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Harnessing *Mycobacterium tuberculosis*–Expanded γδ T-Cells for Tuberculosis Immunotherapy: Emerging Immunological Perspectives

Tüberküloz İmmünoterapisi için *Mycobacterium tuberculosis* ile Genişletilmiş γδ T-Hücrelerinden Yararlanma: Yeni Ortaya Çıkan İmmünolojik Bakış Açıları

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ABSTRACT

The rising incidence of multidrug-resistant and extensively drug-resistant tuberculosis and the persistent syndemic interaction between *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus have substantially intensified the global tuberculosis burden. These challenges have renewed scientific interest in understanding the immunological mechanisms that regulate host resistance, as well as the sophisticated virulence strategies employed by Mtb. Tuberculosis infection is typically initiated through inhalation of aerosolized bacilli, which are first encountered by alveolar macrophages within the pulmonary microenvironment. Acting as frontline immunological sentinels, these cells recognize conserved microbial patterns through diverse pattern-recognition receptors—including Toll-like receptors, C-type lectin receptors, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, and nucleotide-binding oligomerization domain-like receptors—thereby activating intracellular antimicrobial and inflammatory signaling pathways. Although tuberculosis immunology has been extensively investigated, earlier reviews have largely focused on conventional immune pathways, providing comparatively limited attention to the immunotherapeutic potential of Mtb–expanded gamma delta (γδ) T-cells. A comprehensive synthesis addressing their expansion

ÖZ

Çoklu ilaca dirençli ve yaygın ilaca dirençli tüberküloz vakalarının artması ve *Mycobacterium tuberculosis* (Mtb) ile insan immün yetmezlik virüsü (HIV) arasındaki sürekli sendemik etkileşim, küresel tüberküloz yükünü önemli ölçüde artırmıştır. Bu zorluklar, konak direncini düzenleyen immünolojik mekanizmaları ve Mtb tarafından kullanılan karmaşık virülans stratejilerini anlamaya yönelik bilimsel ilgiyi yeniden canlandırmıştır. Tüberküloz enfeksiyonu tipik olarak, akciğer mikroortamındaki alveoler makrofajlar tarafından ilk kez karşılaşılan aerosol halindeki basillerin solunmasıyla başlar. Ön cephe immünolojik bekçileri olarak hareket eden bu hücreler, Toll benzeri reseptörler, C tipi lektin reseptörleri, dendritik hücreye özgü hücreler arası yapışma molekülü-3 yakalayan non-integrin ve nükleotid bağlayıcı oligomerizasyon alanı benzeri reseptörler de dahil olmak üzere çeşitli patern tanıma reseptörleri aracılığıyla korunmuş mikrobiyal paternleri tanır ve böylece hücre içi antimikrobiyal ve inflamatuar sinyal yollarını aktive eder. Tüberküloz immünolojisi kapsamlı bir şekilde araştırılmış olsa da, önceki incelemeler büyük ölçüde geleneksel immün yollara odaklanmış ve Mtb tarafından genişletilmiş gama delta (γδ) T hücrelerinin immünoterapötik potansiyeline nispeten sınırlı bir dikkat göstermiştir. Genişleme mekanizmalarını, immünomodülatör fonksiyonlarını ve tüberküloz immünoterapisindeki translasyonel

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ABSTRACT

mechanisms, immunomodulatory functions, and translational significance in tuberculosis immunotherapy remains insufficiently explored. Consequently, a focused evaluation of the emerging role of γδ T-cells in host defense against tuberculosis is warranted. This review provides an integrated overview of the immunological functions and therapeutic relevance of γδ T-cells in tuberculosis. It discusses the role of γδ T-cells during Mtb infection, emphasizing their early antimicrobial responses and their contribution to innate-like immunity. The review further examines the interactions between γδ T-cells and dendritiC-cells, highlighting their cooperative role in antigen presentation and immune modulation. The mechanisms underlying γδ T-cell activation, interactions, and maturation during Mtb infection are addressed. Finally, emerging γδ T-cell–based immunotherapeutic strategies are being explored as potential host-directed approaches to complement conventional tuberculosis treatment. By consolidating recent advances in γδ T-cell biology and in understanding their role in tuberculosis immunity, this review addresses existing gaps in the literature and underscores their potential as targets for innovative therapeutic interventions against increasingly drug-resistant tuberculosis.

Keywords: *Mycobacterium tuberculosis*, γδ T-cells, tuberculosis immunology, host-directed therapy, dendritic cell interaction, drug-resistant tuberculosis

ÖZ

önemini ele alan kapsamlı bir sentez yeterince araştırılmamıştır. Sonuç olarak, tüberküloza karşı konak savunmasında γδ T hücrelerinin ortaya çıkan rolünün odaklanmış bir değerlendirmesi gereklidir. Bu inceleme, tüberkülozda γδ T hücrelerinin immünolojik fonksiyonları ve terapötik önemine ilişkin bütünleşik bir genel bakış sunmaktadır. Mtb enfeksiyonu sırasında γδ T hücrelerinin rolünü tartışarak, erken antimikrobiyal yanıtlarını ve doğuştan gelen bağışıklığa katkılarını vurgulamaktadır. İnceleme ayrıca, γδ T hücreleri ile dendritik hücreler arasındaki etkileşimleri inceleyerek, antijen sunumu ve immün modülasyondaki işbirlikçi rollerini vurgulamaktadır. Bu derlemede, Mtb enfeksiyonu sırasında γδ T hücre aktivasyonu, etkileşimleri ve olgunlaşmasının altında yatan mekanizmalar ele alınmaktadır. Son olarak, geleneksel tüberküloz tedavisini tamamlayıcı potansiyel konakçı odaklı yaklaşımlar olarak ortaya çıkan γδ T hücre tabanlı immünoterapötik stratejiler araştırılmaktadır. γδ T hücre biyolojisindeki ve tüberküloz bağışıklığındaki rollerinin anlaşılmasındaki son gelişmelerin bir araya getirilmesiyle, bu derleme literatürdeki mevcut boşlukları ele almakta ve giderek artan ilaç dirençli tüberküloza karşı yenilikçi terapötik müdahaleler için potansiyel hedefleri vurgulamaktadır.

