

Review

Human $\gamma\delta$ TCR Repertoires in Health and Disease

Alina Suzann Fichtner ^{1,*}, Sarina Ravens ^{1,2} and Immo Prinz ^{1,2} 

¹ Institute of Immunology, Hannover Medical School, 30625 Hannover, Germany; Ravens.Sarina@mh-hannover.de (S.R.); Prinz.Immo@mh-hannover.de (I.P.)

² Cluster of Excellence RESIST (EXC 2155), Hannover Medical School, 30625 Hannover, Germany

* Correspondence: Fichtner.Alina@mh-hannover.de; Tel.: +(0511) 532-9738

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Abstract: The T cell receptor (TCR) repertoires of $\gamma\delta$ T cells are very different to those of $\alpha\beta$ T cells. While the theoretical TCR repertoire diversity of $\gamma\delta$ T cells is estimated to exceed the diversity of $\alpha\beta$ T cells by far, $\gamma\delta$ T cells are still understood as more invariant T cells that only use a limited set of $\gamma\delta$ TCRs. Most of our current knowledge of human $\gamma\delta$ T cell receptor diversity builds on specific monoclonal antibodies that discriminate between the two major subsets, namely $V\delta 2^+$ and $V\delta 1^+$ T cells. Of those two subsets, $V\delta 2^+$ T cells seem to better fit into a role of innate T cells with semi-invariant TCR usage, as compared to an adaptive-like biology of some $V\delta 1^+$ subsets. Yet, this distinction into innate-like $V\delta 2^+$ and adaptive-like $V\delta 1^+$ $\gamma\delta$ T cells does not quite recapitulate the full diversity of $\gamma\delta$ T cell subsets, ligands and interaction modes. Here, we review how the recent introduction of high-throughput TCR repertoire sequencing has boosted our knowledge of $\gamma\delta$ T cell repertoire diversity beyond $V\delta 2^+$ and $V\delta 1^+$ T cells. We discuss the current understanding of clonal composition and the dynamics of human $\gamma\delta$ TCR repertoires in health and disease.

Keywords: $\gamma\delta$ T cells; $\gamma\delta$ TCR repertoires; TCR diversity; innate T cells

1. Introduction

$\gamma\delta$ T cells are detected at frequencies of 3–10% of T cells in the peripheral blood of human adults and are often enriched as resident cells within solid organs and mucosal tissues [1–3]. The biology of $\gamma\delta$ T cells in blood and tissues is incompletely understood, although they exert pleiotropic functions such as cytokine production, tissue regulation, B cell help and cytotoxicity [4]. First, the defining characteristic of the $\gamma\delta$ T lymphocyte subset is their specific T cell receptor (TCR), composed of a γ -chain (TRG) and a δ -chain (TRD). The genes encoding TRG and TRD rearrange during $\gamma\delta$ T cell maturation in the thymus.

Briefly, the somatic DNA recombination of variable (V), diversity (D, only in TRD), and joining (J) elements creates combinatorial diversity of the individual TCR chains, a process called V(D)J-recombination [5]. Next to a multiplication of the potential TCR variety by the pairing of TRG and TRD chains, overall diversity is greatly amplified by junctional diversity, through the insertion of palindromic sequences (P nucleotides) and of non-templated nucleotides by the terminal deoxynucleotidyl transferase (TdT) enzyme (N nucleotides) at the V(D)J junction (CDR3 region) [6]. Therefore, all $\gamma\delta$ T cells together possess a large repertoire of unique TCRs, termed clonotypes, that in theory could comprise up to 10^{18} TRG/TRD combinations [5]. However, the number of clonotypes found in an individual's $\gamma\delta$ TCR repertoire is probably much smaller, and the composition of human $\gamma\delta$ TCR repertoires in health and disease is an active field of research.

For a long time, the general understanding of $\gamma\delta$ T cell biology was that $\gamma\delta$ T cells are innate-like T lymphocytes, similar to invariant natural killer T (NKT) or mucosa-associated invariant T (MAIT) cells. This was in part because, in contrast to $\alpha\beta$ T cells that recognize peptide antigens in a conserved

MHC-restricted mechanism, ligands and factors that shape the $\gamma\delta$ TCR repertoire and activation remained largely enigmatic. Only a few direct TCR ligands were identified to date. Those are either endogenous MHC-related (e.g., endothelial protein C receptor (EPCR), MR1 or CD1d) or MHC-unrelated proteins (e.g., annexin A2) [7–10]. In particular, EPCR and annexin A2, as well as phosphorylated metabolites of isoprenoid synthesis, were described as serving as self-antigens that indicate cellular stress [5,11–13]. Most importantly, B7 receptor family-like butyrophilin (BTN) and butyrophilin-like (BTNL) molecules have been implied in the development of specific epithelial and circulating $\gamma\delta$ T cell subsets [14–17] and as direct $\gamma\delta$ TCRs ligands [18–21]. Advances in next-generation sequencing (NGS) analysis of human $\gamma\delta$ TCR repertoires, together with the recent identification of $\gamma\delta$ TCR ligands, shed light on the vast TCR diversity of human $\gamma\delta$ T cells, thereby pointing to a complex role in health and disease. These studies support the idea that $\gamma\delta$ T cells have features of innate and adaptive immune cells, that may depend on their developmental origin and priming, and hence may explain their multifaceted roles in tissue homeostasis, autoimmunity, pro- and anti-tumor activity, and during infectious diseases.

