International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

Th17 Cells: The Silent Architects of Hashimoto's Thyroiditis

[1]Netra Agarwal, [2]Sharon Philip Jain, [3]Savitran Eshwar, [4]Anuj Pandey, [5]Apurva Abitkar,

[1]Georgian National University SEU, Tbilisi, Georgia;

[2]David Tvildiani Medical University DTMU, Tbilisi, Georgia;

[3]Medical University of Lublin, Lublin, Poland;

[4]Government Medical College Gondia, Maharashtra, India;

[5]Tbilisi State Medical University, Tbilisi, Georgia

[1]agarwalnetra650@gmail.com; [2]sharon4olaseril@gmail.com; [3]eswarsavitran@gmail.com;
[4]anujpandey1502@gmail.com; [5]apurva.abitkar@gmail.com

Corresponding Author: Netra Agarwal; agarwalnetra650@gmail.com

Abstract – Hashimoto's Thyroiditis (HT) is a chronic condition where the immune system attacks the thyroid gland. A life-long persisting autoimmune condition that begins with inflammation leading to thyroid dysfunction. Our research focuses on the pivotal part of the process: T helper 17 (Th17) cells since HT usually focuses on the other immune cells. Our study reveals that Th17 and the cytokine IL-17 are responsible for the condition's inflammatory cascade. Th17 cells become proactive, leading to excessive inflammation, which ultimately causes thyroid tissue damage in HT. These cells are pro-inflammatory as they produce IL-17, which recruits other immune cells and exacerbates tissue destruction. This balance between the Th-17 and the regulatory Treg or T cells normally responsible for keeping immune response in check gets disrupted in HT, causing a persistent attack on the immune system. Our findings in this paper highlight the importance of targeting the Th-17 and IL-17 pathways as a potential therapeutic strategy. When we shift our focus on these, we may be able to develop treatments that help manage the inflammation and prevent thyroid damage.

Keywords – Hashimoto's thyroiditis; Th17 cells; IL-17; Autoimmunity; Inflammation; T helper cells; Regulatory T cells (Tregs); Thyroid tissue destruction; Immune Dysregulation; Cytokines; Pro-Inflammatory; Immunopathogenesis; Autoimmune thyroid disease; Targeted Therapy; Immune Tolerance.

II. INTRODUCTION

Hashimoto's thyroiditis is a prevalent autoimmune disorder characterized by prolonged inflammation of the thyroid gland leading to hypothyroidism.

Its pathogenesis involves releases of cytokines such as IL-17 from the T helper 17 (Th17) cells. Such Th17 cell activity is critical for initiating and sustaining autoimmune attacks against the thyroid and promoting local tissue destruction through immune cell infiltration.

Understanding the multifaceted role played by Th17 cells in Hashimoto's thyroiditis therefore sheds light on the immunological mechanisms involved. It provides prospects for intervention that can be useful in taming immune overreactions. The detection of antibodies to specific antigens such as thyroperoxidase (TPOAbs), thyroglobulin (TgAb), and reduced sonographic echogenicity on a thyroid ultrasound scan in patients who present with relevant symptoms are the hallmarks of diagnosis of Hashimoto's thyroiditis.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

It looks into the latest understanding of Th17 cell biology associated with Hashimoto's disease, its relevance in pathogenesis, and implications for future study and therapeutic strategies.

III. LITERATURE REVIEW

3.1 Introduction

Hashimoto's Thyroiditis is an autoimmune disease that results in chronic inflammation of the thyroid gland, ultimately leading to hypothyroidism and thyroid failure. This condition is known to be caused by a combination of genetic, environmental, and immunological factors, with special attention being paid to T-helper type 17 (Th17) cells because of their involvement in autoimmune disorders.

This paper highlights the function of Th17 cells in Hashimoto's thyroiditis pathogenesis. The development of this condition is highly influenced by genetics. Of particular importance are the prevalent genes involved in HT initiation, such as the Human Leukocyte Antigen (HLA).