Anahtar Sözcükler: *Mycobacterium tuberculosis*, γδ T-hücreleri, tüberküloz immunolojisi, konağa yönelik tedavi, dendritik hücre etkileşimi, ilaca dirençli tüberküloz

INTRODUCTION

The emergence of multidrug-resistant and extensively drug-resistant tuberculosis, compounded by the persistent syndemic interplay between *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus (HIV), has profoundly aggravated the global tuberculosis burden. These converging pressures have renewed attention to the immunological architecture governing host resistance and to the sophisticated virulence mechanisms employed by the pathogen. Infection is initiated predominantly through inhalation of aerosolized bacilli, after which alveolar macrophages act as the primary immunological sentinels within the pulmonary milieu. Through diverse pattern-recognition receptors—including Toll-like receptors, C-type lectin receptors, dendritic cell (DC)-specific intercellular adhesion molecule-3-grabbing non-integrin, and nucleotide-binding oligomerization domain-like receptors—these cells identify conserved microbial signatures and activate intracellular antimicrobial cascades. In immunocompetent hosts, containment is typically achieved through the coordinated engagement of adaptive immunity, frequently evidenced by tuberculin skin test reactivity, which reflects immunologic sensitization rather than overt disease. Central to this containment is the granuloma, an organized cellular structure composed of activated macrophages, multinucleated giant cells, surrounded by T-lymphocytes, representing the histopathological hallmark of protective immunity. Its formation and maintenance depend largely upon T-cell–mediated processes. The variable efficacy of Bacillus Calmette–Guérin (BCG) vaccination and the limitations of existing chemotherapeutic regimens highlight the urgent need for innovative vaccine strategies and host-directed immunomodulatory approaches. Advancements in tuberculosis control require a more refined elucidation of immunopathogenic networks to identify dependable correlates of protection and inform the rational design of next-generation vaccines and adjunctive therapeutics.

Deterioration of host immune competence substantially compromises the ability to restrict Mtb replication. The bacillus subverts intracellular killing by interfering with phagolysosomal maturation, inhibiting vesicular acidification, and preventing phagosome–lysosome fusion (1), thereby establishing a permissive intracellular niche. Continued replication may ultimately induce host-cell necrosis, facilitating local tissue destruction and hematogenous dissemination. Protective immunity is orchestrated primarily by $CD4^+$ and $CD8^+$ T-lymphocytes, whose cytokine secretion profiles are indispensable for antimycobacterial defense (2). However, antigen-specific adaptive responses evolve slowly; several weeks are required for effective T-cell priming and accumulation at infection sites. This temporal delay enables substantial early bacillary expansion and constitutes a critical barrier to sterilizing immunity. Effective control depends on the differentiation of $CD4^+$ T-cells into functionally specialized subsets tailored to intracellular pathogens, particularly interferon-γ (IFN-γ)–producing T helper 1 (Th1) cells and, to a lesser extent, interleukin (IL)-4–secreting Th2 cells. While robust cell-mediated immunity is fundamental, additional immune components contribute to disease containment. Mtb produces structural and secreted virulence factors that modulate innate signaling pathways, and intrinsic host regulatory mechanisms often temper inflammatory responses, promoting equilibrium rather than complete eradication. Among the earliest lymphocyte populations mobilized during infection are gamma delta (γδ) T-cells, a highly responsive and functionally versatile subset that demonstrates distinct activation kinetics in both acute and chronic stages of mycobacterial disease in humans and experimental models.

A diverse array of T-cell lineages participates in immune responses to mycobacterial antigens, including $CD4^+$ and $CD8^+$ αβ T-cell receptor (TCR)–expressing lymphocytes, γδ TCR^+ cells, and CD1-restricted αβ T-cell subsets (3). Although the indispensable role of $CD4^+$ T-cells in human antimycobacterial immunity is well established, the precise

contributions and cooperative dynamics of other T-cell populations remain incompletely defined. Since the recognition of γδ TCR–bearing lymphocytes as a distinct lineage, studies in murine systems and human cohorts have substantiated their active engagement in host defense against Mtb (4). Conventionally, adaptive immunity is distinguished by antigen specificity and durable memory, whereas innate immunity relies on conserved recognition strategies and has historically been regarded as lacking memory capacity. γδ T-cells occupy an intermediate conceptual and functional position between these paradigms. Predominantly localized to peripheral tissues, the primary interfaces of microbial invasion act in concert with natural killer (NK) cells and interact closely with DCs, the principal antigen-presenting cells (APCs) responsible for translating localized inflammatory cues into systemic adaptive responses. Despite their relatively limited representation in peripheral blood, γδ T-cells exhibit distinctive migratory behavior and effector functions that differentiate them from conventional αβ T-lymphocytes. Emerging evidence, including observations from non-human primate studies, indicates that γδ T-cells may acquire adaptive-like attributes, notably memory-associated expansion. These cells recognize phosphoantigens generated during mycobacterial isoprenoid biosynthesis, in particular isopentenyl pyrophosphate (IPP) and (E)-1-hydroxy-2-methyl-but-2-enyl-4-diphosphate (HMBPP) (5). Experimental depletion of pulmonary γδ T-cells in macaque models has been associated with elevated bacterial burdens following Mtb challenge, stressing their crucial role in early containment. Collectively, these findings position γδ T-lymphocytes as pivotal immunological intermediaries that operate at the nexus of innate and adaptive immune defenses in tuberculosis.

