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Human Vγ9/Vδ2 T cells: Innate adaptors of the immune system

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ABSTRACT

Unconventional T cells are gaining center stage as important effector and regulatory cells that orchestrate innate and adaptive immune responses. Human Vγ9/Vδ2 T cells are amongst the best understood unconventional T cells, as they are easily accessible in peripheral blood, can readily be expanded and manipulated *in vitro*, respond to microbial infections *in vivo* and can be exploited for novel tumor immunotherapies. We here review findings that suggest that Vγ9/Vδ2 T cells, and possibly other unconventional human T cells, play an important role in bridging innate and adaptive immunity by promoting the activation and differentiation of various types of antigen-presenting cells (APCs) and even turning into APCs themselves, and thereby pave the way for antigen-specific effector responses and long-term immunological memory. Although the direct physiological relevance for most of these mechanisms still needs to be demonstrated *in vivo*, these findings may have implications for novel therapies, diagnostic tests and vaccines.

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Introduction

γδ T cells represent a third lineage of lymphocytes expressing re-arranged antigen receptors that co-evolved with 'classical' B cells and αβ T cells over 400 million years, arguing for a crucial and non-redundant contribution of each lymphocyte to effective immune responses, and hence the evolutionary survival of all jawed vertebrate species [1]. 30 years have passed since the accidental and unexpected cloning of the γδ T cell receptor (TCR) and the subsequent realization that αβ T cells and γδ T cells are fundamentally different with respect to the types of antigens they recognize and the distinct effector functions triggered upon such recognition. However, the manifold contributions of γδ T cells to homeostasis, inflammation, infection and tumor surveillance have historically been neglected and are only beginning to be integrated into comprehensive models of the immune system [1–7].

Abbreviations: APC, antigen presenting cell; BCG, bacillus Calmette–Guérin; BTN3A, butyrophilin 3A (CD277); DC, dendritic cell; DMAPP, dimethylallyl pyrophosphate; α-GC, α-galactosylceramide; HMB-PP, (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; ICOS, inducible T cell costimulator; iNKT cell, invariant natural killer T cells; IPP, isopentenyl pyrophosphate; MAIT cell, mucosal-associated invariant T cell; TCR, T cell receptor; T_{FH} cell, follicular B helper T cell; TLR, Toll-like receptor.

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1. Innate-like pattern recognition by human Vγ9/Vδ2 T cells

Like other 'unconventional' T cells carrying an αβ TCR such as mucosal-associated invariant T (MAIT) cells and natural killer T (NKT) cells, γδ T cells are characterized by a markedly restricted TCR usage that allows them to recognize self and non-self molecules in the absence of classical antigen presentation via MHC I or MHC II. Vγ9/Vδ2$^+$ γδ T cells represent the major γδ T cell subset in human peripheral blood where they typically comprise 1–5% in healthy adults [8]. In many microbial infections, Vγ9/Vδ2 T cells increase locally and/or systemically [9,10] and can reach in excess of 50% of all peripheral T cells within a matter of days [11], revealing a fundamental role of this unconventional T cell population in acute disease and suggesting their exploitation for diagnostic and therapeutic purposes [12–14].

Vγ9/Vδ2 T cells uniformly respond to a class of low molecular weight molecules often referred to as 'phosphoantigens' that represent metabolites of the isoprenoid biosynthesis, or synthetic analogs thereof. By far the most potent of these 'phosphoantigens' is (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), an intermediate of the non-mevalonate pathway that is found in the majority of Gram-negative bacteria and many Gram-positive species as well as apicomplexan parasites such as *Plasmodium falciparum* and *Toxoplasma gondii* [11,15]. In these organisms, HMB-PP is converted into isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), two further 'phosphoantigens' with a

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bioactivity approx. 10,000-fold lower than that of HMB-PP [11,16]. In all other bacteria as well as in higher eukaryotes including humans, IPP and DMAPP are generated via the mevalonate pathway that is closely regulated by the action of 3-hydroxy-3-methyl-glutaryl-CoA reductase and downstream enzymes such as farnesyl pyrophosphate synthase. Overproduction of the low bioactivity compounds IPP and DMAPP as a result of a dysregulation of the mevalonate pathway in human cells, be it in metabolically active tissues including tumor cells or through inhibition of farnesyl pyrophosphate synthase by aminobisphophonates such as zoledronate, is thought to render such cells targets of Vγ9/Vδ2 T cells, despite the absence of the high bioactivity metabolite HMB-PP in this context [11,16–18]. Zoledronate and related drugs are therefore receiving substantial attention as Vγ9/Vδ2 T cell-stimulating agents *in vivo* especially with respect to immunotherapies against advanced solid and hematological tumors [19–21].

The recent landmark discovery of butyrophilin 3A (BTN3A/CD277) as the long-sought unconventional 'presenting' molecule for HMB-PP and IPP provided a molecular mechanism that elegantly integrates the action of endogenous and exogenous stimuli via binding of phosphoantigens to the intracellular B30.2 (PRY-SPRY) domain of BTN3A [22–25]. This intracellular recognition of HMB-PP and IPP evokes similar cases of B30.2-mediated innate responses through proteins such as TRIM5α and TRIM21 [26,27], thereby adding BTN3A to the rapidly growing number of innate pattern recognition receptors. Despite this progress, the precise mechanism of how the HMB-PP/BTN3A complex might engage the TCR of Vγ9/Vδ2 T cells awaits further elucidation.

Once activated, Vγ9/Vδ2 T cells exert a range of different effector functions by killing infected and stressed target cells, driving inflammatory and wound healing processes, promoting survival of monocytes and neutrophils, inducing maturation of dendritic cells (DCs), providing B cell help, and priming $CD4^+$ and $CD8^+$ T cells [1–7]. In the following chapters we will review findings showing that Vγ9/Vδ2 T cells, and possibly other unconventional human T cells, play an important role in bridging innate and adaptive immunity by promoting the activation and differentiation of various types of antigen-presenting cells (APCs) and even turning into APCs themselves, and thereby pave the way for antigen-specific effector responses and long-term immunological memory (Fig. 1).

