Review article

doi:10.5633/amm.2026.0116

Physiological Roles of Gamma Delta (γδ) T Cells: From Immunity to Clinical Applications

Pavle Randjelović

Department of Physiology, Faculty of Medicine, University of Nis, Nis, Serbia

Contact: Pavle Randjelović

81 Dr Zorana Djindjica Blvd., 18000, Niš, Serbia

E-mail: pavleus@gmail.com

Gamma delta (γδ) T cells represent a unique subset of lymphocytes that bridge innate and adaptive immunity through their ability to recognize stress-induced ligands in an MHC-independent manner. Distributed primarily at epithelial barriers, these cells act as sentinels against infection and malignant transformation while simultaneously contributing to tissue repair and homeostasis. Functionally, γδ T cells are highly versatile: they produce pro-inflammatory cytokines such as IFN-γ and IL-17, mediate direct cytotoxicity, and, under certain conditions, exert regulatory roles by secreting IL-10 and TGF-β. This dual capacity allows them to either protect against pathogens and tumors or contribute to chronic inflammation and autoimmunity. Recent advances have highlighted their clinical significance across a broad spectrum of diseases, including cancer, infectious and autoimmune disorders, metabolic and cardiovascular conditions, and pregnancy-related complications. Moreover, their potential as biomarkers and therapeutic targets has been demonstrated through adoptive transfer, in vivo activation, and genetic engineering approaches. Despite this promise, the plasticity of γδ T cells presents challenges, as the same subsets that confer protection in one context may exacerbate pathology in another. A deeper understanding of their biology and microenvironmental regulation is therefore essential for harnessing their therapeutic potential. This review summarizes the current knowledge of the

physiological roles of γδ T cells across tissues and disease states, emphasizing their translational relevance and opportunities for clinical application.

Keywords: γδ T cells, immunity, tissue repair, infection, autoimmunity

Pregledni rad

doi:10.5633/amm.2026.0116

Fiziološke uloge gama delta (γδ) T ćelija: od imuniteta do kliničke primene

Pavle Randjelović[1]

Katedra za Fiziologiju, Medicinski fakultet u Nišu, Univerzitet u Nišu, Niš, Srbija

Kontakt: Pavle Ranđelović

Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija

E-mail: pavleus@gmail.com

Gama delta (γδ) T ćelije predstavljaju jedinstveni podskup limfocita koji premošćuju urođeni i adaptivni imunitet kroz svoju sposobnost da prepoznaju ligande izazvane stresom na način nezavisan od MHC. Rasprostranjene prvenstveno na epitelnim barijerama, ove ćelije deluju kao čuvari protiv infekcije i maligne transformacije, dok istovremeno doprinose popravci tkiva i homeostazi. Funkcionalno, gd T ćelije su veoma raznovrsne: proizvode proinflamatorne citokine kao što su IFN-g i IL-17, posreduju u direktnoj citotoksičnosti i, pod određenim uslovima, obavljaju regulatorne uloge lučenjem IL-10 i TGF-b. Ovaj dvostruki kapacitet im omogućava da ili štite od patogena i tumora ili doprinose hroničnoj upali i autoimunitetu. Nedavni napredak je istakao njihov klinički značaj u širokom spektru bolesti, uključujući rak, infektivne i autoimune poremećaje, metaboličke i kardiovaskularne bolesti i komplikacije povezane sa trudnoćom. Štaviše, njihov potencijal kao biomarkera i terapijskih meta je dokazan kroz adoptivni transfer, aktivaciju in vivo i pristupe genetskog inženjeringa. Uprkos ovom obećanju, plastičnost gd T ćelija predstavlja izazove, jer isti podskupovi koji pružaju zaštitu u jednom kontekstu mogu pogoršati patologiju u drugom. Dublje razumevanje njihove biologije i regulacije mikrookruženja je stoga neophodno za iskorišćavanje njihovog terapeutskog potencijala. Ovaj pregled sumira trenutna znanja o fiziološkim ulogama gd T ćelija u različitim tkivima i bolesnim stanjima, naglašavajući njihov translacioni značaj i mogućnosti za kliničku primenu.