γδ T-lymphocytes, long recognized for their participation in antimicrobial defense, also play a pivotal role in tumor immunosurveillance. Their antineoplastic capacity derives from an inherent ability to detect metabolic perturbations accompanying malignant transformation. Rapidly proliferating tumor cells exhibit increased flux through the mevalonate pathway, culminating in intracellular accumulation of IPP and related prenyl intermediates (6). These phosphoantigenic metabolites serve as potent stimuli for γδ T-cell activation, initiating cytotoxic effector responses. Beyond direct lysis of transformed cells, γδ T-lymphocytes augment antitumor immunity through dynamic interactions with other immune populations (7). Upon activation, they may acquire features of professional APCs, including expression of HLA-DR and delivery of costimulatory signals that promote αβ T-cell priming and differentiation into cytotoxic effectors. Modulation of receptors such as CD36 further facilitates clearance of tumor-derived debris and amplifies inflammatory signaling within the tumor microenvironment (8). Despite a comparatively restricted TCR repertoire, γδ T-cells recognize a broad array of phosphoantigenic structures, encompassing pyrophosphate-containing intermediates and prenyl metabolites generated by Mtb. In humans, the circulating Vγ9Vδ2 subset predominates in adulthood and constitutes the principal population responsive to mycobacterial phosphoantigens (9). These cells mediate antimycobacterial activity by granule-dependent cytotoxicity and by constraining bacillary replication within infected macrophages. γδ T-lymphocytes may function as unconventional APCs, promoting αβ T-cell expansion through CD40-mediated costimulation and reinforcing adaptive immune containment. Their capacity to enhance DC maturation and to engage in bidirectional TCR-dependent crosstalk further intensifies immune activation and contributes to the control of persistent intracellular infection.

During chronic Mtb infection, selective clonal expansion of discrete γδ T-cell subsets occurs, accompanied by acquisition of effector memory phenotypes characterized by increased cytokine secretion and augmented cytolytic potential (10). These expanded populations respond robustly to complex mycobacterial antigens, including whole-cell lysates, indicating participation in long-term immunological surveillance. γδ T-cells derived from tuberculosis-naïve infants exhibit measurable reactivity to mycobacterial lysates but display limited responsiveness to defined phosphoantigens such as HMBPP, suggesting that full functional maturation of this lineage depends on developmental progression and cumulative antigenic exposure. Although $CD4^+$ T-lymphocytes remain central to protective immunity against Mtb, their effectiveness may be diminished in states of immunodeficiency, particularly during HIV coinfection, wherein immune exhaustion attenuates antigen-specific responses. Under such circumstances, γδ T-cells may provide complementary or compensatory immune functions. Experimental murine models further delineate the context-dependent nature of γδ T-cell activation. Administration of complete Freund's adjuvant (CFA) induces marked expansion of γδ T-cells within draining lymph nodes (11). At the same time, repeated pulmonary exposure to purified protein derivative (PPD) increases the proportion of $CD3^+$ T-cells in lung tissue that CD4 and CD8 expression. Although CFA promotes in vivo proliferation of γδ T-lymphocytes within lymphoid organs, subsequent antigenic challenge does not elicit classical recall responses, implying that activation in this setting is driven primarily by inflammatory cues rather than by strict antigen specificity.

Functional studies provide additional insight into their role in host defense. Depletion of γδ T-cells exerts minimal impact on early bacterial loads following low-dose Mtb infection, indicating that they are not the principal mediators of initial microbial clearance (12). However, γδ TCR-deficient mice subjected to high-dose challenge exhibit disorganized granulomatous structures, characterized by enlarged lesions and excessive neutrophilic infiltration. These observations suggest that γδ T-lymphocytes contribute predominantly to immunoregulatory mechanisms that shape granuloma architecture (13), a structural determinant critical for containment of mycobacterial dissemination during advanced disease. Parallel findings in Listeria monocytogenes infection models, wherein γδ TCR-deficient animals display aberrant neutrophil recruitment and hepatic abscess formation, further stresses their role in orchestrating inflammatory patterning rather than serving as dominant antimicrobial effectors (14). Effective resistance to microbial invasion reflects the coordinated integration of innate and adaptive immunity. Because pathogens typically invade peripheral tissues while naïve αβ T-cells reside within secondary lymphoid compartments, early containment relies upon tissue-resident and rapidly mobilized immune populations. Within this interface, γδ T-lymphocytes occupy a distinctive intermediary position. Their antigen receptors exhibit structural diversity within complementarity-determining regions, enabling recognition of conserved molecular motifs independently of classical MHC restriction. This functional adaptability supports their characterization as rapid-response sentinels capable of exerting

both local and systemic immunomodulatory effects in accordance with the inflammatory context. Although numerically limited within the circulating lymphocyte pool, γδ T-cells constitute a phenotypically distinct $CD3^+$ subset with established contributions to both antimicrobial defense and tumor immunity.

Within the paradigm of tumor immunosurveillance, γδ T-lymphocytes are distinguished by their prompt secretion of IFN-γ and potent cytolytic capacity. They detect cellular distress through activating receptors most prominently NKG2D which engage stress-induced ligands such as MICA, MICB, and retinoic acid inducible molecules expressed on transformed or damaged cells (15). Upregulation of these ligands in malignant tissues, including melanoma, renders tumor cells more susceptible to γδ T-cell–mediated destruction. The interaction between activating receptors and their ligands provides critical costimulatory signals that facilitate targeted elimination of neoplastic cells. Unlike conventional αβ T-lymphocytes that recognize antigen in a major histocompatibility complex (MHC)-restricted manner and display extensive TCR variability, γδ T-cells exhibit comparatively constrained V-region diversity. In humans, the predominant Vγ9Vδ2 subset responds to low-molecular-weight, non-peptidic phosphorylated metabolites known as phosphoantigens (16), which arise from microbial biosynthetic routes or endogenous metabolic pathways. Among these, HMBPP, generated via the non-mevalonate pathway in numerous microbes and plants, represents one of the most potent activators (17). Endogenous IPP can stimulate these cells, generally at higher concentrations, while alkylamines enhance responsiveness by promoting intracellular accumulation of mevalonate pathway intermediates. Although TCR expression is unequivocally necessary for phosphoantigen recognition, an observation substantiated by gene-transfer studies, the precise molecular mechanisms underlying antigen sensing by γδ T-cells remain to be fully elucidated.

