

Review

From Host Defense to Metabolic Signatures: Unveiling the Role of $\gamma\delta$ T Cells in Bacterial Infections

Namya Nanda and Martin P. Alphonse * 

Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA; nnanda4@jh.edu

* Correspondence: malphon1@jhmi.edu

Abstract: The growth of antibiotic-resistant bacterial infections necessitates focusing on host-derived immunotherapies. $\gamma\delta$ T cells are an unconventional T cell subset, making up a relatively small portion of healthy circulating lymphocytes but a substantially increased proportion in mucosal and epithelial tissues. $\gamma\delta$ T cells are activated and expanded in response to bacterial infection, having the capability to produce proinflammatory cytokines to recruit neutrophils and clear infection. They also play a significant role in dampening immune response to control inflammation and protecting the host against secondary challenge, making them promising targets when developing immunotherapy. Importantly, $\gamma\delta$ T cells have differential metabolic states influencing their cytokine profile and subsequent inflammatory capacity. Though these differential metabolic states have not been well studied or reviewed in the context of bacterial infection, they are critical in understanding the mechanistic underpinnings of the host's innate immune response. Therefore, this review will focus on the context-specific host defense conferred by $\gamma\delta$ T cells during infection with *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, and *Mycobacterium tuberculosis*.

Keywords: $\gamma\delta$ T cells; immunometabolism; bacterial infection



Citation: Nanda, N.; Alphonse, M.P. From Host Defense to Metabolic Signatures: Unveiling the Role of $\gamma\delta$ T Cells in Bacterial Infections. *Biomolecules* **2024**, *14*, 225. <https://doi.org/10.3390/biom14020225>

Academic Editor: Ilan Bank

Received: 30 December 2023

Revised: 12 February 2024

Accepted: 12 February 2024

Published: 15 February 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

$\gamma\delta$ T cells are an unconventional T cell subset, making up about 1–5% of circulating lymphocytes in most healthy animal species [1]. However, in healthy mucosal or epithelial tissue, these cells can comprise up to 50% of the T cell population [2]. Furthermore, $\gamma\delta$ T cell population increases dramatically in response to invading pathogens [3]. Along with Mucosal associated invariant T cells (MAIT), Natural Killer T cells (NKT), and Intraepithelial lymphocytes (IEL), and other unconventional T cell subsets, $\gamma\delta$ T cells are non-MHC restricted, can recognize a host of diverse self- and foreign molecules, and have both innate and adaptive immune cell features [4].

$\gamma\delta$ T cells are classified by their TCR γ and TCR δ chain usage. In humans, this is primarily divided into V δ 1+ and V δ 2+ subsets, which arise during fetal development. V δ 1+ subsets typically associate with the V γ 1+ group, including V γ 2,3,4,5, and 8 [5], and are found in the mucosal epithelium [6,7]. V δ 2+ subsets typically only associate with the V γ 2+ group, including V γ 9 [5], and form the largest $\gamma\delta$ T cell population in the peripheral blood [6,7]. The functions of human V γ 9V δ 2+ T cells are well studied, including cytokine production, killing of infected target cells, regulation of monocyte and Dendritic cell (DC) differentiation and maturation, and antigen presentation [8–11].

In mice, however, $\gamma\delta$ T cells are classified primarily via their V γ chain expression and can be resident to specific tissues with non-redundant functions [12]. The first $\gamma\delta$ T cell population to arise in the thymus are V γ 5V δ 1 T cells, which migrate to the epidermis and become dendritic epidermal T cells (DETCs), a population not found in humans [13]. DETC progenitors are found between embryonic days 14–16 [14]. In the dermis, however, $\gamma\delta$ T cells are primarily V γ 6+, arising at around embryonic day 5, but found obviously

on day 3 in mice [12]. These cells are bona fide resident dermal cells and are essential in neonatal skin immunity [12]. $V\gamma 4+$ cells increase in number through development [12]. $V\gamma 4+$ $\gamma\delta$ T cells typically make $IFN\gamma$ cytokine, while $V\gamma 6+$ $\gamma\delta$ T cells typically make IL-17 and IL-22 [15]. Thymic signals regulate these cells' subsequent effector function and critical role during early infection stages [16].

$\gamma\delta$ T cells may also have memory functions, although it is unclear if these functions are entirely analogous to $\alpha\beta$ T cell memory functions [17–20]. Though not fully elucidated, human $V\gamma 9V\delta 2$ T cells respond to (E)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), an intermediate in the non-mevalonate (MEP) pathway of isoprenoid synthesis in some pathogenic bacterial species [8,9,21,22]; isopentenyl phosphate (IPP) an intermediate in the mevalonate pathway of isoprenoid synthesis [21]; and superantigens [23]. Other subsets of $\gamma\delta$ T cells respond to antigens such as CMV virus and MHC-related molecules [24].

$\gamma\delta$ T cells are thus important in understanding the host response to bacterial infection. Part of the host immune response includes metabolic reprogramming, coined as immunometabolism, driving subsequent cytokine, chemokine, and interferon responses [25]. This review aims to elucidate the immunometabolic role of $\gamma\delta$ T cells during *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, and *M. tuberculosis* infections, focusing on their contextual roles in pro- and anti-inflammatory signaling.

2. Immunometabolism of $\gamma\delta$ T Cells during Bacterial Infection

Murine $\gamma\delta$ T cells can be functionally divided into two subsets via the expression of CD27 and their subsequent metabolic states [26,27] (Figure 1A). CD27+ $\gamma\delta$ T cells are generally splenic-resident, ligand-experienced, and secrete $IFN\gamma$ [26,27]. Alternatively, CD27– $\gamma\delta$ T cells are found in the lymph nodes (LNs), are ligand naive, and secrete IL-17 [26,27]. The transcription factor c-Maf is an essential regulator of IL-17 producing $\gamma\delta$ T cells by increasing chromatin availability of genes involved in producing Th17 cytokines, *Rorc*, *Il17a*, and *Blk*, and downregulating *TCF1*, which limits IL-17 producing $\gamma\delta$ T cell differentiation [28]. These two cell sets have differential metabolic states established during thymic development [29]. $IFN\gamma$ producing cells are dependent on glycolysis, while IL-17-producing cells rely on oxidative phosphorylation [29], controlled by c-Maf regulation of rate-limiting enzyme isocitrate dehydrogenase 2 (IDH2) [30].

While glucose metabolic pathways may mark differential $\gamma\delta$ T cell subsets by cytokine production, lipid metabolic changes may impact the severity of inflammation in inflammatory disease (Figure 1B). In a psoriasis model, dietary cholesterol metabolites, such as oxysterol, regulate IL-17+ $\gamma\delta$ T cell development and trafficking to the skin, with a higher fat diet in mice being associated with more severe psoriasis [31]. Similarly, IL-17+ $\gamma\delta$ T cells had increased lipid metabolism and storage in murine breast adenocarcinoma, colon adenocarcinoma, and melanoma models [29].

Amino acid metabolism in T cells has been well studied, particularly in the context of cancer; however, recent studies aim to relate amino acid metabolism in $\gamma\delta$ T cells to changes in inflammation severity in psoriasis and polymicrobial sepsis (Figure 1C). For example, glutamine metabolism was upregulated in IL-17+ $\gamma\delta$ T cells during psoriasis, promoting acetylation of the *Il17a* promoter and increasing IL-17 production [32,33]. Additionally, CD69 interacted with the heterodimeric LAT1-CD98 amino acid transporter to upregulate tryptophan uptake during psoriasis, leading to mTORC- and AhR-mediated IL-22 production and increased inflammation [33]. Furthermore, glutamine metabolism is also implicated in mouse models of polymicrobial sepsis. Mice treated with glutamine administration had increased $\gamma\delta$ T cell populations, decreased inflammatory lesions, and reduced lung damage compared with mice treated with saline [34]. While these metabolic states were established and studied in both an inflammatory and tumor microenvironment, these metabolic changes have not yet been fully elucidated during bacterial infection. To this end, our lab is currently studying immunometabolic states of immune cells, including con-

ventional and unconventional T cell types, including $\gamma\delta$ T cell and MAIT cell populations, during *S. aureus* infection.

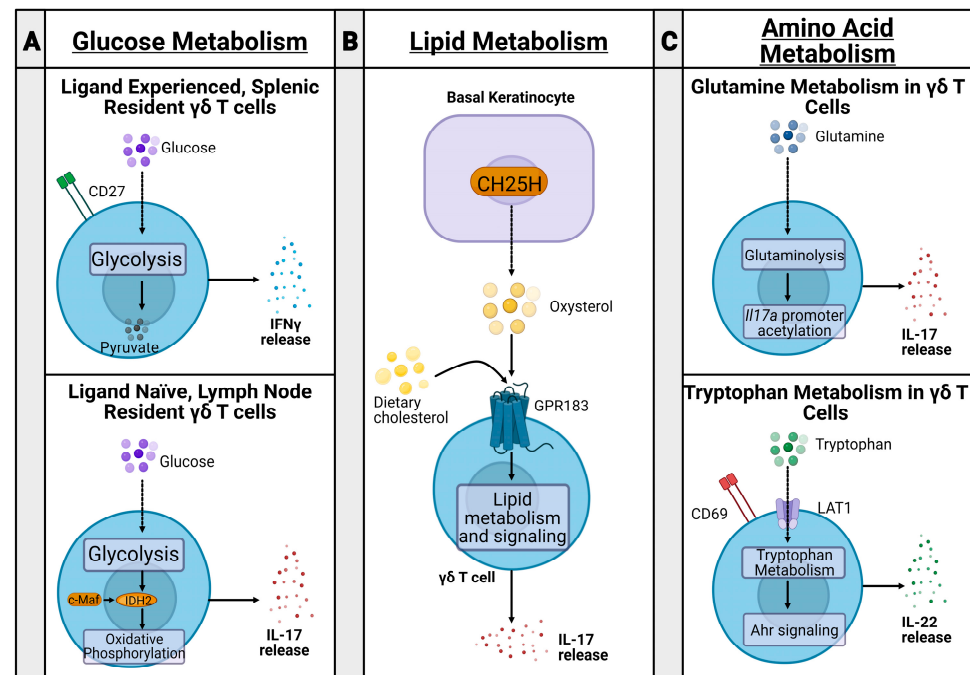


Figure 1. Immune metabolism of $\gamma\delta$ T cells. **(A)** CD27+ $\gamma\delta$ T cells are ligand-experienced and splenic resident. They undergo glycolysis after thymic development and release IFN γ . CD27− $\gamma\delta$ T cells, however, are ligand naïve and lymph node resident. They undergo oxidative phosphorylation, governed by c-Maf regulation of rate-limiting enzyme isocitrate dehydrogenase 2 (IDH2) and Th17 cytokine-producing genes *Rorc*, *Il17a*, and *Blk*. **(B)** In inflammatory psoriasis, basal keratinocytes produce oxysterols through the enzyme cholesterol-25-hydroxylase (CH25H). The oxysterols are ligands for the G-protein-coupled receptor GPR183 on $\gamma\delta$ T cells. Subsequent lipid metabolism and signaling leads to IL-17 release and inflammation. In a mouse model, dietary cholesterol contributes to this signaling cascade, worsening psoriasis. **(C)** During psoriasis, $\gamma\delta$ T cells undergo glutaminolysis, promoting subsequent acetylation of the *Il17a* promoter and releasing IL-17, increasing inflammation. CD69 and LAT1 expression on $\gamma\delta$ T cells promote tryptophan uptake and metabolism in psoriasis. The resulting Ahr signaling cascade leads to IL-22 release and increased inflammation.