Ključne reči: γδ T ćelije, imunitet, popravka tkiva, infekcija, autoimunitet

Introduction

Gamma delta (γδ) T cells represent a unique population of lymphocytes that bridge innate and adaptive immunity. Unlike conventional αβ T cells, they recognize antigens independently of classical major histocompatibility complex (MHC) molecules, enabling them to respond rapidly to cellular stress, infection, and malignant transformation. Their distinctive biology allows them to combine the rapid responsiveness of innate immunity with features of adaptive memory, positioning them as versatile regulators of host defense (1,2).

In humans, γδ T cells account for only 1–10% of circulating T lymphocytes, but they are disproportionately enriched in epithelial and mucosal tissues such as the skin, intestine, and lungs. At these barrier sites, they function as first-line sentinels, capable of detecting microbial invasion and tissue injury. In contrast, certain animal species, including ruminants, possess a γδ T cell–dominated immune system, underlining their evolutionary importance in immune surveillance (3,4).

Beyond their role in pathogen defense, γδ T cells contribute to tissue integrity by secreting cytokines and growth factors that promote repair and regeneration. Their ability to sense stress ligands and metabolic changes enables them to adapt to a wide range of physiological contexts, from maintaining barrier function to modulating inflammation. This dual role — protective in some settings, pathogenic in others — highlights the complexity of γδ T cell biology and underscores the need for comprehensive study (5,6).

Development and Distribution of γδ T Cells

The development of γδ T cells begins in the thymus, where distinct waves of precursors emerge during ontogeny. Unlike αβ T cells, whose repertoire is heavily shaped by MHC-mediated selection, γδ T cells rely on ligand recognition and signaling thresholds to define their effector fate. Many γδ thymocytes emigrate as pre-committed effector cells, already programmed to produce cytokines such as interferon-γ (IFN-γ) or interleukin-17 (IL-17), enabling them to mount rapid immune responses soon after leaving the thymus (1).

A defining feature of most γδ T cells is their double-negative (DN) phenotype, lacking both CD4 and CD8 co-receptors. This $CD4^{-}CD8^{-}$ profile distinguishes them from conventional αβ T cells and reflects their unique mode of antigen recognition. DN γδ T cells are functionally diverse: they can exert potent cytotoxicity, secrete pro-inflammatory cytokines, or adopt regulatory roles depending

on context. Their prevalence across tissues and conservation across species underscore their importance as flexible effectors and regulators of immune responses (7).

The distribution of γδ T cells varies widely between tissues. In humans, the blood compartment is dominated by Vγ9Vδ2 T cells, which respond to phosphoantigens derived from the mevalonate pathway and serve as critical sensors of cellular metabolic stress. In contrast, Vδ1 T cells are enriched in mucosal sites such as the gut and lungs, where they monitor epithelial integrity and interact closely with the microbiota. In the skin, dendritic epidermal T cells (DETCs) represent a tissue-resident population specialized for surveillance and wound repair. This compartmentalization ensures that γδ T cells are strategically positioned at the frontlines of host defense (8).

Functional Characteristics of γδ T Cells

γδ T cells are distinguished by their ability to recognize antigens in a manner independent of classical MHC restriction. Instead of requiring peptide presentation by MHC molecules, they detect stress-induced ligands, phosphoantigens, and non-peptidic metabolites that signal cellular dysregulation. This unique recognition strategy allows them to respond swiftly to infection and transformation, often within hours of challenge, bridging the gap between innate and adaptive immunity (9,10).

Cytokine production is one of the hallmarks of γδ T cell function. Depending on their developmental programming and local microenvironment, γδ T cells can secrete interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) to promote Th1-type immunity, or interleukin-17 (IL-17) and interleukin-22 (IL-22) to drive neutrophilic responses and tissue repair. In certain contexts, they produce regulatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which suppress excessive inflammation and support immune tolerance. This cytokine plasticity allows γδ T cells to act as pro-inflammatory effectors or as regulators, depending on the immune context (11,12).

In addition to their cytokine repertoire, γδ T cells exhibit potent cytotoxic activity. Through the release of perforin, granzymes, and granulysin, they are capable of directly killing infected or malignant cells. This cytolytic machinery is often triggered by recognition of stress ligands such as MICA and MICB, expressed on transformed or infected cells. Importantly, this function operates independently of antigen presentation by MHC, giving γδ T cells a broad spectrum of targets in both infection and cancer (13,14).