Accumulating data further indicate that Vγ9Vδ2 T-cells can acquire adaptive-like characteristics analogous to immunological memory (18). Investigations in nonhuman primate models of tuberculosis have demonstrated marked clonal expansion following primary immunization, accompanied by a more rapid and robust response upon re-exposure to antigen (19). In addition to these memory-like properties, γδ T-cells, alongside NK cells, serve as an early source of IFN-γ during the initial stages of immune activation, preceding the full participation of conventional αβ T-cells. This early cytokine output is principally driven by IL-12 and IL-18 produced by APCs, reflecting the intermediary role of γδ T-cells at the interface of innate and adaptive immunity (20). Their translational significance is underscored by ongoing early-phase oncologic studies assessing nonpeptidic pharmacological agents designed to selectively stimulate γδ T-cells, thereby highlighting their promise in vaccine development and cancer immunotherapy.

From a developmental standpoint, γδ T-cells constitute the earliest T-cell lineage to emerge in the murine thymus and subsequently colonize peripheral epithelial tissues. In the human fetal thymus, the dominant population typically expresses the Vδ1 chain paired with diverse Vγ chains and preferentially homes to epithelial compartments, particularly the intestinal mucosa (21). Although Vδ1 cells represent a minor fraction of circulating peripheral blood lymphocytes, they form a substantial component of intraepithelial lymphocytes and are often expanded in epithelial malignancies and certain lymphoproliferative conditions. Experimental depletion of pulmonary γδ T-cells has been associated with enhanced microbial clearance, suggesting a regulatory role in limiting excessive Th1-driven inflammatory responses. Moreover, both Vδ1 and Vδ2 subsets demonstrate cytotoxic activity *in vitro* against cells infected by viruses, parasites, or bacteria, as well as against transformed targets. Preferential expansion of Vδ1 T-cells has also been observed in individuals with HIV infection and in immunocompromised patients experiencing cytomegalovirus reactivation, stressing their integral role in host defense and immune homeostasis under conditions of immune perturbation.

γδ T in MTb Infection

γδ T-lymphocytes have been documented within granulomatous cutaneous lesions in patients with leprosy, and γδ T-cell lines established from these individuals demonstrate robust proliferative responses upon exposure to mycobacterial extracts (22). Accumulating experimental data further substantiate the capacity of MTb to directly stimulate γδ T-cells. Limiting dilution studies conducted by Kabelitz and co-investigators revealed that a substantial proportion of circulating γδ T-cells proliferate following stimulation with inactivated MTb, predominantly within the Vγ9/Vδ2 subset—the major γδ T-cell population in the peripheral blood of healthy adults (23). Parallel investigations by Havlir et al. (24) showed that monocytes harboring viable MTb possess a markedly enhanced ability to drive Vγ9/Vδ2 T-cell expansion compared with monocytes treated with heat-killed organisms or soluble mycobacterial derivatives such as PPD. These studies further clarified that heat shock protein 65 is not a strong mitogenic trigger for γδ T-cells.

Despite these observations, the precise antigenic determinants engaged by the Vγ9/Vδ2 TCR during MTb infection remain incompletely characterized. Although the Vγ and Vδ gene repertoires exhibit more restricted variability than the Vα and Vβ chains of conventional αβ T-lymphocytes, recombination events involving diversity (D) and joining (J) gene segments generate considerable junctional diversity, thereby enabling broad antigenic recognition (25). The definitive role of γδ T-cells in protective immunity against tuberculosis remains unresolved. Barnes and associates reported diminished *in vitro* expansion of γδ T-cells from individuals with pulmonary or disseminated tuberculosis following stimulation with heat-inactivated MTb and IL-2, although marked interindividual heterogeneity was observed (26). While certain studies have described elevated frequencies of circulating γδ T-cells in active tuberculosis and among healthcare workers with occupational exposure, these findings have not been uniformly replicated. Moreover, although γδ T-cells are present within pulmonary granulomas, their abundance does not surpass that of αβ TCR-expressing T-cells and generally mirrors the frequencies detected in peripheral blood or in unaffected lung parenchyma. Their localization within granulomatous tissue aligns with the role of alveolar macrophages as APCs capable of facilitating γδ T-cell activation.

Substantial evidence indicates a prominent expansion of Vγ9Vδ2 T-cells in the peripheral blood of patients with tuberculosis, as well as in diverse infectious conditions, including leprosy, malaria, Salmonella infection, and *Streptococcus pneumoniae* infection.

Furthermore, γδ T-cell clones isolated from the synovial fluid of individuals with rheumatoid arthritis recover proliferative capacity upon re-exposure to mycobacterial antigens after prior sensitization (27). Limiting dilution analyses provide compelling support for MTb-driven γδ T-cell activation, demonstrating significant expansion of peripheral γδ T-cells following interaction with killed bacilli. Within the pulmonary microenvironment, alveolar macrophages, the principal cellular targets of inhaled mycobacteria, function as non-MHC-restricted accessory cells that promote γδ T-cell activation. Significant functional distinctions exist between alveolar macrophages and circulating monocytes. Under steady-state conditions, where macrophages outnumber T-cells in the alveolar compartment, baseline γδ T-cell proliferation may be restrained through contact- and dose-dependent regulatory mechanisms. However, upon MTb infection, alveolar macrophages acquire enhanced immunostimulatory properties, thereby fostering localized γδ T-cell responses. Optimal γδ T-cell proliferation, cytokine secretion, and cytolytic activity require appropriate costimulatory signaling. Comparative analyses of MTb-stimulated $CD4^+$ and γδ T-cells from tuberculin-positive healthy donors have demonstrated comparable intracellular IFN-γ production, confirming the capacity of γδ T-cells to generate this critical effector cytokine (28). In contrast, $CD4^+$ T-cells produce greater amounts of IL-2, a difference that may partially account for the relatively limited proliferative expansion typically observed within γδ T-cell populations.