2. Maturation of DCs: provision of fully functional APCs

Dendritic cells (DCs) as the prototype of professional APCs play a crucial role in initiating adaptive responses by presenting antigens to conventional αβ T cells. In this context, the process of DC maturation is a critical component of mounting an effective immune response, and involves several distinct stages; the upregulation of antigen presenting and co-stimulatory molecules, the secretion of distinct sets of cytokines/chemokines, a switch in the migratory profile, the reduction of endocytic and phagocytic ability, and the stabilization of MHC/peptide complexes on the cell surface [28]. DC maturation typically occurs upon recognition of danger signals via pattern recognition receptors, the most well defined of which being Toll-like receptors (TLRs). However, host-derived factors are also capable of inducing DC maturation, such as the cytokines IFN-γ and TNF-α [29].

Unconventional T cells including Vγ9/Vδ2 T cells represent a significant source of IFN-γ and TNF-α upon stimulation and are well placed to encounter immature DCs in the blood or periphery to promote DC maturation [30–32] (Fig. 1). In return, DCs have been shown to activate Vγ9/Vδ2 T cells via TCR-independent mechanisms, predominantly by the release of type I IFNs [33–35]. Effects on Vγ9/Vδ2 T cells include the induction and enhancement of proliferation [36] and the expression of cytotoxic and pro-inflammatory mediators such as perforin, IFN-γ and TNF-α [34,37,38], thereby forming a positive feedback loop for mutual stimulation of both cell types.

Upregulation of APC markers and co-stimulatory molecules is an important step in the DC maturation process, due to their vital role in triggering appropriate adaptive responses to any given challenge. Ismaili and colleagues [39] were the first to report that activated Vγ9/Vδ2 T cells stimulate the upregulation of HLA-DR, CD86 and CD83 on immature DCs, in the absence of other stimuli. Further Vγ9/Vδ2 T cell-induced APC markers on DCs may include MHC class I, CD25, CD40, CD80 and others, depending on the culture conditions [37,40–42], suggesting a certain degree of plasticity under the influence of the microenvironment, albeit with unclear physiological implications. Besides inducing DC maturation on their own, Vγ9/Vδ2 T cell-derived factors also synergize with other signals and as such enhance DC maturation triggered by TLR ligands [40,41,43]. Irrespective of *de novo* maturation of DCs or enhancement of TLR-mediated maturation, the upregulation of several costimulatory molecules was identified as predominantly TNF-α mediated, with IFN-γ having little effect [39,43]. In contrast to mice where γδ T cells have been shown to induce DC maturation via CD40L [44], contact-dependent mechanisms have not yet been described in human γδ-DC interactions.

Upon maturation, DCs exhibit a switch in the expression of chemokine receptors, thereby allowing these cells to progress from inflammatory homing iDCs expressing CCR5 to DCs capable of transporting antigens to secondary lymphoid tissues to initiate T cell responses via expression of the lymph node homing receptor CCR7. Indeed, culture of Vγ9/Vδ2 T cells with immature DCs leads to the upregulation of CCR7 and downregulation of CCR5 surface expression, either alone or with the addition of TLR ligands [40–42].

Maturation of DCs is also accompanied by the loss of endocytic and phagocytic capacity. In support, the Vγ9/Vδ2 T cell-mediated maturation of DCs leads to a reduced ability of DC to take up soluble antigen in comparison with immature DCs, exhibiting a similar effect as LPS-triggered maturation [43]. Alongside generally impaired antigen uptake, DCs display improved cross-presentation of antigens upon maturation. NK cells were recently shown to stimulate the cross-presenting capacity of DCs via secretion of IFN-γ and TNF-α [45]. Given that γδ T cells represent a significant source of these two cytokines, it is likely that Vγ9/Vδ2 T cells are able to mediate this process as well.

A number of studies investigated the maturation of DCs pre-infected with HMB-PP producing pathogens that possess the capacity to activate Vγ9/Vδ2 T cells. In this context, DCs infected with *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) undergo maturation by Vγ9/Vδ2 T cells, activated either with zoledronate/phosphoantigens or by the BCG infected DCs themselves [37,46]. Meraviglia et al. [47] reported that DCs, partially matured upon infection with *Mycobacterium tuberculosis*, were able to activate Vγ9/Vδ2 T cells and become fully matured in return. Lastly, Ni et al. [48] described a system whereby DCs infected with *Brucella* exhibited an inhibition of maturation, but upon co-culture with Vγ9/Vδ2 T cells underwent full maturation with regard to upregulation of costimulatory molecules.

Secretion of polarizing cytokines by mature DCs is essential for the skewing of naive $CD4^+$ T cell responses in the lymph nodes. Activated Vγ9/Vδ2 T cells are able to induce the production of IL-12 by mature DCs, either alone or in combination with TLR stimulation [32]. In striking contrast to the differential effect of Vγ9/Vδ2 T cell-derived cytokines on the upregulation of costimulatory molecules, induction of IL-12 is mediated almost exclusively by IFN-γ, and not by TNF-α [39,40,48]. Unlike IL-12, IL-10 is not induced upon Vγ9/Vδ2 T cell mediated DC maturation, and Vγ9/Vδ2 T cell co-culture actually suppresses the LPS-mediated IL-10 expression