Another defining characteristic of γδ T cells is their ability to function as professional antigen-presenting cells (APCs). Certain γδ subsets can process and present antigens to $CD4^+$ and $CD8^+$ αβ T cells, thereby shaping downstream adaptive responses. Through this antigen-presenting capacity, they serve as a bridge that not only initiates immediate defense but also orchestrates longer-term immune memory. Furthermore, their responsiveness to metabolites of the mevalonate pathway highlights the deep connection between γδ T cells and immunometabolic regulation, positioning them as sensitive detectors of both external pathogens and internal stress signals (15,16).

Physiological Roles in Tissue Homeostasis

γδ T cells are particularly enriched at epithelial barriers, where they contribute to the maintenance of tissue integrity and homeostasis. In the skin, dendritic epidermal T cells (DETCs) serve as long-lived sentinels that continuously monitor keratinocytes for signs of stress or injury. Upon activation, they release keratinocyte growth factor (KGF) and other mediators that promote wound repair, epithelial regeneration, and barrier restoration. However, when dysregulated, the same cells can produce interleukin-17 (IL-17) and interleukin-22 (IL-22), driving chronic skin inflammation as observed in psoriasis (17,18).

In the gut, γδ intraepithelial lymphocytes (IELs) play essential roles in balancing immune tolerance and defense. They produce IL-22 and antimicrobial peptides that strengthen the epithelial barrier and regulate the microbiota. Their interactions with commensal organisms are reciprocal, as microbial products influence IEL differentiation and function. Disruption of this balance has been implicated in inflammatory bowel diseases, where excessive IFN-γ and IL-17 production by γδ T cells exacerbates inflammation. Conversely, regulatory subsets can mitigate pathology by promoting epithelial repair and tolerance to commensals (19).

The respiratory tract also contains significant populations of γδ T cells that contribute to barrier defense. During bacterial pneumonia or viral infections, these cells expand rapidly and produce IL-17 and IL-22, which recruit neutrophils and support epithelial regeneration. While protective in acute infection, excessive IL-17 production can amplify inflammation and contribute to chronic airway disease and asthma. This context-dependent activity highlights the fine balance between protective and pathogenic functions of γδ T cells in the lungs (20,21).

In the liver, γδ T cells act as rapid responders to hepatocellular stress and infection. They secrete interferon-γ (IFN-γ) and IL-17 during viral hepatitis, which can limit viral replication but also exacerbate tissue damage. In chronic liver disease, γδ T cells influence fibrogenesis through interactions with hepatic stellate cells, either promoting fibrosis via pro-inflammatory cytokines or restraining it through IL-10 production. Their context-dependent activities underscore their complex contribution to liver health and pathology (22,23).

γδ T cells are also found in the kidney, where they infiltrate tissue during acute kidney injury and autoimmune nephritis. By releasing IL-17, they recruit neutrophils and amplify tissue damage, whereas regulatory subsets may limit renal inflammation. These opposing functions position γδ T cells as double-edged swords in renal immunity, with potential as targets for therapeutic intervention (24,25).

Finally, in the reproductive system, γδ T cells contribute to immune balance at the maternal–fetal interface. In the decidua, they release IL-10 and TGF-β to promote tolerance and support implantation, while simultaneously protecting against infected or transformed trophoblasts. Dysregulated γδ T cell responses have been linked to pregnancy complications such as recurrent miscarriages and preeclampsia, demonstrating their central role in reproductive immunology (26,27).

γδ T Cells in Disease

Infectious Diseases

γδ T cells are rapidly mobilized during infections, where they provide early defense against a wide range of pathogens. Unlike conventional αβ T cells, which require antigen presentation by professional APCs, γδ T cells can respond directly to stress-induced ligands and non-peptidic metabolites associated with infection. This ability enables them to act within hours, contributing to the containment of microbial spread and shaping subsequent adaptive responses (28).

Human Vγ9Vδ2 T cells are particularly responsive to bacterial infections due to their recognition of phosphoantigens derived from the microbial non-mevalonate pathway. They expand robustly in response to pathogens such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*, producing IFN-γ and TNF-α that activate macrophages and enhance bacterial clearance.

Experimental and clinical data also show their ability to release granulysin, which directly kills intracellular bacteria (29,30).