Administration of BCG has consistently been associated with preferential amplification of circulating Vγ9Vδ2 T-lymphocytes. At the same time, other γδ T-cell subsets exhibit comparatively limited fluctuations, underscoring the antigen-selective nature of this response during mycobacterial exposure. Beyond the peripheral blood, elevated frequencies of Vγ9Vδ2 cells have been observed in the pulmonary and intestinal compartments following systemic BCG immunization. In contrast, secondary lymphoid organs, including draining lymph nodes, demonstrate only modest changes. This spatial distribution implies that mucosal and barrier tissues constitute primary sites for γδ T-cell expansion and effector activity in the context of mycobacterial challenge. Both antigen dose and route of administration critically shape γδ T-cell dynamics; systemic delivery of BCG promotes dose-dependent increases in γδ, $CD4^+$, and $CD8^+$ T-cell populations, with particularly pronounced enrichment of γδ T-cells within the lung microenvironment (29). The dominant Vγ9Vδ2 subset detects non-peptidic phosphorylated intermediates via TCR–dependent recognition. These phosphoantigens originate predominantly from the mevalonate pathway, a fundamental metabolic cascade essential for sterol biosynthesis and cellular equilibrium. In parallel with TCR-mediated signaling, human γδ T-cells express diverse NK receptors that fine-tune activation thresholds. Stimulatory engagement of NKG2D by stress-inducible ligands such as MICA and MICB delivers crucial costimulatory signals, whereas inhibitory complexes, including CD94/NKG2A, restrain cytotoxic activity against targets bearing MHC class I molecules (30). Additional receptor pairings, notably CD94/NKG2C and various killer immunoglobulin-like receptors, further calibrate functional responsiveness.

The potential of Vγ9Vδ2 T-lymphocytes to establish long-lived immunological memory remains an area of active inquiry. Evidence from nonhuman primate tuberculosis models reveals clonal expansion of phosphoantigen-reactive Vγ9Vδ2 populations after primary immunization, followed by accelerated and augmented secondary responses upon re-exposure, consistent with memory-like attributes (31). The mechanism of γδ T-lymphocyte activation and immune response is illustrated in Figure 1. Phenotypic heterogeneity within this subset parallels the differentiation continuum characteristic of conventional αβ T-cells. It may be stratified by CD45RA and CD27 expression into naïve, central memory, effector memory, and terminal effector states. Early upregulation of CD45RO signifies commitment toward a memory phenotype analogous to developmental pathways described for $CD8^+$ T-cells. Effector memory cells display enhanced trafficking to peripheral tissues and may subsequently transition into $CD45RA^+CD27^-$ terminal effectors, distinguished by potent cytokine production and cytolytic capacity (32). Upon encountering infected or metabolically perturbed cells, Vγ9Vδ2 T-lymphocytes promptly secrete chemokines and Th1-polarized cytokines, mostly IFN-γ, thereby playing a pivotal role in the initiation and amplification of early antimicrobial defense mechanisms.

Extensive evidence obtained from histopathological analyses, rigorously controlled *in vitro* systems, and diverse animal models confirms the presence of persistent bidirectional crosstalk between γδ T-lymphocytes and myeloid-lineage cells. Such reciprocal communication highlights the distinctive placement of γδ T-cells at the interface of innate and adaptive immune responses. Experimental observations, including those reported by Ismaili and collaborators, have demonstrated that phosphoantigen-stimulated human γδ T-cells facilitate the differentiation and maturation of monocyte-derived DCs *in vitro* (33). This maturation is accompanied by a marked increase in the expression of antigen-presenting and co-stimulatory molecules, notably HLA-DR, CD86, and CD83. Mechanistically, these effects are largely mediated by cytokines, as activated γδ T-cells release substantial amounts of tumor necrosis factor-α and IFN-γ upon phosphoantigen exposure. The regulatory influence of γδ T-cells extends beyond soluble mediators; direct cell–cell interactions also play a pivotal role, forming an integrated and multifaceted network of immune modulation.

Within the peripheral circulation, the Vγ9Vδ2 subset constitutes the dominant γδ T-cell population and undergoes significant clonal

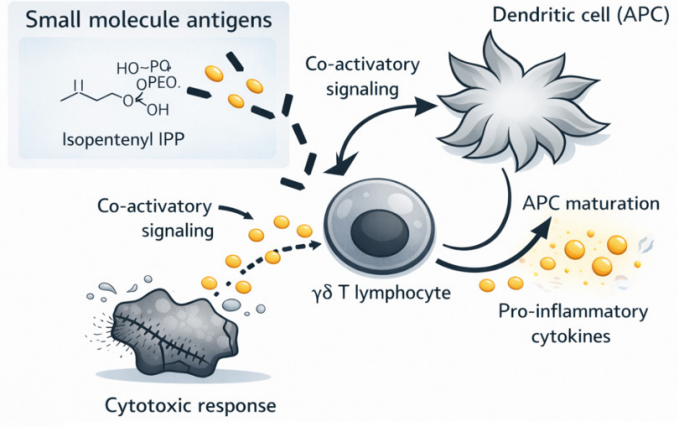

Figure 1. Mechanism of γδ T-lymphocyte activation and immune response. γδ T and dendritic cells.