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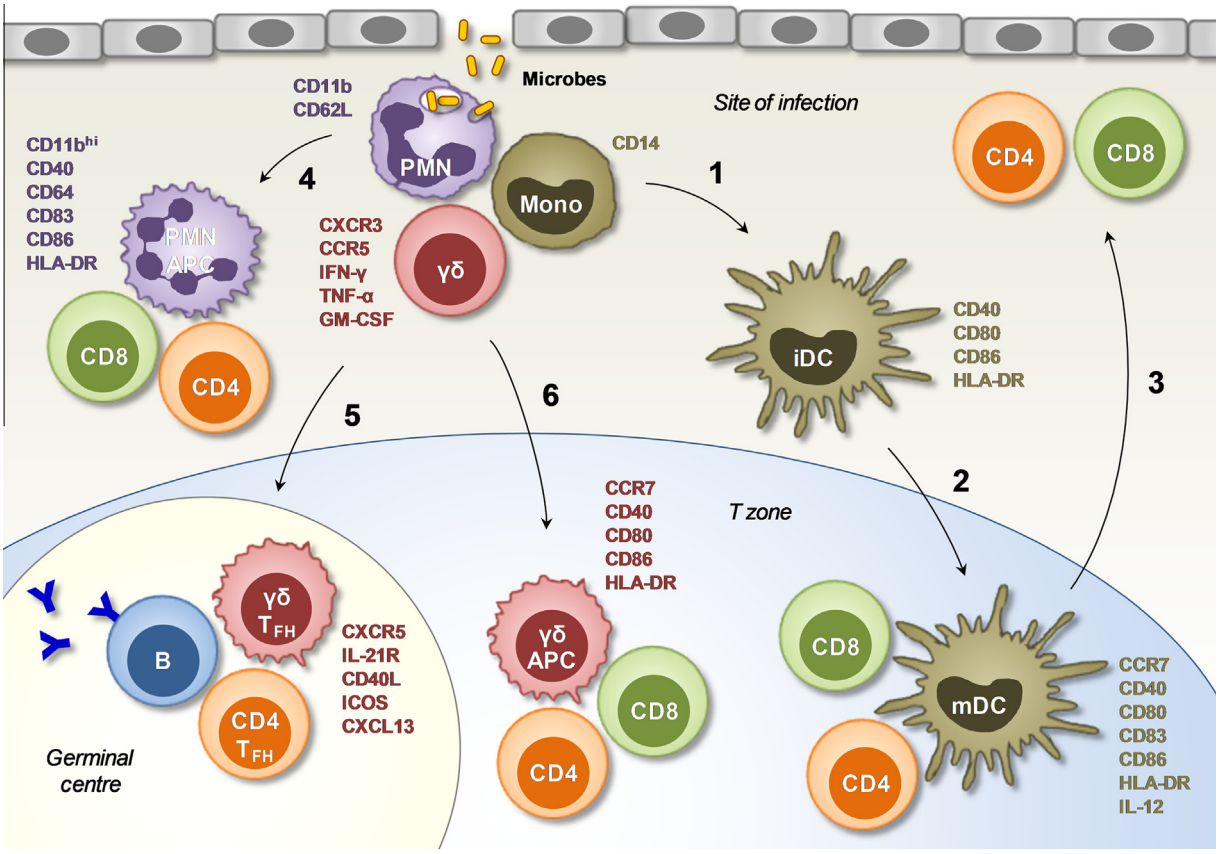

Fig. 1. Bridging innate and adaptive immunity as a result of anti-microbial responses by human Vγ9/Vδ2 T cells. At the site of infection Vγ9/Vδ2 T cells become exposed to microbial compounds, in the context of infiltrating neutrophils (PMN) and monocytes (Mono), leading to the release of cytokines including IFN-γ, TNF-α and GM-CSF. Under the influence of these pro-inflammatory conditions, local monocytes differentiate into inflammatory DCs (1). Vγ9/Vδ2 T cells will induce inflammatory and tissue-resident DCs to mature, migrate to the draining lymph nodes and prime antigen-specific $CD4^+$ and $CD8^+$ T cells (2) that will eventually traffic back to the site of infection (3). Local neutrophils will also acquire APC features, which will enable them to present microbial antigens to tissue-resident memory or newly recruited effector $CD4^+$ and $CD8^+$ T cells (4). The activated Vγ9/Vδ2 T cells themselves will enter secondary lymphoid tissues where they interact with B cells and T_{FH} cells in the germinal centers to stimulate the production of antimicrobial antibodies (5), and as γδ T-APCs present antigens directly to naive and memory $CD4^+$ and $CD8^+$ T cells in the T zone (6). Highlighted molecules represent defining surface markers and effector molecules for the different cell types shown. Not depicted, for the sake of clarity, are possible scenarios in which γδ T-APCs or γδ T cell-induced DCs present antigens locally to tissue-resident or newly arrived $CD4^+$ and $CD8^+$ T cells, or in which APC-like neutrophils enter the draining lymph node.

by maturing DCs [42], thereby favoring Th1 polarizing conditions. In addition to the induction of IL-12, Martino et al. [46] observed the upregulation of TNF-α and IL-15 production by maturing DCs in response to activated Vγ9/Vδ2 T cells.

Since Vγ9/Vδ2 T cells alter the expression of polarizing cytokines by DCs, several studies consequently examined the effects of Vγ9/Vδ2 T cell-matured DCs on naive $CD4^+$ T cell responses. In functional assays, Vγ9/Vδ2 T cell-matured DCs were able to polarize $CD4^+$ T cells towards a Th1 phenotype as default pathway, characterized by increased IFN-γ production and decreased IL-4 and IL-5 production [39–41,46]. However, given the functional plasticity of Vγ9/Vδ2 T cells [49], it remains to be investigated whether under certain conditions they may also instruct DCs to polarize naive $CD4^+$ T cells toward other phenotypes (Th2, Th17, Th22, Treg). Futhermore, little is known about the potential of γδ T cell-matured DCs to induce $CD8^+$ T cell responses [50]. While it has been shown that induction of cytotoxic T cells requires TLR stimulation of DCs [51], it will be interesting to test whether Vγ9/Vδ2 T cell mediated maturation can overcome this necessity, and whether $CD8^+$ T cell phenotypes can be similarly regulated as their $CD4^+$ T cell counterparts [52].

Finally, it is worth emphasizing that the concept of Vγ9/Vδ2 T cell mediated-maturation of DCs is entirely based on using monocyte-derived DCs. Consequently, more research is needed into applying these findings to the breadth of human DC subsets that differ in expression of costimulatory molecules, pathogen recognition receptors and cytokines as well as their anatomical location, migratory properties and their ability to induce naïve $CD4^+$ and $CD8^+$ T cell responses and polarize them toward distinct phenotypes [53]. In this respect it is encouraging that Poccia et al. [54] observed an expansion of peripheral Vγ9/Vδ2 T cells in HIV patients upon treatment with zoledronate and IL-2, which was accompanied by an increased expression of CD80 on circulating $CD11c^+$ $HLA\text{-}DR^+$ DCs.

3. Differentiation of monocytes: local generation of inflammatory DCs

The origin of tissue-resident and inflammatory DCs is a matter of intensive research [55,56]. In mice, circulating monocytes can give rise to inflammatory DCs *in vivo* but whether the same holds true for humans remains unclear [57]. The observation that human monocytes can readily be differentiated into monocyte-derived DCs in the presence of GM-CSF and IL-4 *in vitro* [58] fundamentally transformed our understanding of DC-driven immune responses and facilitated investigations into many aspects of human DC biology including their potential as cellular vaccines [59]. Yet, the physiological relevance of these monocyte-derived DCs and the processes that drive monocyte differentiation into professional APCs *in vivo* are still only poorly understood.

