Review Article

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HASHIMOTO'S DISEASE REVISITED: THE γδ T CELL PERSPECTIVE

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ABSTRACT

Hashimoto's disease is a prevalent autoimmune disorder characterized by chronic thyroid gland inflammation. With an emphasis on CD4+ and CD8+ T cells, several research has been done on T cells in connection to Hashimoto's disease. Gamma delta (γδ) T cell involvement in the immunological dysregulation of Hashimoto's disease is not well understood, yet. This review aims to comprehensively examine the impact of γδ T cells on the pathophysiology of Hashimoto's disease, exploring their mechanisms of action and discussing their potential as therapeutic targets. The study utilizes a literature review approach based on current literature and available data. γδ T cells are a distinct subgroup with distinct tissue distribution, antigen recognition, and functional characteristics. Recent research suggests they may contribute to the genesis of Hashimoto's disease according to evidence of their existence and altered subsets in thyroid tissue. It may be possible to understand the precise role of γδ T cells in the immunopathogenesis of the disorder by learning more about their interactions with thyroid autoantigens and regulatory capabilities. Based on the reviewed literature and available data, this study highlights the need for further research on the role of γδ T cells in Hashimoto's disease. Understanding their mechanisms of action, interactions with thyroid autoantigens, and regulatory capacities could lead to the development of therapeutic targets for the disease.

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INTRODUCTION

Hashimoto's disease is an autoimmune disorder characterized by chronic thyroid gland inflammation. According to Chaker et al., it is the leading cause of hypothyroidism worldwide[1]. Several genetic, environmental, and immunological variables interact in a complicated manner throughout the etiology of Hashimoto's disease[2]. Gamma delta (γδ) T cells are involved in the immunological dysregulation of Hashimoto's disease, but their involvement has not gotten nearly as much attention as $CD4^+$ and $CD8^+$ T cells. A unique T cell receptor (TCR) made up of gamma and delta chains is expressed by γδ T cells, a subpopulation of T lymphocytes. They differ from conventional alpha-beta (αβ) T cells in terms of antigen recognition, tissue distribution, and functional traits[3]. γδ T cells have been connected to a variety of immune responses, such as host defense against infections and the management of autoimmune conditions[4,5].

Recent evidence suggests that γδ T cells may be involved in the development of Hashimoto's disease. Several studies have discovered γδ T cells in the thyroid tissue of people with Hashimoto's disease, proving that these cells have been locally activated and have migrated to the site of inflammation[6,7]. Furthermore,

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research on Hashimoto's disease has shown altered γδ T cell subsets and functions, suggesting that these cells may contribute to the disordered immune response seen in this condition[6].

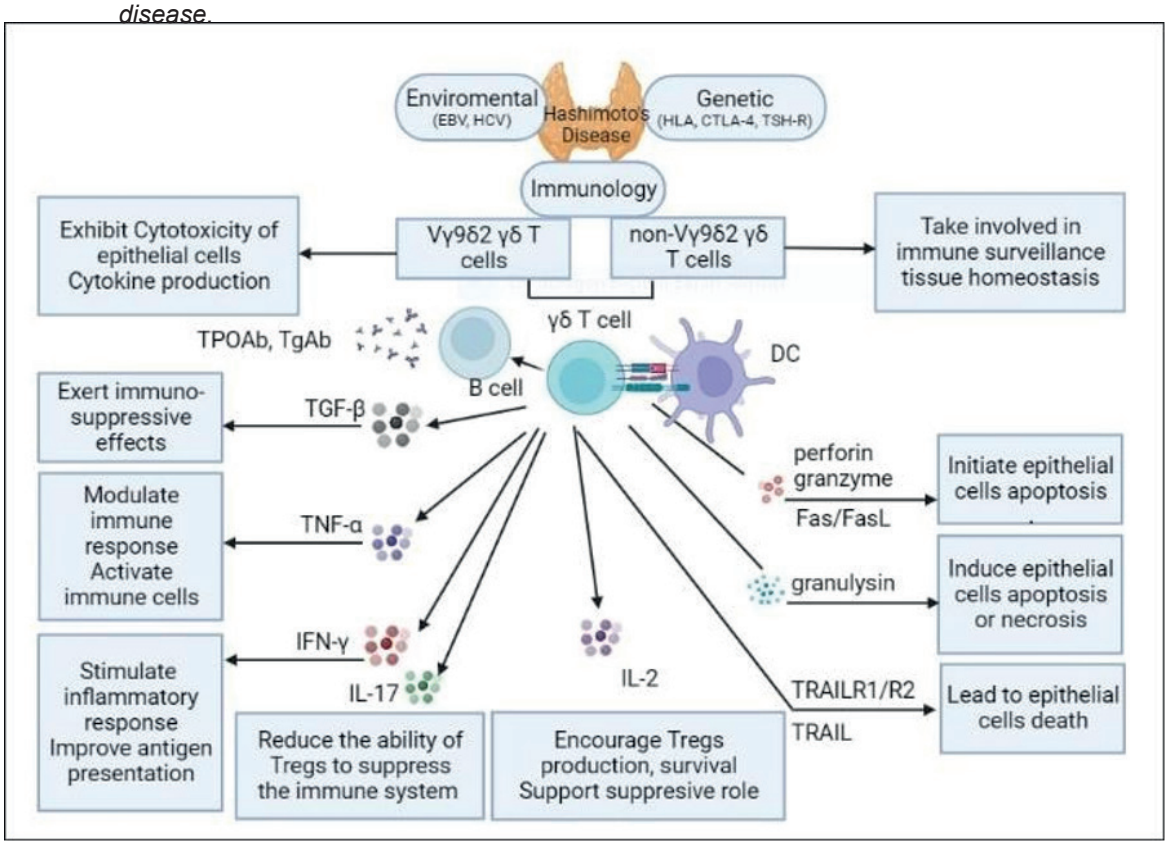
For the complicated immunological mechanisms underpinning the onset and course of the ailment, it is crucial to understand the specific role that γδ T cells play in Hashimoto's disease pathogenesis. Understanding the regulatory and effector functions of γδ T lymphocytes in relation to thyroid autoantigens may help to clarify the immunopathogenesis of Hashimoto's disease and open up new treatment avenues. This review's goal is to extensively analyze how γδ T cells impact the pathogenesis of Hashimoto's disease. We will examine the evidence for the involvement of γδ T cells in the immune dysregulation seen in Hashimoto's disease, elucidate their mechanisms of action, and discuss their potential as diagnostic markers and therapeutic targets by reviewing the current literature and synthesizing the data that is available.