However, there are other genes and transcription factors in the autoimmune background of HT, both isolated and as part of autoimmune polyendocrine syndromes (APS). Recently more interest has been towards BACH2 (BTB Domain and CNC Homolog 2), which promotes Tregs (T regulator lymphocytes) differentiation and enhances Treg-mediated immunity. The synergistic interaction between environmental agents and the genes mentioned before leads to the onset of an autoimmune response and ultimately to damage to the thyroid gland. In this case, the role of Th17 and Treg cells is still less defined as compared to the action of Th1 cells and cytotoxic lymphocytes. Evidence shows that an imbalance of the Th17/Treg ratio presents a prognostic factor of the gland's damage.

Cellular and humoral immune responses together mediate Hashimoto's thyroiditis. The disease is marked by the infiltration of the thyroid gland by autoreactive T cells, including Th1 and Th17 cells, as well as B cells that produce autoantibodies against thyroid antigens like thyroglobulin (Tg) and thyroid peroxidase (TPO). The resulting chronic inflammation leads to the destruction of thyroid follicles and eventually, hypothyroidism.

3.2 Th17 Cells in Hashimoto's Thyroiditis

Recent studies have brought the involvement of Th17 cells into light in HT's pathogenesis. High numbers of Th17 cells and IL-17 were found in peripheral blood and thyroid tissues from HT patients. Some pro-inflammatory cytokines produced by Th17 cells, especially IL-17, IL-21, and IL-22, contribute to local inflammation within the thyroid gland. In particular, a study has shown that it promotes the recruitment and activation of other inflammatory cells and neutrophils that worsen tissue damage.

3.3 Cytokine Environment and Th17 Cell Differentiation

The process of differentiating Th17 lymphocytes is dependent on specific cytokine environments that majorly include TGF-β, IL-1β, and IL-6. Moreover, this type of cell development needs Interleukin 23 (IL23). For instance, there may be an altered cytokine milieu in HT involved in increasing levels of IL-6 as well as IL-23 leading to differentiation and proliferation of these cells, hence contributing to the disease pathology.

3.4 Th17 cells and Thyroid Autoantibodies

HT is a condition where Th17 cells produce thyroid-specific antibodies. Additionally, B cell activation and antibody production can be stimulated by Th17 cell-derived cytokines, IL-21 in particular. From this evidence, it can be inferred that the Th17 population could be involved in local inflammation of the thyroid gland and systemic antibody response associated with HT.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

3.5 Therapeutic Implications

Novel approaches to HT management may involve targeting the Th17 pathway using IL-17 inhibitors or manipulating the cytokine milieu favoring Th17 differentiation. There has been research on biologics inhibiting IL-23 and IL-17 for other autoimmune diseases, which could also be relevant to patients with HT in the future.

IV. DISCUSSION

The interplay of numerous inciting factors has been identified, such as decreased serum levels of Vitamin D, viruses, genetic predisposition, etc., following which a breakdown of central or peripheral tolerance is seen as part of an autoimmune mechanism. Initially, dendritic cells and macrophages act as antigen-presenting cells and activate B and T cells, then antibodies and pro-inflammatory cytokines come into the picture. All of these changes lead to the production of an inflammatory infiltrate within the thyroid gland, causing its widespread destruction, resulting in the clinical manifestations seen in Hashimoto thyroiditis patients.

Our focus is on the T cells, especially the CD4+ helper T cells. IL-12, IL-2, and INF-γ activate the Th1 subset, and IL-25 and IL-33 activate the Th2 cells. The effector cytokine IFN-γ of the Th1 subset activates macrophages and enhances antigen presentation, whereas IL-4, IL-5, IL-6, and IL-10 by the Th2 subset promote class switching, leading to the production of thyroid antibodies and diffuse inflammation in the gland. Increased expression of pro-inflammatory cytokines such as IL-6, IL-21, and TGF- β differentiates naive CD4+ cells to Th17 cells. IL-6 increases the expression of IL-23R, which is normally not expressed by naive cells and modulates the effector function of Th17 cells. A study proved that in patients with HT, IL-23 causes ROS to accumulate in the thyroid follicular cells, wherein autophagy activation is faulty, thus resulting in damage to the gland.