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Monocytes are critical for the activation and proliferation of Vγ9/Vδ2 T cells in response to neutrophil-released microbial compounds [9,10], and are thus likely to drive early inflammatory responses in acute microbial infections [60], which can be mimicked *in vitro* by providing soluble HMB-PP [61,62]. In addition, monocytes are also essential for Vγ9/Vδ2 T cell responses to aminobisphosphonates such as zoledronate by facilitating uptake of these compounds through endocytosis and intracellular accumulation of IPP [63–65]. However, only a few studies have examined the feedback of activated Vγ9/Vδ2 T cells on monocytes.

Monocytes are relatively short-lived cells that rapidly undergo apoptosis *in vitro* but can be rescued by a variety of different stimuli including pro-inflammatory cytokines. Ottones et al. [66] reported morphological changes of monocytes co-cultured together with activated Vγ9/Vδ2 T cells yet did not characterize those activated monocytes in more detail. Other studies showed an induction of CD40, high-mobility group box 1 protein (HMGB-1) and tissue factor (TF) by monocytes in PBMC cultures treated with IPP or zoledronate [67,68]. Our own research demonstrated that HMB-PP activated Vγ9/Vδ2 T cells trigger monocyte survival and activation in a highly sensitive and dose-dependent manner. These effects are still measurable at HMB-PP concentrations of down to 0.1 nM and ratios of up to 500 monocytes per Vγ9/Vδ2 T cells, and are thus likely to be of physiological relevance at the site of inflammation [61]. Of note, overactivation by Vγ9/Vδ2 T cells may also induce apoptosis of monocytes [69]. Most importantly, Vγ9/Vδ2 T cell-primed monocytes lose expression of CD14 and upregulate a whole set of APC markers, most notably CD40, CD86 and HLA-DR (Fig. 1), and also express DC-related markers such as CD83 and CD209, thereby acquiring a phenotype reminiscent of inflammatory DCs [61].

While Vγ9/Vδ2 T cells are typically portrayed as pro-inflammatory [70] they nevertheless co-express factors such as IL-4 [71–74]. Indeed, most effects of Vγ9/Vδ2 T cells on monocytes are largely mediated via IFN-γ and TNF-α as well as GM-CSF, yet IL-4 may make an additional contribution to shaping the phenotype and function of Vγ9/Vδ2 T cell-triggered inflammatory DCs [61]. In addition to soluble mediators, cell–cell contact is crucial for the γδ T cell-driven activation of monocytes, as cluster formation as well as loss of CD14 and upregulation of CD40 and CD86 is abrogated in the presence of neutralizing antibodies against LFA-1 [61]. Of note, the induction of CCR7 appears to require the presence of further microbial compounds such as LPS and peptidoglycan [[61]; B.M. and M.E, unpublished], suggesting a complex two-step differentiation and maturation process depending on a variety of microbial and environmental cues.

In functional assays, Vγ9/Vδ2 T cell-primed monocytes present bacterial proteins or superantigens to autologous $CD4^+$ T cells, typically resulting in the induction of IFN-γ secreting $CD4^+$ T cells [61]. However, Vγ9/Vδ2 T cell-primed monocytes exposed to microbial compounds such as LPS or peptidoglycan readily induce IL-17 secreting $CD4^+$ T cells, indicating that the prevailing conditions in the local microenvironment may eventually dictate the outcome of such interactions and affect the balance between Th1 and Th17 dominated responses [60]. This notwithstanding, functional proof of this Vγ9/Vδ2 T cell-driven generation of inflammatory DCs *in vivo* is missing, especially during microbial infection in affected tissues.

Indirect evidence that Vγ9/Vδ2 T cells do trigger monocyte activation *in vivo* comes from studies in patients upon intravenous administration of zoledronate, a treatment that frequently causes acute phase reactions characterized by fever, fatigue, muscle pain, headache, and/or joint pain [75]. In reminiscence of the earlier observation of CD80 upregulation on circulating DCs in zoledronate-treated HIV patients [54], our own clinical trial in otherwise healthy individuals with osteoporosis demonstrated a significant although transient increase in the surface expression of CD14, CD40, CD80, and HLA-DR of circulating $CD14^+$ monocytes after first time treatment with zoledronate [65]. This study also identified pre-treatment levels of monocytes and central/memory Vγ9/Vδ2 T cells as predictive risk factors for the occurrence of subclinical and clinical symptoms, in support of the interaction of these two cell types *in vivo*.

4. Interaction with neutrophils: unexpected generation of APC-like neutrophils

Neutrophils are the earliest immune cells recruited to sites of acute inflammation, especially in the context of microbial infections. However, there is also emerging evidence supporting a role for neutrophils in antiviral defense [76]. Neutrophils turn out to be far more versatile and sophisticated than originally perceived and have been shown to engage in complex mutual interactions with other immune and non-immune cells to regulate acute inflammation as well as resolution and tissue repair [77,78]. As a result of this crosstalk, neutrophils receive potent signals that trigger a substantial extension of their life span and allow them to acquire distinct phenotypes and functions including the capacity to facilitate monocyte differentiation and DC maturation, and to interact with T cells [78–80]. It is this intriguing APC-like aspect of neutrophil biology that is most relevant to this review.

In mice, neutrophils were recently shown to differentiate into "neutrophil-DC hybrids" that express markers typical of both neutrophils and DCs [81,82]. Of note, those intermediate cells exhibit a blend of neutrophil features such as phagocytosis, release of neutrophil extracellular traps and bacterial killing, and APC properties including DC-like morphology and migration, cytokine production and antigen presentation to naive $CD4^+$ T cells. In humans, neutrophils expressing MHC class II and other APC-related surface markers can be found in diverse inflammatory and infectious scenarios, yet a clear function of such neutrophils as APCs, especially under physiological conditions *in vivo*, remains to be validated [83,84].