2. Human $\gamma\delta$ T Cell Subsets Are Defined by Their TCR δ Chain

In mice, tissue localization and effector function of $\gamma\delta$ T cells is typically correlating to their expressed TCR γ chain. For instance, (according to the Heilig and Tonegawa nomenclature [22]) skin-surveilling $V\gamma 5^+$ T cells exclusively locate to the skin epidermis. In contrast, $V\gamma 7^+$ T cells reside as specialized intraepithelial lymphocytes in the gut, and $V\gamma 1^+$ T cells circulate as naïve or IFN- γ -committed T cells in the periphery. Furthermore, IL-17-producing $V\gamma 4^+$ or $V\gamma 6^+$ T cells are enriched in tissues such as the dermis, oral mucosa, brain, joints or reproductive tracts [23,24]. Similarly, human $\gamma\delta$ T cells can be roughly grouped by V-gene usage (Table 1).

Table 1. Human $\gamma\delta$ T cell subsets by high-throughput TCR sequencing. Table summarizes features of γ -chain (TRG) and δ -chain (TRD) repertoires of the major $V\gamma 9V\delta 2^+$ (fetal and adult-like) and non- $V\gamma 9V\delta 2^+$ T cell subsets ($V\gamma 9^-V\delta 2^+$, $V\delta 1^+$, $V\delta 3^+$, $V\gamma 8V\delta 1/2^+$ and $V\gamma 4^+$). Nomenclature of gene segments according to Lefranc/Forster [25], in brackets according to IMGT [26] and Strauss et al. [27].

Human $\gamma\delta$ Subsets	TRG Repertoire	TRD Repertoire	Characteristics
Fetal $V\gamma 9V\delta 2^+$ [28]	- Semi-invariant $V\gamma 9JP$ (IMGT: TRGV9/TRGJP, Strauss: $V\gamma 2/J\gamma 1.2$)	- Predominant $V\delta 2J\delta 3$ usage (IMGT: TRDV2/TRDJ3)	- Phosphoantigen-reactive $\gamma\delta$ T cell subset
	- Shared CDR3 γ sequences and length homogenization	- Private and shared CDR3 δ	- Polyclonal expansion upon antigen stimulation
	- Germline-encoded clonotypes: Short-homology repeats	- Shorter CDR3 δ lengths	- Extrathymic, postnatal expansion
Adult-like $V\gamma 9V\delta 2^+$ [28–30]	- Semi-invariant $V\gamma 9JP$	- Predominant $V\delta 2J\delta 1$ usage (IMGT: TRDV2/TRDJ1)	- Phosphoantigen-reactive $\gamma\delta$ T cell subset
	- Shared CDR3 γ sequences and length homogenization	- Private CDR3 δ	- Originate from postnatal thymus
	- Germline-encoded clonotypes: N additions		- Polyclonal expansion upon antigen stimulation
$V\gamma 9^-V\delta 2^+$ [31,32]	- Diverse $V\gamma$ chains	- Private CDR3 δ	- Extrathymic expansion
	- Private CDR3 γ		- Clonal expansion in CMV Liver infiltrating/tissue homing
$V\delta 1^+$ [33,34]	- Diverse $V\gamma$ chains	- $V\delta 1$ usage (IMGT: TRDV1)	- Clonal expansion in CMV
	- Private CDR3 γ	- Private CDR3 δ	
$V\delta 3^+$ [34,35]		- $V\delta 3$ usage (IMGT: TRDV3)	- Clonal expansion in some HCV patients
	- Diverse $V\gamma$ chains?	- Clonal/oligoclonal repertoire?	- Moderate clonal focusing
		- Private CDR3 δ	

Table 1. Cont.

Human $\gamma\delta$ Subsets	TRG Repertoire	TRD Repertoire	Characteristics
Fetal $V\gamma 8V\delta 1/2^+$ [36,37]	- $V\gamma 8JP1$ usage (IMGT: TRGV8/TRGJP1, Strauss: $V\gamma 1.8/J\gamma 1.1$) - Public, short CDR3 γ - Germline-encoded clonotypes: Short-homology repeats	- $V\delta 1$ or $V\delta 2$ usage - Public, short CDR3 δ - Germline-encoded clonotypes: Short-homology repeats	- CMV-responsive in utero - Lin 28b-driven intrinsic priming for IFN- γ and granzyme expression - Invariant/public clonotypes - Not present in adults
$V\gamma 4^+$ [38,39]	- Public $V\gamma 4$ chains (IMGT: TRGV4, Strauss: $V\gamma 1.4$) - Clonal repertoire	- Private $V\delta 1$ chains - Clonal repertoire	- Intestinal epithelial $\gamma\delta$ T cell subset - Innate-like phenotype - Loss of $V\gamma 4^+$ in celiac disease

According to the international ImMunoGeneTics information system®(IMGT) [26], the human TRG locus is encoded on chromosome 7 and contains six functional V gene segments, called $V\gamma 2$ to $V\gamma 5$, $V\gamma 8$ and $V\gamma 9$ (TRGV2, TRGV3, TRGV4, TRGV5, TRGV8 and TRGV9), five J-elements (TRGJ1, J2, JP1, JP2 and JP) and two constant gene regions (TRGC1, TRGC2) [25,26,40,41]. The V-genes TRGV2-5 and TRGV8 have a relatively high sequence similarity and differ from the TRGV9 sequence. TCRs using the latter TRGV9 element are therefore sometimes still (misleadingly) called $V\gamma 2^+$ instead of $V\gamma 9^+$ [27].