3. Response of Human V γ 9V δ 2 T Cells to Phosphoantigens

Human V γ 9V δ 2 T cells have remarkably rapid responses to phosphoantigens. IPP, an intermediate in the mevalonate pathway of isoprenoid synthesis, is a stimulator of human V γ 9V δ 2 T cells, though less potent than HMB-PP [24]. Zoledronate (ZOL) and pamidronate (PAM) are aminobisphosphonate drugs and stimulators of human V γ 9V δ 2 T cells [35]. They work by inhibiting farnesyl diphosphate synthase, an enzyme that metabolizes IPP, which leads to an accumulation of IPP, and subsequent activation of V γ 9V δ 2 T cells [35]. The microbial side of $\gamma\delta$ T cell immunometabolism largely centers around HMB-PP, one of the most potent stimulators of human V γ 9V δ 2 T cells. HMB-PP is a microbial prenyl phosphate metabolite recognized as a pathogen-associated molecular pattern (PAMP) [35]. To be stimulated by HMB-PP, $\gamma\delta$ T cells require butyrophilin membrane proteins [36]. Phosphoantigens like HMB-PP interact with and bind to the B30.2 and juxtamembrane domains within the intracellular domain of BTN3A to modulate phosphoantigen sensing [35].

Furthermore, in V γ 9V δ 2 T cells, HMB-PP alone is not sufficient to trigger proliferation; IL-2, IL-17, IL-22, and IL-23 have all been implicated as co-stimulatory cytokines, with IL-23 co-stimulation seen during memory response challenge [36]. This expansion of V δ 2+ cells was found to be a marker for HMB-PP-producing bacterial infection, including *E. coli*,

K. pneumoniae, *P. aeruginosa*, *C. striatum*, and *L. monocytogenes*. It produced TNF α and IFN γ [8,22,37].

HMB-PP stimulated $\gamma\delta$ T cells are notably expanded during acute bacterial peritonitis in kidney disease patients [22]. In these patients, HMB-PP stimulated $\gamma\delta$ T cells underwent crosstalk with mesothelial cells and peritoneal fibroblasts to induce the proinflammatory response of CCL2, CXCL8, CXCL10, and IL-6 production [22]. These $\gamma\delta$ T cells promote short-term neutrophil survival and activation and respond further to neutrophil-phagocytosed bacteria through crosstalk with monocytes [8]. Cell-cell interactions are necessary for such crosstalk, and induce an APC-like phenotype in monocytes, characterized by upregulation of CD40, CD86, and HLA-DR, causing a subsequent inflammatory positive feedback loop [9]. Neutrophils stimulated by V δ 2+ $\gamma\delta$ T cells also obtained a unique APC-like phenotype, not found in other circulating neutrophils, again expressing CD40, CD64, CD86, HLA-DR, CD54, and HLA-ABC [38].

Interestingly, exposure to TNF α or IFN γ derived from HMB-PP stimulated $\gamma\delta$ T cell supernatant induced a morphological change in primary omentum-derived mesothelial cells, causing them to become fibroblastic, coupled with an upregulation of the mesenchymal marker fibronectin [22]. This cellular remodeling may impact the integrity of the peritoneal membrane and could explain increased peritoneal dialysis technique failure rates in patients with bacterial peritonitis [22], making $\gamma\delta$ T cell activation by HMB-PP a salient target for therapeutics. Taken in sum, evidence from initial studies marks $\gamma\delta$ T cell immunometabolism as a promising field of study in better understanding the microbe and subsequent host response to bacterial invasion.

4. The Site-Specific $\gamma\delta$ T Cell Response to *S. aureus* Infection

S. aureus is a gram-positive bacterium that is highly pathogenic and is the major cause of skin and soft tissue infection (SSTI), infective endocarditis, bone and joint infection, medical device-related infection, and bacteremia. [39]. Mainly, community-associated methicillin-resistant *S. aureus* (CA-MRSA) infection is a looming threat, claiming over 20,000 lives in the US annually [40]. Furthermore, vaccine efforts against *S. aureus* to date have been unsuccessful [41,42]. As a result, alternative approaches to combat the threat have become essential, and immunotherapies against *S. aureus* infection have emerged in recent years [43,44].

There are various non-pore-forming toxins, pore-forming toxins, and bacterial components from *S. aureus* that are antigenic to the host. $\gamma\delta$ T cells have been reportedly involved in early immune responses to *S. aureus* infection. $\gamma\delta$ T cells respond to staphylococcal superantigens, including staphylococcal enterotoxin A (SEA) and toxic shock syndrome toxin 1 (TSST-1) [45]. In conventional T cells, staphylococcal superantigens bind outside the MHCII-TCR antigen presenting complex, leading to rapid T cell expansion and inflammation [46].

In human adults, V γ 2+ T cell response and proliferation to SEA in specific requires APC presentation, particularly on MHC II [23,47]. SEA recognition requires the N terminal third of the toxin for partial $\gamma\delta$ T cell activity and the N terminal two-thirds of the protein for optimal activity, most critically needing amino acid residues 20–27 [23]. Subsequent reactivity to SEA was also dependent on and specific to the V γ 9 region of the TCR, which may explain why V γ 2+ cells are largely extrathymic [47].

The $\gamma\delta$ T cell cytokine response to superantigens primarily involves IFN γ and IL-17A. IFN γ production by $\gamma\delta$ T cells in response to SEA proceeds through an IL-12-dependent pathway and helps induce the expansion of memory-like CD45RO+ V γ 9V δ 2 T cells [41,45]. This finding was echoed in bovine WC1+ $\gamma\delta$ T cells [48]. On the other hand, SEA-induced IL-17A production by $\gamma\delta$ T cells has a unique role in lung host response. In a lung immunity model, Kumar and colleagues found that $\gamma\delta$ T cells were the primary source of proinflammatory cytokine IL-17A after the SEA challenge [49].

Interestingly, however, after the SEA challenge, there was no decrease in neutrophil and monocyte recruitment in TCR δ (–/–) mice, and $\alpha\beta$ T cells were found to be responsible

for neutrophil and monocyte recruitment to the infection site [49]. Neutrophil recruitment is critical for clearance of *S. aureus*: individuals with impaired neutrophil function or decreased neutrophil count display increased infection susceptibility [50]. Since IL-17A is known to play a critical role in neutrophil recruitment [51], the researchers hypothesized that IL-17A production was being compensated by CD3 + CD8 $\alpha\beta$ T cells in TCR $\delta(-/-)$ mice [49]. In a follow-up study, IL-17 producing $\gamma\delta$ T cells in the lung were termed lung granular $\gamma\delta$ T cells due to their increased side scatter measured during flow cytometry analysis [52]. Lung granular $\gamma\delta$ T cells were activated by inflammasome-derived IL-1 β and IL-2 to produce IL-17 in a JAK/STAT-dependent manner, marking a novel mechanism by which $\gamma\delta$ T cells respond to superantigen exposure [52]. Interestingly, this finding contrasts the widely accepted paradigm of IL-2 inhibition of Th17 differentiation [53], though the exact function of $\gamma\delta$ T cell-derived IL-17 in this context has not yet been elucidated.

Unlike SEA stimulation, TSST-1 stimulation of $\gamma\delta$ T cells upregulated secretion of proinflammatory cytokines IFN γ , TNF α , and IL-2 and suppressed anti-inflammatory IL-10 production [54]. This response was specific to TSST-1 stimulation and was not demonstrated in other staphylococcal toxins [54].

While staphylococcal superantigens were shown to activate the inflammatory response of $\gamma\delta$ T cells, *S. aureus* α toxin was contrastingly found to delay IL-17+ $\gamma\delta$ T cell recruitment to the infection site, slowing neutrophil recruitment and worsening infection in a mouse dermonecrosis model [55]. These studies indicate a critical role for $\gamma\delta$ T cells in activating or suppressing host immune responses against *S. aureus* in response to toxins the bacterium produces. The following section of the review will explore current literature elucidating the host $\gamma\delta$ T cell response to *S. aureus* in different infection sites and contexts.

4.1. Cutaneous Infection

Cutaneous $\gamma\delta$ T cells are important in early immune defense against *S. aureus* skin infection [56] (Figure 2). In a murine in vivo study of *S. aureus* skin infection, epidermal V γ 5+ $\gamma\delta$ T cells induced by IL-1R and IL-23 signaling were protective against worsened infection; $\gamma\delta$ T cell deficient mice had more significant lesion sizes, increased bacterial burdens, and lessened neutrophil recruitment and activity compared to both $\alpha\beta$ T cell deficient mice and wild type (WT) mice [57]. This protective role is mediated by IL-17 production. $\gamma\delta$ T cells comprise most of the IL-17-producing cells in *S. aureus*-infected skin [57,58]. Treatment of $\gamma\delta$ T cell-deficient mice with a single dose of IL-17 abrogated the detrimental effects of $\gamma\delta$ T cell deficiency [57]. IL-17+ $\gamma\delta$ T and Th17 cells also play a compensatory role, promoting neutrophil recruitment in IL-1 β deficient mice [59].

A study from our research group supported the importance of IL-17 producing $\gamma\delta$ T cell populations during *S. aureus* skin infection, finding that these cells were being trafficked from the LNs [60]. T cell receptor (TCR) RNA sequencing revealed clonotypic expansion of V γ 6+ V δ 4+ T cells but not V γ 5+ $\gamma\delta$ T cells in the skin and LNs [60]. This expansion was specific to *S. aureus* infection; however, during *P. aeruginosa* infection, both TRGV6 and V5 were expanded [60]. The trafficked V γ 6 + V δ 4+ T cells enhanced the neutrophilic response during secondary *S. aureus* infection in IL-1 β deficient mice [61]. These cells produced not only IL-17 but also other proinflammatory cytokines like TNF α , IL-22, and IFN γ [60]. IL-17A and IL-17F produced by LN-trafficked $\gamma\delta$ T cells have compensatory roles to one another in the skin, as they do during mucocutaneous *S. aureus* infection [62]. Both cytokines had to be neutralized to note any differences in mouse lesion size or bacterial burden after cutaneous *S. aureus* infection [60]. While IL-17 plays a critical role in $\gamma\delta$ T cell signaling in cutaneous infection, it is important to note that this is not the case in all infection contexts. For example, response to early IL-1R signaling, but surprisingly not IL-17 or TNF α signaling, in $\gamma\delta$ T cells promotes host survival and monocyte recruitment to the spleen in an *S. aureus*-induced bacteremia model [63].

