Understanding the complexity of γδ T cell subsets in mouse and human

Dick John Pang[*], Joana F. Neves[*,†], Nital Sumaria[*], and Daniel J. Pennington[*]

[*]Blizard Institute, Barts and The London School of Medicine, Queen Mary University of London, 4 Newark Street, London, E1 2AT, United Kingdom.

[†]Programa Doutoral de Biologia Experimental e Biomedicina, Centro de Neurociências e Biologia Celular, Universidade de Coimbra, Coimbra, Portugal.

Corresponding author: D.J.Pe.

Tel: +44 20 7882 2302; *Fax:* +44 20 7882 2181; *e-mail:* d.pennington@qmul.ac.uk

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Summary

γδ T cells are increasingly recognised as having important functional roles in a range of disease scenarios such as infection, allergy, autoimmunity, and cancer. With this has come realisation that γδ cells are not a homogeneous population of cells with a single physiological role. Instead, ever increasing complexity in both phenotype and function is being ascribed to γδ cell subsets from various tissues and locations, and in both mouse and human. Here, we review this complexity by describing how diverse γδ cell subsets are generated in the mouse thymus, and how these events relate to subsequent γδ subset function and location in the periphery. We then review the two major γδ cell populations in human, highlighting the several similarities of $V\delta1^{(+)}$ cells to certain murine γδ subsets, and describing the remarkable functional plasticity of human $V\delta2^{(+)}$ cells. A better understanding of this spectrum of γδ cell phenotypes should facilitate more targeted approaches to utilise their tremendous functional potential in the clinic.

Introduction

The initial perception of γδ cells as innate cells with limited functional potential is now distinctly outdated. Instead, γδ cells display considerable subset heterogeneity, with complex patterns of effector function that range from T cell help to antigen presentation. Understanding this heterogeneity, and how it develops, is central to understanding the role of γδ cells in complex disease scenarios, and will provide an important foundation for harnessing these enigmatic cells for multiple future therapeutic opportunities in the clinic.

Commitment to the γδ cell lineage; pre-commitment and signal strength

In the murine thymus, commitment to the γδ lineage occurs at the immature $CD4^{(-)}CD8^{(-)}$ double negative (DN) stage of thymocyte development[1]. Early DN cells with potential to develop as either γδ or αβ T cells rearrange their TCRγ, TCRδ, and TCRβ loci in an attempt to generate a productive TCRγδ or preTCR (TCRβ paired with the invariant preTCRα chain) that compete to drive γδ or αβ T cell development, respectively[1-3]. Despite initial suggestions that TCRγδ and preTCR "instruct" DN cells into their respective lineages, it now appears that signal strength, rather than identity of the expressed TCR complex, is the critical factor in fate determination; strong signalling committing DN cells to the γδ lineage; weak signalling committing cells to the αβ lineage[4,5]. Nonetheless, this effectively equates to an instructional model, as under normal circumstances preTCR signals weakly while TCRγδ signalling is stronger.

Although this strength-of-signal model is now widely accepted, there is significant evidence to suggest that factors operating prior to, or contemporaneously with, TCR rearrangement and signalling may also influence γδ/αβ fate determination. Thus, $CD44^{(+)}CD25^{(+)}$ DN2

cells that express CD127 (IL-7Rα chain)[6], or Sox13[(ref 7)], appear more likely to enter the γδ lineage, while adult DN cells, or DN cells from the later CD44$^{(-)}$CD25$^{(+)}$ DN3, or CD44$^{(-)}$CD25$^{(-)}$ DN4 subsets appear biased toward αβ T cell development[3,8]. Thus, commitment to a γδ fate requires strong signalling from successfully rearranged TCRγδ complexes in DN cells that are permissive for entry into the γδ cell lineage[3].

Thymic γδ subsets in mouse; the consequence of strong TCRγδ signals

The earliest murine TCRγδ$^{(+)}$ thymic progenitors are CD24$^{(+)}$CD25$^{(+)}$CD27$^{(+)}$ cells that express relatively low levels of surface TCRγδ, but are highly proliferative[9,10]. At this stage, TCRγδ signalling initiates, leading to CD25 down-regulation, up-regulation of TCRγδ, and generation of cells with a CD24$^{(+)}$CD25$^{(-)}$CD27$^{(+)}$ phenotype[9]. These uncommitted cells likely represent precursors of several distinct mature CD24$^{(-)}$TCRγδ$^{(+)}$ thymocyte populations (**Figure 1A**, and see below), that must have arisen from TCRγδ signalling that exceeds a critical commitment threshold. Nonetheless, evidence now suggests that mechanisms of TCRγδ signal initiation that underpin these commitment events may significantly differ[3,11,12].

