and IL-17 production in γδ *versus* CD4^{+} T cells. One possibility is that the two cell types differentiate and participate at different stages of the immune response and this requires distinct networks activated by different stimuli. In particular, since many γδ T cells are functionally programmed in the thymus, this will likely involve a series of thymic signals that may be qualitatively or quantitatively different in secondary lymphoid organs where CD4^{+} T cells differentiate. Along these lines, the role of TCRγδ signaling during the developmental pre-programming of γδ T cells clearly deserves further investigation: to what degree, if any, does this involve endogenous ligands for the γδ TCRs?

One explanation for pre-programming is that the cells are required in the periphery to respond very rapidly. In adults, this would be consistent with innate-like γδ T cells providing a first line of defence and mobilization in response to the stress of infection and/or non-microbial challenges, *e.g.* toxins. Moreover, in the very young – when γδ T cells are particularly abundant – pre-programming may equip γδ T cells to provide immediate responses to diverse environmental challenges. Indeed, our own work has recently shown that αβ T cells in human neonates display disproportionately high levels of innate-like relative to adaptive functions [92]. Whatever the most important roles prove to be, pre-programming of gene regulatory networks and their enforcement at the level of epigenetics are key steps in equipping the T cell compartments to provide meaningful responses in appropriate time and space. In this respect, it remains a conspicuous fact that among body surface T cells, IFNγ production is a property of intraepithelial lymphocytes, whereas IL-17 production is a feature of sub-epithelial cells, such as those in the dermis and intestinal lamina propria.

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