Neutrophils and other innate cells including Vγ9/Vδ2 T cells are often co-recruited to sites of infection, and hence are likely to interact with each other *in vivo*. Activated Vγ9/Vδ2 T cells in fact induce chemotaxis and phagocytosis of neutrophils [85,86], and in return microbial compounds released by neutrophils upon phagocytosis of different pathogens are sensed by Vγ9/Vδ2 T cells [9,10], suggesting an intimate crosstalk of the two cell types, typically leading to their mutual activation. However, recent supports also suggest that under certain conditions neutrophils may actually suppress Vγ9/Vδ2 T cell responses [87,88], indicative of a fine-tuned regulatory interplay between the two cell types depending on the microenvironment [89].

The contact with locally activated Vγ9/Vδ2 T cells is likely to have profound consequences for the phenotype and function of co-recruited neutrophils. Davey et al. [9] demonstrated a striking anti-apoptotic effect of Vγ9/Vδ2 T cells on human neutrophils that significantly extends the lifespan of cultured neutrophils. Over a period of 48 h these surviving neutrophils show signs of strong activation such as the presence of hypersegmented nuclei together with an upregulated surface expression of CD11b and CD66b and complete shedding of CD62L [10]. Most importantly, such neutrophils exposed to activated Vγ9/Vδ2 T cells also acquire numerous APC-related markers such as high levels of expression of CD40, CD54, CD64 and CD83 as well as MHC class I and class II molecules (Fig. 1). On a functional level, Vγ9/Vδ2 T cell-primed neutrophils not only readily take up soluble antigens and process microbial material for presentation to antigen-specific $CD4^+$ T cells but are also capable of shuttling exogenous antigens via the cross-presentation pathway for an effective induction of antigen-specific $CD8^+$ T cells [10].

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These findings support a model in which Vγ9/Vδ2 T cells (as well as other unconventional T cells such as MAIT cells) respond rapidly to neutrophils after phagocytosis of a broad range of microbial pathogens at the site of infection, and in turn mediate the local differentiation of bystander neutrophils into APCs for both $CD4^+$ and $CD8^+$ T cells through rapid production of pro-inflammatory cytokines including GM-CSF, IFN-γ and TNF-α [10]. Since local Vγ9/Vδ2 T cells are far more abundant at the site of infection than $CD4^+$ and $CD8^+$ T cells specific for individual antigenic epitopes, it can be envisaged that Vγ9/Vδ2 T cells cells represent early and abundant sources of such pro-inflammatory cytokines. The rapid and local generation of such APC-like neutrophils may allow to present microbial antigens to tissue-resident memory T cells or freshly recruited effector T cells, thereby aiding the anti-microbial immune response and contributing to pathogen clearance. It can be speculated that even though neutrophils may be less potent than DCs in processing and presenting antigenic peptides to T cells and be less relevant for the induction of primary T cell responses in the draining lymph nodes, the sheer quantity of neutrophils rapidly recruited to the site of infection will easily outnumber local DCs that are relatively sparse in peripheral tissues. Indirect evidence for the existence of APC-like neutrophils comes from studies in patients with various infectious and non-infectious inflammatory diseases [90–96], most notably in acute sepsis where circulating neutrophils possess a phenotype similar to Vγ9/Vδ2 T cell-primed neutrophils and are similarly capable of cross-presenting soluble proteins to antigen-specific $CD8^+$ T cells [10]. These findings support the existence of an effective sentinel network comprised of Vγ9/Vδ2 T cells and their crosstalk with neighboring immune and non-immune cells [4], and identify a novel role for human unconventional T cells in shaping the transition of the innate to the adaptive phase of anti-microbial responses.

5. Provision of B cell help: boosting humoral immunity

Effective control of many infections depends on the production of specific antibodies that are generated through somatic hypermutation, class switch recombination and affinity maturation of activated B cells in the germinal centers of secondary lymphoid organs. While these processes typically depend on cognate help provided by follicular B helper T (T_{FH}) cells [97,98], early studies in $TCR\alpha^{-/-}$ and $TCR\beta^{-/-}$ mice demonstrated that lymph nodes in animals lacking αβ T cells still contain germinal centers [99–101]. Similarly, patients with selective deficiencies in αβ T cells due to mutations in recombinase activating gene 1 (*RAG1*), TCRα subunit constant gene (*TRAC*) or *CD3D* show normal or even elevated levels of antibody production [102–104]. Functional proof that γδ T cells are sufficient to orchestrate follicular responses came from adoptive transfer experiments in SCID mice [105,106]. However, such studies also indicated that γδ T cell-dependent B cell responses result in increased titers of self-reactive antibodies, suggesting that αβ T cells may be crucial for the effective regulation of affinity maturation and clonal selection. These findings were mirrored by the description of γδ T cell lines isolated from lupus patients that were capable of inducing autoantibody production by autologous B cells [107]. Although not directly addressing the underlying mechanism, the link between γδ T cell responses and antibody production is also supported by the observation that antigens encountered in the context of cutaneous epithelial stress sensed by γδ T cells induce strong primary and secondary Th2-type atopic responses in mice [108].

In humans, γδ T cells can readily be found in secondary lymphoid tissues [109,110], both in the T zone and within germinal centers [111], supporting the notion that γδ T cells interact with other lymphocytes and participate in the generation of antigen-specific T cell and B cell responses. Indeed, microarray studies revealed that Vγ9/Vδ2 T cells primed in the presence of IL-21 assume features typically associated with human T_{FH} cells, most notably the expression of the B cell attracting chemokine, CXCL13, which is key in recruiting B cells to secondary lymphoid tissue and establishing germinal centers [74]. On a functional level, activated Vγ9/Vδ2 T cells readily provide B cell help *in vitro*, with a particular contribution of Vγ9/Vδ2 T cell-expressed CD40L and inducible T cell co-stimulator (ICOS) as well as IL-4 and IL-10 [111,112]. These findings identify an intimate tripartite crosstalk between antigen-specific $CD4^+$ T_{FH} cells, HMB-PP responsive Vγ9/Vδ2 T cells and follicular B cells in which both $CD4^+$ and γδ T cells regulate the recruitment of further cells to the germinal center and the production and affinity maturation of class-switched antibodies [113,114] (Fig. 1). Of note, activated Vγ9/Vδ2 T cells also drive the expression of APC markers by B cells, most notably CD40, CD86 and HLA-DR [113,115], thereby enhancing the potential of follicular B cells to engage T_{FH} cells and amplify antigen-specific immune responses. Similarly, activated Vγ9/Vδ2 T cells themselves may acquire APC characteristics [116], as discussed in the subsequent chapter, and may present antigens to T_{FH} cells. This potent amplification of the germinal center response places Vγ9/Vδ2 T cells at a key position in the regulation of humoral immunity, with implications for the efficient generation of high affinity antibodies in microbial infections but also for potential collateral damage resulting from an overshooting immune response and increased titers of self-reactive antibodies.