Strong TCR signals of the type that commit DN cells to the γδ lineage are generally considered a consequence of agonist-ligand binding. However, a general TCRγδ restricting element, analogous to MHC-I or MHC-II for TCRαβ, has not been identified, and in mouse only one confirmed TCRγδ-ligand, the MHC class Ib thymus leukaemia (TL) molecule, has thus far been found[13]. Nonetheless, there is reasonable evidence, although mostly indirect, for TCRγδ-ligand binding during generation of thymic progenitors of at least three peripheral γδ cell subsets; dendritic epidermal T cells (DETC) that use TCRγ chain variable region-5 (Vγ5) (nomenclature from[14]), and TCRδ chain variable region-1 (Vδ1)[11], NKT-like

γδ cells that use a Vγ1Vδ6.3/6.4$^{(+)}$ TCR[15,16], and γδ cells whose TCRs recognise the TL molecules T10^{b} and T22^{b} (~0.5-1.0% of all γδ cells)[17-20]. In each case, the TCRs used by these subsets already show restricted CDR3 length and amino acid composition in the thymus, indicative of thymic ligand-driven TCR selection[11,15,21]. Moreover, these CD27$^{(+)}$ thymic progenitors display a CD44$^{(+)}$CD62L$^{(-)}$CD122$^{(+)}$ phenotype that is generally associated with ligand engagement (**Figure 1A**).

A further subset of mature TCRγδ$^{(+)}$ thymocytes, that express a Vγ6Vδ1$^{(+)}$ TCR, have also been reported to show evidence of CDR3-mediated TCR selection[21]. These cells are progenitors of those that populate the female reproductive tract and peritoneal cavity, and appear shortly after Vγ5Vδ1$^{(+)}$ DETC progenitors at approximately embryonic day-16[(ref 1)]. Notably, Vγ6Vδ1$^{(+)}$ γδ cells differ from DETC, NKT-like γδ cells and (ligand-selected) TL-specific γδ cells in their capacity to produce IL-17A[22]. This IL-17A-secreting effector potential is additionally shared by CD27$^{(-)}$CCR6$^{(+)}$ γδ thymocytes[9,23] (**Figure 1A**), that are also CD44$^{(+)}$CD62L$^{(-)}$, consistent with a previous TCRγδ/ligand interaction. However, CD27$^{(-)}$ γδ cells do not express CD122, and conspicuously fail to develop in foetal thymic organ cultures (FTOCs) supplemented with TCRγδ antibodies that induce strong TCR signals[9,23]. Thus, any putative ligand interaction for the development of CD27$^{(-)}$ IL-17A-secreting γδ cells must necessarily induce an attenuated (or at least qualitatively different) TCR signal that cannot readily be reproduced by classical antibody cross-linking of the TCR[9,11,19].

The development of IL-17A-secreting γδ cells has also been suggested to result from ligand-independent TCRγδ signalling in the thymus, possibly as a result of oligomerization of TCRγδ induced by the variable domain of TCRδ[19]. However, a TCRγδ that lacks both Vγ and Vδ can still signal effectively in DN thymocytes, resulting in generation of γδ

thymocytes with IFNγ-secreting potential[12]. These cells evoke a subset of mature (i.e. $CD24^{(-)}$) $CD27^{(+)}$ γδ thymocytes that show IFN-γ-secreting potential and display a "naive" $CD44^{(-)}CD62L^{(+)}$ phenotype consistent with an absence of previous TCRγδ/ligand interactions (**Figure 1A**)[9]. Thus, several distinct subsets of mature γδ thymocytes can be identified that are likely the result of distinct mechanisms of thymic TCRγδ signal initiation[3].

Mouse peripheral γδ subsets

Several distinct populations of peripheral murine γδ cells have now been identified (**Figure 1B**). Perhaps the best studied are $Vγ5Vδ1^{(+)}$ DETC from the murine (but not human) epidermis that display "innate-like" properties, in that they are thought to respond *en masse* to relatively few stress-associated TCR-ligands[24]. These cells are $CD44^{(+)}CD62L^{(-)}CD103^{(+)}$, and express CD122 consistent with their dependence on IL-15[ref 25,26]. DETC secrete IFNγ when activated, but can also drive IL-13-mediated Th2-associated responses on recognition of NKG2D-ligands expressed on stressed epithelial cells[27]. A $CD44^{(+)}CD62L^{(-)}CD122^{(+)}$ phenotype is also shared by a $CD90^{(dull)}CD27^{(+)}$ NKT-like γδ subset that uses a restricted $Vγ1Vδ6.3/6.4^{(+)}$ TCR and secretes both IFNγ and IL-4 when activated[15,28], and by IFNγ-secreting TL-specific lymphoid γδ cells that develop in a $T10^b/T22^b$-expressing background[19].