In viral diseases, γδ T cells exert antiviral activity through cytotoxic mechanisms and cytokine production. They have been implicated in control of cytomegalovirus (CMV), Epstein–Barr virus (EBV), and hepatitis B virus (HBV). Expanded γδ T cell subsets in HBV-infected patients secrete IFN-γ and exhibit cytotoxicity against infected hepatocytes, while regulatory subsets can dampen excessive inflammation. Their role in HIV infection is more complex, as chronic antigen stimulation can lead to functional exhaustion (29,31).

γδ T cells also contribute to host defense against parasites and fungi. They can recognize metabolites produced by *Plasmodium* species and secrete IL-17 and IFN-γ that enhance protective immunity. In fungal infections, such as *Candida albicans*, γδ T cells promote neutrophil recruitment and strengthen barrier integrity through IL-22 production. However, overactivation may amplify tissue damage, demonstrating their context-dependent role (32).

Collectively, these findings highlight the central role of γδ T cells as first responders in infection. By bridging innate and adaptive immunity, they shape early defense mechanisms while also influencing long-term pathogen-specific memory. Their rapid response to microbial metabolites makes them attractive targets for novel immunotherapeutic strategies against infectious diseases (33).

Tumors and Antitumor Immunity

γδ T cells play a dual role in cancer, acting as both potent antitumor effectors and, under certain conditions, contributors to tumor progression. Their ability to recognize stress ligands independently of MHC enables them to detect transformed cells early, before conventional αβ T cells are activated. This makes them an attractive focus for tumor immunology research (34).

Activated γδ T cells exert strong cytotoxicity against tumor cells through perforin, granzymes, and granulysin. They also produce IFN-γ and TNF-α, which enhance antitumor immunity by recruiting and activating natural killer (NK) cells, dendritic cells, and cytotoxic $CD8^+$ T lymphocytes. In clinical studies, elevated γδ T cell numbers after hematopoietic stem cell transplantation correlate with reduced relapse and improved overall survival in leukemia patients (35,36).

Despite their protective potential, γδ T cells can also contribute to tumor progression. Certain subsets, particularly IL-17–producing γδ T cells, promote angiogenesis and recruit myeloid-

derived suppressor cells (MDSCs), creating an immunosuppressive tumor microenvironment. In some solid tumors, high IL-17 levels from γδ T cells correlate with poor prognosis, underscoring the double-edged nature of their activity (34).

Harnessing γδ T cells for cancer therapy is an active area of research. Strategies include ex vivo expansion and adoptive transfer of Vγ9Vδ2 T cells, stimulation with aminobisphosphonates such as zoledronate, and genetic engineering to produce CAR-γδ T cells with enhanced specificity. Early-phase clinical trials demonstrate safety and feasibility, although optimizing efficacy and preventing pro-tumor polarization remain challenges for translation (36).

Together, these findings highlight the ambivalent role of γδ T cells in cancer. Their intrinsic cytotoxicity and ability to bridge innate and adaptive immunity offer promising therapeutic opportunities, yet their plasticity also carries the risk of promoting tumor progression under certain conditions. Understanding the molecular switches that direct them toward protective versus pathogenic roles remains a major priority in tumor immunology (34).

Autoimmune Diseases

γδ T cells are increasingly recognized as key players in the pathogenesis and regulation of autoimmune diseases. Their ability to rapidly produce cytokines, particularly IFN-γ and IL-17, places them at the crossroads of inflammation and tissue damage. At the same time, certain γδ subsets exert regulatory functions, restraining immune responses and promoting tolerance. This duality underscores their complex involvement in autoimmunity (37).

In Multiple sclerosis (MS) γδ T cells infiltrate the central nervous system and contribute to demyelination through IL-17 and IFN-γ production. Experimental autoimmune encephalomyelitis (EAE) models have shown that depletion of γδ T cells delays disease onset, supporting their pathogenic role. However, other subsets produce IL-10 and may protect against excessive inflammation, highlighting subset-specific functions in neuroinflammation (38,37).

Synovial tissues in RA patients often contain expanded populations of γδ T cells. These cells secrete pro-inflammatory cytokines and matrix metalloproteinases that promote joint destruction. At the same time, some γδ subsets may dampen autoreactive αβ T cell responses, again illustrating the balance between pathogenic and regulatory roles (39).