The TRD locus is situated within the α -chain (TRA) locus on chromosome 14 and includes eight functional V gene segments called $V\delta 1$ to $V\delta 8$ (TRDV1, TRDV2, TRDV3, TRAV14/DV4, TRAV29/DV5, TRAV23/DV6, TRAV36/DV7 and TRAV38/DV8), with TRDV1-3 genes being used most frequently, along with three diversity (TRDD1-3), four joining (TRDJ1-4) and one constant (TRDC) gene region [26,40,41]. It is well established that most $V\gamma 9^+$ chains assemble with the TRGJ element “JP” and often pair with $V\delta 2^+$ sequences. The resulting semi-invariant $V\gamma 9(JP)V\delta 2^+$ TCR is expressed by innate-like $V\gamma 9V\delta 2^+$ T cells [42–45]. $V\gamma 9V\delta 2^+$ T cells are considered the main circulating $\gamma\delta$ T cell subset in humans [31,33,46]. They are the major $\gamma\delta$ T cell fraction in the peripheral blood of most adults and expand after birth, likely upon the sensing of host- or microbe-derived prenyl pyrophosphates, also called phosphoantigens (pAgs) [11,12,44,47–49] (Figure 1). In brief, pAgs are metabolic products that interact with the butyrophilin family member BTN3A1 and activate $V\gamma 9V\delta 2$ T cells in a BTN2A1-dependent manner [15,16,18,21,50–52]. BTN2A1 has been shown to interact with BTN3A1 and binds $V\gamma 9^+$ chains via germline-encoded residues in the hypervariable region 4 (HV4) and CDR2, similar to BTNL3 interactions with $V\gamma 4^+$ chains [18,19,21]. According to Rigau and colleagues, phosphoantigen reactivity depends on the $V\gamma 9JP$ CDR3 loop and CDR2 residues of $V\delta 2$ chains, that seem to form a second interaction site with another molecule (potentially BTN3A1) on the TCR surface [43,45,53]. Conversely, Karunakaran et al. confirmed the BTN2A1-CDR2 δ interaction and also observed CDR3 δ to be crucial for pAg reactivity, but proposed a composite ligand model involving $V\gamma 9$ germline-mediated BTN2A1 recognition and CDR3-dependent binding to one or more separate ligands [21]. Phosphoantigens are produced by several bacteria and stressed cells (e.g. virus-infected or transformed cells) and are potent antigens leading to the rapid anti-bacterial, anti-viral or anti-cancer responses of $V\gamma 9V\delta 2^+$ T cells [12,13,54]. These small molecules interact with an intracellular domain of BTN3A1 (B30.2) and are thought to induce conformational changes that lead to $V\gamma 9V\delta 2^+$ T cell activation [15,17,50].