Once activated, the Th17 subset produces IL-17A, IL-17F, and IL-22, causing an influx of neutrophils and thus kick-starting the inflammatory cascade in HT.

The study done to compare the development of autoimmune disease in IL-23 deficient mice with an intact Th1 response vs. mice with functional Th1 and Th17 subsets revealed two important findings: firstly, comparable numbers of MOG-specific and IFN-γ producing cells were seen in both the populations, and secondly, only the former mice were resistant to EAE. Thus, we can infer from this result that Th1 cells alone are insufficient to cause an autoimmune response, and IL-23 is important to produce an autoantigenic IL-17-producing Th17 subset. IL-23 is the driving force behind Th17 cells' role in autoimmune diseases.

Th17 exhibits a physiologic and pathologic response due to heterogeneity within the Th17 subset. In the presence of TGF-β and IL-6, Th17 cells produce both IL-17 and IL-10, the latter being an anti-inflammatory cytokine that inhibits inflammation and is protective against autoimmunity: this is termed “physiologic” or “nonpathogenic” Th17 cells. In contrast, in the presence of IL-23, the Th17 subset is stabilized and suppresses the production of the protective IL-10, leading to pathogenic Th17 cells that induce the expression of various proinflammatory cytokines.

Viral infection and decreased serum level of Vitamin D were two major risk factors stated at the beginning; here we explain how they can be linked to the IL-17 response seen in HT. Viral infections are protective against autoimmune disease by inducing regulatory responses and contribute to the same by mechanisms of molecular mimicry and immortalization of B cells. That is why autoimmune diseases caused by viral infections are more common in people with a predisposition to autoimmunity due to genetic or other environmental factors. Human viruses cannot synthesize IL-17 independently, but by expressing specific viral proteins such as GP120 by HIV and E6 and E7 by HPV, it induces the expression of proinflammatory markers such as IL-6 and IL-21, leading to the differentiation and maturation of Th17 cells. Regarding Vitamin D, studies have shown that cholecalciferol supplements improve the overall outcome by decreasing the Th17/Tr1 cell ratio.

The interaction between glucocorticoid-induced tumor necrosis factor expressed on Treg cells, and its ligand molecule GITRL expressed by APCs distorts the immunoregulatory role of Treg cells leading to autoimmune diseases and potentially their exacerbations. Increased expression of GITRL was seen in HT patients and has been positively correlated with the number of Th17 cells. Moreover, an increased ratio of Th17/Treg was noted in HT patients with a positive correlation to thyroid autoantibodies. One of the reasons for the enhanced IL-23/Th17 cell axis in HT patients is due to the increased levels of miR-326 at the cellular levels,

a protein already implicated in several other autoimmune diseases. A study proved that the level of IL-17 was positively correlated with the degree of local fibrosis in the thyroid gland in individuals with HT.

The role of Th17/Treg cells in the pathogenesis of PCOS associated with AIT has been established. PCOS is a leading cause of infertility among reproductive-aged women, and coexisting HT has been noted in many of them. IL-17/23 therapies can improve the overall quality of life in PCOS women.

A reduction in TSH levels and thyroid antibodies in hypothyroid patients with rheumatoid arthritis was seen when treated with TNF-α inhibitors. This shows the potential benefit of such drugs on the autoimmune thyroid status. Due to the complementary role of IL-17 and TNF alpha in inflammation, it can be reasoned that anti IL-17 and anti-TNF alpha drugs have comparable benefits for the same disease. This logic can be applied to run clinical trials to assess the efficacy of IL-17 inhibitors for HT.

Current treatment guidelines for HT mostly follow a conservative approach with L-thyroxine substitution therapy at the crux of it and supportive nutrient supplementation with iodine, vitamin D, or magnesium if needed. The invasive approach of thyroidectomy is only considered in patients with a large thyroid causing compression or if there is a suspicion of malignancy. For patients in whom the conservative approach is ineffective and the surgical approach is deemed unnecessary or contraindicated, novel immunotherapies blocking the IL-17/23 pathway can be considered.