By contrast to DETC that primarily make IFNγ, γδ cells from the murine dermis predominantly secrete IL-17A. These cells are biased towards use of a Vγ4-containing TCRγδ, are $CD44^{(+)}CD122^{(-)}$, and express both CCR6 and SCART2[refs 25,29-31]. This phenotype closely resembles that of IL-17A-secreting γδ cells from the female reproductive tract, tongue, and peritoneal cavity, that are $CD27^{(-)}CD25^{(+)}$ and predominantly use a $Vγ6Vδ1^{(+)}$ TCR[22,32], and also of $CD27^{(-)}$ γδ cells from secondary lymphoid organs[9] (**Figure 1B**). A common feature of these γδ subsets is their potent IL-17A secretion *en masse* in

response to cytokines such as IL-1β and IL-23[ref 33,34]. Indeed, this characteristic strongly predicts an innate-like role for these γδ subsets in diverse immune responses.

The capacity to secrete IFNγ is also a feature of murine γδ cell populations that are found in secondary lymphoid tissues, and organs such as the lung[9]. Unlike the IFNγ-secreting DETC and NKT-like γδ subset, these $CD27^{(+)}$ γδ cells display a naive $CD44^{(-)}CD62L^{(+)}CD122^{(-)}$ phenotype consistent with an absence of TCR ligation during development[3,9]. They also possess a polyclonal TCR repertoire (using mainly Vγ1 or Vγ4), and expand extensively when activated through TCRγδ[9,35]. However, it remains to be determined whether these cells respond to environmental stimuli *en masse* in an innate-like manner, or whether their diverse TCRγδ specificities and considerable proliferative potential allow adaptive-like TCR-driven clonal expansions in response to foreign antigen challenge.

A sizable yet enigmatic subset of γδ cells permanently resides in the epithelial layers of the gastro-intestinal tract[36]. These γδ intraepithelial lymphocytes (IELs) can be generated in gut-associated lymphoid tissue (e.g. cryptopatches[37]) and are present (to ~25% of normal levels) in athymic *nude* animals[38]. γδ IELs use predominantly $Vγ1^{(+)}$ or $Vγ7^{(+)}$ TCRs with limited junctional diversity, although their TCR specificities remain unknown[39]. γδ IELs lack expression of the conventional T cell co-receptors CD4 and CD8αβ, but often express CD8αα[36]. The vast majority of γδ IELs are $CD27^{(+)}CD122^{(lo)}CCR9^{(+)}$, but do not express either CD90 or CD2[ref 9,18,40,41]. Functionally, γδ IELs are cytolytic effector cells with an immunoprotective role in the gut[36,40], especially in young animals[42], and largely through the production of cytokines such as IFNγ[43]. Nonetheless, γδ IELs are also immuno-modulatory. For example, adult mice lacking γδ IELs display exaggerated intestinal damage in response to *Eimeria vermiformis* infection, due to a failure to control αβ T cell responses[44].

Human γδ cells

Human γδ cells, like their murine counterparts, are a minor population (1-10% of nucleated cells) in peripheral blood but are abundant in tissues, especially in epithelial layers[24]. For identification purposes, they are usually sub-divided based on use of one of two variable regions of TCRδ; Vδ1 or Vδ2(ref 1). Vδ1$^{(+)}$ γδ cells are the predominant subset found at mucosal surfaces, and thus share certain characteristics with murine γδ IELs (see below). By contrast, Vδ2$^{(+)}$ γδ cells (that are almost exclusively Vγ9$^{(+)}$) largely dominate the peripheral blood (Vγ9 is often referred to as Vγ2 in an alternative nomenclature[45-48]). Indeed, γδ cells expressing a Vγ9Vδ2$^{(+)}$ TCRγδ can sometimes identify >50% of blood leucocytes after certain bacterial or parasitic infections[49].

Vγ9Vδ2$^{(+)}$ γδ cells

A γδ population with the specific features of Vγ9Vδ2$^{(+)}$ cells are found only in humans and higher primates (the absence of an equivalent subset in rodents making study of Vγ9Vδ2$^{(+)}$ cells problematic). Vγ9Vδ2$^{(+)}$ cells are unique in their recognition of low molecular weight non-peptide phosphoantigens; e.g. (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), an intermediate metabolite from the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway of microbial isoprenoid biosynthesis[50-52]. Nanomoler concentrations of HMB-PP lead to rapid TCR-dependent activation of Vγ9Vδ2$^{(+)}$ cells, enabling them to respond to a diverse range of pathogens, including *Mycobacterium tuberculosis*[53] and *Plasmodium falciparum*[54]. Vγ9Vδ2$^{(+)}$ cells are also indirectly activated by aminobisphosphonates and alkylamines. These compounds inhibit farnesyl diphosphate synthase (FDPS), an enzyme in the mevalonate pathway of isoprenoid synthesis (used by eukaryotic cells), leading to accumulation of the stimulatory phosphoantigen isopentenyl pyrophosphate (IPP)[55]. Interestingly, elevated IPP levels are also characteristic of many

human tumours, rendering them potential targets for Vγ9Vδ2$^{(+)}$ cells[56-58]. Indeed, although the mechanism by which phosphoantigens activate the Vγ9Vδ2$^{(+)}$ TCR remains unclear, administration of bisphosphonates such as zoledronate (plus IL-2) are presently generating encouraging Vγ9Vδ2$^{(+)}$ cell responses against a range of tumours in the clinic[57,58].