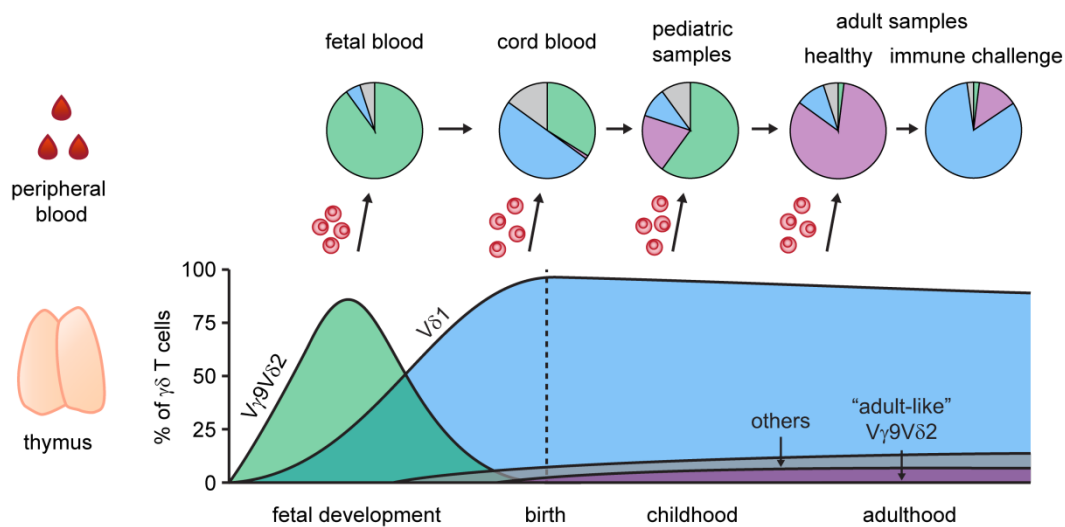


Figure 1. Developmental waves of human $\gamma\delta$ T cells. The $\gamma\delta$ T cell population in the human thymus shows characteristic waves of $\gamma\delta$ T cell subpopulations, with distinct V-gene usage (lower panel). Schematic proportions of $V\gamma9V\delta2^+$ (fetal: green, adult-like: purple), $V\delta1$ (blue) and $\gamma\delta$ T cells using other V-genes (“others”: gray) are shown as a percentage of all thymic $\gamma\delta$ T cells. Migration of thymic $\gamma\delta$ T cells and extrathymic changes subsequently contribute to the formation of the adult peripheral blood $\gamma\delta$ T cell compartment (upper panel). The composition of peripheral blood $\gamma\delta$ T cells from second trimester fetal blood to adults is illustrated by pie charts. Typical clonal expansions of $V\delta1^+$ T cells were observed in a multitude of immune challenges (e.g., CMV), and indicate an adaptive-like $\gamma\delta$ T cell response.

Other human $\gamma\delta$ T cell subsets are non-reactive to phosphoantigens, and include cells that use $V\delta2$ chains paired with non- $V\gamma9$ chains, also known as $V\gamma9^-V\delta2^+$ T cells, or display $V\delta1^+$ or $V\delta3^+$ $\gamma\delta$ TCRs [31,33,34,42]. Such non- $V\gamma9V\delta2^+$ T cells can undergo clonal expansion and often represent the dominant $\gamma\delta$ T cell fraction in tissues; albeit some adult individuals also display high frequencies in peripheral blood [33,34].

3. $\gamma\delta$ T Cell Subsets Arise Early during Ontogeny

In mice, the development of several waves of $\gamma\delta$ T cell subsets, such as $V\gamma5V\delta1^+$ dendritic epidermal T cells (DETCs) or $V\gamma6V\delta1^+$ IL-17-producing $\gamma\delta$ T cells, exclusively takes place in the fetal thymus and these cells are maintained as long-lived effector cells after birth [23,24]. Early ontogenetic murine $\gamma\delta$ T cell subsets are characterized by the expression of highly invariant and public TCRs that are shared among individual mice [55]. This publicity is presumably caused by simple gene rearrangements and/or positive selection during thymic development [56]. While $V\gamma6V\delta1^+$ T cells are prewired to become IL-17 producers even before TCR expression [57,58], a strong TCR-signal mediated via Skint1, a butyrophilin-like molecule expressed on thymic epithelial cells, will induce the IFN- γ phenotype of $V\gamma5V\delta1^+$ DETCs during thymic development. Later on, the murine thymus produces different $\gamma\delta$ T cell subsets that often display a high TCR repertoire diversity.

Recent advances showed that, comparable to the mouse $\gamma\delta$ T cell compartment, it is likely that human $\gamma\delta$ T cells also arise in developmental waves. During fetal development, $V\delta1^+$ TCR rearrangements dominate the fetal thymus $\gamma\delta$ T cell receptor sequences (gestational week 15 and 16) [59]. Later in gestation, both $V\delta1^+$ and $V\delta2^+$ TCRs can be detected, with a prominence of $V\delta2^+$ chains [59–61]. Along that line, the predominant $\gamma\delta$ T cell subset in the fetal blood consists of $V\gamma9V\delta2^+$ T cells (75%–80%) in the second trimester and low frequencies of $V\delta1^+$ and $V\delta3^+$ $\gamma\delta$ T cells (< 5%), indicating a first wave of $V\gamma9V\delta2^+$ T cells before gestational week 30 [62]. These fetal $V\gamma9V\delta2^+$ T cells are characterized by a semi-invariant $V\gamma9V\delta2^+$ TCR with characteristics of pAg-reactive TCRs, like TRGV9-TRGJP rearrangements and restricted CDR3 γ lengths [43], and were shown to be reactive to the

phosphoantigen (*E*)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) [62]. Interestingly, fetal blood $V\gamma 9V\delta 2^+$ T cells show an enrichment of a public germline-encoded CDR3 nucleotide sequence “5'-TGTGCCCTTGTGGGAGGTGCAAGAGTTGGGCAAAAAAATCAAGGTATTT-3'” (translation: “CALWEVQELGKKIKVF”), formed without the addition of N nucleotides, but using short homology repeats (GCA) [28,62]. TdT expression in thymocytes increases with age and low levels were shown to favor the generation of such germline-encoded TCR clones (without N nucleotides) during early thymic development. Later on during ontogeny, the length of each CDR3 region is more variable, and a higher number of N insertions is used. Thus, in adults, this specific public germline-encoded clone is found in varying frequencies, and is mostly generated using N additions. This leads to a differential nucleotide usage of fetal and adult germline $V\gamma 9J\text{P}$ clones [28,33,63]. Its CDR3 region seems to be prototypic for pAg recognition by $V\gamma 9V\delta 2^+$ T cells, and is a major contributor to the length homogenization to around 14 amino acids observed in the $V\gamma 9$ chain repertoire [62,64,65]. We might speculate that this simple rearrangement, and thus the length homogenization, coevolved with the pAg sensing ability of $V\gamma 9V\delta 2^+$ TCRs and the conserved binding of $V\gamma 9$ to BTN2A1 [18,21]. Thus, by retaining the binding capacity to BTN2A1, the $V\gamma 9J\text{P}$ chain may pair with a multitude of $V\delta 2^+$ chains in the blood [66], creating a high TCR repertoire diversity of $V\gamma 9V\delta 2^+$ T cells. Further studies should address the effect of BTN2A1, and potentially other factors, to positively select $V\gamma 9V\delta 2^+$ T cells during thymic development.