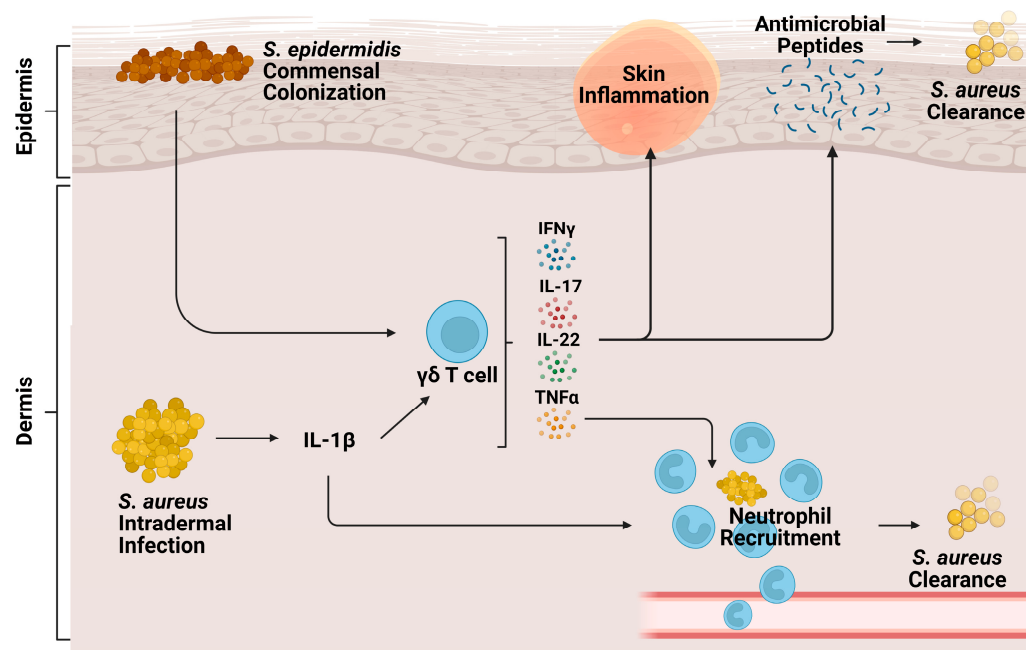


Figure 2. Role of $\gamma\delta$ T cells during cutaneous *S. aureus* infection. Intradermal *S. aureus* infection and subsequent IL-1 β signaling stimulate cutaneous $\gamma\delta$ T cells to produce proinflammatory cytokines IFN γ , TNF α , IL-22, and IL-17. These cytokines contribute to neutrophil recruitment, production of antimicrobial peptides, skin inflammation, and eventual bacterial clearance. Commensal *S. epidermidis*, skin colonization, stimulates $\gamma\delta$ T cells to produce perforin-2, a pore-forming cytolyisin that helps clear *S. aureus* infection.

$\gamma\delta$ T cells also have memory-like function during skin inflammation and *S. aureus* infection [61,64]. In an imiquimod model of inflammation, IL-17 producing V γ 4+ $\gamma\delta$ T cells leave the LNs and are trafficked to the skin, with previously sensitized mice showing more significant $\gamma\delta$ T cell-induced inflammation proliferation and IL-17 production, indicating a memory-like role [64]. In the context of *S. aureus* infection, our colleagues found that while the primary challenge of IL-1 β deficient mice led to decreased bacterial clearance, greater lesions, and impaired neutrophil abscess formation, these functions were restored upon secondary infection by LN draining $\gamma\delta$ T cells through TLR2/MyD88 signaling to produce IFN γ and TNF [61]. Overall, inflammatory cytokine production in the skin by LN-draining $\gamma\delta$ T cells seems to confer protective immunity against primary and secondary *S. aureus* infections.

Along with inherent host protective responses to *S. aureus* infection, commensal bacteria may protect the host against *S. aureus* infection by driving host antimicrobial peptide production by $\gamma\delta$ T cells [65]. One study finds that *S. epidermidis* commensal colonization of the skin induces $\gamma\delta$ T cells to upregulate perforin-2 expression, a cytolyisin constitutively expressed by $\gamma\delta$ T cells to form pores in bacterial membranes [66], along with upregulating other cytotoxicity markers against MRSA infection [67]. As such, *S. epidermidis* co-colonization with *S. aureus* on the skin led to an increased anti-*S. aureus* effect [67].

Lactobacilli have also been identified as commensal bacteria that may modulate host immune protection (Figure 2). One study found that in vitro co-colonization of human PBMCs with *S. aureus* and Lactobacillus strains dampened IFN γ secretion in $\gamma\delta$ T cells, MAIT cells, and NK cells stimulated by *S. aureus* cell free supernatants [68]. However, recent other studies utilize Lactobacillus recombinant strains as vaccine models against *S. aureus* due to the commensal bacteria's ability to induce a robust immune response [69,70]. Thus, it is evident that during *S. aureus* infection, lactobacilli have differential effects in vitro versus in vivo and must be studied contextually.

4.2. Pneumonia

In the lung, the major subsets of $\gamma\delta$ T cells are V γ 1+ and V γ 4+ and accumulate after *S. aureus*-induced pneumonia [71]. While murine $\gamma\delta$ T cells are involved in decreasing the bacterial burden and increasing neutrophil infiltration, with corresponding increases in keratinocyte-derived chemokine (KC), MIP2, GM-CSF, IL-6, and TNF α , acute lung damage was decreased in $\gamma\delta$ T cell deficient mice, likely due to tamped inflammation from reduced neutrophil recruitment [71]. An early burst of $\gamma\delta$ T cell-produced IL-17 was also implicated in increased lung damage post-pneumonia [71], indicating a possibly detrimental role for $\gamma\delta$ T cells in this model.

Interestingly, nociceptor sensory neurons in the lung may have an immunosuppressive role on pulmonary $\gamma\delta$ T cell function during MRSA infection. Selective ablation of TRPV1+, an ion channel expressed on nociceptors mediating airway allergic pathways, increased absolute V γ 1+ $\gamma\delta$ T cell population, increased survival, and increased bacterial clearance [72]. This neuroimmunological finding is important as it marks sensory neurons as targets to protect against *S. aureus* pneumonia.

Cell death pathways, including the necroptotic pathway, may also suppress the host immune response against *S. aureus*-induced pneumonia by targeting IL-17 signaling by lung $\gamma\delta$ T cells [73]. α toxin from *S. aureus* is known to activate the NLRP3 inflammasome in vitro [74]. NLRC4, an NLR family protein involved in inflammasome assembly, is upregulated during *S. aureus*-induced pneumonia in myeloid and non-myeloid cells [73]. Furthermore, α toxin from *S. aureus* induces necroptosis leading to increased IL-18 and IL-1 β production and suppressed $\gamma\delta$ T cell recruitment, dampening the IL-17 response, leading to decreased neutrophil recruitment and inflammation [73]. However, necroptotic suppression of IL-17 response is site-specific; in a surgical site *S. aureus* infection model, IL-17 producing $\gamma\delta$ T cells at the wound site relied by NLRP3/IL-1 β signaling for IL-17A production. It is interesting to note that these observed during infection with SH1000 *S. aureus* strain, but not PS80 [37].

Therefore, the pneumonia model indicates the necessity of balance in the $\gamma\delta$ T cell response; too much IL-17 signaling may lead to excessive inflammation and tissue damage, while too little may hinder bacterial clearance.

4.3. Peritonitis

Similar to cutaneous and pulmonary infection, $\gamma\delta$ T cells are the primary source of IL-1 β -dependent IL-17 in a primary challenge during a recurrent peritonitis murine model of *S. aureus* infection [18]. Some mice in this study were also found to have a biphasic wave of IL-17 production, with one peak at 3 h and the second at 72 h post-infection, with V γ 4+ $\gamma\delta$ T cells at 72 h being primed for later infection and IL-1 β independent IL-17 production [18], suggesting a memory function for $\gamma\delta$ T cells during acute peritonitis as well. In the kidney, chronic systemic *S. aureus* infection induced the expansion of a population of kidney-resident $\gamma\delta$ T cells that constitutively express CD69 and provide protection against *S. aureus* [15]. Thus, in mice, *S. aureus* infection seems to expand both resident and memory $\gamma\delta$ T cells.

In human peritoneal dialysis (PD) patients, on the other hand, it is unclear whether *S. aureus*-induced peritonitis expands $\gamma\delta$ T cells or not. In one study, peritoneal V δ 2+ $\gamma\delta$ T cells were reduced during acute peritonitis [37]. However, this was not specific to *S. aureus*-induced peritonitis and was used partially as an immune fingerprint to classify gram-positive acute peritonitis [37]. On the other hand, other studies found V δ 2+ $\gamma\delta$ T cell recruitment and response to *S. aureus*-induced peritonitis in PD patients, possibly due to superantigen recognition [22,23].

5. $\gamma\delta$ T Cell Response during *S. pneumoniae* Infection

S. pneumoniae infection is the leading cause of community-acquired pneumonia, meningitis, and bacteremia, inflicting a heavy disease burden [75]. Despite vaccination against *S. pneumoniae*, multidrug-resistant bacterial infections run rampant, causing 19,336 hospi-

talizations in the US annually and millions of dollars in medical and other costs [76]. The immune response to *S. pneumoniae* infection utilizes neutrophil recruitment, subsequent accumulation in the alveolar spaces, and killing through both phagocytosis and, more critically, degranulation [77,78]. Proinflammatory cytokine synthesis and release induced by V α 14+ NKT cells, another unconventional T cell subset, has been shown to promote rapid neutrophil recruitment to the infection site [79]. Alveolar macrophages function to control the resolution of inflammation [80]. $\gamma\delta$ T cells have also been critically implicated during innate immune response to *S. pneumoniae* in the lung.

S. pneumoniae infection stimulated human peripheral V γ 9V δ 2 T cells in an in vitro study [81]. In mice, however, V γ 4+ $\gamma\delta$ T cells accumulated in the lungs after pulmonary infection [78] due to their lung-homing capability [82]. TCR V γ 4(−/−) mice had increased bacterial burden, increased mortality, decreased neutrophil accumulation, and decreased TNF α and MIP2 production early after *S. pneumoniae* infection, indicating a role for $\gamma\delta$ T cells during initial innate immunity [78]. In the lung, V γ 4+ $\gamma\delta$ T cells produce IL-17 in response to infection [82]. IL-17 production was stimulated by IL-23 and IL-1 β , further recruiting neutrophils [83]. Neutrophils, via NLRP3 inflammasome activation, were in turn the greatest source of IL-1 β in the interstitial area of the lung, activated by alveolar macrophage-derived TNF α and pneumolysin, a pore-forming virulence toxin [83].

The lung $\gamma\delta$ T cell population is regulated to prevent excess inflammation. IL-17-producing $\gamma\delta$ T cells are regulated by *S. pneumoniae*-activated regulatory T cells with up-regulated TNFR2; lack of TNFR2 caused a dysregulated IL-17 response and increased lung damage due to excessive inflammation [84]. The lung's inflammatory state may also regulate $\gamma\delta$ T cell responses [85]. In one study, mice deficient in SOD3, the main enzyme involved in clearing damaging ROS, had increased phagosomal ROS levels [85]. This led to early neutrophil apoptosis in *S. pneumoniae* infection, thereby hampering the subsequent pro-inflammatory $\gamma\delta$ T cell response [85]. As such, the above data suggest that $\gamma\delta$ T cells have a regulated proinflammatory role during early *S. pneumoniae* clearance in the lung.

$\gamma\delta$ T cells have also been found to play an important part in inflammation resolution during *S. pneumoniae* infection. In a murine model, the lung $\gamma\delta$ T cell population increased by 30 fold, 7–10 days post-challenge, when no more bacterial burden was detectable [80], indicating that these cells were not involved in bacterial clearance. Instead, lung $\gamma\delta$ T cells were cytotoxic towards both naive and challenged host-derived inflammatory alveolar macrophages and pulmonary dendritic cells, thus aiding in dampening inflammation [80], similar to *S. aureus*-induced pneumonia [71]. $\gamma\delta$ T cells are also involved in non-bacterial inflammation resolution in the lungs, interacting with M2 macrophages to promote clearance of apoptotic cells during ozone-induced pulmonary inflammation [86]. In summary, early $\gamma\delta$ T cell response to *S. pneumoniae* promotes neutrophil recruitment and bacterial clearance, while an end-stage response assists more during the resolution phase of infection.