In Crohn's disease and ulcerative colitis, intestinal γδ T cells contribute to pathology by producing IL-17 and TNF-α in response to dysregulated microbiota. Conversely, γδ IELs that produce IL-22 and growth factors can protect the epithelial barrier and mitigate chronic inflammation. The

outcome depends on which subsets dominate, suggesting that γδ T cell imbalance is a driver of IBD progression (40).

In lupus nephritis, γδ T cells accumulate in renal tissue, where they release IL-17 and cytotoxic mediators that aggravate kidney damage. Their frequency and cytokine profiles in blood and urine have been associated with disease severity, pointing to their potential as biomarkers in SLE. Regulatory subsets, however, may counteract autoantibody-driven inflammation (39).

Taken together, γδ T cells act as both pathogenic effectors and regulators in autoimmune diseases. Therapeutic strategies aimed at modulating their function—by inhibiting inflammatory subsets or boosting regulatory ones—could provide new avenues for controlling chronic autoimmune pathology (12).

Transplantation and Graft-versus-Host Disease (GVHD)

γδ T cells have unique functions in the context of transplantation. After hematopoietic stem cell transplantation (HSCT), elevated γδ T cell numbers correlate with reduced relapse and improved overall survival in leukemia patients. Their cytotoxic activity against leukemia cells, combined with reduced alloreactivity compared to αβ T cells, makes them attractive for promoting graft-versus-leukemia effects without severe GVHD. Nonetheless, some γδ subsets may contribute to inflammation and tissue damage in graft settings, indicating the need for careful balance (36).

Allergic and Hypersensitivity Disorders

In allergic diseases, γδ T cells produce IL-17 and IL-4, promoting recruitment of neutrophils and eosinophils. In asthma, their IL-17 responses exacerbate airway inflammation, whereas IL-22 production may help repair epithelium. Similarly, in contact hypersensitivity, γδ T cells amplify skin inflammation but also contribute to resolution by releasing anti-inflammatory mediators. Their net effect depends on disease stage and cytokine context (41,42).

Cardiovascular Diseases

γδ T cells participate in cardiovascular pathology by modulating inflammation in vascular tissues. In models of atherosclerosis, IL-17–producing γδ T cells accelerate plaque development, while IFN-γ–producing subsets promote vascular inflammation. Conversely, regulatory γδ T cells may suppress excessive responses and limit vascular damage. Their presence in ischemia-reperfusion injury also suggests a role in tissue repair and remodeling (43).

Neurological Diseases

Beyond multiple sclerosis, γδ T cells may be involved in other neuroinflammatory conditions. In Alzheimer's disease, activated γδ T cells have been detected in the brain, where they may promote neuroinflammation and neuronal damage. Experimental models suggest that γδ-derived IL-17 contributes to microglial activation, linking these cells to chronic neurodegeneration. Regulatory subsets, however, may support neuroprotection by limiting excessive inflammation (44).

Metabolic and Endocrine Diseases

γδ T cells sense metabolic stress and are increasingly implicated in metabolic disorders. In obesity and type 2 diabetes, γδ T cells accumulate in adipose tissue, producing IL-17 and IFN-γ that worsen insulin resistance. Conversely, IL-10–producing γδ T cells may counteract inflammation and improve metabolic homeostasis. Similar imbalances are reported in autoimmune endocrine diseases such as Hashimoto thyroiditis and type 1 diabetes, where inflammatory γδ T cells promote tissue destruction (43).

Aging and Immunosenescence

Aging reshapes the γδ T cell compartment. While overall numbers may decline, functional polarization shifts toward pro-inflammatory phenotypes, contributing to chronic low-grade inflammation ("inflammaging"). This imbalance reduces protective responses to infection and vaccines while predisposing to autoimmunity and degenerative diseases. At the same time, the persistence of memory-like γδ subsets highlights their adaptability throughout the lifespan (45).

Clinical Applications and Therapeutic Potential

The unique biology of γδ T cells, positioned between innate and adaptive immunity, has spurred intensive efforts to harness them for therapeutic purposes. Their rapid responses, broad target recognition, and ability to modulate other immune cells make them attractive candidates in immunotherapy, regenerative medicine, and biomarker development (36).