Overview of Hashimoto's Disease

Hashimoto's disease is an autoimmune disorder in which the immune system mistakenly attacks the thyroid gland, leading to persistent inflammation[8]. The illness primarily affects women, with an about 10:1 female-to-male ratio[9]. It is widespread in iodine-sufficient regions including North America, Europe, and some regions of Asia. Hashimoto's disease is likely to have a hereditary and environmental component, while its exact cause is yet unclear. A genetic predisposition plays a significant role, as evidenced by the increased concordance rate in monozygotic twins[10]. The human leukocyte antigen (HLA), TSH receptor, and cytotoxic T-lymphocyte antigen-4 (CTLA-4) genes have all been connected to Hashimoto's disease[11].

Environmental triggers or exacerbations of the autoimmune response in vulnerable individuals include virus infections and exposure to certain substances[12]. Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) are examples of autoantibodies that are produced when the immune system detects thyroid-specific antigens[13]. These autoantibodies interfere with hormone production and the destruction of thyroid cells (Figure 1).

Figure 1. *Genetic, environmental, and immunological factors contribute to the etiology of Hashimoto's disease.*



Vγ9Vδ2 and non-Vγ9Vδ2 T cells are the two types of γδ T cells. Vγ9Vδ2 T cells are capable of producing cytokines and cytotoxicity, among other powerful effector actions. Non-Vγ9Vδ2 T cells, on the other hand, have unique functional traits and tissue-specific distribution patterns that suggest they play specialized roles in local immune responses. Dendrite cell-γδ T cell interaction contributes to immunological control, stimulates cytokine synthesis, and has an impact on other immune cells. The autoimmune process may become more intense if γδ T cells and B cells interact. γδ T cells can release cytotoxic substances that kill thyroid epithelial cells.

Importance of Investigating γδ T Cells in Hashimoto's Disease

The pathogenesis of Hashimoto's disease is complex and involves a number of immune cell subtypes. According to current data, its development may be greatly controlled by γδ T cells. According to research, the thyroid glands of people with Hashimoto's disease contain γδ T cells[14]. Since these cells can be found in thyroid tissue, it is possible that they contribute to local immune responses. The thyroid's stimulation and recruitment of γδ T cells may play a role in the ongoing tissue damage and inflammation that are symptoms of Hashimoto's disease[6].

IFN-γ and IL-17, two cytokines that γδ T cells can produce, have an impact on the thyroid gland and immune system performance[15]. The imbalance between pro-inflammatory and regulatory immunological responses seen in Hashimoto's disease may be caused by altered cytokine production by γδ T cells. The existence of autoantibodies against thyroid-specific antigens like TPO and Tg is a defining feature of Hashimoto's disease. γδ T cells may be involved in the autoimmune response by interacting with B cells and promoting the production of autoantibodies[14]. It may be possible to comprehend the mechanisms causing autoantibody development in Hashimoto's disease by learning how γδ T cells and B cells interact.

Pathogenesis of Hashimoto's Disease

Hashimoto's disease involves a complex interplay of genetic, environmental, and immunological factors. The onset of Hashimoto's disease is significantly influenced by genetic factors[16]. According to studies, there is a substantial familial correlation, which points to a hereditary propensity[17]. HLA genes, CTLA-4 gene, protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene, and forkhead box P3 (FOXP3) gene are just a few of the genes that have been linked to the pathogenesis[2]. These genes have an impact on immunological responses and immune tolerance, which helps to cause Hashimoto's disease.

The pathophysiology of Hashimoto's disease is also influenced by environmental variables. Viral infections (e.g., Epstein-Barr virus, hepatitis C virus) and exposure to environmental pollutants are just two examples of certain triggers that have been linked to the beginning or worsening of the autoimmune response[18]. These catalysts may cause the immune system to get activated, target thyroid antigens, and start the autoimmune process[18]. Research is currently being done to determine the precise pathways that lead to the loss of self-tolerance and the activation of autoreactive T cells[19].