The earliest T cells, namely the subset of pAg-specific $V\gamma 9V\delta 2^+$ T cells, are followed by $V\delta 1^+$ T cells that can be detected in fetal blood at week 25 and increase to become the major population of $\gamma\delta$ T cells at term-delivery [37,62,67] (Figure 1). The $\gamma\delta$ TCR repertoire of fetal non- $V\gamma 9V\delta 2^+$ thymocytes was shown to comprise an oligoclonal TRG repertoire, a diverse TRGV usage (including the non-functional TRGV10) and usage of mainly TRDV2 rearrangements paired with TRDJ2 or TRDJ3 [36]. Those fetal thymocytes use few N insertions, and TdT expression at this stage is low [36]. Similar to germline-encoded $V\gamma 9J\text{P}$ rearrangements, invariant TCRs (TRGV8JP1, TRGV10JP1, TRDV2D3, TRDV1D3) were found to be expressed by fetal non- $V\gamma 9V\delta 2^+$ thymocytes, and recombination is thought to be similarly dictated by short homology repeats [36]. Using OP9DL1 cultures, Tieppo and colleagues showed the involvement of Lin28b in the induction of an effector program, the inhibition of TdT expression and the formation of germline-encoded CDR3 γ and δ sequences in fetal thymocytes. The fact that fetal non- $V\gamma 9V\delta 2^+$ T cells (in particular one $V\gamma 8V\delta 1^+$ T cell clone) can already mount efficient immune responses against in utero cytomegalovirus (CMV) infections [37] supports the idea that $\gamma\delta$ T cells are an important innate immune cell subset during fetal life and in neonates.

4. Development and Maintenance of $\gamma\delta$ T Cells in Child- and Adulthood

In the postnatal thymus, $V\delta 1^+$ T cells are the most abundant $\gamma\delta$ T cell population and $V\delta 2^+$ chains are found at very low levels [28,47,61,68,69]. The FACS monitoring of $\gamma\delta$ T cell frequencies ($V\delta 1^+$ and $V\delta 2^+$) in peripheral blood lymphocytes of young children and pediatric thymi lead to the conclusion that $\gamma\delta$ T cells undergo an extrathymic, postnatal maturation in response to environmental stimuli during early childhood [47]. Moreover, human immature $\gamma\delta$ T cells (mainly $V\delta 1^+$) leave the postnatal thymus to differentiate into cytotoxic T cells in the periphery [68]. Recent NGS studies have supported this view, as human $\gamma\delta$ TCR repertoires are highly polyclonal in the pediatric thymus and cord blood [33,34,69–72] and adult TCR repertoires appear less diverse and highly focused [33,34,71]. Thus, circulating fetal-derived $V\gamma 9V\delta 2^+$ T cells probably undergo a postnatal expansion, driven by the exposure to phosphoantigens of bacterial origin or food products after birth [47,54,73] (Figure 1). For $V\gamma 9V\delta 2^+$ T cells, TRD repertoires of fetal blood lymphocytes are characterized by shorter CDR3 lengths, as compared to adult $V\delta 2^+$ TRD repertoires, and the preferential usage of $V\delta 2$ rearrangements with TRDJ3, and to a lesser extent TRDJ2 and TRDJ1 gene segments [28]. In contrast, adult $V\delta 2^+$ chains show a bias for TRDJ1 usage [28,29,33] and contain different nucleotides encoding the germline-derived public $V\gamma 9J\text{P}$ clone that is present in every individual [31,33,63]. This led to speculation on whether postnatal selection or postnatal thymic output can explain this major change in the J-usage of human $V\gamma 9V\delta 2^+$

TCR repertoires [31,62]. Recently, Papadopoulou and colleagues tracked the lineage relationship of $V\gamma 9V\delta 2^+$ T cells and confirmed that the majority of adult blood $V\gamma 9V\delta 2^+$ T cells derive from a small subset of postnatal $V\gamma 9V\delta 2^+$ thymocytes that show adult-like features, e.g., TRDJ1 usage, and represents around 6% of postnatal thymocytes [28]. Interestingly, the phosphoantigen-dependent expansion of neonatal or adult $V\gamma 9V\delta 2^+$ T cells in in vitro assays did not affect TRDJ usage or diversity [28,30], and the proliferated cells retained a high oligoclonality. This suggests that adult $V\gamma 9V\delta 2^+$ TCR repertoires represent a blend of adult-like $V\gamma 9V\delta 2^+$ TCR clonotypes and a few remaining fetal-derived clonotypes that underwent postnatal expansion events. Nevertheless, it is tempting to speculate that recurrent pAg education might induce a slow, still polyclonal, outgrowth of some $V\gamma 9V\delta 2^+$ T cell clones, as observed in some adults [29].