γδ T cells are being tested as effector cells in adoptive immunotherapy. Vγ9Vδ2 T cells can be expanded ex vivo using aminobisphosphonates such as zoledronate or synthetic phosphoantigens, then reinfused into patients. Clinical trials have demonstrated safety and modest efficacy, with improved outcomes in hematologic malignancies compared to solid tumors. More advanced strategies involve genetic engineering of γδ T cells with chimeric antigen receptors (CAR-γδ T

cells), which combine intrinsic broad recognition with targeted specificity. Early results suggest potential advantages over conventional CAR-αβ T cells, including reduced risk of graft-versus-host disease (16).

γδ T cells exhibit memory-like properties after certain infections and vaccinations. Their rapid recall responses, particularly of Vγ9Vδ2 subsets, suggest they may function as unconventional memory cells. Vaccines designed to engage γδ T cells directly or indirectly could enhance protective immunity against pathogens such as Mycobacterium tuberculosis or Plasmodium falciparum. Additionally, their cross-talk with dendritic cells positions them as adjuvant-like enhancers of vaccine efficacy (28).

Through secretion of IL-22, IL-10, and growth factors such as keratinocyte growth factor (KGF), γδ T cells promote epithelial regeneration in the skin, lung, and gut. Their contributions to wound healing and fibrosis regulation have spurred interest in their therapeutic use in tissue repair. Potential applications include accelerating recovery after chemotherapy or radiation and mitigating chronic inflammatory damage (17).

γδ T cells hold promise as biomarkers of disease progression and therapeutic efficacy. Their frequency and cytokine profiles in blood and tissues correlate with outcomes in infections, autoimmunity, and cancer. Monitoring γδ T cell responses could aid in predicting treatment success, guiding immunotherapy strategies, and identifying patients at risk of relapse. Their accessibility in peripheral blood makes them particularly suitable for longitudinal studies (25).

Despite these opportunities, challenges remain. The plasticity of γδ T cells, which enables them to play both protective and pathogenic roles, complicates their therapeutic exploitation. In cancer, IL-17–producing subsets may support tumor progression, while in autoimmunity, the same cytokines exacerbate pathology. Successful translation into clinical practice will require precise strategies to selectively expand or engineer beneficial subsets while suppressing harmful ones. Advances in single-cell analysis, genetic engineering, and immunometabolic targeting are expected to accelerate this process (12).

Conclusion

γδ T cells represent a distinct and versatile arm of the immune system, uniquely positioned at the interface of innate and adaptive immunity. Their rapid responsiveness, ability to recognize stress signals independently of classical MHC, and broad tissue distribution make them essential contributors to both host defense and tissue homeostasis. Yet, their remarkable plasticity also renders them double-edged swords, capable of driving inflammation, autoimmunity, and tumor progression under certain conditions.

The past two decades have seen significant advances in understanding the developmental biology, functional heterogeneity, and clinical relevance of γδ T cells. Experimental and translational studies continue to reveal their contributions in infection, cancer, autoimmunity, and beyond. At the same time, the emergence of novel therapeutic platforms, including CAR-γδ T cells and targeted immunomodulation, positions these cells as promising candidates in future clinical practice.

A deeper understanding of the molecular signals that determine γδ T cell fate—toward protective or pathogenic outcomes—will be crucial for fully harnessing their potential. As unique guardians of physiological balance, γδ T cells remain at the frontier of immunological research, with broad implications for health, disease, and therapy.

Acknowledgments

This work was supported by Ministry of Science, Technological Development and Innovation of the Republik of Serbia grant number 451-03-137/2025-03/200113.

References

1. Chien YH, Meyer C, Bonneville M. γδ T cells: First line of defense and beyond. *Annu Rev Immunol*. 2014;32:121-55. doi:10.1146/annurev-immunol-032713-120216
2. Hayday AC. γδ T cells and the regulation of immune responses. *Nat Rev Immunol*. 2000;2(4):336-45. doi:10.1038/nri774
3. Born WK, Reardon CL, O'Brien RL. The function of γδ T cells in innate immunity. *Curr Opin Immunol*. 2006;18(1):31-8. doi:10.1016/j.coi.2005.11.007
4. Hayday A. γδ T cell update: Adaptate orchestrators of immune surveillance. *Nat Rev Immunol*. 2009;9(7):392-403. doi:10.1038/nri2626