Role of Thyroid Autoantigens

Tg and TPO are two thyroid autoantigens that are important initiators of the abnormal immune response in Hashimoto's disease. These primarily thyroid-expressed autoantigens are recognized by autoreactive T cells and B cells, which sets off a series of immunological responses[16]. The thyroid gland is attacked by the immune system as a consequence of the coaction between autoantigens and immune cells, which causes persistent inflammation and consequent tissue destruction[20]. A distinguishing feature of Hashimoto's disease is the development of autoantibodies against thyroid autoantigens. TgAb and TPOAb are examples of autoantibodies that are produced by autoreactive B cells that are triggered by autoreactive T cells[21]. When these autoantibodies connect to their specific target antigens and enter the thyroid gland through circulation, further immune-mediated death of thyroid tissue is triggered. The interaction of thyroid autoantigens and autoantibodies intensifies the autoimmune response, causing chronic inflammation and aiding in the development of Hashimoto's disease's clinical symptoms[22].

Immune Dysregulation in Hashimoto's Disease

Immunological dysregulation, which is the result of complex interactions between various immune cell types and signaling molecules, has a significant impact on the pathophysiology of the

disease. In Hashimoto's disease, immune cells—particularly T and B cells—are inappropriately active[23]. Pro-inflammatory cytokines including IFN-γ and IL-17 are secreted by activated γδ T cells and have been associated with thyroid tissue inflammation and damage. When B cells interact with autoreactive T cells to transform into plasma cells and produce autoantibodies against thyroid antigens, the autoimmune response is maintained[24] (Figure 1).

Overview and Functions of γδ T Cells

Unlike αβ T cells, which are mostly found in secondary lymphoid organs like the lymph nodes and spleen, γδ T cells are distributed in a range of tissues throughout the body. They are particularly common in epithelial tissues including the skin, gastrointestinal tract, and lung mucosa, according to Hayday et al.[25]. Their specific role in immune protection and monitoring at barrier regions is shown by their distinctive tissue localization. γδ T cells are very functionally adaptable. Unlike αβT cells, which largely identify peptide antigens presented by major histocompatibility complex (MHC) molecules, γδ T cells may detect a range of antigens, including microbial products, stress-induced molecules, and self-antigens[26]. They can mount quick immune responses thanks to this property in situations including infection, and tumor surveillance. γδ T cells can also create cytokines, influence other immune cells, and take part in immunological regulation[27]. They can also cause direct cytotoxicity. As shown by their ability to integrate innate and adaptive immune responses, they are crucial in bridging innate and adaptive immunity.

Due to their special characteristics, γδ T cells offer an exciting potential for participation in a variety of physiological and pathological processes. γδ T cells may help maintain immunological homeostasis, defend against pathogens, and monitor the immune system in barrier locations, according to recent research[27,28]. Furthermore, both autoimmune diseases and inflammatory disorders have been linked to dysregulation or modification in the activity of γδ T cells[29,30]. Future research on the complex biology of γδ T cells could result in the creation of brand-new therapeutic targets and therapy regimens.

Vγ9Vδ2 and non-Vγ9Vδ2 T cells are the two main categories of γδ T cells, which can be broadly classified based on the expression of different gamma and delta chain combinations. The majority of the circulating population of γδ T cells in adult humans is made up of Vγ9Vδ2 cells. They exhibit the Vγ9 and Vδ2 chains and respond to phosphoantigens such as isopentenyl pyrophosphate (IPP), which are produced by microorganisms or stressed cells[31]. Vγ9Vδ2 T cells exhibit potent effector functions, including cytokine production and cytotoxicity, enabling them to respond rapidly to infections and malignancies. However, non-Vγ9Vδ2 T cells, which do not express Vγ9 and Vδ2, are made up of a wide variety of T cells that express various gamma and delta chain combinations. Non-Vγ9Vδ2 T cells have distinct functional characteristics and tissue-specific distribution patterns, which point to specialized roles in local immune responses[32]. They are involved in immune surveillance and tissue homeostasis and are capable of recognizing a wide range of antigens, including self-antigens (Figure 1).

γδ T cells can offer early immunological protection because of their quick and innate-like responses. Through the production of cytotoxic chemicals like perforin and granzymes, γδ T cells may specifically identify and eliminate infected or altered cells[33]. They can destroy infections and target malignant cells thanks to their cytotoxic activity. γδ T cells also secrete a variety of cytokines, including TNF-α, IFN-γ, and IL-17, which help to modulate immune responses, activate other immune cells, and have antimicrobial effects[3] (Figure 1).

γδ T cells bridge innate and adaptive immunity by their uncommon ability to combine features of adaptive immune cells with prompt innate responses. Dendritic cells and conventional T cells that receive antigens from γδ T cells can influence immunological responses and shape adaptive immunity[26]. Other immune cells can receive co-stimulatory signals from γδ T cells, which promotes their activation, proliferation, and the development of effective immune responses[27]. γδ T cells are also engaged in immunological regulation, which prevents the immune system from overreacting and keeps it under control. γδ T cells have the ability to modify the actions of other immune cells such as conventional T cells, B cells, and dendritic cells in order to regulate immunological responses and prevent immunopathology[4,34]. One subtype of γδ T cells called regulatory γδ T cells suppresses autoreactive immune responses and delays the onset of autoimmune diseases[27,35].