6. Priming of $CD4^+$ and $CD8^+$ T cells by Vγ9/Vδ2 T cells: a new type of professional APC

In addition to the indirect promotion of adaptive immune responses via maturation of DCs and induction of APC features in monocytes, neutrophils and B cells, Vγ9/Vδ2 T cells themselves can also directly act as APCs [116]. Expression of HLA-DR is a well known attribute of activated T cells, and such activated T cells may be able to present antigens in appropriate contexts [117]. However, only Vγ9/Vδ2 T cells have been shown to be able to act as truly professional APCs, as characterized by the effective uptake and processing of exogenous antigens through endocytosis [118] and even phagocytosis [119], and the priming and differentiation of naive $CD4^+$ and $CD8^+$ T cells [116,120] (Fig. 1). While membrane transfer from other cells via trogocytosis may contribute to the expression of APC markers [121,122], the mobilisation of an efficient APC machinery and the potential to load exogenous antigens onto both MHC class I and class II molecules is an intrinsic feature of activated human Vγ9/Vδ2 T cells. As such, these 'Vγ9/Vδ2 T-APCs' are capable of inducing MHC class II restricted $CD4^+$ T cell responses upon presentation of the staphylococcal superantigen toxic shock syndrome toxin 1 (TSST-1) that crosslinks HLA-DR on the APC surface with the TCR of responder cells carrying a Vβ2 chain, and in mixed lymphocyte responses as a reaction to donor mismatched MHC class II alleles [116]. Moreover, Vγ9/Vδ2 T-APCs have also been shown to induce antigen-specific $CD4^+$ T cell responses upon direct presentation of antigenic peptides or upon uptake and intracellular processing of microbial antigens like *M. tuberculosis* PPD and tetanus toxoid [116,123].

With regard to the functional outcome of Vγ9/Vδ2 T-APC driven $CD4^+$ T cell responses, the abundant expression of pro-inflammatory cytokine such as IFN-γ and TNF-α by activated Vγ9/Vδ2 T cells may mainly induce a polarization of $CD4^+$ T cells toward a Th1 phenotype, although at low APC ratios an expression of IL-4 by $CD4^+$ T cells was observed [116]. Depending on the culture conditions,

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Vγ9/Vδ2 T cells clearly assume different functions including distinct cytokine profiles [49,74,72,124–126], and hence more research is needed to delineate whether Vγ9/Vδ2 T-APCs may induce different 'flavors' of $CD4^+$ T cell responses (Th1, Th2, Th17, Th22, Treg), and what the signals involved in such a polarization are. In this respect, our preliminary findings suggest that under appropriate conditions Vγ9/Vδ2 T-APCs are able to induce considerable IL-22 expression in naive $CD4^+$ T cells [C.J.T., M.E. and B.M., unpublished], supporting an unexpected plasticity in Vγ9/Vδ2 T cell-driven $CD4^+$ T cell responses.

The true potential of Vγ9/Vδ2 T-APCs as novel type of professional APC becomes apparent when considering their capacity to take up soluble proteins from the microenvironment and load antigenic peptides onto newly translated MHC class I molecules for efficient presentation to $CD8^+$ T cells, in a mechanism usually referred to as antigen cross-presentation [120]. Activated Vγ9/Vδ2 T cells turned out to be well equipped cross-presenting APCs capable of processing not only defined proteins but also complex material such as cell debris and whole bacteria, and shuttle endocytosed antigens into the cytosol for degradation by the proteasome [118–120]. As Vγ9/Vδ2 T cells retain their cytolytic potential when they acquire APC functions [127], this unique combination of direct target cytotoxicity and APC machinery allows for scenarios in which Vγ9/Vδ2 T cells would lyse transformed, stressed or infected cells, and take up and process released proteins for presentation to both $CD4^+$ and $CD8^+$ T cells, with enormous implications for novel immunotherapies and vaccines [128–132]. In this context, Himoudi et al. [130] proposed a role for opsonizing antibodies in the efficient 'licensing' of Vγ9/Vδ2 T-APCs, by enhancing uptake of antibody-bound material via Fc receptors like CD16, which is expressed by Vγ9/Vδ2 T cells under certain stimulation conditions and on distinct subsets [133,134]. Such a licensing pathway to boost cross-presentation of tumor-derived antigens could be exploited by using monoclonal antibodies specifically targeting tumor cells, such as rituximab (anti-CD20), trastuzumab (anti-HER2/neu) or ch14.18 (anti-GD2), and contribute to the effectiveness of combination therapies [135–137].

Irrespective of this progress in our understanding of γδ T-APC triggered responses *in vitro*, there is a paucity of data on the relevance of Vγ9/Vδ2 T cells acting as APCs *in vivo*, be it under homeostatic conditions in healthy tissues or in acute and chronic inflammatory scenarios including microbial infections. Naturally, local access to inflamed tissues and draining lymph nodes in humans is very limited, thereby severely compromising investigations into the APC function of Vγ9/Vδ2 T cells – or, as a matter of fact, into the APC function of any human immune cell. Indirect support for a possible role as APC stems from observations that HLA-DR is expressed by activated Vγ9/Vδ2 T cells in patients with severe inflammation or during acute infection [123,138–140], and in patients receiving intravenous zoledronate with and without IL-2 [65,141,142]. However, functional evidence into the potential of activated Vγ9/Vδ2 T cells to act as APC *ex vivo* is only beginning to emerge [123,143].

7. Other unconventional T cells bridging innate and adaptive immunity: parallels between Vγ9/Vδ2 T cells and iNKT cells

In addition to Vγ9/Vδ2 T cells, other unconventional T cells can contribute directly and indirectly to adaptive immune responses by promoting antigen presentation, polarizing T cell differentiation into distinct types of effector cells, and promoting B cell and antibody responses. These innate T cell populations differ from Vγ9/Vδ2 T cells and from each other in their TCR ligand specificities, frequencies and locations in the body. Most of our understanding of innate T cell roles and functions comes from nearly three decades of research on natural killer T (NKT) cells, however, more recent research is focusing on other γδ T cell subsets such as $V\delta1^+$ and $V\delta3^+$ T cells, and MAIT cells, which are more abundant in humans.