6. $\gamma\delta$ T Cell Response during *L. monocytogenes* Infection

L. monocytogenes is one of the deadliest food-borne pathogens and can cause listeriosis, which results in a 90% hospitalization rate [87]. V γ 9V δ 2+ T cells have a site-specific proliferative response in the liver and spleen to secreted ligands from the bacterium, indicating a possible role for $\gamma\delta$ T cells during immunity [88,89]. HMB-PP is a particularly potent stimulator of human V γ 9V δ 2+ T cells. *L. monocytogenes* undergoes both the mevalonate and non-mevalonate pathways for isoprenoid biosynthesis, producing both IPP and HMB-PP. However, HMB-PP affects a greater response in $\gamma\delta$ T cell expansion [90,91]. This is evidenced by the finding that in vitro, human V γ 9V δ 2+ T cells were more bioactive when co-cultured with an *L. monocytogenes* mutant strain with a deficiency in the LytB (HMB-PP reductase) enzyme leading to HMB-PP overproduction [90]. HMB-PP is also important in developing V γ 9V δ 2 T cells with a memory phenotype, which was demonstrated in a macaque model using an attenuated *L. monocytogenes* immunization [91].

$\gamma\delta$ T cell activation seems to have a protective role against *L. monocytogenes* infection, though the exact $\gamma\delta$ subset involved is unclear. In a murine intraperitoneal infection model,

administration of an anti-V γ 1 antibody led to increased bacterial burden in the spleen and liver, indicating a role for V γ 1V δ 6+ T cells during early infection in mice [92]. In contrast, another study found that, despite an overall increase in $\gamma\delta$ T cell population after *L. monocytogenes* infection, there was a relative decrease in the frequency of V γ 1+ $\gamma\delta$ T cells in the liver, while V γ 6+ T cells increased in frequency [93]. In another inflammation study, V γ 6+ $\gamma\delta$ T cells also seemed to have a proportionally increased response compared to other $\gamma\delta$ T cell subsets [94].

Intravenous injection of *L. monocytogenes* into a lateral tail vein led to $\gamma\delta$ T cell activation, which, though non-essential for survival, helped control the inflammatory response in the liver by promoting macrophage influx via MCP-1 production and reducing neutrophil influx [95]. $\alpha\beta$ T cells, as opposed to $\gamma\delta$ T cells, are critical in survival and protection against necrotic hepatitis [95]. During early infection, IL-17-producing $\gamma\delta$ T cells are vital in cytotoxic T cell recruitment. They act on dendritic cells to upregulate MHC I, increasing the production of IL-12, IL-6, and IL-1 β , thus leading to the cross-priming and proliferation of CD8+ T cells [59]. In the murine liver, these early IL-17-producing cells are activated by IL-23 from macrophages or dendritic cells, express V γ 4 or V γ 6, and are involved not only in neutrophil recruitment and host protection but also in negatively regulating granuloma formation [59]. V γ 6V δ 1 T cells, in specific, play a protective role during infection and produce IFN γ along with IL-17 [96]. On the other hand, V γ 4+ $\gamma\delta$ T cells are protective against CD8+ T cell-mediated liver injury in an IL-10-dependent fashion by controlling TNF α production and dysregulation [97]. IL-10 production in this context occurs in response to signaling from activated splenic macrophages and *L. monocytogenes*-elicited CD8+ T cells.

$\gamma\delta$ T cells have also been shown to have an immunomodulatory response during *L. monocytogenes* infection. Infection in TCR δ deficient mice led to an accumulation of activated macrophages and neutrophils in the infected mice's peritoneum, leading to overwhelming hepatic necrosis [98], indicating a suppressive role for $\gamma\delta$ T cells. Macrophages had decreased apoptosis in TCR δ deficient mice, indicating that $\gamma\delta$ T cells are cytotoxic towards macrophages via either the TNF α or the Fas pathway towards the end of *L. monocytogenes* infection [98]. The binding between $\gamma\delta$ T cells and macrophages is TCR-mediated [99].

During *L. monocytogenes* infection, $\gamma\delta$ T cells also have memory functions. In a mouse oral inoculation model that closely replicates human enteric *L. monocytogenes* infection, mesenteric lymph node-derived V γ 4V δ 1 T cells produced both IL-17A and IFN γ and were identified as a unique CD27[−]CD44^{hi} memory subset that persisted for at least 5 months and launched a robust and rapid proliferative response to secondary challenge [19]. Though it is unclear what causes this memory-like expansion, the secondary memory response was infection route dependent; intravenous infection of mice did not elicit a similar $\gamma\delta$ T cell expansion and response [19]. A subsequent study found that V γ 4+ $\gamma\delta$ T cells were bona fide resident memory T cells, expressing gut-homing genes like integrin b7, CCR2, CCR5, CXCR3, and CXCR6 [20]. Though these cells had restricted motility, they rapidly formed clusters with neutrophils and monocytes in an IL-17-dependent manner at bacterial replication foci to quickly clear infection after a secondary challenge [20]. A similar $\gamma\delta$ T cell population was found in an imiquimod sensitization model of psoriasis, in which they produced elevated levels of IL-17, upregulated IL-1R1 expression, and increasingly responded to IL-1 β stimulation [64]. Interestingly, memory V γ 4+ $\gamma\delta$ T cells were resistant to cellular senescence [100]. Their adaptive-like response to food-borne *L. monocytogenes* infection increased with age, making these memory T cells an essential target for antibacterial therapies in elderly patients [100]. Thus, $\gamma\delta$ T cells have multi-faceted functions, including early protection, inflammatory resolution, and memory functions, during *L. monocytogenes* infection.

7. $\gamma\delta$ T Cell Response during *M. tuberculosis* Infection

Tuberculosis is the leading cause of death worldwide from a single infectious agent, primarily due to latent tuberculosis infection [101]. In *M. tuberculosis*-infected lung cells, $\gamma\delta$ T cells produce IL-17, dependent upon IL-23 production from infected dendritic cells

in mice, and IL-2 co-stimulation and HMB-PP stimulation in primates [36,102,103]. Post expansion, IL-17 producing $\gamma\delta$ T cells upregulate expression of ICAM-1 and LFA-1 in macrophages [104,105]. ICAM-1 and LFA-1 are involved in forming granulomas in the lung, thereby helping to sequester and kill the mycobacteria [104,105]. $\gamma\delta$ T cell expansion also led to IL-12 production, enhancing the Th1 cytokine response of Ag-specific CD4 and CD8 T cells [36,103]. Macrophages have been implicated in the chemotaxis of $\gamma\delta$ T cells to the infection site via secretion of IP-10, inducing changes in chemokine expression pattern [106]; after being trafficked to the pulmonary compartment, V γ 9V δ 2 T cells can differentiate into IFN γ -, perforin-, and granzyme-producing cells, thus reducing bacterial burden and increasing immune resistance against *M. tuberculosis* [36,103].

In vitro, HMB-PP-stimulated expansion and effector function are also driven by Th17 cytokines, particularly IL-23 [107]. In one study, IL-2 facilitated IL-23 mediated expansion of HMB-PP stimulated V γ 9V δ 2 T cells from human patients with latent tuberculosis infection [108]. However, tuberculosis infection also selectively impaired IL-23 stimulated expansion during human latent tuberculosis by inhibiting JAK-STAT signaling, leading to loss of effector function and cytokine production [108]. This indicates a mechanism by which *M. tuberculosis* can suppress infection clearance. Specifically, miRNAs hsa-miR-337-3p and hsa-miR-125b-5p were found to be upregulated during tuberculosis infection, inhibiting STAT3 expression and IL-23 stimulated $\gamma\delta$ T cell expansion; silencing of these miRNAs restored expansion [108]. *M. tuberculosis* infection may also site-specifically impair V γ 9V δ 2 T cell activation in response to antigen recognition. In human tuberculosis patients, $\gamma\delta$ T cells isolated from bronchoalveolar lavage had downmodulation of CD3 ϵ , as compared to $\gamma\delta$ T cells from the peripheral blood [109]. Therefore, the *M. tuberculosis* model represents an arms race between the bacteria and the corresponding innate immune response.

8. Future Clinical Role for $\gamma\delta$ T Cells

Given the immunoprotective role of $\gamma\delta$ T cells, several new therapies have emerged involving stimulation of $\gamma\delta$ T cell expansion. $\gamma\delta$ T cell-related therapeutics have to date primarily focused on anti-cancer therapeutics. Initially, bisphosphonate-based drugs, such as PAM, ZOL, and IL-2, were found to stimulate V γ 9V δ 2 T cells but were not clinically effective in cancer models [110]. However, due to MHC independence and lessened graft vs. host disease risk, $\gamma\delta$ T cells have been identified as a potential target for allogeneic T cell transfer immunotherapy in many cancer states [110,111]. In fact, an ongoing clinical trial is using an expanded $\gamma\delta$ T cell infusion intending to increase host defense in leukemia and myelodysplastic patients while reducing the risk of graft vs. host disease seen in conventional bone marrow transplants [110], (Clinical trial ID: NCT03533816). Additionally, induced pluripotent stem cell-derived CAR-modified $\gamma\delta$ T cells seem to be effective against tumors in a xenograft mouse model, and there are several commercial entities now developing CAR $\gamma\delta$ T cell therapies [110]. A recent murine study found that genetically modified $\gamma\delta$ T cells that expressed NY-ESO-1 (a cancer-testis antigen widely expressed in a number of cancers) specific $\alpha\beta$ TCR are effective in killing NY-ESO-1 expressing tumors [112]. Interestingly, these $\alpha\beta$ T cell-transduced $\gamma\delta$ T cells seemed to undergo oxidative phosphorylation at a higher rate, with IFN γ production being dependent on ATP production [112]. Mitochondria have been demonstrated to play an important role in sustained CD8 T cell cytotoxicity [113], which may apply to these $\alpha\beta$ T cell transduced $\gamma\delta$ T cells as well. Though a further examination of the metabolic state of $\gamma\delta$ T cells in therapeutic models is required, it could further our understanding of $\gamma\delta$ T cell-mediated cytotoxicity, as demonstrated in cancer models.

Apart from cancer models, vaccine development in nonhuman primate tuberculosis models is currently ongoing and focuses on stimulating V γ 9V δ 2 T cells via phosphoantigen delivery. ZOL, in particular, is known to expand $\gamma\delta$ T cells, and initial studies focused on adequately promoting $\gamma\delta$ T cells to use during immunization. In vitro, ZOL coupled with IL-2 (ZOL/IL-2) stimulation was found to expand IFN γ and TNF α producing $\gamma\delta$ T cells [114]. Direct ZOL/IL-2 administration led to an in vivo expansion of V γ 9V δ 2 T cells

during multidrug-resistant *M. tuberculosis* infection [36,114]. These cells then traveled to the pulmonary compartment, producing IFN γ , perforin, and TNF α , thereby decreasing bacterial burden and disease state [36,114]. An initial proof of concept study then found that adoptive transfer of ZOL/IL-2-expanded V γ 9V δ 2 T cells in macaques infected with *M. tuberculosis* had reduced bacterial burden in the lung and reduced bacterial dissemination [115]. In another study, a mutant HMB-PP-producing *L. monocytogenes* vector was used to selectively immunize V γ 9V δ 2 T cells, which conferred protection against *M. tuberculosis* in macaques [116]. Vaccine development efforts against *M. tuberculosis* are a promising yet ongoing field of research.