Involvement of γδ T Cells in Hashimoto's Disease

Through the use of flow cytometry and immunohistochemistry, γδ T cells have been discovered inside the thyroid gland[14]. Due to their proximity to lymphoid clusters and inflammatory infiltrates, these cells may be implicated in the thyroid tissue's local immune response. Additionally, research has revealed that Hashimoto's thyroiditis patients have a higher frequency of γδ T cells in their peripheral blood than healthy individuals. Higher percentages of γδ T cells, particularly the Vδ2 subset, were seen in the patient's peripheral blood samples after being subjected to flow cytometry analysis[36]. The increasing of γδ T cells in the circulation suggests their systemic involvement in the immune dysregulation observed in Hashimoto's disease. γδ T cells have been discovered to have cytotoxic action against thyroid epithelial cells[37]. The loss of thyroid tissue and the subsequent onset of hypothyroidism may be caused by this cytotoxicity. γδ T cells are hypothesized to support the maintenance of the autoimmune response in the thyroid gland, which causes ongoing tissue damage and inflammation[14]. Furthermore, the autoimmune process may become more severe as a result of γδ T cells' interactions with B cells and regular T (Treg) cells[38].

Modulation of Immune Response by γδ T Cells

γδ T cells have a variety of skills that help maintain and regulate immunological homeostasis. The control of immunological responses by γδ T cells has an impact on the development of therapeutic strategies as well as physiological immune regulation[39]. γδ T cells produce a variety of cytokines to regulate the immune response. Depending on the exact situation, these cytokines may have pro-inflammatory or anti-inflammatory effects. γδ T cells generate IL-17, a chemical that is essential for triggering inflammation and enticing immune cells to areas of infection or tissue injury[40]. In addition, IL-17 can promote autoimmune and inflammatory disease development. IFN-γ, a cytokine having a variety of immunomodulatory effects, is produced in large quantities by γδ T cells[41]. IFN-γ may increase cytotoxic responses and activate macrophages. Additionally, it affects immune cell movement and controls adaptive immunological responses[28]. Some subsets of γδ T cells can generate TGF-β, which has immunosuppressive effects and can regulate immune cell development, proliferation, and survival[42,43]. TGF-β promotes immunological tolerance as well as the maturation of Tregs. γδ T cells can also regulate other immune cells' activities, influencing immunological responses and protecting immune homeostasis[44]. γδ T cells and dendritic cells can communicate with one another and affect how each other develops, presents antigens, and produces cytokines[45]. This contact may influence the ensuing immunological response and aid in immune control. γδ T cells can impact the activation, proliferation, and differentiation of conventional T cells through interactions[30]. The balance between effector and regulatory T-cell responses may be impacted by this crosstalk, which also supports immunological control[27].

Interaction between γδ T Cells and Thyroid Autoantigens

The interaction between γδ T cells and thyroid autoantigens is an area of ongoing research in the context of autoimmune thyroid disorders. Understanding the interplay between γδ T cells and thyroid autoantigens may provide insights into the mechanisms driving autoimmune thyroid disorders, such as Hashimoto's disease[46]. γδ T cells may be able to recognize and react to thyroid autoantigens in autoimmune thyroid diseases, according to the newly available information. Some investigations have shed light on the coaction between γδ T cells and thyroid autoantigens, even though the precise mechanisms are not yet fully understood. Tg, a key protein found in thyroid follicles, has been linked to autoimmune thyroiditis as a possible target for γδ T cells[47]. γδ T cells may be involved in the immune response to thyroid-specific antigens as studies have demonstrated that they can recognize and react to peptides produced from Tg. A thyroid hormone production enzyme called TPO has also been linked to the interaction with γδ T cells[48]. Studies have shown that TPO-specific γδ T cells are present in the thyroid tissue of people with autoimmune thyroiditis, indicating that these cells may play a part in autoimmune reactions that target TPO.

The etiology of autoimmune thyroid diseases may be influenced by the mutual effect between γδ T cells and thyroid autoantigens. The local inflammatory response seen in autoimmune thyroid diseases may be influenced by γδ T cells' identification of thyroid autoantigens within the thyroid gland[49]. The autoimmune process may continue to develop if thyroid autoantigens activate γδ T cells, releasing pro-inflammatory cytokines. γδ T cell-mediated cytotoxicity, induced by thyroid autoantigen recognition, may

be a factor in thyroid follicular cell apoptosis seen in autoimmune thyroiditis[2]. The onset of thyroid dysfunction and the clinical symptoms of autoimmune thyroid diseases may be influenced by this cytotoxic action.

Mechanisms of Action of γδ T Cells in Hashimoto's Disease

γδ T cells are capable of a variety of cytotoxic actions that aid in immune monitoring, anticancer responses, and host defense against infections. These abilities include the ability to directly kill cells as well as the ability to produce cytotoxic substances and activate death receptors[50]. Contact-dependent mechanisms enable γδ T cells to directly kill target cells. This direct cell killing is caused by a number of mechanisms, including the release of granzymes, serine proteases, and perforin by γδ T cells into the immunological synapse made with target cells[51]. Perforin, which makes holes in the target cell's membrane so that granzymes can enter the cytoplasm and start apoptosis, causes target cell death. By expressing the FasL protein on their cell surface, γδ T lymphocytes can interact with the Fas receptors on target cells[3]. The apoptotic signaling pathways of the target cells are activated through this interaction, resulting in programmed cell death.