Heterogeneity within the Vγ9Vδ2$^{(+)}$ subset

Vγ9Vδ2$^{(+)}$ cells are often sub-divided on surface expression of CD45RA and CD27 (**Figure 2A**); markers more commonly used to identify the naive, effector or memory status of conventional αβ T cells[59]. Nonetheless, CD27 does not obviously identify a γδ subset in human comparable to the CD27$^{(+)}$ γδ subset in mouse (i.e. pre-committed to robust IFNγ secretion). Instead, CD27 and CD45RA identify four Vγ9Vδ2$^{(+)}$ subsets. "Naive" (T_{naive}) CD45RA$^{(+)}$CD27$^{(+)}$ Vγ9Vδ2$^{(+)}$ cells generally comprise 10-20% of those in peripheral blood (addition of a further marker; CD11a, suggests a slightly lower percentage[60]), but are the major Vγ9Vδ2$^{(+)}$ subset in lymph nodes, in keeping with their expression of CCR7 and CD62L but absence of CCR2, CCR5, CCR6, or CXCR3. T_{naive} cells proliferate at relatively high concentrations of IPP (10^{-4} to 10^{-3}M), but do not secrete IFNγ[59]. After activation for 12 days with IPP+IL-2, T_{naive} cells become largely CD45RA$^{(-)}$CD27$^{(+)}$. These "Central Memory" (T_{CM}) cells are CD45RO$^{(+)}$, but remain CCR7$^{(+)}$CD62L$^{(+)}$ (**Figure 2A**). In healthy individuals T_{CM} cells represent ~25% and ~50% of Vγ9Vδ2$^{(+)}$ cells in lymph nodes and peripheral blood, respectively. T_{CM} cells appear to proliferate at much lower concentrations of IPP (10^{-6} to 10^{-7}M), but can secrete only low levels of IFNγ[59].

After 12-day activation with IPP plus IL-2, T_{CM} cells generate CD45RA$^{(-)}$CD27$^{(-)}$ "Effector Memory" (T_{EM}) cells that are CD45RO$^{(+)}$, CCR7$^{(-)}$CD62L$^{(-)}$, but positive for the tissue-associated chemokine receptors CCR2, CCR5, CCR6, and CXCR3[(ref 59)] (**Figure 2A**).

Unsurprisingly, T_{EM} cells are scarce in lymph nodes, but are readily detected in blood and inflammatory sites. T_{EM} secrete abundant IFNγ and TNFα when activated with IPP+IL-2, but their capacity for proliferation is much reduced compared with T_{naive} and T_{CM} cells. T_{CM} cells also appear to generate a CD45RA$^{(+)}$ effector memory (T_{EMRA}) population when activated with IL-15[ref 61]. These cells are virtually absent from blood, are CD27$^{(-)}$, CCR7$^{(-)}$, and CD62L$^{(-)}$, but express CCR5 and CXCR3, a phenotype shared by a subset of CD8$^{(+)}$ $\alpha\beta$ T cells that display robust cytotoxic potential. Consistent with this, T_{EMRA} cells express abundant perforin, granulysin and BLT-esterase, and readily display cytolytic activity (but little production of IFNγ). They also express CD16, KIR2DL1-3 and NKG2A/CD94. However, T_{EMRA} cells are un-responsive to further TCR stimulation and have little proliferative capacity, a phenotype consistent with a terminally differentiated state.

Although T_{naive}, T_{CM}, T_{EM}, and T_{EMRA} Vγ9Vδ2$^{(+)}$ subsets can be identified, whether these represent true naive, effector and memory subsets, comparable to those observed for $\alpha\beta$ T cells, is still unclear[62]. Nonetheless, the assessment of Vγ9Vδ2$^{(+)}$ cells on these criteria appears to correlate with objective clinical outcomes[63]. For example, in a phase I trial of patients with advanced solid tumours, increased proportions of T_{CM} and T_{EM} from patients' peripheral blood was predictive for good cell expansion *in vitro* with zoledronate+IL-2, which in turn correlated with better clinical responses after subsequent adoptive transfer[64].