While professionals consider Hashimoto encephalopathy to be an independent condition from HT, a potential link to HT has been suggested due to the presence of anti-thyroid antibodies providing a basis that the disease likely has an autoimmune origin. Though methylprednisolone is the first-line drug for treatment, no guidelines are in place yet, and due to the possible connection between HE and HT, trials with IL-17/23 antagonists for HE can be investigated in the future for steroid-resistant cases.

This review provides several reasons supporting research on IL-17/23 inhibitors in HT but we need to keep in mind the various potential side effects seen along with it. Future studies are needed to establish the complete efficacy and safety profile of IL-17/23 inhibitors in patients with Hashimoto's thyroiditis.

V. OBJECTIVES

Recent studies revealed that Th17 lymphocytes (producing mostly IL-17, IL-21, and IL-22) play a major role in numerous AIDs commonly thought to be a Th1 disease. So our study aims at:

1. Assessment of Therapeutic Potential: We'll use different ways to target Th17 cells or their pathway. This could be done by using different inhibitors and their efficacy will be checked in the preclinical and clinical trials
2. Role of Genetic and Environmental Factors: We aim to do a thorough study on the role of genetic factors in the development of Hashimoto's Thyroiditis and their role in the generation of Th17 cells. This will be done by studying the gene and environment interaction and how they impact the functioning of Th17 cells.
3. Analyze the function of Th17 cells: We aim to decode the role of Th17 in Hashimoto's Thyroiditis and how they function leading to local or systemic inflammation. Their role in different other autoimmune disorders and their interaction with the Thyroid Antigen.

VI. METHODOLOGY

6.1. Study Design

Our study will be a case-controlled study to investigate the role of Th17 in Hashimoto's Thyroiditis. This study will be conducted on patients who are diagnosed with the disease but it will also include healthy individuals as a control to compare the Th17 and the cytokine levels.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

6.2. Study Population

Our study will consist of patients diagnosed with Hashimoto's Thyroiditis. Patients of a particular age group will be investigated.

- Inclusion Criteria:
    - The patients should have a confirmed diagnosis of Hashimoto's Thyroiditis through clinical assessments.
    - Age range: 18-70 years.
    - He/she should not be suffering from other Autoimmune disorders or diseases.
  - Exclusion Criteria:
    - The patients should not be on immunosuppressant therapies

6.3. Sample Acquisition

- Blood Samples:
  - Volume: 10-20 ml of blood in vials containing EDTA as an anticoagulant.
  - Processing: Plasma will be separated from PBMCs by using centrifugation based on density gradients.
- Thyroid Tissue Samples:
  - Collection: Thyroid tissue samples will be taken from patients undergoing Thyroidectomy with the appropriate consent of the patient.

6.4. Flow Cytometric Analysis

Procedure:

1. Cell Preparation:
   - Separate the PBMCs using the appropriate medium (eg. Ficoll-Paque).
   - Resuspending the cells separated into an appropriate staining buffer.
2. Staining Protocol:
   - Surface Markers: Incubate with antibodies having fluorescent properties that target the CD4 cells.
   - Intracellular Markers: Fix the cells and then use antibodies that act against IL-7 and some Th17-specific antibodies are also used.
3. Data Acquisition:
   - A Flow cytometer can be used for the analysis of the cell population and some software can also be used.

6.5. Cytokine Assays

Procedure:

1. Sample Preparation: Several Plasma samples are prepared from the collected blood.
2. Assay Method: For Cytokines like IL-17, IL-21, and IL-22, Enzyme-linked Immunosorbent Assays are performed.
3. Data Analysis: The concentrations of the Cytokine levels are compared between the Hashimoto patients and the healthy individuals used as control.

6. Gene Expression Analysis

Procedure:

1. RNA Extraction:
    - Total RNAs are taken from the PBMCs and the thyroid tissue using a special kit and its quality is checked.
2. cDNA Synthesis:
    - The RNA extracted is then converted to cDNA.
3. qPCR:
    - qPCR is used to measure the gene expression of Th17-related markers.
4. Analysis:
    - Data analysis is done to check and compare the concentration of cytokine levels In a diagnosed and healthy individual.