γδ T cells have the ability to release cytotoxic substances that kill target cells. γδ T cells have the ability to create TNF-α, a cytokine that can kill target cells[52]. TNF-α, which also induces apoptosis and can activate more immune cells, further destroys target cells. Granulysin, a cytolytic protein that may quickly kill a target cell, is produced by γδ T cells[53]. Granulysin disrupts target cell membranes and causes either apoptosis or necrosis, depending on the dose. Additionally, γδ T cells can connect with target cells' death receptors to activate apoptotic signaling pathways. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which γδ T cells can express on their cell surfaces, binds to the death receptors TRAIL-R1 and TRAIL-R2 on target cells[33]. Target cell death results from the activation of caspase-mediated apoptotic pathways by the binding of TRAIL to its receptors (Figure 1).

γδ T Cell-Mediated Inflammation

γδ T cells, a vital component of the immune system, play a critical role in mediating inflammation. γδ T cells can affect the inflammatory milieu in a number of normal and pathological settings because they create pro-inflammatory cytokines, activate immune cells, and draw tissue. The cytokine IL-17, which is crucial for causing inflammation, is mostly produced by γδ T cells[40]. IL-17 activates neutrophils, encourages the draw of immune cells to inflammatory areas, and boosts the production of additional pro-inflammatory cytokines and chemokines. IFN-γ, a cytokine with pro-inflammatory properties, can also be produced by γδ T cells[41]. IFN-γ may stimulate the inflammatory response, activate macrophages, and improve antigen presentation. γδ T cells can activate and modify the activities of other immune cells, which supports the inflammatory response. T cells can interact with DCs to help them mature, present antigens, and produce cytokines[54]. Through this contact, additional immune cells are more effectively activated by DCs, and inflammatory responses are more effectively launched. γδ T cells can induce macrophages to generate cytokines and chemokines that promote inflammation[27,55]. By increasing their phagocytic and antibacterial capabilities, macrophage activation causes tissue inflammation. γδ T cells may help draw immune cells to areas of inflammation, so enhancing the inflammatory response.

Additionally, chemokines like CCL3, CCL4, and CXCL8 that γδ T cells are capable of producing help draw immune cells to inflamed areas[56]. These chemokines draw immune cells like neutrophils and monocytes to the area of inflammation, where they trigger the inflammatory cascade. Adhesion molecules whose expression can be enhanced by γδ T lymphocytes include intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). Its expression promotes immune cell migration and adhesion, which feeds the inflammatory response[57].

Duty of γδ T Cells in Regulatory T Cell Imbalance

γδ T cells, are important for controlling immunological responses. γδ T cells may have an impact on Treg production, survival, and suppressive ability, altering immunological control and perhaps causing autoimmune disorders and immune dysregulation. Interleukin-2 (IL-2) is a cytokine that γδ T cells can produce and is crucial for the growth and maintenance of Tregs[58]. IL-2 supports Treg survival and growth while simultaneously promoting their suppressive function. γδ T cells may operate as a source of IL-2, assisting Treg homeostasis. Indoleamine 2, 3-dioxygenase (IDO) is activated by γδ T cells,

which helps Treg formation and function[59]. By creating an immunosuppressive environment, IDO-mediated tryptophan metabolism promotes the production and activation of Treg.

γδ T cells may potentially obstruct Treg action, upsetting the immune system's delicate balance. γδ T cells have the capacity to release IL-17, which has been shown to lessen Tregs' capacity to inhibit the immune system[60]. The disruption of Treg stability and function by IL-17 may have an effect on immune dysregulation. When IL-23, a cytokine associated with inflammatory reactions, activates γδ T cells, Treg function may be inhibited[34]. γδ T cells activated by IL-23 release chemicals that inhibit the immune system's capacity to be suppressed by Treg[61]. The ratio of γδ T cells to Tregs may affect immunological dysregulation and autoimmune diseases[62].

Clinical Implications and Therapeutic Potential

γδ T cells have drawn interest as potential prognostic and diagnostic biomarkers for many diseases. This section examines the importance of γδ T cells for diagnosis and prognosis, emphasizing their potential use in clinical settings. γδ T cells show potential as useful indicators in the assessment and management of various medical disorders due to their correlation with disease activity and predictive usefulness for therapy response and patient outcomes[63]. γδ T cells link to numerous autoimmune disorders as diagnostic indicators. Autoimmune diseases such as rheumatoid arthritis[64], systemic lupus erythematosus[36], and multiple sclerosis[65] have abnormal amounts or dysregulated functions of γδ T cells.