There is also increasing evidence for bisphosphonate-based drugs as an immunotherapy in other bacterial infection states. ZOL activates circulating $\gamma\delta$ T cells via monocyte accumulation of IPP and its stereoisomer DMAPP [35,117]. In one study, human septic PBMCs treated with ZOL led to monocyte activation, marked by upregulated HLA-DR, CD40, and CD64, allowing for downstream activation of V γ 9V δ 4 $\gamma\delta$ T cells [118]. PAM, a known safe human V γ 9V δ 2 T cell-specific aminobisphosphonate drug [119], may also be a promising therapeutic agent. A chimeric SCID mouse model was used to elucidate the role of memory V γ 9V δ 2 T cells in antibacterial resistance, finding that treatment with PAM rendered PBMCs 100x more efficient in clearing both *S. aureus* and *E. coli* infection [120].

9. Conclusions

In summary, this review outlines the critical role of $\gamma\delta$ T cells during bacterial infection, focusing on the microenvironment and promising advances in studying immune metabolism. $\gamma\delta$ T cells are part in all stages of infection—early defense, inflammatory resolution, and defense during reinfection—making these unconventional T lymphocytes a potential target for therapeutics against hard-to-treat bacterial infection. As such, further research must focus on utilizing $\gamma\delta$ T cells in immunotherapies to provide lasting protection against the threat of antibiotic-resistant microbes.

Author Contributions: Conceptualization, M.P.A.; writing—original draft preparation, N.N.; writing—review and editing, N.N. and M.P.A. visualization, N.N. and M.P.A.; supervision, M.P.A.; funding acquisition, M.P.A. All authors have read and agreed to the published version of the manuscript.

Funding: MPA is funded by Research Career Development Award from Dermatology Foundation, USA (Funding number: 140819-22043024).

Conflicts of Interest: The authors declare no conflict of interest.

References

- Carding, S.R.; Egan, P.J. $\gamma\delta$ T Cells: Functional Plasticity and Heterogeneity. *Nat. Rev. Immunol.* **2002**, *2*, 336–345. [\[CrossRef\]](#)
- Kabelitz, D.; Wesch, D.; Hinz, T. Gamma Delta T Cells, Their T Cell Receptor Usage and Role in Human Diseases. In *Springer Seminars in Immunopathology*; Springer International: Berlin, Germany, 1999; Volume 21, pp. 55–75.
- Brown, A.F.; Murphy, A.G.; Lalor, S.J.; Leech, J.M.; O’Keeffe, K.M.; Mac Aogáin, M.; O’Halloran, D.P.; Lacey, K.A.; Tavakol, M.; Hearnden, C.H.; et al. Memory Th1 Cells Are Protective in Invasive *Staphylococcus aureus* Infection. *PLoS Pathog.* **2015**, *11*, e1005226. [\[CrossRef\]](#)
- Mayassi, T.; Barreiro, L.B.; Rossjohn, J.; Jabri, B. A Multilayered Immune System through the Lens of Unconventional T Cells. *Nature* **2021**, *595*, 501–510. [\[CrossRef\]](#) [\[PubMed\]](#)
- Wesch, D. Analysis of the TCR Vgamma Repertoire in Healthy Donors and HIV-1-Infected Individuals. *Int. Immunol.* **1998**, *10*, 1067–1075. [\[CrossRef\]](#) [\[PubMed\]](#)
- Lee, D.; Rosenthal, C.J.; Penn, N.E.; Dunn, Z.S.; Zhou, Y.; Yang, L. Human $\gamma\delta$ T Cell Subsets and Their Clinical Applications for Cancer Immunotherapy. *Cancers* **2022**, *14*, 3005. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zhao, Y.; Lin, L.; Xiao, Z.; Li, M.; Wu, X.; Li, W.; Li, X.; Zhao, Q.; Wu, Y.; Zhang, H.; et al. Protective Role of $\gamma\delta$ T Cells in Different Pathogen Infections and Its Potential Clinical Application. *J. Immunol. Res.* **2018**, *2018*, 5081634. [\[CrossRef\]](#) [\[PubMed\]](#)
- Davey, M.S.; Lin, C.-Y.; Roberts, G.W.; Heuston, S.; Brown, A.C.; Chess, J.A.; Toleman, M.A.; Gahan, C.G.M.; Hill, C.; Parish, T.; et al. Human Neutrophil Clearance of Bacterial Pathogens Triggers Antimicrobial $\gamma\delta$ T Cell Responses in Early Infection. *PLoS Pathog.* **2011**, *7*, e1002040. [\[CrossRef\]](#)
- Eberl, M.; Roberts, G.W.; Meuter, S.; Williams, J.D.; Topley, N.; Moser, B. A Rapid Crosstalk of Human $\gamma\delta$ T Cells and Monocytes Drives the Acute Inflammation in Bacterial Infections. *PLoS Pathog.* **2009**, *5*, e1000308. [\[CrossRef\]](#)

10. Leslie, D.S.; Vincent, M.S.; Spada, F.M.; Das, H.; Sugita, M.; Morita, C.T.; Brenner, M.B. CD1-Mediated γ/δ T Cell Maturation of Dendritic Cells. *J. Exp. Med.* **2002**, *196*, 1575–1584. [\[CrossRef\]](#)
11. Skeen, M.J.; Freeman, M.M.; Ziegler, H.K. Changes in Peritoneal Myeloid Populations and Their Proinflammatory Cytokine Expression during Infection with *Listeria monocytogenes* Are Altered in the Absence of Gamma/Delta T Cells. *J. Leukoc. Biol.* **2004**, *76*, 104–115. [\[CrossRef\]](#)
12. Cai, Y.; Xue, F.; Fleming, C.; Yang, J.; Ding, C.; Ma, Y.; Liu, M.; Zhang, H.; Zheng, J.; Xiong, N.; et al. Differential Developmental Requirement and Peripheral Regulation for Dermal V γ 4 and V γ 6T17 Cells in Health and Inflammation. *Nat. Commun.* **2014**, *5*, 3986. [\[CrossRef\]](#)
13. Vermijlen, D.; Prinz, I. Ontogeny of Innate T Lymphocytes—Some Innate Lymphocytes Are More Innate than Others. *Front. Immunol.* **2014**, *5*, 486. [\[CrossRef\]](#)
14. Sutoh, Y.; Mohamed, R.H.; Kasahara, M. Origin and Evolution of Dendritic Epidermal T Cells. *Front. Immunol.* **2018**, *9*, 1059. [\[CrossRef\]](#)
15. Bertram, T.; Reimers, D.; Lory, N.C.; Schmidt, C.; Schmid, J.C.; Heinig, L.; Bradtke, P.; Rattay, G.; Zielinski, S.; Hellmig, M.; et al. Kidney-Resident Innate-like Memory $\gamma\delta$ T Cells Control Chronic *Staphylococcus aureus* Infection of Mice. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2210490120. [\[CrossRef\]](#)
16. Fiala, G.J.; Gomes, A.Q.; Silva-Santos, B. From Thymus to Periphery: Molecular Basis of Effector $\gamma\delta$ -T Cell Differentiation. *Immunol. Rev.* **2020**, *298*, 47–60. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Zheng, J.; Liu, Y.; Lau, Y.-L.; Tu, W. $\gamma\delta$ -T Cells: An Unpolished Sword in Human Anti-Infection Immunity. *Cell. Mol. Immunol.* **2013**, *10*, 50–57. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Murphy, A.G.; O’Keeffe, K.M.; Lalor, S.J.; Maher, B.M.; Mills, K.H.G.; McLoughlin, R.M. *Staphylococcus aureus* Infection of Mice Expands a Population of Memory $\gamma\delta$ T Cells That Are Protective against Subsequent Infection. *J. Immunol.* **2014**, *192*, 3697–3708. [\[CrossRef\]](#)
19. Sheridan, B.S.; Romagnoli, P.A.; Pham, Q.-M.; Fu, H.-H.; Alonzo, F.; Schubert, W.-D.; Freitag, N.E.; Lefrançois, L. $\gamma\delta$ T Cells Exhibit Multifunctional and Protective Memory in Intestinal Tissues. *Immunity* **2013**, *39*, 184–195. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Romagnoli, P.A.; Sheridan, B.S.; Pham, Q.-M.; Lefrançois, L.; Khanna, K.M. IL-17A-Producing Resident Memory $\gamma\delta$ T Cells Orchestrate the Innate Immune Response to Secondary Oral *Listeria monocytogenes* Infection. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 8502–8507. [\[CrossRef\]](#) [\[PubMed\]](#)
21. Morita, C.T.; Jin, C.; Sarikonda, G.; Wang, H. Nonpeptide Antigens, Presentation Mechanisms, and Immunological Memory of Human V γ 2V δ 2 T Cells: Discriminating Friend from Foe through the Recognition of Prenyl Pyrophosphate Antigens. *Immunol. Rev.* **2007**, *215*, 59–76. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Liuzzi, A.R.; Kift-Morgan, A.; Lopez-Anton, M.; Friberg, I.M.; Zhang, J.; Brook, A.C.; Roberts, G.W.; Donovan, K.L.; Colmont, C.S.; Toleman, M.A.; et al. Unconventional Human T Cells Accumulate at the Site of Infection in Response to Microbial Ligands and Induce Local Tissue Remodeling. *J. Immunol.* **2016**, *197*, 2195–2207. [\[CrossRef\]](#)
23. Morita, C.T.; Li, H.; Lamphear, J.G.; Rich, R.R.; Fraser, J.D.; Mariuzza, R.A.; Lee, H.K. Superantigen Recognition by $\gamma\delta$ T Cells. *Immunity* **2001**, *14*, 331–344. [\[CrossRef\]](#)
24. Vermijlen, D.; Gatti, D.; Kouzeli, A.; Rus, T.; Eberl, M. $\gamma\delta$ T Cell Responses: How Many Ligands Will It Take till We Know? In *Seminars in Cell & Developmental Biology*; Academic Press: Cambridge, MA, USA, 2018; Volume 84, pp. 75–86. [\[CrossRef\]](#)
25. Rosenberg, G.; Riquelme, S.; Prince, A.; Avraham, R. Immunometabolic Crosstalk during Bacterial Infection. *Nat. Microbiol.* **2022**, *7*, 497–507. [\[CrossRef\]](#)
26. Jensen, K.D.C.; Su, X.; Shin, S.; Li, L.; Youssef, S.; Yamasaki, S.; Steinman, L.; Saito, T.; Locksley, R.M.; Davis, M.M.; et al. Thymic Selection Determines $\gamma\delta$ T Cell Effector Fate: Antigen-Naive Cells Make Interleukin-17 and Antigen-Experienced Cells Make Interferon γ . *Immunity* **2008**, *29*, 90–100. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Ribot, J.C.; deBarros, A.; Pang, D.J.; Neves, J.F.; Peperzak, V.; Roberts, S.J.; Girardi, M.; Borst, J.; Hayday, A.C.; Pennington, D.J.; et al. CD27 Is a Thymic Determinant of the Balance between Interferon- γ - and Interleukin 17-Producing $\gamma\delta$ T Cell Subsets. *Nat. Immunol.* **2009**, *10*, 427–436. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Zuberbuehler, M.K.; Parker, M.E.; Wheaton, J.D.; Espinosa, J.R.; Salzler, H.R.; Park, E.; Ciofani, M. The Transcription Factor C-Maf Is Essential for the Commitment of IL-17-Producing $\gamma\delta$ T Cells. *Nat. Immunol.* **2019**, *20*, 73–85. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Lopes, N.; McIntyre, C.; Martin, S.; Raverdeau, M.; Sumaria, N.; Kohlgruber, A.C.; Fiala, G.J.; Agudelo, L.Z.; Dyck, L.; Kane, H.; et al. Distinct Metabolic Programs Established in the Thymus Control Effector Functions of $\gamma\delta$ T Cell Subsets in Tumor Microenvironments. *Nat. Immunol.* **2021**, *22*, 179–192. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Chen, X.; Cai, Y.; Hu, X.; Ding, C.; He, L.; Zhang, X.; Chen, F.; Yan, J. Differential Metabolic Requirement Governed by Transcription Factor C-Maf Dictates Innate $\gamma\delta$ T17 Effector Functionality in Mice and Humans. *Sci. Adv.* **2022**, *8*, eabm9120. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Frascoli, M.; Ferraj, E.; Miu, B.; Malin, J.; Spidale, N.A.; Cowan, J.; Shissler, S.C.; Brink, R.; Xu, Y.; Cyster, J.G.; et al. Skin $g\delta$ T Cell Inflammatory Responses Are Hardwired in the Thymus by Oxysterol Sensing via GPR183 and Calibrated by Dietary Cholesterol. *Immunity* **2023**, *56*, 562–575.e6. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Xia, X.; Cao, G.; Sun, G.; Zhu, L.; Tian, Y.; Song, Y.; Guo, C.; Wang, X.; Zhong, J.; Zhou, W.; et al. GLS1-Mediated Glutaminolysis Unbridled by MALT1 Protease Promotes Psoriasis Pathogenesis. *J. Clin. Investig.* **2020**, *130*, 5180–5196. [\[CrossRef\]](#)