The TCR repertoires of postnatal thymic non- $V\gamma 9V\delta 2^+$ T cells, mostly $V\delta 1^+$, have been reported to be extremely polyclonal [36,69,70]. In the thymus, postnatal $V\delta 1^+$ T cells use various TRGV gene segments, yet with a distinct preference for TRGJ1. In addition, $V\delta 1^+$ T cells use a high fraction of shared TRG sequences, whereas the corresponding TRD repertoires are largely non-overlapping, and were thus described as mostly private [69]. In contrast to fetal thymocytes, TdT expression is high in the postnatal thymus, and thus the usage of short homology repeats is inhibited, while the number of N additions used increases, leading to a repertoire distinct from fetal repertoires [36,74].

A key question of studying TCR repertoire composition is whether snapshots of repertoires are representative of a steady state, or how volatile $\gamma\delta$ TCR repertoires are in a healthy individual's life. We do not have longitudinal data from cord blood to adulthood, however, systematic comparison of adult peripheral blood versus cord blood-derived total $\gamma\delta$ or $V\delta 1^+$ TCR repertoires points out that single clonotypes can expand from a diverse neonatal $V\delta 1^+$ T cell pool [33,34]. In healthy adult individuals, $\gamma\delta$ TCR repertoires were shown to remain stable over a time of at least 90 days, indicating that changes in the $\gamma\delta$ repertoire are most likely caused by more severe immunological challenges and do not usually happen at steady state [33]. The fact that some healthy adults showed no expanded single $V\delta 1^+$ clonotypes, further leads to the conclusion that postnatal $V\delta 1^+$ repertoire focusing is not generally caused by T cell maturation, but is more likely an effect of specific antigenic challenges [34]. In line with this, stable $\gamma\delta$ TCR repertoires in chronic hepatitis virus C (HCV) patients and during direct-acting antiviral drug therapy were observed [35]. Intriguingly, the *de novo* generation of human $\gamma\delta$ T cell repertoires from stem cells, after allogeneic hematopoietic stem cell transplantation (alloHSCT), led to a reconstitution of $\gamma\delta$ TCR repertoires that showed comparable diversity and quality to repertoires of healthy adults [33]. Interestingly, the same study revealed that distinct new $V\delta 1^+$ and $V\delta 2^+$ clonotypes arose from donor stem cells, indicating *de novo* generation in the adult thymus. It will be interesting to investigate whether the same level of functionality of those newly generated $\gamma\delta$ TCR repertoires is restored in alloHSCT recipients [33,72].

Upon ageing, Kallemeijn and colleagues reported shrinking of the naïve $\gamma\delta$ T cell population ($CD45RA^+CD27^+CD197^+$), while repertoire diversity was maintained [70,75]. Moreover, a tendency for a decreased $V\gamma 9$ usage and an increase of $V\gamma 2-5$ and $V\gamma 8$ chain usage in elderly individuals was shown for effector ($CD45RA^-CD45RO^+CD27^-CD197^-$) and central memory $\gamma\delta$ T cells ($CD45RA^-CD45RO^+CD27^+CD197^+$) [70,75], as well as a general reduction of paired $V\gamma 9V\delta 2^+$ TCRs in some individuals [66]. Furthermore, $\gamma\delta$ TCR repertoires in healthy elderly individuals are characterized by large clonal expansions of particular non- $V\gamma 9V\delta 2^+$ clonotypes that could reflect the history of antigen challenge [66].

5. Impact of Infectious Diseases on $\gamma\delta$ TCR Repertoires

A role for $\gamma\delta$ T cells in the course of viral, bacterial or parasitic infections has been proposed by many studies via flow cytometric assessment of $\gamma\delta$ T cell quantities and/or qualities in the onset, progression and prognosis of infections [76–78]. Recent advances in the NGS analysis of peripheral human $\gamma\delta$ TCR repertoires gave strong evidence that non- $V\gamma 9V\delta 2^+$ T cell subsets can mount an

adaptive-like immune response [33,34]. Yet, data monitoring the TCR repertoire of $\gamma\delta$ T cells during infections is still scarce and only a limited number of diseases have been studied.