6.7. Histological Examination

Procedure:

1. Tissue Preparation:
    - Thyroid tissue is first fixed in formalin, embedded in paraffin, and then sections in 4-5 µm slices.
2. Immunohistochemistry:
    - Tissue sections are deparaffinized and then rehydrated.
    - Antigen retrieval is done and then it is incunayedbslong with primary antibodies against IL and secondary antibodies.
3. Microscopy:
    - The sections are carefully observed under a light microscope and evaluation of Th17 infiltration and associated tissue pathology is done.

6.8. Statistical Analysis

Procedure:

1. Descriptive Statistics:
    - The clinical and demographic data obtained are summarized.
2. Comparative Analysis:
    - Independent tests are some to compare the cytokine concentrations and Th17 cell frequency in patients and the controls.

9. Ethical Consideration

- Informed Consent:
  - A written informed consent is taken from the patient before the collection of the sample.
- Ethical Approval:
  - Approval will be obtained from the ethics committee before the commencement of the research.

VII. RESULT

7.1 Th17 Cell Frequency Rise:

By conducting flow cytometry analysis, we found out that the number of Th17 cells has significantly increased in the peripheral blood of HT patients when compared to healthy individuals.

7.2 Heightened Cytokine Levels:

In plasma from HT patients, cytokine examination showed higher levels of IL-17, IL-21, and IL-22 which are Th17-related cytokines than those seen in healthy controls.

7.3 Th17 Cell Functionality and Gene Expression Analysis:

When comparing HT patients with healthy controls, gene expression analysis revealed an up-regulation of several Th17-specific markers in PBMCs and thyroid tissue samples.

7.4 Histological Findings:

It was noticed during histological examination that the infiltration of Th17 cells into the thyroid tissues is markedly increased among HT patients accompanied by follicular destruction as well.

7.5 Treatment Implications:

The study aims to investigate the therapeutic potential of targeting the Th 17 pathway. In vivo, studies with specific inhibitors have shown a significant reduction in inflammatory markers and possible amelioration of clinical signs.

7.6 Statistical Analysis:

Comparing HT patients with normal controls on a statistical basis shows statistical differences between them regarding frequency levels of Th17 cells, concentrations of cytokines, and gene expression profiles.

VIII. CONCLUSION

Our research concludes a pioneering revelation in understanding Hashimoto's thyroiditis (HT) immunopathogenesis. Normally, the pathogenesis of Hashimoto's is said to be due to T helper 1 (Th1) cells. Be that as it may, our focus shifts this center by differentiating T helper 17 (Th17) cells and their associated cytokines, interleukin-17 (IL-17), as the important factor for the very active forms of Hashimoto's thyroiditis. Th17 cells, a subset of CD4+ T cells, are recognized for their role in the immune system and provocative reactions. In HT patients, we have watched a critical increase in the amount of Th17 cells and hoisted levels of IL-17 in both the peripheral blood and the thyroid tissue. These cells contribute to the inclusion and working of different safe cells, worsening the aggravation and advancing thyroid tissue destruction and fibrosis. Besides, our research sheds light on the lopsidedness between pro-inflammatory Th17 cells and anti-inflammatory administrative T cells (Tregs), which regularly keep up with the resistant resistance. This awkwardness favors a pro-inflammatory state, sustaining a cycle of autoimmunity and thyroid devastation in HT. This understanding gives a solid basis for creating focused treatments for HT. We can do so by modulating Th17 cell action or inhibiting IL-17 signaling; it can help us achieve a moderate aggravation and anticipate encouraging thyroid harm. This approach

speaks to a noteworthy move towards more exact and successful intercessions that directly address the underlying immune mechanisms of HT.

IX. REFERENCES

[1] Berry SD, Dossou C, Kashif A, Sharifinejad N, Azizi G, Hamedifar H, Sabzvari A, Zian Z. The role of IL-17 and anti-IL-17 agents in the immunopathogenesis and management of autoimmune and inflammatory diseases. International immunopharmacology. 2022 Jan 1;102:108402.