Notwithstanding the utility of CD45RA and CD27 to describe functional subsets of Vγ9Vδ2$^{(+)}$ cells, further useful surface markers have also been identified. For example, cytotoxic potential appears to correlate with increased CD56 and CD16 expression following activation of Vγ9Vδ2$^{(+)}$ cells with phosphoantigen and IL-2 for 10-14 days[65]. IPP-expanded CD56$^{(+)}$, but not CD56$^{(-)}$, Vγ9Vδ2$^{(+)}$ cells efficiently killed several tumour lines, in a perforin/granzyme-dependent manner that also required NKG2D. Interestingly, tracking individual clones using Vγ9 CDR3 regions appeared to reveal that the capacity for CD56

expression was a stable pre-existing characteristic of individual Vγ9Vδ2$^{(+)}$ cells that is unrelated to TCR specificity[66]. However, whether this reveals a cytotoxic lineage for Vγ9Vδ2$^{(+)}$ cells remains uncertain.

Finally, approximately half the Vγ9Vδ2$^{(+)}$ subset also expresses the skin homing receptor CLA[67]. These dermal CLA$^{(+)}$ γδ cells were recently implicated in psoriasis, in which they secrete abundant IFNγ and TNFα, and high levels of CCL3, CCL4, CCL5 and CXCL8. However, as with CD56 and CD16, it is still unclear how the use of CLA to identify Vγ9Vδ2$^{(+)}$ subsets overlaps with the method defined by CD45RA and CD27.

Remarkable plasticity of activated Vγ9Vδ2$^{(+)}$ cells

For a cell type generally considered innate, the Vγ9Vδ2$^{(+)}$ subset displays remarkable functional plasticity upon TCR activation that is easily comparable with their more illustrious cousin; the CD4$^{(+)}$ αβ T helper cell. Such plasticity was initially demonstrated *in vitro* through polarisation of IPP-activated Vγ9Vδ2$^{(+)}$ cells; IL-12 and anti-IL-4 antibody generating IFNγ-secreting Th1-like cells; IL-4 plus anti-IL-12 antibody generating IL-4-producing Th2-like cells[68]. An IFNγ/TNFα-secreting Th1-like phenotype is also generated following activation with HMB-PP plus IL-2, although the Th2-associated cytokines IL-5 and IL-13 are also produced[69] (**Figure 2B**). By contrast, HMB-PP activation of Vγ9Vδ2$^{(+)}$ cells in the presence of IL-21 promotes a follicular helper (T_{FH})-like phenotype that is characterised by increased expression of IL-21R, CD244, CXCL10 and CXCL13, and trafficking to lymph node germinal centres[70]. Somewhat surprisingly, Vγ9Vδ2$^{(+)}$ cells have also been reported to express Foxp3 and to display regulatory activity after IPP activation with IL-15 and TGFβ[71], while 18-24hr IPP stimulation (alone) of tonsillar Vγ9Vδ2$^{(+)}$ cells appears to induce considerable APC-like activity, with accompanying surface expression of MHC-II, CD80, CD86, CD40 and CD54[(Ref 72)].

The production of IL-17 by human γδ cells, unlike for murine γδ cells, has been difficult to demonstrate[73]. Nonetheless, T_{naive} Vγ9Vδ2$^{(+)}$ cells (especially those from neonates[74]) can adopt an IL-17-secreting Th17-like phenotype if cultured in the presence of various combinations of IL-1β, IL-6, TGFβ and IL-23 in media containing aromatic hydrocarbons[75]. These IL-17$^{(+)}$ Vγ9Vδ2$^{(+)}$ cells are CD161$^{(+)}$CCR6$^{(+)}$TRAIL$^{(+)}$FasL$^{(+)}$ with a largely CD45RA$^{(+)}$CD27$^{(-)}$ T_{EMRA} phenotype, and have been identified in psoriasis[67], and in the CSF of patients with bacterial meningitis[75]. However, these IL-17-expressing T_{EMRA} cells appear distinct from the previously described cytotoxic T_{EMRA} cells as they do not express perforin or NKG2D[75].

The extensive plasticity of activated Vγ9Vδ2$^{(+)}$ cells contrasts sharply with murine γδ cells that demonstrate considerable pre-commitment to cytokine production in the thymus[9]. However, it is still unclear whether this plasticity relates equally well to all CD45RA/CD27-defined Vγ9Vδ2$^{(+)}$ subsets[75], or to what extent possible pre-commitment, for example to a CD56$^{(+)}$ cytotoxic fate[66], regulates subsequent effector function.

Human Vδ1$^{(+)}$ cells; the cousin of murine γδ IELs?