γδ: Gamma delta.

expansion during infectious processes, occasionally comprising a considerable fraction of circulating T-lymphocytes. In contrast to conventional αβ T-cells, these cells exhibit a relatively restricted TCR repertoire, reflecting their evolutionarily conserved and specialized immunological functions. Their activation profile is contingent upon the nature of the stimulating signal. Pamidronate-induced activation requires close interaction with immature DCs to achieve full functional competence, whereas stimulation with IPP can occur independently of obligatory cellular contact (34). In both scenarios, cytokines within the microenvironment, particularly tumor necrosis factor-α and IFN-γ, serve as critical determinants of subsequent immune outcomes. Pamidronate, an aminobisphosphonate widely prescribed for osteoporosis and malignancy-associated bone disease, elicits robust γδ T-cell activation only in the presence of DCs, as reflected by upregulated expression of activation markers such as CD25 and CD69 and increased cytokine secretion; exposure in isolation produces comparatively modest effects (35). Moreover, γδ T-cells stimulated by IPP act synergistically with DCs undergoing lipopolysaccharide-driven maturation, leading to mutual amplification of activation signals and cytokine production. Collectively, these observations stress that microbial and pharmacologic stimuli enhance immune responsiveness through coordinated intercellular cooperation rather than isolated signaling events.

IL-15 further potentiates IFN-γ production by $CD4^+$ and $CD8^+$ T-lymphocytes, thereby reinforcing host defenses against mycobacterial pathogens. DCs infected and subsequently cultured with activated γδ T-cells display an increased capacity to direct naïve $CD4^+$ T-cells toward IFN-γ–producing phenotypes, compared with infected DCs maintained alone. This finding substantiates the concept that γδ T-cell engagement augments DC–mediated T-cell polarization and promotes pro-inflammatory cytokine responses. The pronounced expansion of γδ T-cells in response to BCG-infected DCs, even in the absence of supplemental cytokines, suggests the operation of self-sustaining reciprocal activation circuits that maintain localized inflammatory responses. Functional diversity emerges according to the mode of γδ T-cell expansion: Vγ9Vδ2 T cells expanded with IPP demonstrate limited capacity to restrict intracellular mycobacterial proliferation, whereas those expanded in response to BCG exhibit substantial antimycobacterial activity. These findings indicate that Vγ9Vδ2 T-cells play a critical role in preserving immunological homeostasis during bacterial infection by constraining pathogen dissemination, eliminating infected monocytes, and maintaining the antigen-presenting integrity of DCs. The interaction and activation pathways between DCs and Vγ9Vδ2 T-cells are illustrated in Figure 2.

Comprehensive transcriptomic profiling revealed that stimulation of peripheral blood mononuclear cells (PBMCs) with hemagglutinin antigen (HAg) induces a profound reorganization of global gene expression patterns. This remodeling was characterized by a significant enrichment of immunoregulatory signaling cascades, particularly those associated with tumour necrosis factor (TNF), IL-17, and JAK–STAT pathways. Quantitative real-time PCR validation corroborated these high-throughput findings, demonstrating robust upregulation of cytokine-encoding genes integral to antimycobacterial immunity following antigenic exposure. Functionally, γδ T-lymphocytes isolated from HAg-stimulated PBMCs of tuberculosis patients produced substantially higher levels of IFN-γ than those healthy individuals, indicating enhanced antigen sensitivity and effector competence. These HAg-primed γδ T-cells maintained IFN-γ secretion even under Th2-skewing conditions. This preserved functionality coincided with the expansion of Th1-like ($IFN\text{-}\gamma^+IL\text{-}4^-$) and Th0-like ($IFN\text{-}\gamma^+IL\text{-}4^+$) γδ T-cell subsets, alongside upregulation of the master transcription factors T-bet and GATA-3. Contrary to the classical model, which proposes mutual antagonism between these lineage regulators, the evidence does not support a definitive reciprocal inhibitory interaction. Experimental observations in murine systems further suggested that T-bet predominantly augments IFN-γ production while constraining IL-4 synthesis, whereas GATA-3 exerts limited suppressive influence on T-bet–mediated IFN-γ expression (36).

In addition to Th1-associated cytokines, HAg stimulation amplified γδ T-cell production of IL-17 and IL-22, with $Vδ2^+$ subsets exhibiting particularly pronounced responses following supplementation with exogenous IL-1β and IL-23 (37). Beyond γδ T-cells, NK cells demonstrated the capacity to develop durable, antigen-specific adaptive-like responses independent of classical B-cell and αβ T-cell pathways. $CD45RO^+$ NK cells isolated from pleural effusions of individuals with tuberculous pleuritis responded to HAg exposure by producing IL-22 and mounting recall responses against MTb, in contrast to NK cells from healthy PBMCs. Combined stimulation with IL-12, IL-15, and BCG further potentiated NK-cell activation, as reflected by increased expression of NKG2D, CD25, CD69, and granzyme B (38). These activated NK-cell populations were associated with the mitigation of inflammatory tissue injury and the preservation of pulmonary mucosal integrity. Collectively, these findings implicate HAg as a promising immunological adjuvant capable of strengthening BCG-induced protective immunity. Moreover, HAg-expanded γδ T-cells exhibited cytotoxic activity against hepatocellular carcinoma cells through mechanisms involving NKG2D engagement and ERK1/2 signaling (39). The role of Vγ9Vδ2 T-cells in tuberculosis-associated immune responses is summarized in Figure 3.