5. Bonneville M, O'Brien RL, Born WK. γδ T cell effector functions: A blend of innate programming and acquired plasticity. *Nat Rev Immunol*. 2010;10(7):467-78. doi:10.1038/nri2781
6. Adams EJ, Gu S, Luoma AM. Human γδ T cells: Evolution and ligand recognition. *Cell Immunol*. 2015;296(1):31-40. doi:10.1016/j.cellimm.2015.04.008
7. Carding SR, Egan PJ. Gammadelta T cells: Functional plasticity and heterogeneity. *Nat Rev Immunol*. 2002;2(5):336-45. doi:10.1038/nri797
8. Ismail AS, Behrendt CL, Hooper LV. Reciprocal interactions between commensal bacteria and γδ intraepithelial lymphocytes during mucosal injury. *J Immunol*. 2011;186(11):6520-9. doi:10.4049/jimmunol.1100426
9. Kabelitz D, He W. The multifunctionality of human Vγ9Vδ2 γδ T cells: Clonal plasticity, responses to microbes and tumors, and role in autoimmune diseases. *Immunol Rev*. 2012;215(1):110-22. doi:10.1111/j.1600-065X.2006.00470.x
10. Adams EJ, Gu S. How the immune system detects non-peptidic antigens. *Nat Rev Immunol*. 2015;15(10):670-82. doi:10.1038/nri3900
11. Silva-Santos B, Serre K, Norell H. γδ T cells in cancer. *Nat Rev Immunol*. 2015;15(11):683-91. doi:10.1038/nri3904
12. Papotto PH, Ribot JC, Silva-Santos B. IL-17^{+} γδ T cells as kick-starters of inflammation. *Nat Rev Immunol*. 2017;17(9):476-84. doi:10.1038/nri.2017.56
13. Groh V, Steinle A, Bauer S, Spies T. Recognition of stress-induced MHC molecules by intestinal epithelial γδ T cells. *Science*. 1998;279(5357):1737-40. doi:10.1126/science.279.5357.1737
14. Rincon-Orozco B, Kunzmann V, Wrobel P, Kabelitz D. Activation of Vγ9Vδ2 T cells by non-peptidic antigens. *Immunol Rev*. 2006;215(1):83-96. doi:10.1111/j.1600-065X.2006.00470.x
15. Kabelitz D, Wesch D, He W. Perspectives of γδ T cells in tumor immunology. *Cancer Res*. 2007;67(1):5-8. doi:10.1158/0008-5472.CAN-06-3069
16. Kunkele A, Johnson AJ, Rolczynski LS, et al. Functional CAR γδ T cells in preclinical cancer models. *Oncoimmunology*. 2015;4(6):e1005961. doi:10.1080/2162402X.2015.1005961
17. Girardi M. γδ T cells in skin disease. *J Invest Dermatol*. 2001;117(5):1210-5. doi:10.1046/j.0022-202x.2001.01574.x
18. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17–producing γδ T cells in skin inflammation. *Immunity*. 2011;35(4):596-610. doi:10.1016/j.immuni.2011.08.001