Human Vδ1$^{(+)}$ cells are the major γδ population at epithelial sites such as the intestine and skin[76,77]. Similar to murine γδ IELs, Vδ1$^{(+)}$ cells frequently express CD8, and display a cytotoxic, Th1-like phenotype characterised by IFNγ secretion[76]. This notwithstanding, Vδ1$^{(+)}$ cells also appear to play a significant role in tissue homeostasis and repair, as demonstrated by IGF-1 production in wound healing[78]. Indeed, consistent with epithelial immunosurveillance[24], Vδ1$^{(+)}$ cells kill a range of epithelial tumours[79,80], possibly through recognition of stress-induced MHC class I-related molecules MICA and MICB[80,81]. Vδ1$^{(+)}$ cells are also known to respond to autologous and/or endogenous phospholipids

presented by CD1[(ref 82)], and display TCR-driven clonal expansions in response to CMV (along with the very minor Vδ3$^{(+)}$ and Vδ5$^{(+)}$ subsets)[83,84], and possibly HIV[85], and malaria[86].

Like Vδ2$^{(+)}$ cells, Vδ1$^{(+)}$ cells can be sub-divided based on CD45RA and CD27 expression[60]. By contrast to Vδ2$^{(+)}$ cells, the majority of adult blood Vδ1$^{(+)}$ cells are CD45RA$^{(+)}$, being evenly split into an IL-2-secreting CD27$^{(+)}$CD11a$^{(lo)}$ "naive" subset, and an IFNγ-secreting CD27$^{(-)}$CD11a$^{(hi)}$ "non-naive" population[60]. Unsurprisingly, ~80% of cord blood Vδ1$^{(+)}$ cells are naive (compared with ~50-60% for Vδ2$^{(+)}$ cells), dropping to ~30-40% by two years of age[60]. By contrast, <5% of Vδ2$^{(+)}$ cells are naive by one year of age, reflecting significant expansion of a restricted number of phosphoantigen-reactive Vγ9Vδ2$^{(+)}$ clones. The fact that the percentage of naive Vδ1$^{(+)}$ cells remains relatively constant in peripheral blood until late middle age may suggest a constant thymic production[60].

In addition to expressing common surface markers such as CD2, ICAM-1 and NKG2D[87], Vδ1$^{(+)}$ cells also display several notable differences when compared with Vδ2$^{(+)}$ cells. For example, they are CD5$^{(dull)}$CD28$^{(lo)}$, but express abundant CD57 that correlates with high perforin expression[88]. On activation of Vδ1$^{(+)}$ cells through their TCR (e.g. with PHA), in the presence of either IL-2 or IL-15, the natural cytotoxicity receptors (NCRs) NKp30, NKp44 and NKp46 are upregulated, which correlates with potent tumour-directed cytotoxicity and CD56 expression[89,90]. By contrast, HMB-PP+IL-2-activated Vδ2$^{(+)}$ cells do not express NCRs, instead mainly utilising the NKG2D pathway as their main mechanism of targeting tumours[89,91].

Concluding remarks

Recent studies have begun to characterise the subset complexity of mouse and human γδ cells. Interestingly, certain subsets, such as murine DETC or human Vγ9Vδ2$^{(+)}$ cells, are

restricted to certain species, while certain useful surface markers, such as CD27, do not appear to identify comparable subsets across species. Nonetheless, this methodical dissection of γδ cell repertoires has exposed the critically important innate-like, and possibly adaptive-like, functional roles for γδ cells in diverse disease scenarios. A further understanding of this largely unanticipated γδ cell biology should reveal much about the relationship between early tissue-associated immune surveillance and the powerful adaptive responses that follow, and should perhaps provide unexpected therapeutic opportunities for the clinic.

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Figure Legends

Figure 1 Mouse γδ cell subsets in the thymus and periphery. (A) Thymic γδ subsets described by surface expression of; yellow triangles – CD27; green triangles – CD24; blue triangles CD44; purple triangles – CD25; and red triangles – CD122. Proposed developmental relationships between subsets are indicated by arrows, and potential for cytokine secretion is shown. **(B)** Peripheral γδ subsets described by tissue location, potential for cytokine secretion and surface markers are described for (A). Gut γδ cells (i.e. γδ IELs) express only low levels of CD122.

Figure 2. Human Vγ9Vδ2$^{(+)}$ γδ cells can be sub-divided using surface expression of CD45RA and CD27, and show remarkable functional plasticity after activation. (A) CD45RA$^{(+)}$CD27$^{(+)}$ T_{naive} cells give rise to CD45RA$^{(-)}$CD27$^{(+)}$ T_{CM} cells on activation with

IPP+IL-2, but do not secrete IFNγ. T_{CM} cells generate $CD45RA^{(-)}CD27^{(-)}$ T_{EM} cells after activation with IPP+IL-2, or $CD45RA^{(+)}CD27^{(-)}$ T_{EMRA} cells in the presence of IL-15. T_{EM} cells can secrete abundant IFNγ, while T_{EMRA} cells are mainly cytotoxic. Prol; proliferative capacity, Kill; cytotoxic capacity; red triangles indicate CD27 expression; blue triangles indicate CD45RA expression; green triangles indicate CD62L expression; **(B)** $V\gamma9V\delta2^{(+)}$ cells display extensive plasticity after activation with phosphoantigen (HMB-PP or IPP) in the presence or absence of various cytokines as indicated. "?" indicates uncertainty as to the potential of T_{naive}, T_{CM}, T_{EM} and T_{EMRA} to generate the indicated effector subsets. Expression of functionally relevant genes and characteristics are indicated.