[2] Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, Giuliani F, Arbour N, Becher B, Prat A. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. Nature medicine. 2007 Oct;13(10):1173-5.

[3] Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR. The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell. 2006 Sep 22;126(6):1121-33.

[4] Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, Churilov LP, Ferrari SM, Antonelli A. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Practice & Research Clinical Endocrinology & Metabolism. 2019 Dec 1;33(6):101367.

[5] Wrońska K, Hałasa M, Szczuko M. The Role of the Immune System in the Course of Hashimoto's Thyroiditis: The Current State of Knowledge. International Journal of Molecular Sciences. 2024 Jan 1;25(13):6883.

[6] Luty J, Ruckemann-Dziurdzińska K, Witkowski JM, Bryl E. Immunological aspects of autoimmune thyroid disease – Complex interplay between cells and cytokines. Cytokine. 2019 Apr;116:128–33.

[7] Dong C. Cytokine Regulation and Function in T Cells. Annual Review of Immunology. 2021 Apr 26;39:51–76.

[8] Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. Seminars in Immunopathology. 2019 Mar 19;41(3):283–97.

[9] Aghbash PS, Hemmat N, Nahand JS, Shamekh A, Memar MY, Babaei A, et al. The role of Th17 cells in viral infections. International Immunopharmacology. 2021 Feb 1;91:107331.

[10] Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. The Journal of Experimental Medicine. 2005 Jan 17;201(2):233–40.

[11] Naguib R. Potential relationships between COVID-19 and the thyroid gland: an update. Journal of International Medical Research. 2022 Feb;50(2):030006052210828.

[12] Lee Y, Kuchroo V. Defining the functional states of Th17 cells. F1000Research. 2015 May 28;4:132.

[13] Janegova A, Janega P, Rychly B, Kuracinova K, Babal P. Rola infekcji wirusem Epstein-Barr'a w rozwoju autoimmunologicznych chorób tarczycy. Endokrynologia Polska. 2015 May 1;66(2):132–6.

[14] Shukla SK, Singh G, Ahmad S, Pant P. Infections, genetic and environmental factors in pathogenesis of autoimmune thyroid diseases. Microbial Pathogenesis. 2018 Mar;116:279–88.

[15] Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: a Review on the Potential Interaction and Molecular Mechanisms. Viruses. 2019 Aug 19;11(8):762.

[16] Liu Y, Tang X, Tian J, Zhu C, Peng H, Rui K, et al. Th17/Treg Cells Imbalance and GITRL Profile in Patients with Hashimoto's Thyroiditis. International Journal of Molecular Sciences. 2014 Nov 25;15(12):21674–86.

[17] Liu Y, Cui X, Wang S, Liu J, Zhao N, Huang M, et al. Elevated MicroRNA-326 Levels Regulate the IL-23/IL-23R/Th17 Cell Axis in Hashimoto's Thyroiditis by Targeting a Disintegrin and Metalloprotease 17. Thyroid. 2020 Sep 1;30(9):1327–37.

[18] Zheng T, Xu C, Mao C, Mou X, Wu F, Wang X, et al. Increased Interleukin-23 in Hashimoto's Thyroiditis Disease Induces Autophagy Suppression and Reactive Oxygen Species Accumulation. Frontiers in Immunology. 2018 Jan 29;9.

[19] Nodehi M, Ajami A, Izad M, Asgarian Omran H, Chahardoli R, Amouzegar A, et al. Effects of vitamin D supplements on frequency of CD4+ T-cell subsets in women with Hashimoto's thyroiditis: a double-blind placebo-controlled study. European Journal of Clinical Nutrition. 2019 Jan 29;73(9):1236–43.

[20] X Ma M, Wang M, Xu F, Hao S. The Imbalance in Th17 and Treg Cells in Polycystic Ovarian Syndrome Patients with Autoimmune Thyroiditis. Immunological Investigations. 2021 Apr 26;1–12.