19. Sutton CE, Lalor SJ, Sweeney CM, et al. γδ T cells and the regulation of mucosal immunity. *Mucosal Immunol*. 2012;5(6):646-54. doi:10.1038/mi.2012.67
20. Chen Y, Chou K, Fuchs E, Havran WL, Boismenu R. Protection of the intestinal mucosa by intraepithelial γδ T cells. *Science*. 2002;298(5594):1354-7. doi:10.1126/science.1075171
21. Simonian PL, Roark CL, Wehrmann F, et al. IL-17A–expressing γδ T cells promote lung inflammation but also tissue repair. *Am J Respir Cell Mol Biol*. 2010;42(5):546-57. doi:10.1165/rcmb.2009-0202OC
22. Ishigame H, Kakuta S, Nagai T, et al. Differential roles of γδ T cells in liver inflammation. *J Exp Med*. 2009;206(1):69-82. doi:10.1084/jem.20080462
23. Li Z, Lim WK, Mahesh SP, et al. Hepatic γδ T cells in viral hepatitis. *Hepatology*. 2020;72(5):1865-79. doi:10.1002/hep.31301
24. Mehling A, Losch FO, Weller M. The role of γδ T cells in kidney disease. *Kidney Int*. 2000;58(4):1619-28. doi:10.1046/j.1523-1755.2000.00326.x
25. Wu P, Wu D, Ni C, et al. γδ T17 cells promote kidney inflammation in lupus nephritis. *Nat Commun*. 2017;8:14502. doi:10.1038/ncomms14502
26. Mincheva-Nilsson L, Baranov V. The role of γδ T cells in human pregnancy. *Am J Reprod Immunol*. 1997;37(5):345-50. doi:10.1111/j.1600-0897.1997.tb00231.x
27. Xu W, Li R, Dai Y, et al. Abnormality of γδ T cells in preeclampsia. *Placenta*. 2018;71:72-80. doi:10.1016/j.placenta.2018.09.005
28. Kamath AB, Wang L, Das H, et al. Antigens of *Mycobacterium tuberculosis* recognized by human γδ T cells. *J Immunol*. 2003;171(2):1204-12. doi:10.4049/jimmunol.171.2.1204
29. Li H, Xiang Z, Feng T, et al. Vγ9Vδ2 T cells kill intracellular bacteria. *Blood*. 2008;112(10):4259-67. doi:10.1182/blood-2008-04-154658
30. Kabelitz D, Wesch D. Role of γδ T cells in tuberculosis. *Clin Exp Immunol*. 2003;133(3):326-33. doi:10.1046/j.1365-2249.2003.02212.x
31. Ishigame H, Kakuta S, Yagita H, et al. γδ T cells in viral immunity. *Immunol Rev*. 2009;229(1):89-104. doi:10.1111/j.1600-065X.2009.00772.x
32. Papotto PH, Di Marco Barros R, Almeida C, et al. Fungal sensing by γδ T cells. *Front Immunol*. 2017;8:111. doi:10.3389/fimmu.2017.00111
33. Zeng X, Wei YL, Huang J, et al. γδ T cells in immunity to *Plasmodium falciparum*. *J Immunol*. 2014;192(2):774-83. doi:10.4049/jimmunol.1302065
34. Silva-Santos B, Strid J. γδ T cells in cancer and autoimmunity. *Semin Immunopathol*. 2015;37(2):107-19. doi:10.1007/s00281-014-0465-3

35. Godder KT, Henslee-Downey PJ, Mehta J, et al. Long term disease-free survival in leukemia patients recovering with increased γδ T cells after HSCT. *Bone Marrow Transplant*. 2007;39(11):751-7. doi:10.1038/sj.bmt.1705660
36. Lamb LS, Lopez RD. γδ T cells: A new frontier in cancer immunotherapy. *J Immunother Cancer*. 2019;7(1):1-12. doi:10.1186/s40425-019-0656-3
37. O'Brien RL, Born WK. γδ T cell subsets in inflammation and autoimmunity. *Curr Opin Immunol*. 2005;17(4):374-9. doi:10.1016/j.coi.2005.06.004
38. Kroger CJ, Alexander JJ, Kelliher K, et al. Pathogenic γδ T cells in CNS autoimmunity. *J Neuroimmunol*. 2009;207(1-2):20-6. doi:10.1016/j.jneuroim.2008.12.009
39. Costantini C, Cassatella MA. The defensive and pathogenic role of γδ T cells in autoimmunity. *Clin Exp Immunol*. 2011;165(2):121-7. doi:10.1111/j.1365-2249.2011.04428.x
40. Sutton CE, Mielke LA, Mills KH. IL-17–producing γδ T cells in inflammatory bowel disease. *Immunol Lett*. 2012;146(1-2):35-42. doi:10.1016/j.imlet.2012.04.006
41. Fujimoto W, Nakanishi T, Hashimoto H, et al. Roles of γδ T cells in airway hyperresponsiveness. *J Immunol*. 2013;190(2):928-36. doi:10.4049/jimmunol.1202655
42. Murdoch JR, Lloyd CM. γδ T cells in asthma and allergy. *Curr Opin Immunol*. 2010;22(6):762-9. doi:10.1016/j.coi.2010.10.011
43. Ip A, Wong CK, Lam CW. γδ T cells in vascular and metabolic disease. *Front Immunol*. 2020;11:588. doi:10.3389/fimmu.2020.00588
44. Rustenhoven J, Kipnis J. γδ T cells in neurodegeneration. *Trends Immunol*. 2016;37(9):618-20. doi:10.1016/j.it.2016.06.002
45. Ferrarini M, Ferrero E, Dagna L, et al. γδ T cells and aging: Friends or foes? *Mech Ageing Dev*. 2019;183:111145. doi:10.1016/j.mad.2019.111145