Future Directions and Research Opportunities

γδ T cell research is an area that is still being explored and has exciting potential. Continued research, which involves looking at new targets and looking into developing technology, may help unlock the full potential of γδ T cells in various disease scenarios. Additional investigation into the diversity and characteristics of γδ T cell subsets may produce illuminating findings. Understanding the distinctive behaviors and therapeutic potential of tissue-specific γδ T cell subsets may be possible[66]. It is possible to gain knowledge on the heterogeneity, flexibility, and functional states of γδ T cells in intricate immunological settings by combining single-cell sequencing and high-dimensional profiling approaches[67,68]. Research into the therapeutic potential and functional roles of γδ T cells is accelerated by the use of genome editing tools like CRISPR-Cas9, which can enable precise genetic modifications in these cells[69,70].

CONCLUSION

The functions and therapeutic potential of γδ T cells have been clarified by a number of important discoveries. To create tailored therapeutic strategies, it is essential to understand how γδ T cells activate, how their effectors work, and how they interact with tissues. γδ T cells are linked to autoimmune thyroid disorders, changing immune responses and causing cytotoxicity and inflammation. In order to enable tailored therapeutic interventions, they operate as markers for disease activity, therapy response, and patient outcomes. Overall, γδ T cells are a unique and adaptable class of immune cells with therapeutic potential, providing chances for cutting-edge therapies.

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CONFLICT OF INTEREST

No conflict of interest is reported by the authors.

REFERENCES

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism and hypertension: fact or myth? Authors' reply. *The Lancet*. 2018; 391.10115: 30.

2. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: Clinical and diagnostic criteria. *Autoimmunity Reviews*. 2014; 13(4-5): 391-397.

3. Vantourout P, Hayday A. Six-of-the-best: Unique Contributions of γδ T Cells to Immunology. *Nature Reviews Immunology*. 2013; 13(2): 88-100.

4. Chien YH, Meyer C, Bonneville M. γδ T cells: First line of defense and beyond. *Annual Review of Immunology*. 2014; 32: 121-155.

5. Wesch D, Peters C, Oberg HH, Pietschmann K, Kabelitz D. Modulation of γδ T cell responses by TLR ligands. *Cell Mol Life Sci*. 2011; 68: 2357-2370.

6. Paul S, Lal G. Role of gamma-delta (γδ) T cells in autoimmunity. *Journal of leukocyte biology*. 2015; 97(2): 259-271.

7. Pacheco Y, Acosta-Ampudia Y, Monsalve DM, Chang C, Gershwin ME, Anaya JM. Bystander activation and autoimmunity. *J Autoimmun*. 2019; 103:102301.

8. Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, et al. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmunity Reviews*. 2020; 19(10), p.102649.

9. Chiovato L, Bassi P, Santini F, Mammoli C, Lapi P, Carayon P, et al. Antibodies producing complement-mediated thyroid cytotoxicity in patients with atrophic or goitrous autoimmune thyroiditis. *The Journal of Clinical Endocrinology & Metabolism*. 1993; 77(6): 1700-1705.

10. Brix TH, Hegedüs L. Twin studies as a model for exploring the etiology of autoimmune thyroid disease. *Clinical Endocrinology*. 2012; 76(4): 457-464.

11. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: Celebrating the centennial through the lens of the Johns Hopkins Hospital surgical pathology records. *Thyroid*. 2013; 23(2): 142-150.

12. Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. *Endocrine Reviews*. 1993; 14(1): 107-120.

13. Prummel MF, Wiersinga WM. Thyroid peroxidase autoantibodies in euthyroid subjects. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2005; 19(1): 1-15.

14. Liu H, Zheng T, Mao Y, Xu C, Wu F, Bu L, et al. γδ T cells enhance B cells for antibody production in Hashimoto's thyroiditis, and retinoic acid induces apoptosis of the γδ T cell. *Endocrine*. 2016; 51: 113-122.

15. Nielsen MM, Witherden DA, Havran WL. γδ T cells in homeostasis and host defense of epithelial barrier tissues. *Nature Reviews Immunology*. 2017; 17(12): 733-745.

16. Tomer Y, Huber A. The etiology of autoimmune thyroid disease: A story of genes and environment. *Journal of Autoimmunity*. 2009; 32(3-4): 231-239.

17. Ban Y, Davies TF, Greenberg DA, Concepcion ES, Tomer Y. The influence of human leucocyte antigen (HLA) genes on autoimmune thyroid disease (AITD): results of studies in HLA-DR3-positive AITD families. *Clin Endocrinol (Oxf)*. 2002; 57(1): 363-370.

18. Nakamura H, Fujieda Y, Yasuda S, Nakai M, Atsumi T. Remission of nephrotic syndrome after therapy for chronic hepatitis C virus infection in a patient with systemic lupus erythematosus. *Ann Intern Med*. 2018; 169(5):352-353.

19. Wang J, Lo JC, Foster A, Yu P, Chen HM, Wang Y, et al. The regulation of T cell homeostasis and autoimmunity by T cell–derived LIGHT. *The Journal of Clinical Investigation*. 2001; 108(12): 1771-1780.

20. Rydzewska M, Jaromin M, Pasierowska IE, Stożek K, Bossowski A. Role of the T and B lymphocytes in the pathogenesis of autoimmune thyroid diseases. *Thyroid research*. 2018; 11(1): 1-11.

21. Weetman AP. Determinants of autoimmune thyroid disease. *Nat Immunol*. 2001; 2(9): 769-770.

22. McLachlan SM, Rapoport B. Autoimmune response to the thyroid in humans: Thyroid peroxidase—The common autoantigenic denominator. *International Reviews of Immunology*. 2000; 19(6): 587-618.