NKT cells are a heterogeneous group of T cells that share properties of both T cells and NK cells [144–146]. Two classes of NKT cells are found in humans and mice. Type 1 or invariant NKT (iNKT) cells express a TCR composed of an invariant TCR α-chain (Vα24-Jα18 in human and Vα14-Jα18 in mice), whereas type 2 NKT cells express a diverse array of TCRs that recognize the MHC class I-like molecule CD1d. Type 1 and type 2 NKT cells also express a number of NK cell stimulatory receptors, such as NK1.1 in mice and NKG2C and NKG2D in humans. While iNKT cells recognize a number of self [147,148] and microbial [149–151] glycosphingolipids, most of our understanding of NKT cells comes from studies of murine and human iNKT cells stimulated with the xenogeneic glycolipid, α-galactosylceramide (α-GC). Upon activation with α-GC *in vitro*, iNKT cells can kill target cells and secrete a diverse range of growth factors and cytokines [144–146]. Murine and human iNKT cells are unique in their ability to produce Th1 (IFN-γ, TNF-α), Th2 (IL-4, IL-5, IL-13), Th9 (IL-9), Th17 (IL-17A, IL-22) and regulatory T cell (IL-10) cytokines, at times simultaneously [152–155]. Cytokines released by iNKT cells contribute to the activation of T cells [156], NK cells [156,157], macrophages [158] and suppression of functions of neutrophils and myeloid-derived suppressor cells [159,160].

Activated iNKT cells can interact directly with DCs, causing them to mature into APCs. This adjuvant activity was first reported by Kitamura et al. [161] who found that α-GC-stimulated murine iNKT cells induced IL-12 production by DC through CD40/CD40L interactions between iNKT cells and DCs. Subsequently, Vincent et al. [162] showed that human T cell clones reactive against all isotypes of CD1 (CD1a, CD1b, CD1c and CD1d) in the absence of foreign antigen could induce the expression of CD83 and CD86, cell surface localization of MHC class II and release of IL-12 by DC, but different CD1-restricted T cells costimulated DC to different degrees inducing profoundly different amounts of IL-12. The adjuvant effect of iNKT cells for DC was also demonstrated *in vivo* by Fujii et al. [163] who found that a single intravenous dose of α-GC stimulated the full maturation of DCs, which led to the induction of $CD4^+$ and $CD8^+$ T cell responses to a coadministered protein. Of note, a subset of iNKT cells can also kill DCs [164]. In contrast to this wealth of data on the interaction of iNKT cells with DCs in mouse and humans, less is known about the crosstalk of iNKT cells with monocytes as possible precursors of DCs and macrophages. While activated Vγ9/Vδ2 T cells can drive the differentiation of monocytes into inflammatory DCs [60,61], it is unclear whether iNKT cells can do the same. Instead, iNKT cells appear to promote the differentiation of monocytes into IL-10 secreting myeloid-derived suppressor cells (MDSCs) [165,166].

Similarly to Vγ9/Vδ2 T cells, iNKT cells can also provide help for B cell maturation and antibody production. In murine models, CD1d and iNKT cells are required for the generation of protective antibody responses against microbial pathogens [167–169]. Co-administration of α-GC with immunizing antigen to mice results in enhanced production of antibodies specific for the antigen [170–172], demonstrating that the adjuvant effect of iNKT cells is antigen-specific. This help provided by iNKT cells results in the induction of long-lived antibody-secreting plasma cells, affinity maturation and the generation of memory B cells [172–175]. iNKT cells can also provide help for B cells specific for lipid-containing antigens internalized through the B cell receptor [176,177]. Marginal zone B cells are the most efficient B cell subset at presenting glycolipids to iNKT cells [177], which frequently possess a T_{FH}-like phenotype ($CXCR5^+$, $PD\text{-}1^+$, $CD28^+$, $IL\text{-}21^+$) [178]. Crosstalk between the two cell types involves CD40/CD40L interactions but does not

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appear to depend on IFN-γ or IL-4 [172]. The contribution of human iNKT cells to B cell help was first reported by Galli et al. [179], who co-cultured expanded $CD4^+$ and $CD4^-$ iNKT cell lines with B cells *in vitro* and found that both subsets induced B cell proliferation and antibody production. This finding was later confirmed using fresh human iNKT cells [180]. In our own work, we investigated the effects of co-culturing expanded human $CD4^+$, $CD8\alpha^+$ and $CD4^-CD8\alpha^-$ iNKT cells with autologous peripheral B cells *in vitro* and found that all iNKT cell subsets induced IgM, IgA and IgG release by B cells by a mechanism that required CD1d but not added glycolipid, such as α-GC [181]. All iNKT cell subsets induced the expression of CD40, CD86 and HLA-DR by B cells, but iNKT cell-matured B cells were less able to drive proliferation of autologous and alloreactive conventional T cells than B cells cultured in the absence of iNKT cells. Additionally, $CD4^+$ iNKT cells induced expansions of cells with phenotypes of regulatory B cells. Therefore, human iNKT cell subsets may differentially promote and regulate antibody production and T cell activation by B cells [181].

The adjuvant effects of iNKT cells, together with their cytotoxic activities and capacity to secrete diverse cytokines, and the ease by which these cells can be expanded using conserved antigens have placed these cells as important immunomodulators in the tissues and potential targets for immunotherapy. Therapeutic activation of iNKT cells in murine models can prevent tumor growth [182–184], ameliorate autoimmune [185,186] and metabolic [187] disease, and protect against microbial infection [188]. Numerical and functional iNKT cell deficiencies have been reported in a number of human diseases [189–192]. These findings led to clinical trials in humans for cancer involving the adoptive transfer of *ex vivo* expanded autologous DC, pulsed with α-GC, in the absence or presence of expanded iNKT cells [193–195]. Although these treatments were well-tolerated and resulted in the generation of antitumor $CD4^+$ and $CD8^+$ T cell responses, clinical responses have been limited and future refinements are required to optimize the generation of efficient antitumor immunity.