33. Meng, Z.; Cao, G.; Yang, Q.; Yang, H.; Hao, J.; Yin, Z. Metabolic Control of $\gamma\delta$ T Cell Function. *Infect. Microbes Dis.* **2021**, *3*, 142–148. [\[CrossRef\]](#)
34. Hu, Y.-M.; Yeh, C.-L.; Pai, M.-H.; Lee, W.-Y.; Yeh, S.-L. Glutamine Administration Modulates Lung $\gamma\delta$ T Lymphocyte Expression in Mice with Polymicrobial Sepsis. *Shock* **2014**, *41*, 115–122. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Herrmann, T.; Fichtner, A.S.; Karunakaran, M.M. An Update on the Molecular Basis of Phosphoantigen Recognition by V γ 9V δ 2 T Cells. *Cells* **2020**, *9*, 1433. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Chen, Z.W. Protective Immune Responses of Major V γ 2V δ 2 T-Cell Subset in *M. tuberculosis* Infection. *Curr. Opin. Immunol.* **2016**, *42*, 105–112. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Lin, C.-Y.; Roberts, G.W.; Kift-Morgan, A.; Donovan, K.L.; Topley, N.; Eberl, M. Pathogen-Specific Local Immune Fingerprints Diagnose Bacterial Infection in Peritoneal Dialysis Patients. *J. Am. Soc. Nephrol.* **2013**, *24*, 2002–2009. [\[CrossRef\]](#)
38. Davey, M.S.; Morgan, M.P.; Liuzzi, A.R.; Tyler, C.J.; Khan, M.W.A.; Szakmany, T.; Hall, J.E.; Moser, B.; Eberl, M. Microbe-Specific Unconventional T Cells Induce Human Neutrophil Differentiation into Antigen Cross-Presenting Cells. *J. Immunol.* **2014**, *193*, 3704–3716. [\[CrossRef\]](#)
39. Tong, S.Y.C.; Davis, J.S.; Eichenberger, E.; Holland, T.L.; Fowler, V.G. *Staphylococcus aureus* Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. *Clin. Microbiol. Rev.* **2015**, *28*, 603–661. [\[CrossRef\]](#)
40. Kourtis, A.P.; Hatfield, K.; Baggs, J.; Mu, Y.; See, L.; Epton, E.; Nadle, J.; Kainer, M.A.; Dumyati, G.; Petit, S.; et al. Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections—United States. *MMWR Morb. Mortal. Wkly. Rep.* **2019**, *68*, 214–219. [\[CrossRef\]](#)
41. Cooper, A.J.R.; Lator, S.J.; McLoughlin, R.M. Activation of Human V δ 2+ $\gamma\delta$ T Cells by *Staphylococcus aureus* Promotes Enhanced Anti-Staphylococcal Adaptive Immunity. *J. Immunol.* **2020**, *205*, 1039–1049. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Clegg, J.; Soldaini, E.; McLoughlin, R.M.; Rittenhouse, S.; Bagnoli, F.; Phogat, S. *Staphylococcus aureus* Vaccine Research and Development: The Past, Present and Future, Including Novel Therapeutic Strategies. *Front. Immunol.* **2021**, *12*, 705360. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Alphonse, M.P.; Rubens, J.H.; Ortines, R.V.; Orlando, N.A.; Patel, A.M.; Dikeman, D.; Wang, Y.; Vuong, I.; Joyce, D.P.; Zhang, J.; et al. Pan-Caspase Inhibition as a Potential Host-Directed Immunotherapy against MRSA and Other Bacterial Skin Infections. *Sci. Transl. Med.* **2021**, *13*, eabe9887. [\[CrossRef\]](#)
44. Cahill, E.; Oladipo, O.O.; Dikeman, D.; Prifti, D.; Mento, S.J.; Miller, L.S.; Alphonse, M.P. An Oral Caspase Inhibitor as Monotherapy or with Antibiotics Eradicates MRSA Skin Infections in Mice. *Drug Dev. Res.* **2023**, *84*, 1567–1571. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Mata Forsberg, M.; Arasa, C.; Van Zwol, W.; Uzunçayır, S.; Schönbichler, A.; Regenthal, P.; Schelin, J.; Lindkvist-Petersson, K.; Björkander, S.; Sverremark-Ekström, E. Activation of Human $\gamma\delta$ T Cells and NK Cells by Staphylococcal Enterotoxins Requires Both Monocytes and Conventional T Cells. *J. Leukoc. Biol.* **2022**, *111*, 597–609. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Pinchuk, I.V.; Beswick, E.J.; Reyes, V.E. Staphylococcal Enterotoxins. *Toxins* **2010**, *2*, 2177–2197. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Rust, C.J.J.; Verreck, F.; Vietor, H.; Koning, F. Specific Recognition of Staphylococcal Enterotoxin A by Human T Cells Bearing Receptors with the V γ 9 Region. *Nature* **1990**, *346*, 572–574. [\[CrossRef\]](#)
48. Fikri, Y.; Denis, O.; Pastoret, P.-P.; Nyabenda, J. Purified Bovine WC1+ $\gamma\delta$ T Lymphocytes Are Activated by Staphylococcal Enterotoxins and Toxic Shock Syndrome Toxin-1 Superantigens: Proliferation Response, TCR V γ Profile and Cytokines Expression. *Immunol. Lett.* **2001**, *77*, 87–95. [\[CrossRef\]](#)
49. Kumar, S.; Colpitts, S.L.; Ménoret, A.; Budelsky, A.L.; Lefrançois, L.; Vella, A.T. Rapid $\alpha\beta$ T-Cell Responses Orchestrate Innate Immunity in Response to Staphylococcal Enterotoxin A. *Mucosal Immunol.* **2013**, *6*, 1006–1015. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Miller, L.S.; Cho, J.S. Immunity against *Staphylococcus aureus* Cutaneous Infections. *Nat. Rev. Immunol.* **2011**, *11*, 505–518. [\[CrossRef\]](#)
51. Zenobia, C.; Hajishengallis, G. Basic Biology and Role of Interleukin-17 in Immunity and Inflammation. *Periodontology 2000* **2015**, *69*, 142–159. [\[CrossRef\]](#)
52. Ménoret, A.; Buturla, J.A.; Xu, M.M.; Svedova, J.; Kumar, S.; Rathinam, V.A.K.; Vella, A.T. T Cell-Directed IL-17 Production by Lung Granular $\gamma\delta$ T Cells Is Coordinated by a Novel IL-2 and IL-1 β Circuit. *Mucosal Immunol.* **2018**, *11*, 1398–1407. [\[CrossRef\]](#)
53. Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Hennighausen, L.; et al. Interleukin-2 Signaling via STAT5 Constrains T Helper 17 Cell Generation. *Immunity* **2007**, *26*, 371–381. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Kalyan, S.; Chow, A.W. Human Peripheral $\gamma\delta$ T Cells Potentiate the Early Proinflammatory Cytokine Response to Staphylococcal Toxic Shock Syndrome Toxin-1. *J. Infect. Dis.* **2004**, *189*, 1892–1896. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Tkaczyk, C.; Hamilton, M.M.; Datta, V.; Yang, X.P.; Hilliard, J.J.; Stephens, G.L.; Sadowska, A.; Hua, L.; O'Day, T.; Suzich, J.; et al. *Staphylococcus aureus* Alpha Toxin Suppresses Effective Innate and Adaptive Immune Responses in a Murine Dermonecrosis Model. *PLoS ONE* **2013**, *8*, e75103. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Mölne, L.; Corthay, A.; Holmdahl, R.; Tarkowski, A. Role of Gamma/Delta T Cell Receptor-Expressing Lymphocytes in Cutaneous Infection Caused by *Staphylococcus aureus*. *Clin. Exp. Immunol.* **2003**, *132*, 209–215. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Cho, J.S.; Pietras, E.M.; Garcia, N.C.; Ramos, R.I.; Farzam, D.M.; Monroe, H.R.; Magorien, J.E.; Blauvelt, A.; Kolls, J.K.; Cheung, A.L.; et al. IL-17 Is Essential for Host Defense against Cutaneous *Staphylococcus aureus* Infection in Mice. *J. Clin. Investig.* **2010**, *120*, 1762–1773. [\[CrossRef\]](#) [\[PubMed\]](#)