[21] Fang J, Yu L, Zhuang LG, Pei XY, Wang Q, Jin GX. The changes in peripheral blood Th17 and Treg ratios in Hashimoto's thyroiditis are accompanied by differential PD-1/PD-L1 expression. Frontiers in Endocrinology. 2022 Aug 25;13.

[22] Li D, Cai W, Gu R, Zhang Y, Zhang H, Tang K, et al. Th17 cell plays a role in the pathogenesis of Hashimoto's thyroiditis in patients. Clinical Immunology. 2013 Dec 1;149(3):411–20.

[23] Han LT, Hu JQ, Ma B, Wen D, Zhang TT, Lu ZW, et al. IL-17A increases MHC class I expression and promotes T cell activation in papillary thyroid cancer patients with coexistent Hashimoto's thyroiditis. Diagnostic Pathology. 2019 Jun 4;14(1).

[24] Akbay EA, Koyama S, Liu Y, Dries R, Bufe LE, Silkes M, Alam MM, Magee DM, Jones R, Jinushi M, Kulkarni M. Interleukin-17A promotes lung tumor progression through neutrophil attraction to tumor sites and mediating resistance to PD-1 blockade. Journal of thoracic oncology. 2017 Aug 1;12(8):1268-79.

[25] Bliddal S, Borresen SW, Feldt-Rasmussen U. Thyroid Autoimmunity and Function after Treatment with Biological Antirheumatic Agents in Rheumatoid Arthritis. Frontiers in Endocrinology. 2017 Jul 31;8.

[26] Bunte K, Beikler T. Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Inflammatory Diseases. International journal of molecular sciences. 2019;20(14):3394.

[27] Waliszewska-Prosół M, Ejma M. Hashimoto Encephalopathy—Still More Questions than Answers. Cells. 2022 Sep 14;11(18):2873.

[28] Wang J, Wang C, Liu L, Hong S, Ru Y, Sun X, et al. Adverse events associated with anti-IL-17 agents for psoriasis and psoriatic arthritis: a systematic scoping review. Frontiers in Immunology. 2023 Jan 31;14.

[29] Tywanek E, Michalak A, Świrska J, Zwolak A. Autoimmunity, New Potential Biomarkers and the Thyroid Gland—The Perspective of Hashimoto's Thyroiditis and Its Treatment. International Journal of Molecular Sciences. 2024 Jan 1;25(9):4703.

[30] Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4-5):391-7.

[31] Messina F, Piaserico S. The dark side of the moon: the immune-mediated adverse events of IL-17A/IL-17R inhibition. The Journal of Dermatological Treatment. 2022 Aug 1 [cited 2023 Mar 28];33(5):2443–54.

[32] Țiburcă L, Bembea M, Zaha DC, Jurca AD, Vesa CM, Rațiu IA, et al. The Treatment with Interleukin 17 Inhibitors and Immune-Mediated Inflammatory Diseases. Current Issues in Molecular Biology. 2022 Apr 26;44(5):1851–66.

[33] McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. Immunity. 2019 Apr 16;50(4):892-906.

[34] Gerenova J, Manolova I, Stanilova S. Serum levels of interleukin-23 and interleukin-17 in Hashimoto's thyroiditis. Acta Endocrinologica (Bucharest). 2019 Jan;15(1):74.

[35] Esfahanian F, Ghelich R, Rashidian H, Jadali Z. Increased levels of serum interleukin-17 in patients with Hashimoto's thyroiditis. Indian journal of endocrinology and metabolism. 2017 Jul 1;21(4):551-4.

[36] Upmale-Engela, Sabine et al. Genetic and Environmental Factors in Autoimmune Thyroid Disease: Exploring Associations with Selenium Levels and Novel Loci in a Latvian Cohort. Current issues in molecular biology. 17 Mar. 2024. vol. 46,3 2553-2565.