8. Innate regulation of adaptive immune responses: $V\delta2^+$ versus $V\delta2^{neg}$ human γδ T cells

iNKT cells constititute <1% of the T cell repertoire in most human tissues, one hundred-fold less than in murine tissues [189]. This has prompted the search for other, more abundant, semi-invariant innate T cells as therapeutic agents. In this respect, although human T cell reactivities against CD1a, CD1b, CD1c and CD1d have been described, the lack of invariant TCRs as defining markers of these CD1-restricted T cells has hampered their evaluation as adjuvants for the activation and polarization of adaptive immune responses. Of notable exception is the finding of human CD1-restricted T cells with semi-invariant TCRs within the γδ T cell repertoire. Whilst Vγ9/Vδ2 T cells make up the majority of peripheral human γδ T cells, $V\delta1^+$ and $V\delta3^+$ ('$V\delta2^{neg}$') T cells are the predominant γδ T cell subtypes in human intestine and liver [196,197]. Several studies have demonstrated CD1a, CD1b, CD1c and CD1d reactivity of human $V\delta1^+$ T cells [198–203] and CD1d-reactivity of human $V\delta3^+$ T cells [204]. Roles for CD1-restricted $V\delta1^+$ and $V\delta3^+$ T cells in the induction of adaptive immune responses are evident from studies that have shown that these cells can induce MHC and costimulatory receptor expression and cytokine production by DC, conferring upon DC the capacity to drive alloreactive T cell proliferation [204,205]. Additionally, one report described the ability of CD1-restricted $V\delta1^+$ T cells specific for pollen-derived phosphatidyl-ethanolamine to drive IgE production by B cells [200].

Although CD1 restriction is evident in the $V\delta1^+$ T cell repertoire, the majority of $V\delta1^+$ T cells appear not to be CD1 restricted [201]. Non-CD1-restricted $V\delta1^+$ T cells recognize and kill a variety of tumor cells [206–208] and cells infected with CMV [209,210] and HIV [211,212], and release cytokines in response to bacteria and fungi [213,214]. Once activated, $V\delta1^+$ T cells can drive DC maturation [215] but also kill DCs [216]. In addition, $V\delta1^+$ T cells can display properties of regulatory T cells and suppress immune responses through contact or cytokine dependent interactions [217–220], including the suppression of DC maturation in breast cancer [221,222]. Thus, it appears that the $V\delta1^+$, $V\delta2^+$ and $V\delta3^+$ subsets of γδ T cells as well as iNKT cells all play roles in the induction, polarization and/or regulation of adaptive immune responses in humans. Future studies will ascertain if further unconventional T cells such as MAIT cells have complementary roles in bridging innate and adaptive immunity. Our most recent findings already suggest that the vast majority of invading microbes is likely to be detected by either Vγ9/Vδ2 T cells or MAIT cells, or both, and that both cell types have an equal potential to activate human neutrophils and drive their acquistion of APC features [10].

9. Conclusion and outlook: Vγ9/Vδ2 T cells as natural adjuvants for antigen-specific responses?

Vγ9/Vδ2 T cells and other unconventional T cells in humans and in mice clearly regulate a plethora of distinct immune responses, by interacting with local immune and non-immune cells, and may thereby influence homeostatic, anti-microbial, anti-tumor and tissue repair responses [1–7]. It is conspicuous that the generation and maturation of effective APCs appears to be a common endpoint of Vγ9/Vδ2 T cell-triggered interactions with neutrophils, monocytes and immature DCs as well as B cells, in combination with the unexpected potential of Vγ9/Vδ2 T cells themselves to act as professional APCs (Fig. 1). Even more, other unconventional T cell subsets may drive similar reactions, albeit in response to different stimuli and in different anatomical contexts, arguing for a general role of innate T cell subsets as natural adjuvants to promote protective immune responses. In analogy to the exploitation of iNKT cells in the clinic [193–195,223,224], approaches specifically targeting Vγ9/Vδ2 T cells may have a similar potential as vaccine adjuvant, to boost immune responses against pathogens and tumors and to modulate autoimmune responses.

Administration of Vγ9/Vδ2 T cell stimulating agents and the adoptive transfer of *ex vivo* expanded Vγ9/Vδ2 T cell have proven to be safe in patients [19–21]. The promising role of Vγ9/Vδ2 T cells as cytotoxic effectors against a range of solid and hematological malignancies notwithstanding, there are no detailed reports on anti-tumor αβ T cell or antibody responses in treated individuals. Indirect support for an adjuvant role comes from the observation that HIV patients receiving treatment with zoledronate and IL-2 showed enhanced $CD8^+$ T cell responses against a pool of HIV gag peptides, although the effect of IL-2 administration on HIV-specific and non-specific $CD8^+$ T cell responses was not addressed in that study [54]. In fact, only one study has attempted to specifically address the possible adjuvant effect of Vγ9/Vδ2 T cells *in vivo*, by vaccinating cynomolgus monkeys with a mycobacterial ESAT-6-Ag85B (H1 hybrid) fusion protein in the presence or absence of the synthetic HMB-PP analog Picostim. Cendron et al. [225] concluded that a prime-boost vaccination with the H-1/Picostim subunit combination induced two independent waves of immune responses, an early innate-like one dominated by γδ T cells and a subsequent one comprised of antigen-specific αβ T cells, without an apparent effect of γδ T cells on the ensuing αβ T cell response. Future studies in patients should re-address the wider effect of

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Vγ9/Vδ2 T cell targeting approaches on antigen-specific immune responses in different contexts.

As a flip side of the potential benefit of the adjuvant properties of Vγ9/Vδ2 T cells, a dysregulated generation of APCs under the influence of Vγ9/Vδ2 T cells may eventually result in uncontrolled inflammation and the generation of cellular and humoral autoimmune responses, thereby contributing to the clinical symptoms in scenarios such as psoriasis [226], inflammatory bowel disease [227], celiac disease [196,228], and multiple sclerosis [229]. More research is clearly needed to delineate the complex interactions of Vγ9/Vδ2 T cells (and other unconventional T cells) with different immune and non-immune cells, both locally and systemically, and define how such knowledge can be exploited for therapeutic interventions to either boost protective immune responses or suppress excessive inflammation.

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