5.1. Viral Infections

$V\delta 1^+$ T cells have long been associated with the immune response after human Cytomegalovirus (CMV) infection, as firstly described by the Déchanet-Merville group in the context of kidney transplantation [37,79,80]. More recent NGS TCR repertoire analyses added the important detail that CMV-driven expansions of non- $V\gamma 9V\delta 2^+$ T cells were indeed clonal, e.g., in patients with CMV reactivation after alloHSCT [33] and in CMV-seropositive healthy adults [31,34]. Furthermore, expanded $CD8^+$ $\gamma\delta$ T cells were found in CMV-positive grafts [81]. In stem cell transplant recipients, CMV re-activation induced an immediate clonal expansion of individual non- $V\gamma 9V\delta 2^+$ T cell clones that was still visible after viral clearance, indicating a memory formation of virus-induced $\gamma\delta$ T cell clones [33]. In contrast, patients without CMV reactivation showed high $\gamma\delta$ TCR repertoire stability in longitudinal samples. Similarly, CMV-positive adults have skewed $V\delta 1^+$ TCR repertoires [34]. In addition to $V\delta 1^+$ T cells, $V\gamma 9^-V\delta 2^+$, a prevalent $V\delta 2^+$ subset at birth with diverse $V\gamma$ chain usage, also show clonal expansions and transition from a $CD27^{hi}$ naïve-like to a $CD27^{lo/neg}$ effector-like phenotype after acute CMV [31,32]. Together, these studies support the idea that individual expanded clones are unique to donors and most likely stem from the selection of low frequency clones that expand upon antigen challenge. As a consequence, in contrast to $V\gamma 9V\delta 2^+$ TCR repertoires, these TCR repertoires are extremely diverse, non-overlapping, and therefore private [33,34]. In comparison to CMV infections, where an adaptive-like expansion of $\gamma\delta$ T cells is evident, the $\gamma\delta$ T cell response in HIV-infected individuals seems more complex [82]. Early during HIV infection, $V\delta 1^+$ T cell expansions are observed, leading to an inverted ratio of $V\delta 2^+/V\delta 1^+$ cells [82,83]. Expanded $V\delta 1^+$ cells have been speculated to contribute to the control of HIV replication at mucosal sites of entry [82]. Early spectratyping analysis revealed the polyclonal nature of $V\delta 1^+$ T cell expansions, as no skewing towards specific TRDV1 or TRGV sequences was observed [84,85], and activation and expansion was associated with microbial translocation in the gut of SIV-infected rhesus macaques [86]. In addition to $V\delta 1^+$ T cell expansion, $V\delta 2^+$ T cells are depleted from the circulation correlating with $CD4^+$ T cell counts and a loss of pAg reactivity occurs, most likely because specifically $V\delta 2^+$ cells with $V\gamma 9J\text{P}$ chains disappear, and public clonotypes are lost [87,88]. The depletion of $V\delta 2^+$ T cells is considered a possible immune evasion strategy of the virus. One mechanism of depletion could be that HIV envelope-mediated cell death by CCR5 is possible in $V\delta 2^+$ T cells and not $V\delta 1^+$ T cells [89]. Interestingly, (partial) reconstitution of $V\delta 2^+$ T cell functionality and $V\gamma 9J\text{P}^+$ public clonotypes, including germline-encoded clonotypes, occurs during antiretroviral therapy and is speculated to be mediated by thymic output of $V\gamma 9V\delta 2^+$ cells [88]. In the case of Influenza A virus infections, $V\gamma 9V\delta 2^+$ T cells have been reported to kill infected cells and provide a major source of IFN- γ [90,91]. Recently, synapse formation and direct killing of H1N1/PR8-infected cells by $\gamma\delta$ T cells have been shown *ex vivo* and $V\gamma 9V\delta 2^+$ T cells were described to be the main population of INF- γ producing $\gamma\delta$ T cells [66,92].

5.2. Bacterial Infections

Mycobacteria are a rich source of bacterial phosphoantigens [13], and thus, phosphoantigen-reactive $V\gamma 9V\delta 2^+$ T cells have been implied in protective $\gamma\delta$ T cell responses to *Mycobacterium tuberculosis* infections [77,93]. Expansions of $V\gamma 9V\delta 2^+$ T cells in pulmonary tuberculosis (TB) have been reported [94–96]. Yet, in other reports, comparable to HIV infections, a loss of $V\gamma 9V\delta 2^+$ T cells in the blood has been observed in active TB and correlated with disease severity [92,97,98]. Recently, in lungs from HIV-negative patients with active TB, a dominance of $V\delta 1$ (and $V\delta 3$) usage, a bias for $J\delta 1$ and clonal expansions have been shown and most δ -chains were non-overlapping when lungs and blood samples of the same donor were compared [92]. Moreover, highly localized expansions of $V\delta 1^+$ clonotypes and heterogeneity within individual lung tissues sections in the same study suggested a lung-resident non-recirculating $\gamma\delta$ T cell population.

5.3. Parasitic Infections

Upon infection with *Plasmodium species*, proliferation and phenotypic changes of $\gamma\delta$ T cells have been observed and extensively reviewed elsewhere [99–102]. Importantly, $V\gamma9V\delta2^+$ T cells that recognize pAgs produced by the parasite as well as non- $V\gamma9V\delta2^+$ T cells seem to be implied in the $\gamma\delta$ T cells response during malaria [103,104]. For $V\gamma9V\delta2^+$ T cells, that can be directly cytotoxic for blood stage parasites [104], repertoire studies showed a decrease in JP usage and the occurrence of germline $V\gamma9JP^+$ clones in neonates as an effect of placental malaria [105,106]. Recently, an oligoclonal expansion of $V\delta1^+$ T cells expressing CD38 and PD-1 and lacking the expression of CD27 and CD57, indicative of an early effector phenotype, has been reported in controlled infections of Tanzanian volunteers with *Plasmodium falciparum*, however, as longitudinal data is lacking, it is unclear whether those observations are a result of infection [103].