23. Weetman AP. Cellular immune responses in autoimmune thyroid disease. *Clinical endocrinology*. 2004; 61(4): 405-413.

24. Latif R, Morshed SA, Zaidi M, Davies TF. The thyroid-stimulating hormone receptor: impact of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on multimerization, cleavage, and signaling. *Endocrinology and metabolism clinics of North America*. 2009; 38(2): 319-341.

25. Hayday A, Theodoridis E, Ramsburg E, Shires J. Intraepithelial lymphocytes: Exploring the Third Way in Immunology. *Nature Immunology*. 2001; 2(11): 997-1003.

26. Carding SR, Egan PJ. γδ T Cells: Functional Plasticity and Heterogeneity. *Nature Reviews Immunology*. 2002; 2(5): 336-345.

27. Silva-Santos B, Serre K, Norell H. γδ T cells in cancer. *Nat Rev Immunol*. 2015; 15(11): 683-691.

28. Hayday AC. γδ T Cells and the Lymphoid Stress-Surveillance Response. *Immunity*. 2009; 31(2):184-196.

29. Caccamo N, Todaro M, La Manna MP, Sireci G, Stassi G, Dieli F. IL-21 regulates the differentiation of a human γδ T cell subset equipped with B cell helper activity. *PLoS One*. 2012; 7(7): e41940.

30. Xu W, Lau ZWX, Fulop T, Larbi A. The aging of γδ T cells. *Cells*. 2020; 9(5): 1181.

31. Lee HW, Chung YS, Kim TJ. Heterogeneity of human γδ T cells and their role in cancer immunity. *Immune Network*. 2020; 20(1).

32. Bonneville M, O'Brien RL, Born WK. γδ T cell effector functions: A blend of innate programming and acquired plasticity. *Nature Reviews Immunology*. 2010; 10(7): 467-478.

33. Brandes M, Willimann K, Moser B. Professional Antigen-Presentation Function by Human γδ T Cells. *Science*. 2005; 309(5732): 264-268.

34. Ribot JC, deBarros A, Pang DJ, Neves JF, Peperzak V, Roberts SJ, et al. CD27 is a thymic determinant of the balance between interferon-γ-and interleukin 17-producing γδ T cell subsets. *Nature Immunology*. 2009; 10(4): 427-436.

35. Ma C, Zhang Q, Ye J, Wang F, Zhang Y, Wevers E, et al. Tumor-infiltrating γδ T lymphocytes predict clinical outcome in human breast cancer. *Journal of Immunology*. 2012; 189(10): 5029-5036.

36. Lu Z, Li X, Wang D, SU D, Zhou S, WU Q, et al. Change and clinical significance of peripheral blood γδT cells in patients with systemic lupus erythematosus. *Chinese Journal of Rheumatology*. 2012; 23-26.

37. Paolieri F, Pronzato C, Battifora M, Fiorino N, Canonica GW, Bagnasco M. Infiltrating γ/gd T-cell receptor-positive lymphocytes in Hashimoto's thyroiditis, Graves' disease and papillary thyroid cancer. *Journal of endocrinological investigation*. 1995; 18: 295-298.

38. Mikoś H, Mikoś M, Obara-Moszyńska M, Niedziela M. The role of the immune system and cytokines involved in the pathogenesis of autoimmune thyroid disease (AITD). *Endokrynologia Polska*. 2014; 65(2): 150-155.

39. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing γδ T cells selectively expand in response to pathogen products and environmental signals. *Immunity*. 2009; 31(2): 321-330.

40. Cua DJ, Tato CM. Innate IL-17-producing cells: The sentinels of the immune system. *Nature Reviews Immunology*. 2010; 10(7): 479-489.

41. Gelderblom M, Arunachalam P, Magnus T. γδ T cells as early sensors of tissue damage and mediators of secondary neurodegeneration. *Frontiers in cellular neuroscience*. 2014; 8: 368.

42. Chen Z, Ji Z, Ngiow SF, Manne S, Cai Z, Huang AC, et al. TCF-1-centered transcriptional network drives an effector versus exhausted CD8 T cell-fate decision. *Immunity*. 2019; 51(5): 840-855.

43. Cai Y, Shen X, Ding C, Qi C, Li K, Li X, et al. Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. *Immunity*. 2011; 35(4): 569-610.

44. Giri S, Lal G. Differentiation and functional plasticity of gamma-delta (γδ)T cells under homeostatic and disease conditions. *Molecular Immunology*. 2021; 136:138-149.

45. Holtmeier W, Kabelitz D. γδ T cells link innate and adaptive immune responses. *Chemical Immunology and Allergy*. 2005; 86: 151-183.

46. Navegantes KC, de Souza Gomes R, Pereira PAT, Czaikoski PG, Azevedo CHM, Monteiro MC. Immune modulation of some autoimmune diseases: the critical role of macrophages and neutrophils in the innate and adaptive immunity. *Journal of translational medicine*. 2017; 15(1): 1-21.

47. Adams EJ, Gu S, Luoma AM. Human gamma delta T cells: evolution and ligand recognition. *Cellular immunology*. 2015; 296(1): 31-40.