58. Myles, I.A.; Fontecilla, N.M.; Valdez, P.A.; Vithayathil, P.J.; Naik, S.; Belkaid, Y.; Ouyang, W.; Datta, S.K. Signaling via the IL-20 Receptor Inhibits Cutaneous Production of IL-1 β and IL-17A to Promote Infection with Methicillin-Resistant *Staphylococcus aureus*. *Nat. Immunol.* **2013**, *14*, 804–811. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Hamada, S.; Umemura, M.; Shiono, T.; Tanaka, K.; Yahagi, A.; Begum, M.D.; Oshiro, K.; Okamoto, Y.; Watanabe, H.; Kawakami, K.; et al. IL-17A Produced by Gammadelta T Cells Plays a Critical Role in Innate Immunity against *Listeria monocytogenes* Infection in the Liver. *J. Immunol.* **2008**, *181*, 3456–3463. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Marchitto, M.C.; Dillen, C.A.; Liu, H.; Miller, R.J.; Archer, N.K.; Ortines, R.V.; Alphonse, M.P.; Marusina, A.I.; Merleev, A.A.; Wang, Y.; et al. Clonal V γ 6 + V δ 4 + T Cells Promote IL-17-Mediated Immunity against *Staphylococcus aureus* Skin Infection. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 10917–10926. [\[CrossRef\]](#)
61. Dillen, C.A.; Pinsker, B.L.; Marusina, A.I.; Merleev, A.A.; Farber, O.N.; Liu, H.; Archer, N.K.; Lee, D.B.; Wang, Y.; Ortines, R.V.; et al. Clonally Expanded $\gamma\delta$ T Cells Protect against *Staphylococcus aureus* Skin Reinfection. *J. Clin. Investig.* **2018**, *128*, 1026–1042. [\[CrossRef\]](#)
62. Ishigame, H.; Kakuta, S.; Nagai, T.; Kadoki, M.; Nambu, A.; Komiyama, Y.; Fujikado, N.; Tanahashi, Y.; Akitsu, A.; Kotaki, H.; et al. Differential Roles of Interleukin-17A and -17F in Host Defense against Mucoepithelial Bacterial Infection and Allergic Responses. *Immunity* **2009**, *30*, 108–119. [\[CrossRef\]](#)
63. Wang, Y.; Ahmadi, M.Z.; Dikeman, D.A.; Youn, C.; Archer, N.K. $\gamma\delta$ T Cell-Intrinsic IL-1R Promotes Survival during *Staphylococcus aureus* Bacteremia. *Front. Immunol.* **2023**, *14*, 1171934. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Ramírez-Valle, F.; Gray, E.E.; Cyster, J.G. Inflammation Induces Dermal V γ 4+ $\gamma\delta$ T17 Memory-like Cells That Travel to Distant Skin and Accelerate Secondary IL-17-Driven Responses. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 8046–8051. [\[CrossRef\]](#)
65. Christensen, G.J.M.; Brüggemann, H. Bacterial Skin Commensals and Their Role as Host Guardians. *Benef. Microbes* **2014**, *5*, 201–215. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Strbo, N.; Pastar, I.; Romero, L.; Chen, V.; Vujanac, M.; Sawaya, A.P.; Jozic, I.; Ferreira, A.D.F.; Wong, L.L.; Head, C.; et al. Single Cell Analyses Reveal Specific Distribution of Anti-Bacterial Molecule Perforin-2 in Human Skin and Its Modulation by Wounding and *Staphylococcus aureus* Infection. *Exp. Dermatol.* **2019**, *28*, 225–232. [\[CrossRef\]](#)
67. Pastar, I.; O'Neill, K.; Padula, L.; Head, C.R.; Burgess, J.L.; Chen, V.; Garcia, D.; Stojadinovic, O.; Hower, S.; Plano, G.V.; et al. *Staphylococcus Epidermidis* Boosts Innate Immune Response by Activation of Gamma Delta T Cells and Induction of Perforin-2 in Human Skin. *Front. Immunol.* **2020**, *11*, 550946. [\[CrossRef\]](#)
68. Johansson, M.A.; Björkander, S.; Mata Forsberg, M.; Qazi, K.R.; Salvany Celades, M.; Bittmann, J.; Eberl, M.; Sverremark-Ekström, E. Probiotic Lactobacilli Modulate *Staphylococcus aureus*-Induced Activation of Conventional and Unconventional T Cells and NK Cells. *Front. Immunol.* **2016**, *7*, 273. [\[CrossRef\]](#)
69. Pan, N.; Liu, B.; Bao, X.; Zhang, H.; Sheng, S.; Liang, Y.; Pan, H.; Wang, X. Oral Delivery of Novel Recombinant *Lactobacillus* Elicit High Protection against *Staphylococcus aureus* Pulmonary and Skin Infections. *Vaccines* **2021**, *9*, 984. [\[CrossRef\]](#)
70. Pan, N.; Liu, Y.; Zhang, H.; Xu, Y.; Bao, X.; Sheng, S.; Liang, Y.; Liu, B.; Lyu, Y.; Li, H.; et al. Oral Vaccination with Engineered Probiotic *Limosilactobacillus reuteri* Has Protective Effects against Localized and Systemic *Staphylococcus aureus* Infection. *Microbiol. Spectr.* **2023**, *11*, e0367322. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Cheng, P.; Liu, T.; Zhou, W.-Y.; Zhuang, Y.; Peng, L.; Zhang, J.; Yin, Z.-N.; Mao, X.; Guo, G.; Shi, Y.; et al. Role of Gamma-Delta T Cells in Host Response against *Staphylococcus aureus*-Induced Pneumonia. *BMC Immunol.* **2012**, *13*, 38. [\[CrossRef\]](#)
72. Baral, P.; Umans, B.D.; Li, L.; Wallrapp, A.; Bist, M.; Kirschbaum, T.; Wei, Y.; Zhou, Y.; Kuchroo, V.K.; Burkett, P.R.; et al. Nociceptor Sensory Neurons Suppress Neutrophil and $\gamma\delta$ T Cell Responses in Bacterial Lung Infections and Lethal Pneumonia. *Nat. Med.* **2018**, *24*, 417–426. [\[CrossRef\]](#)
73. Paudel, S.; Ghimire, L.; Jin, L.; Baral, P.; Cai, S.; Jeyaseelan, S. NLR4 Suppresses IL-17A-Mediated Neutrophil-Dependent Host Defense through Upregulation of IL-18 and Induction of Necroptosis during Gram-Positive Pneumonia. *Mucosal Immunol.* **2019**, *12*, 247–257. [\[CrossRef\]](#)
74. Craven, R.R.; Gao, X.; Allen, I.C.; Gris, D.; Wardenburg, J.B.; McElvania-TeKippe, E.; Ting, J.P.; Duncan, J.A. *Staphylococcus aureus* α -Hemolysin Activates the NLRP3-Inflammasome in Human and Mouse Monocytic Cells. *PLoS ONE* **2009**, *4*, e7446. [\[CrossRef\]](#)
75. Kim, L.; McGee, L.; Tomczyk, S.; Beall, B. Biological and Epidemiological Features of Antibiotic-Resistant *Streptococcus pneumoniae* in Pre- and Post-Conjugate Vaccine Eras: A United States Perspective. *Clin. Microbiol. Rev.* **2016**, *29*, 525–552. [\[CrossRef\]](#)
76. Reynolds, C.A.; Finkelstein, J.A.; Ray, G.T.; Moore, M.R.; Huang, S.S. Attributable Healthcare Utilization and Cost of Pneumonia Due to Drug-Resistant *Streptococcus pneumoniae*: A Cost Analysis. *Antimicrob. Resist. Infect. Control* **2014**, *3*, 16. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Palmer, C.S.; Kimmey, J.M. Neutrophil Recruitment in Pneumococcal Pneumonia. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 894644. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Nakasone, C.; Yamamoto, N.; Nakamatsu, M.; Kinjo, T.; Miyagi, K.; Uezu, K.; Nakamura, K.; Higa, F.; Ishikawa, H.; O'Brien, R.L.; et al. Accumulation of Gamma/Delta T Cells in the Lungs and Their Roles in Neutrophil-Mediated Host Defense against Pneumococcal Infection. *Microbes Infect.* **2007**, *9*, 251–258. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Kawakami, K.; Yamamoto, N.; Kinjo, Y.; Miyagi, K.; Nakasone, C.; Uezu, K.; Kinjo, T.; Nakayama, T.; Taniguchi, M.; Saito, A. Critical Role of V α 14+ Natural Killer T Cells in the Innate Phase of Host Protection against *Streptococcus pneumoniae* Infection. *Eur. J. Immunol.* **2003**, *33*, 3322–3330. [\[CrossRef\]](#) [\[PubMed\]](#)