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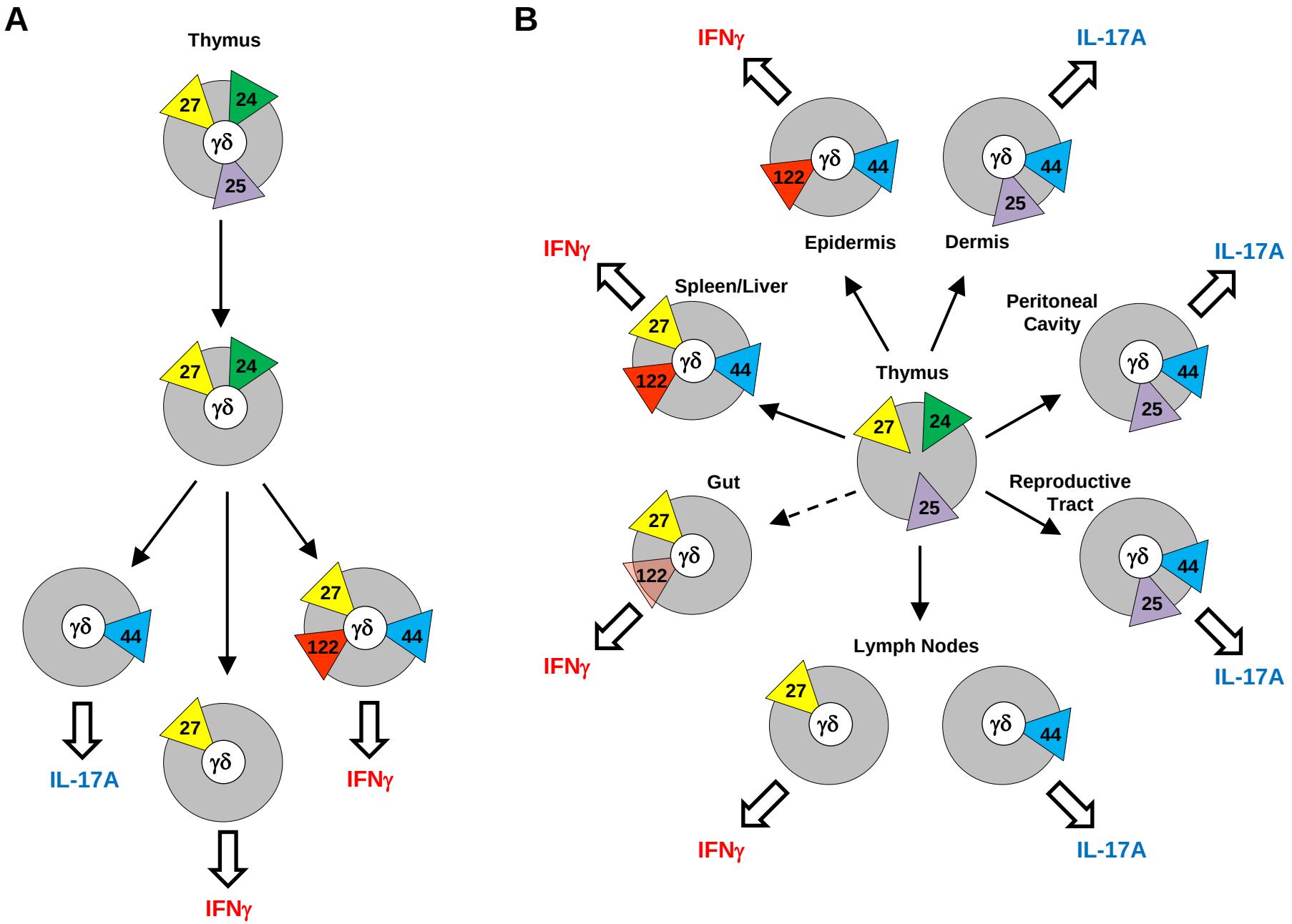
Figure 1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IFNγ
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B
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IL-17A
γδ
122
44
γδ
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25
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Dermis
IFNγ
IL-17A
Spleen/Liver
Peritoneal
Cavity
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γδ
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122
Thymus
γδ
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Gut
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Lymph Nodes
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IFNγ