48. Conti L, Casetti R, Cardone M, Varano B, Martino A, Belardelli F, et al. Reciprocal activating interaction between dendritic cells and pamidronate-stimulated γδ T cells: role of CD86 and inflammatory cytokines. *The Journal of Immunology*. 2005; 174(1): 252-260.

49. Sorokina EV, Bisheva IV, Mishina NV, Stolpnikova VN. Role of γδ T Lymphocytes in the Pathogenesis of Autoimmune Diseases with Skin Lesions. *Biology Bulletin Reviews*. 2023; 13(2): 92-97.

50. Witherden DA, Johnson MD, Havran WL. Coreceptors and their ligands in epithelial γδ T cell biology. *Frontiers in Immunology*. 2018; 9: 731.

51. Casetti R, Martino A. The Plasticity of γδ T Cells: Innate Immunity, Antigen Presentation, and New Immunotherapy. *Cellular & Molecular Immunology*. 2008; 5(3): 161-170.

52. Allez M, Tieng V, Nakazawa A, Treton X, Pacault V, Dulphy N, et al. CD4+NKG2D+ T Cells in Crohn's Disease Mediate Inflammatory and Cytotoxic Responses through MICA Interactions. *Gastroenterology*. 2007; 132(7): 2346-58.

53. Littwitz-Salomon E, Malyshkina A, Schimmer S, Dittmer U. The cytotoxic activity of natural killer cells is suppressed by IL-10+ regulatory T cells during acute retroviral infection. *Frontiers in Immunology*. 2018; 9: 1947.

54. Fang H, Welte T, Zheng X, Chang GJJ, Holbrook MR, Soong L, et al. γδd T Cells Promote the Maturation of Dendritic Cells during West Nile Virus Infection. FEMS Immunology and Medical Microbiology. 2010; 59(1): 71-80.

55. Jensen KD, Su X, Shin S, Li L, Youssef S, Yamasaki S, et al. Thymic selection determines γδ T cell effector fate: antigen-naive cells make interleukin-17 and antigen-experienced cells make interferon γ. *Immunity*. 2008; 29(1): 90-100.

56. Paul S, Singh AK, Shilpi, Lal G. Phenotypic and functional plasticity of gamma–delta (γδ) T cells in inflammation and tolerance. *International Reviews of Immunology*. 2014; 33(6): 537-558.

57. Pistoia V, Tumino N, Vacca P, Veneziani I, Moretta A, Locatelli F, et al. Human γδ T-cells: from surface receptors to the therapy of high-risk leukemias. *Frontiers in Immunology*. 2018; 9: 984.

58. Owen DL, Sjaastad LE, Farrar MA. Regulatory T cell development in the thymus. *The Journal of Immunology*. 2019; 203(8): 2031-2041.

59. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An Interaction between Kynurenine and the Aryl Hydrocarbon Receptor Can Generate Regulatory T Cells. *The Journal of Immunology*. 2010; 185(6): 3190-3198.

60. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, et al. IL-6 programs TH-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nature Immunology*. 2007; 8(9): 967-974.

61. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature*. 2003; 421(6924): 744-748.

62. Su D, Shen M, Li X, Sun L. Roles of T cells in the pathogenesis of autoimmune diseases. *Clinical and Developmental Immunology*. 2013; 2013.

63. Jin Z, Luo Q, Lu S, Wang X, He Z, Lai J, et al. Oligoclonal expansion of TCR Vδ T cells may be a potential immune biomarker for clinical outcome of acute myeloid leukemia. *Journal of Hematology&Oncology*. 2016; 9(1): 1-7.

64. Nguyen CT, Maverakis E, Eberl M, Adamopoulos IE. γδ T cells in rheumatic diseases: from fundamental mechanisms to autoimmunity. *In Seminars in immunopathology*. 2019; 41: 595-605. Springer Berlin Heidelberg.

65. Monteiro A, Cruto C, Rosado P, Martinho A, Rosado L, Fonseca M, et al. Characterization of circulating gamma-delta T cells in relapsing vs remission multiple sclerosis. *Journal of Neuroimmunology*. 2018; 318: 65-71.

66. Silva-Santos B, Strid J. Working in "NK Mode": Natural Killer Group 2 Member D and Natural Cytotoxicity Receptors in Stress-Surveillance by γδ T Cells. *Frontiers in Immunology*. 2018; 9: 851.

67. Chen H, Ye F, Guo G. Revolutionizing immunology with single-cell RNA sequencing. *Cellular&Molecular Immunology*. 2019; 16(3): 242-249.

68. Rozenblatt-Rosen O, Stubbington MJ, Regev A, Teichmann SA. The human cell atlas: from vision to reality. *Nature*. 2017; 550(7667): 451-453.

69. Legut M, Dolton G, Mian AA, Ottmann OG, Sewell AK. CRISPR-mediated TCR replacement generates superior anticancer transgenic T cells. *Blood, The Journal of the American Society of Hematology*. 2018; 131(3): 311-322.

70. Stronen E, Toebes M, Kelderman S, van Buuren MM, Yang W, van Rooij N, et al. Targeting of cancer neoantigens with donor-derived T cell receptor repertoires. *Science*. 2016; 352(6291): 1337-1341.