80. Kirby, A.; Newton, D.; Carding, S.; Kaye, P. Pulmonary Dendritic Cells and Alveolar Macrophages Are Regulated by $\gamma\delta$ T Cells during the Resolution of *S. pneumoniae*-induced Inflammation. *J. Pathol.* **2007**, *212*, 29–37. [[CrossRef](#)] [[PubMed](#)]
81. Bender, A.; Kabelitz, D. Preferential Activation of Peripheral Blood $V\gamma 9+\gamma/\delta$ T Cells by Group A, B and C but Not Group D or F Streptococci. *Clin. Exp. Immunol.* **2008**, *89*, 301–304. [[CrossRef](#)] [[PubMed](#)]
82. De Souza Costa, M.F.; Bastos Trigo De Negreiros, C.; Ugarte Bornstein, V.; Hemmi Valente, R.; Mengel, J.; Henriques, M.D.G.; Farias Benjamim, C.; Penido, C. Murine IL-17+ $V\gamma 4$ T Lymphocytes Accumulate in the Lungs and Play a Protective Role during Severe Sepsis. *BMC Immunol.* **2015**, *16*, 36. [[CrossRef](#)] [[PubMed](#)]
83. Hassane, M.; Demon, D.; Soulard, D.; Fontaine, J.; Keller, L.E.; Patin, E.C.; Porte, R.; Prinz, I.; Ryffel, B.; Kadioglu, A.; et al. Neutrophilic NLRP3 Inflammasome-Dependent IL-1 β Secretion Regulates the $\gamma\delta$ T17 Cell Response in Respiratory Bacterial Infections. *Mucosal Immunol.* **2017**, *10*, 1056–1068. [[CrossRef](#)]
84. Xu, R.; Jacques, L.C.; Khandaker, S.; Beentjes, D.; Leon-Rios, M.; Wei, X.; French, N.; Neill, D.R.; Kadioglu, A. TNFR2+ Regulatory T Cells Protect against Bacteremic Pneumococcal Pneumonia by Suppressing IL-17A-Producing $\gamma\delta$ T Cells in the Lung. *Cell Rep.* **2023**, *42*, 112054. [[CrossRef](#)]
85. Anthony, D.; Papanicolaou, A.; Wang, H.; Seow, H.J.; To, E.E.; Yatmaz, S.; Anderson, G.P.; Wijburg, O.; Selemidis, S.; Vlahos, R.; et al. Excessive Reactive Oxygen Species Inhibit IL-17A+ $\Gamma\delta$ T Cells and Innate Cellular Responses to Bacterial Lung Infection. *Antioxid. Redox Signal.* **2020**, *32*, 943–956. [[CrossRef](#)]
86. Mathews, J.A.; Kasahara, D.I.; Ribeiro, L.; Wurmbrand, A.P.; Ninin, F.M.C.; Shore, S.A. $\gamma\delta$ T Cells Are Required for M2 Macrophage Polarization and Resolution of Ozone-Induced Pulmonary Inflammation in Mice. *PLoS ONE* **2015**, *10*, e0131236. [[CrossRef](#)] [[PubMed](#)]
87. Matle, I.; Mbatha, K.R.; Madoroba, E. A Review of *Listeria monocytogenes* from Meat and Meat Products: Epidemiology, Virulence Factors, Antimicrobial Resistance and Diagnosis. *Onderstepoort J. Vet. Res.* **2020**, *87*, e1–e20. [[CrossRef](#)] [[PubMed](#)]
88. Belles, C.; Kuhl, A.K.; Donoghue, A.J.; Sano, Y.; O'Brien, R.L.; Born, W.; Bottomly, K.; Carding, S.R. Bias in the Gamma Delta T Cell Response to *Listeria monocytogenes*. V Delta 6.3+ Cells Are a Major Component of the Gamma Delta T Cell Response to *Listeria monocytogenes*. *J. Immunol.* **1996**, *156*, 4280–4289. [[CrossRef](#)] [[PubMed](#)]
89. Munk, M.E.; Elser, C.; Kaufmann, S.H. Human Gamma/Delta T-Cell Response to *Listeria monocytogenes* Protein Components In Vitro. *Immunology* **1996**, *87*, 230–235. [[CrossRef](#)] [[PubMed](#)]
90. Begley, M.; Gahan, C.G.M.; Kollas, A.-K.; Hintz, M.; Hill, C.; Jomaa, H.; Eberl, M. The Interplay between Classical and Alternative Isoprenoid Biosynthesis Controls $\gamma\delta$ T Cell Bioactivity of *Listeria monocytogenes*. *FEBS Lett.* **2004**, *561*, 99–104. [[CrossRef](#)] [[PubMed](#)]
91. Frencher, J.T.; Shen, H.; Yan, L.; Wilson, J.O.; Freitag, N.E.; Rizzo, A.N.; Chen, C.Y.; Chen, Z.W. HMBPP-Deficient *Listeria* Mutant Immunization Alters Pulmonary/Systemic Responses, Effector Functions, and Memory Polarization of $V\gamma 2V\delta 2$ T Cells. *J. Leukoc. Biol.* **2014**, *96*, 957–967. [[CrossRef](#)] [[PubMed](#)]
92. Nakamura; Matsuzaki; Nomoto. The Protective Role of T-cell Receptor $V\gamma 1^+$ T Cells in Primary Infection with *Listeria monocytogenes*. *Immunology* **1999**, *96*, 29–34. [[CrossRef](#)] [[PubMed](#)]
93. Roark, C.E.; Vollmer, M.K.; Campbell, P.A.; Born, W.K.; O'Brien, R.L. Response of a Gamma Delta+ T Cell Receptor Invariant Subset during Bacterial Infection. *J. Immunol.* **1996**, *156*, 2214–2220. [[CrossRef](#)]
94. Roark, C.L.; Aydin, M.K.; Lewis, J.; Yin, X.; Lahn, M.; Hahn, Y.-S.; Born, W.K.; Tigelaar, R.E.; O'Brien, R.L. Subset-Specific, Uniform Activation among $V\gamma 6/V\delta 1+$ $\gamma\delta$ T Cells Elicited by Inflammation. *J. Leukoc. Biol.* **2004**, *75*, 68–75. [[CrossRef](#)] [[PubMed](#)]
95. DiTirro, J.; Rhoades, E.R.; Roberts, A.D.; Burke, J.M.; Mukasa, A.; Cooper, A.M.; Frank, A.A.; Born, W.K.; Orme, I.M. Disruption of the Cellular Inflammatory Response to *Listeria monocytogenes* Infection in Mice with Disruptions in Targeted Genes. *Infect. Immun.* **1998**, *66*, 2284–2289. [[CrossRef](#)] [[PubMed](#)]
96. Hamada, S.; Umemura, M.; Shiono, T.; Hara, H.; Kishihara, K.; Tanaka, K.; Mayuzumi, H.; Ohta, T.; Matsuzaki, G. Importance of Murine $V\delta 1$ gammadelta T Cells Expressing Interferon-Gamma and Interleukin-17A in Innate Protection against *Listeria monocytogenes* Infection. *Immunology* **2008**, *125*, 170–177. [[CrossRef](#)] [[PubMed](#)]
97. Rhodes, K.A.; Andrew, E.M.; Newton, D.J.; Tramonti, D.; Carding, S.R. A Subset of IL-10-Producing Gammadelta T Cells Protect the Liver from *Listeria*-Elicited, CD8(+) T Cell-Mediated Injury. *Eur. J. Immunol.* **2008**, *38*, 2274–2283. [[CrossRef](#)]
98. Egan, P.J.; Carding, S.R. Downmodulation of the Inflammatory Response to Bacterial Infection by Gammadelta T Cells Cytotoxic for Activated Macrophages. *J. Exp. Med.* **2000**, *191*, 2145–2158. [[CrossRef](#)]
99. Dalton, J.E.; Pearson, J.; Scott, P.; Carding, S.R. The Interaction of Gamma Delta T Cells with Activated Macrophages Is a Property of the V Gamma 1 Subset. *J. Immunol.* **2003**, *171*, 6488–6494. [[CrossRef](#)]
100. Khairallah, C.; Chu, T.H.; Qiu, Z.; Imperato, J.N.; Yang, D.; Sheridan, B.S. The Accumulation of $V\gamma 4$ T Cells with Aging Is Associated with an Increased Adaptive $V\gamma 4$ T Cell Response after Food-borne *Listeria monocytogenes* Infection of Mice. *Immun. Ageing* **2022**, *19*, 19. [[CrossRef](#)]
101. Ragonnet, R.; Trauer, J.M.; Geard, N.; Scott, N.; McBryde, E.S. Profiling Mycobacterium Tuberculosis Transmission and the Resulting Disease Burden in the Five Highest Tuberculosis Burden Countries. *BMC Med.* **2019**, *17*, 208. [[CrossRef](#)]
102. Lockhart, E.; Green, A.M.; Flynn, J.L. IL-17 Production Is Dominated by $\gamma\delta$ T Cells Rather than CD4 T Cells during *Mycobacterium tuberculosis* Infection. *J. Immunol.* **2006**, *177*, 4662–4669. [[CrossRef](#)]
103. Chen, C.Y.; Yao, S.; Huang, D.; Wei, H.; Sicard, H.; Zeng, G.; Jomaa, H.; Larsen, M.H.; Jacobs, W.R.; Wang, R.; et al. Phospho-antigen/IL2 Expansion and Differentiation of $V\gamma 2V\delta 2$ T Cells Increase Resistance to Tuberculosis in Nonhuman Primates. *PLoS Pathog.* **2013**, *9*, e1003501. [[CrossRef](#)] [[PubMed](#)]

104. Okamoto Yoshida, Y.; Umemura, M.; Yahagi, A.; O'Brien, R.L.; Ikuta, K.; Kishihara, K.; Hara, H.; Nakae, S.; Iwakura, Y.; Matsuzaki, G. Essential Role of IL-17A in the Formation of a Mycobacterial Infection-Induced Granuloma in the Lung. *J. Immunol.* **2010**, *184*, 4414–4422. [\[CrossRef\]](#)
105. Peng, M.Y.; Wang, Z.H.; Yao, C.Y.; Jiang, L.N.; Jin, Q.L.; Wang, J.; Li, B.Q. Interleukin 17-Producing Gamma Delta T Cells Increased in Patients with Active Pulmonary Tuberculosis. *Cell. Mol. Immunol.* **2008**, *5*, 203–208. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Ferrero, E.; Biswas, P.; Vettoretto, K.; Ferrarini, M.; Uguccioni, M.; Piali, L.; Leone, B.E.; Moser, B.; Rugarli, C.; Pardi, R. Macrophages Exposed to *Mycobacterium tuberculosis* Release Chemokines Able to Recruit Selected Leucocyte Subpopulations: Focus on Gammadelta Cells. *Immunology* **2003**, *108*, 365–374. [\[CrossRef\]](#)
107. Shen, H.; Wang, Y.; Chen, C.Y.; Frencher, J.; Huang, D.; Yang, E.; Ryan-Payseur, B.; Chen, Z.W. Th17-Related Cytokines Contribute to Recall-like Expansion/Effector Function of HMBPP-Specific V γ 2V δ 2 T Cells after *Mycobacterium tuberculosis* Infection or Vaccination. *Eur. J. Immunol.* **2015**, *45*, 442–451. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Shen, H.; Gu, J.; Xiao, H.; Liang, S.; Yang, E.; Yang, R.; Huang, D.; Chen, C.; Wang, F.; Shen, L.; et al. Selective Destruction of Interleukin 23-Induced Expansion of a Major Antigen-Specific $\gamma\delta$ T-Cell Subset in Patients With Tuberculosis. *J. Infect. Dis.* **2017**, *215*, 420–430. [\[CrossRef\]](#)
109. El Daker, S.; Sacchi, A.; Montesano, C.; Altieri, A.M.; Galluccio, G.; Colizzi, V.; Martini, F.; Martino, A. An Abnormal Phenotype of Lung V γ 9V δ 2 T Cells Impairs Their Responsiveness in Tuberculosis Patients. *Cell. Immunol.* **2013**, *282*, 106–112. [\[CrossRef\]](#)
110. Saura-Esteller, J.; de Jong, M.; King, L.A.; Ensing, E.; Winograd, B.; de Gruijl, T.D.; Parren, P.W.H.I.; van der Vliet, H.J. Gamma Delta T-Cell Based Cancer Immunotherapy: Past-Present-Future. *Front. Immunol.* **2022**, *13*, 915837. [\[CrossRef\]](#)
111. Kobayashi, H.; Tanaka, Y.; Shimmura, H.; Minato, N.; Tanabe, K. Complete Remission of Lung Metastasis Following Adoptive Immunotherapy Using Activated Autologous Gammadelta T-Cells in a Patient with Renal Cell Carcinoma. *Anticancer Res.* **2010**, *30*, 575–579. [\[PubMed\]](#)
112. Ishihara, M.; Miwa, H.; Fujiwara, H.; Akahori, Y.; Kato, T.; Tanaka, Y.; Tawara, I.; Shiku, H. A β -T Cell Receptor Transduction Gives Superior Mitochondrial Function to $\gamma\delta$ -T Cells with Promising Persistence. *iScience* **2023**, *26*, 107802. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Lisci, M.; Barton, P.R.; Randzavola, L.O.; Ma, C.Y.; Marchingo, J.M.; Cantrell, D.A.; Paupe, V.; Prudent, J.; Stinchcombe, J.C.; Griffiths, G.M. Mitochondrial Translation Is Required for Sustained Killing by Cytotoxic T Cells. *Science* **2021**, *374*, eabe9977. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Shen, H.; Yang, E.; Guo, M.; Yang, R.; Huang, G.; Peng, Y.; Sha, W.; Wang, F.; Shen, L. Adjunctive Zoledronate + IL-2 Administrations Enhance Anti-Tuberculosis V γ 2V δ 2 T-Effector Populations, and Improve Treatment Outcome of Multidrug-Resistant Tuberculosis1. *Emerg. Microbes Infect.* **2022**, *11*, 1790–1805. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Qaqish, A.; Huang, D.; Chen, C.Y.; Zhang, Z.; Wang, R.; Li, S.; Yang, E.; Lu, Y.; Larsen, M.H.; Jacobs, W.R.; et al. Adoptive Transfer of Phosphoantigen-Specific $\Gamma\delta$ T Cell Subset Attenuates *Mycobacterium tuberculosis* Infection in Nonhuman Primates. *J. Immunol.* **2017**, *198*, 4753–4763. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Shen, L.; Frencher, J.; Huang, D.; Wang, W.; Yang, E.; Chen, C.Y.; Zhang, Z.; Wang, R.; Qaqish, A.; Larsen, M.H.; et al. Immunization of V γ 2V δ 2 T Cells Programs Sustained Effector Memory Responses That Control Tuberculosis in Nonhuman Primates. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 6371–6378. [\[CrossRef\]](#)
117. Roelofs, A.J.; Jauhainen, M.; Mönkkönen, H.; Rogers, M.J.; Mönkkönen, J.; Thompson, K. Peripheral Blood Monocytes Are Responsible for Gammadelta T Cell Activation Induced by Zoledronic Acid through Accumulation of IPP/DMAPP. *Br. J. Haematol.* **2009**, *144*, 245–250. [\[CrossRef\]](#)
118. Raffray, L.; Burton, R.J.; Baker, S.E.; Morgan, M.P.; Eberl, M. Zoledronate Rescues Immunosuppressed Monocytes in Sepsis Patients. *Immunology* **2020**, *159*, 88–95. [\[CrossRef\]](#)
119. Zacharin, M.; O'Sullivan, M. Intravenous Pamidronate Treatment of Polyostotic Fibrous Dysplasia Associated with the McCune Albright Syndrome. *J. Pediatr.* **2000**, *137*, 403–409. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Wang, L.; Kamath, A.; Das, H.; Li, L.; Bukowski, J.F. Antibacterial Effect of Human V Gamma 2V Delta 2 T Cells in Vivo. *J. Clin. Investig.* **2001**, *108*, 1349–1357. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.