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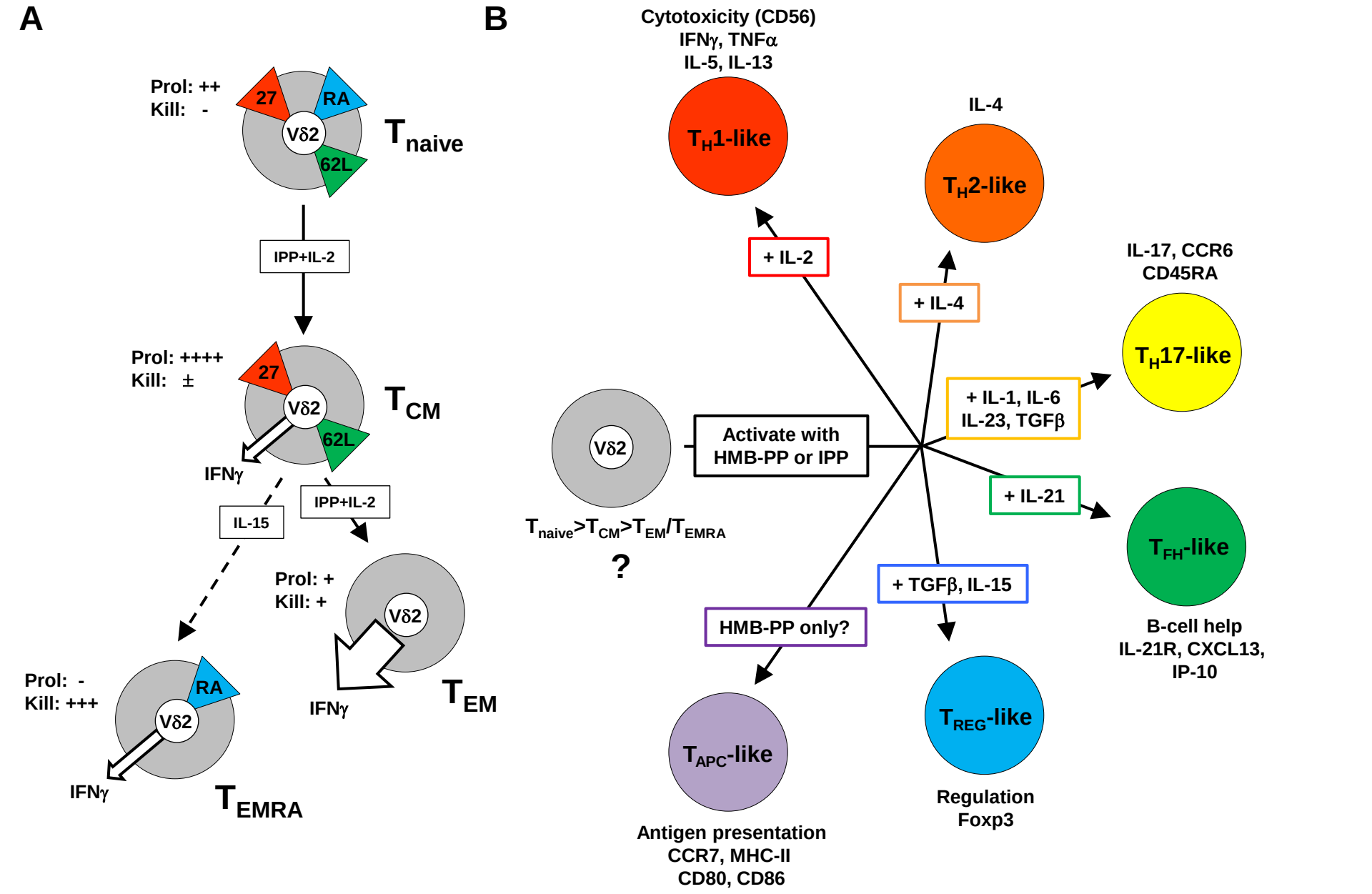
Figure 2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Kill: -
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RA
Vδ2
62L
T naive
IPP+IL-2
Prol: ++++
Kill: ±
27
Vδ2
62L
T CM
IFNγ
IL-15
IPP+IL-2
Prol: +
Kill: +
Vδ2
T EM
IFNγ
Prol: -
Kill: +++
RA
Vδ2
IFNγ
T EMRA
B
Cytotoxicity (CD56)
IFNγ, TNFα
IL-5, IL-13
T H1-like
IL-4
T H2-like
+ IL-2
+ IL-4
IL-17, CCR6
CD45RA
T H17-like
Vδ2
Activate with
HMB-PP or IPP
+ IL-1, IL-6
IL-23, TGFβ
+ IL-21
T FH-like
T naive>T CM>T EM/T EMRA
?
+ TGFβ, IL-15
HMB-PP only?
B-cell help
IL-21R, CXCL13,
IP-10
T APC-like
T REG-like
Regulation
Foxp3
Antigen presentation
CCR7, MHC-II
CD80, CD86