Contemporary models of host defense stress the importance of coordinated interactions among diverse immune cell subsets. Even numerically limited populations within infected tissues may exert substantial immunomodulatory effects through sustained communication with innate effector cells and APCs. During MTb infection, γδ-T-lymphocytes and DCs serve pivotal roles in

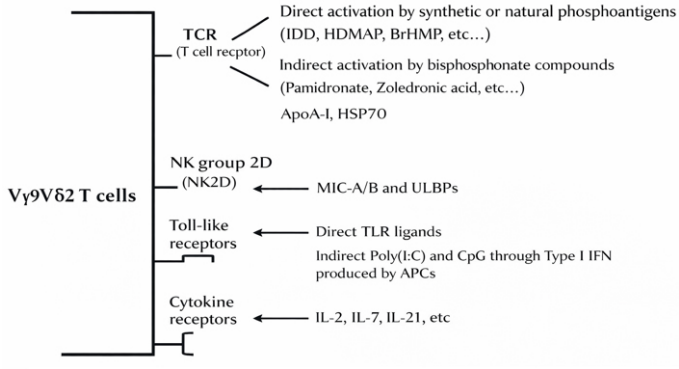

Figure 2. Activation pathways of Vγ9Vδ2 T-cells. γδ T interactions to MTb.
γδ: Gamma delta, MTb: Mycobacterium tuberculosis.

shaping early immune responses. Convergent evidence from histopathological studies, *in vitro* analyses, and *in vivo* models supports continuous, bidirectional crosstalk between γδ T-cells and myeloid compartments. Through secretion of pro-inflammatory mediators such as IFN-γ and TNF-α, as well as chemokines that enhance cytotoxic potential and modulate the local immune milieu, γδ T-cells contribute substantially to frontline antimycobacterial defense (40). Previous investigations have demonstrated that phosphoantigen-activated human γδ T-cells facilitate the maturation of monocyte-derived DCs. Although DCs are recognized as essential orchestrators of cellular immunity in tuberculosis, their functional behavior within infected tissues remains incompletely defined (41). In early disease stages, DCs accumulate at sites of inflammation, undergo pathogen-induced maturation, and subsequently migrate to secondary lymphoid organs, where they prime naïve T-cells by upregulating MHC molecules and co-stimulatory receptors and secreting cytokines such as IL-12.

In vivo studies further indicate that MTb can compromise DC migratory capacity and antigen-presenting function, thereby promoting bacterial persistence. Disruption of myeloid DC trafficking and competency appears to represent a strategic mechanism facilitating chronic infection. Under physiologically relevant conditions, particularly when Vγ9Vδ2 T-cells are activated in the context of incomplete DC maturation additional environmental cues likely influence the activation states of both cellular populations (42). Evidence suggests that Vγ9Vδ2 T-cells can drive the full maturation of MTb-infected immature DCs that would otherwise remain partially differentiated. Whereas infection alone elevates CD86 and HLA-DR expression without significantly increasing CD80 or CD40 expression, co-culture with Vγ9Vδ2 T-cells enhances CD80 and CD40 expression, sustains HLA-DR and CD86 expression, and markedly augments IL-12p70 secretion. Conversely, inadequate differentiation of Vγ9Vδ2 T-cells has been associated with insufficient IL-15 production by infected DCs. Given the critical role of IL-15 in promoting γδ T-cell differentiation toward an effector-memory phenotype—mediated through induction of Bcl-2 and enhanced resistance to apoptosis—deficiency of this cytokine may compromise the establishment of fully effective γδ T-cell–dependent protective immunity.

γδ T Maturation to MTb

Barnes and colleagues reported that patients with pulmonary or disseminated (miliary) tuberculosis exhibited a diminished *in vitro* proliferative response of γδ T-lymphocytes when these cells were stimulated with heat-inactivated Mtb in the presence of IL-2. However, the degree of impairment differed substantially among individuals. Data concerning the circulating proportions of γδ T-cells in individuals with tuberculosis and in healthcare workers exposed to the organism remain inconsistent; studies have reported divergent findings. Histological analyses have confirmed the presence of γδ T-cells within tuberculous pulmonary lesions; however, their abundance does not surpass levels detected in peripheral blood or uninvolved lung parenchyma. Their recruitment to infected tissue is consistent with the established role of alveolar macrophages as competent APCs capable of initiating γδ T-cell activation. Schwander et al. (43) further documented pronounced monocyte infiltration within the alveolar spaces of tuberculous lungs. Given that monocytes likewise possess antigen-presenting capacity, the inflammatory milieu within diseased lung tissue appears conducive to localized activation of γδ T-lymphocytes.

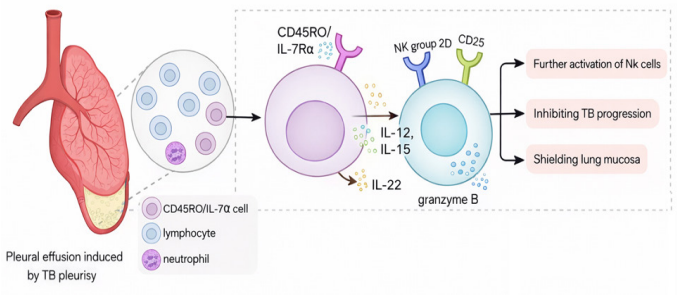

Figure 3. Role of Vγ9Vδ2 T-cells in tuberculosis-associated immune responses.

Robust expansion of Vγ9Vδ2 T-cells has been observed in neonates following BCG vaccination; this response is attributed to specific mycobacterial phosphoantigens. In the setting of active tuberculosis, circulating Vγ9Vδ2 T-cells exhibit transient phenotypic modulation that typically normalizes after successful antimicrobial therapy. Despite maintaining, or in some cases demonstrating, enhanced proliferative responsiveness, these cells produce lower quantities of IFN-γ than cells derived from healthy, tuberculin-reactive individuals. Dieli et al. (44) further demonstrated that this functional compromise extends beyond cytokine production to include reduced granulysin expression, thereby potentially attenuating antimycobacterial cytotoxic activity .

The mechanisms underlying this functional impairment remain incompletely defined. One proposed explanation implicates chronic antigenic stimulation *in vivo* as a driver of activation-induced cell death within the Vγ9Vδ2 subset. Alternatively, defective differentiation of central memory Vγ9Vδ2 cells into effector populations may result from suboptimal cytokine signals provided by Mtb-infected DCs. Experimental findings indicate that progression toward effector memory and terminally differentiated phenotypes depends critically on IL-15, whereas IL-7 is insufficient to substitute for this signal (45). IL-15 facilitates survival during this maturation process through induction of anti-apoptotic mechanisms, including upregulation of Bcl-2. Meraviglia et al. (46) have suggested that DCs harboring Mtb exhibit reduced IL-15 production, not because of an inherent defect in its induction, but as a consequence of pathogen-mediated suppression, thereby limiting effective Vγ9Vδ2 T-cell effector differentiation.