6. Tissue-Resident $\gamma\delta$ TCR Repertoires

The V-gene usage of $\gamma\delta$ T cells is not only associated with their function and ontogeny, but also with their tissue localization. While pAg-inducible $V\gamma9V\delta2^+$ T cells are predominant in peripheral blood lymphocytes, the majority of $\gamma\delta$ T cells localizing to solid organs or mucosal tissues often express non- $V\gamma9V\delta2^+$ TCRs. This phenomenon of V-gene usage linked to tissue distribution seems highly similar to their mouse counterparts (reviewed in [23]). However, knowledge of the human $\gamma\delta$ TCR repertoire composition in healthy and diseased tissues remains fragmented. There is evidence that $\gamma\delta$ TCR repertoires have an oligoclonal distribution in healthy liver, spleen, lymph node and lung [66,107]. An NGS analysis of intrahepatic $V\delta2^-$ $\gamma\delta$ T cells showed that $CD69^+$ tissue-resident $V\delta2^-$ T cells are characterized by unique TCR clones, while expanded TCR clones of liver-infiltrating $V\delta2^-$ T cells are present in the blood of the respective donor, albeit with lower abundance. Interestingly, the recruitment of adaptive-like $V\gamma9^-V\delta2^+$ cell subsets to the liver seems evident [31]. In healthy individuals, lung $\gamma\delta$ T cells are enriched for $V\delta2^+$ T cells, while patients with active tuberculosis were reported to have elevated $V\delta1^+$ T cell numbers that display skewed TCR repertoires. However, there was no dominant $V\delta1^+$ $\gamma\delta$ TCR clone or motif among patients with active tuberculosis. The distribution of TCR repertoires proposed that presumably lung-infiltrating $V\delta1^+$ T cells underwent an adaptive-like clonal expansion during active tuberculosis [92]. In contrast, tissue-resident $NKG2D^+$ and $CD69^+ V\delta1^+$ T cells were reported to have oligoclonal TCR repertoires in healthy breast tissues that remained stable after tumor-infiltration, consistent with their innate-like features such as $NKG2D$ -driven activation [108,109].

Similar innate-like phenotypes can be ascribed to human gut-resident $V\gamma4^+$ intestinal epithelial $\gamma\delta$ T cells (IELs), that are $CD69^+$ and express the natural cytotoxicity receptors $Nkp46$ and/or $Nkp44$ [38,110]. Human $V\gamma4^+$ IELs are shaped and selected by the $BTNL$ -like molecules, $BTNL3$ and $BTNL8$, that are exclusively expressed in the human gut epithelial [14]. TCR repertoire analysis of total or $Nkp46^+$ $\gamma\delta$ IELs isolated from healthy tissues gave evidence for a relatively clonal TRG and TRD repertoire, enriched for public $V\gamma4^+$ and private $V\delta1^+$ T cell clones [38,39,110]. Importantly, celiac disease leads to a loss of the $BTNL$ -induced $V\gamma4^+$ IEL compartment, that cannot be restored after gluten-free diet [38]. Notably, an innovative approach of single-cell TCR repertoire analysis of $\gamma\delta$ IELs of celiac disease patients noticed a higher TCR repertoire diversity, due to loss of innate-like $V\gamma4^+$ IELs, but did not identify public $\gamma\delta$ T cell clones that may recognize defined disease-associated ligands [39]. Moreover, in colorectal cancer patients with higher numbers of innate-like cytotoxic $Nkp46^+ V\gamma4V\delta1^+$ T cells were correlated with a better clinical outcome [110]. Altogether, TCR-seq analysis can be a valuable method to distinguish tissue-resident and circulating $\gamma\delta$ T cell clones and characterize adaptive-like versus innate-like expansions of tissue $\gamma\delta$ T cells in healthy and diseased individuals.

7. Conclusions

$\gamma\delta$ T cells have long been understood as unconventional innate-like T cells with TCRs of only limited diversity, predisposed for rapid recognition of highly conserved antigens. Now, a more

nuanced view of $\gamma\delta$ T cell function is emerging. While $V\gamma 9V\delta 2^+$ T cells are still viewed as largely invariant innate-like T cells, current research focusses on the question whether some versions of the $V\gamma 9V\delta 2^+$ TCR cells are superior to others. Future studies combining single cell TCR and total RNA sequencing should be very instructive. Regarding non- $V\gamma 9V\delta 2^+$ T cells, it is clear that they play a more sophisticated role and can establish a hitherto unrecognized form of individual adaptive immune surveillance [33,34,71,107]. Clonotype-specific expansions of non- $V\gamma 9V\delta 2^+$ T cells occur in multiple diseases, but are also observed in healthy individuals. This has led to the hypothesis that the non- $V\gamma 9V\delta 2^+$ TCR repertoire could serve as a log-file, reflecting the immunological history of individual antigen challenges.

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