γδ T-based Immunotherapy

γδ T-lymphocytes possess potent antimicrobial and antineoplastic capabilities, attributable to their capacity to release proinflammatory cytokines, chemokines, and cytotoxic effector molecules, including perforin and granzymes (47). Through these mechanisms, they play a central role in immune surveillance and are increasingly regarded as valuable candidates in the development of next-generation immunotherapeutic strategies. In addition to their inherent cytolytic activity, γδ T-cells exert important immunomodulatory effects on DCs, promoting their maturation and enhancing antigen-presenting competence (48). This bidirectional interaction between innate-like and adaptive immune compartments is particularly relevant

for individualized immunotherapy, which requires coordinated immune activation. Although other unconventional lymphocyte subsets can stimulate DC function, circulating human γδ T-cells are distinguished by their relative abundance and their efficiency in amplifying DC-mediated immune responses. Their activation can be triggered by a wide array of endogenous and synthetic non-peptidic phosphoantigens, such as IPP, dimethylallyl diphosphate, geranylgeranyl pyrophosphate, and nitrogen-containing bisphosphonates, underscoring the diversity of metabolic and pharmacological signals capable of engaging this population.

Within the tumor microenvironment, malignant cells frequently circumvent immune detection by reducing the expression of tumor-associated antigens, downregulating MHC molecules, and impairing signaling pathways. Unlike conventional αβ T-lymphocytes, γδ T-cells recognize transformed targets in a largely MHC-independent fashion and exhibit diminished dependence on classical costimulatory signals, including CD28-mediated pathways (49). These properties provide a significant advantage in antitumor immunity. Experimental studies have demonstrated their protective function in murine models of chemically induced carcinogenesis and have shown robust cytotoxicity against diverse human tumor cell lines *in vitro* (50). Furthermore, adoptive transfer of *ex vivo* expanded human Vγ9Vδ2 T-cells into immunodeficient mice bearing xenografted malignancies has yielded therapeutic benefit in models of B-cell lymphoma, melanoma, and renal cell carcinoma (51). Pharmacological agents such as zoledronate have been reported to promote *in vivo* expansion of circulating γδ T-cells, thereby augmenting IFN-γ secretion and cytolytic potential (52). Early-phase clinical investigations in metastatic castration-resistant prostate cancer have established the feasibility and tolerability of Vγ9Vδ2 T-cell activation using zoledronate, either as monotherapy or in conjunction with low-dose IL-2, with preliminary signals of antitumor activity. The therapeutic impact observed in solid tumors likely reflects the dual functionality of γδ T-cells, encompassing direct tumor cell destruction following tissue infiltration and indirect enhancement of $CD8^+$ T-cell responses via DC modulation.

Studies in nonhuman primate models have provided additional insight into the adaptive-like attributes of γδ T-cells. Distinct peripheral γδ T-cell subsets —namely naïve, central memory ($CD27^+$), and effector memory ($CD27^-$) populations— have been phenotypically delineated across multiple primate species using monoclonal antibodies targeting human T-cell markers. Their *in vivo* proliferation following phosphoantigen stimulation has been shown to require IL-2. Enhanced immunogenicity to mycobacterial antigens has likewise been observed in cynomolgus macaques subjected to prime–boost vaccination with the H-1 fusion antigen formulated in Lipovac adjuvant, administered alone or together with the synthetic phosphoantigen Picostim (53). Although IC31 advanced to clinical evaluation in combination with the H-1 subunit vaccine, Lipovac was preferentially employed in experimental contexts due to its comparatively limited intrinsic immunostimulatory activity, thereby enabling clearer assessment of phosphoantigen-specific effects (54). Immunization strategies combining phosphoantigens and antituberculous subunit vaccines produced distinct T-cell kinetic patterns, in which booster administration attenuated γδ T-cell effector functions while simultaneously amplifying recall responses in αβ T-lymphocytes.

CONCLUSION

An expanding corpus of scientific literature has delineated the proliferative behavior, intracellular signaling networks, and functional effector properties of γδ T-lymphocytes within the intricate immunopathological landscape of tuberculosis. Findings from animal-based *in vivo* models, complemented by *in vitro* studies using human cellular systems, have progressively elucidated the contribution of γδ T-cells to orchestrating protective immune responses against Mtb. Their translation into clinical practice remains relatively limited. Only a modest number of clinical investigations have examined the therapeutic potential of γδ T-cells—particularly the Vγ9Vδ2 subset—within contemporary tuberculosis treatment frameworks. Unlike conventional αβ T-lymphocyte populations, γδ T-cells circulate at comparatively low frequencies under physiological conditions. Furthermore, the absence of well-established and phenotypically stable *in vitro* cell lines restricts comprehensive mechanistic exploration and translational advancement. Consequently, most experimental methodologies rely heavily on freshly isolated peripheral blood samples, which pose technical challenges associated with efficient cell purification, large-scale *ex vivo* expansion, and preservation of functional integrity and phenotypic stability, thereby imposing substantial practical limitations. Taken together, the unique capacity of γδ T-lymphocytes to function at the interface of innate and adaptive immunity, enabling rapid recognition of phosphoantigen-producing mycobacteria and other intracellular pathogens highlights their considerable promise as strategic candidates for the development of next-generation immunotherapeutic approaches in the management of tuberculosis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.D., Concept: S.R.A., N.S., Design: S.R.A., N.S., Data Collection or Processing: A.D., Analysis or Interpretation: R.G., V.J.L., R.K.V., Literature Search: A.D., Writing: A.D.

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