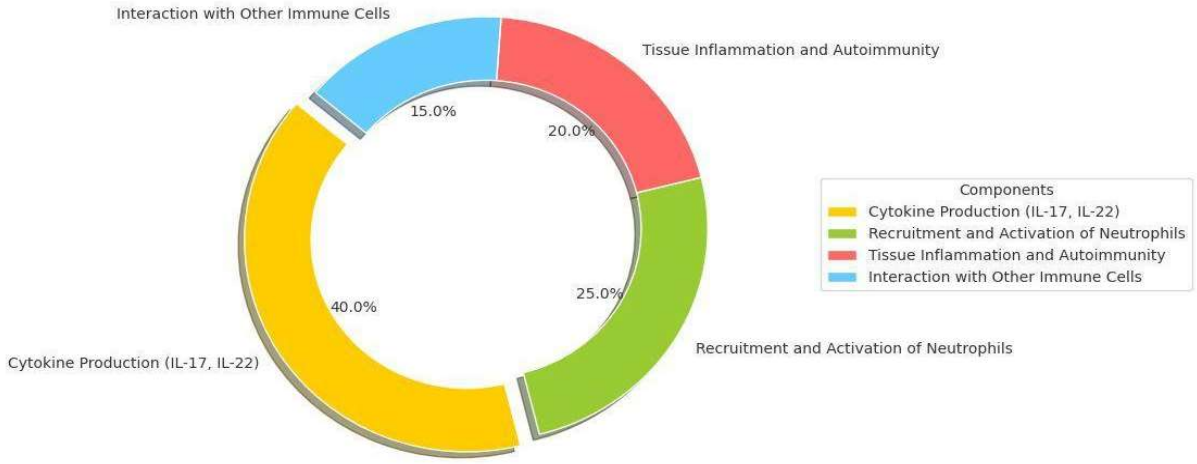
[37] Klubo-Gwiezdzinska J, Wartofsky L. Hashimoto thyroiditis: an evidence-based guide to etiology, diagnosis and treatment. Pol Arch Intern Med. 2022.

[38] Yoo, Won Sang, and Hyun Kyung Chung. Recent Advances in Autoimmune Thyroid Diseases. Endocrinology and metabolism (Seoul, Korea). 2016, vol. 31,3.

X. APPENDIX

10.1 Appendix A: Pie chart on the role of Th17 cells in Hashimoto's thyroiditis

Diagram 1: Components of Th17 cells pathophysiology



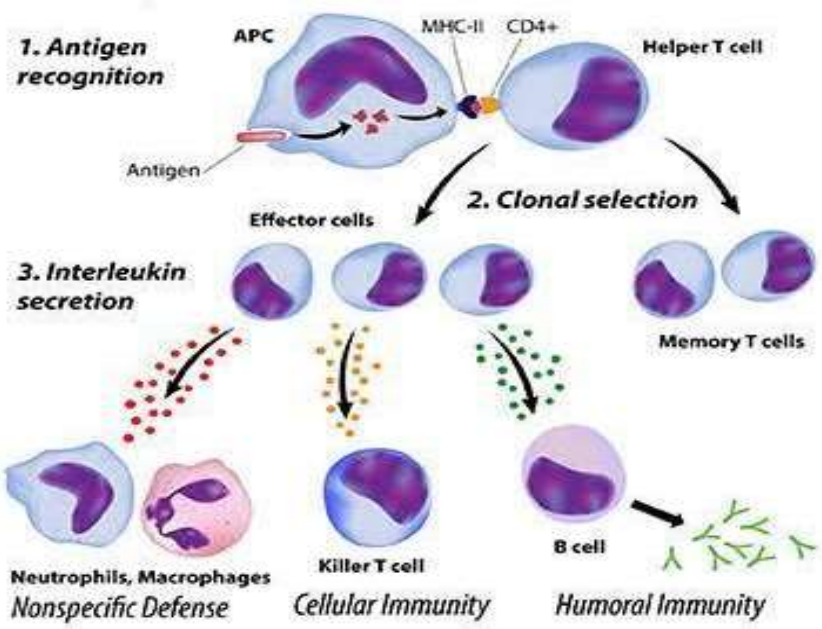
Description: The above figure shows the percentage of contribution by each of the components of Th17 cells in Hashimoto's thyroiditis

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

10.2 Appendix B: Picture of Helper T cell activation and function

Diagram 2: Stages of T cell activation



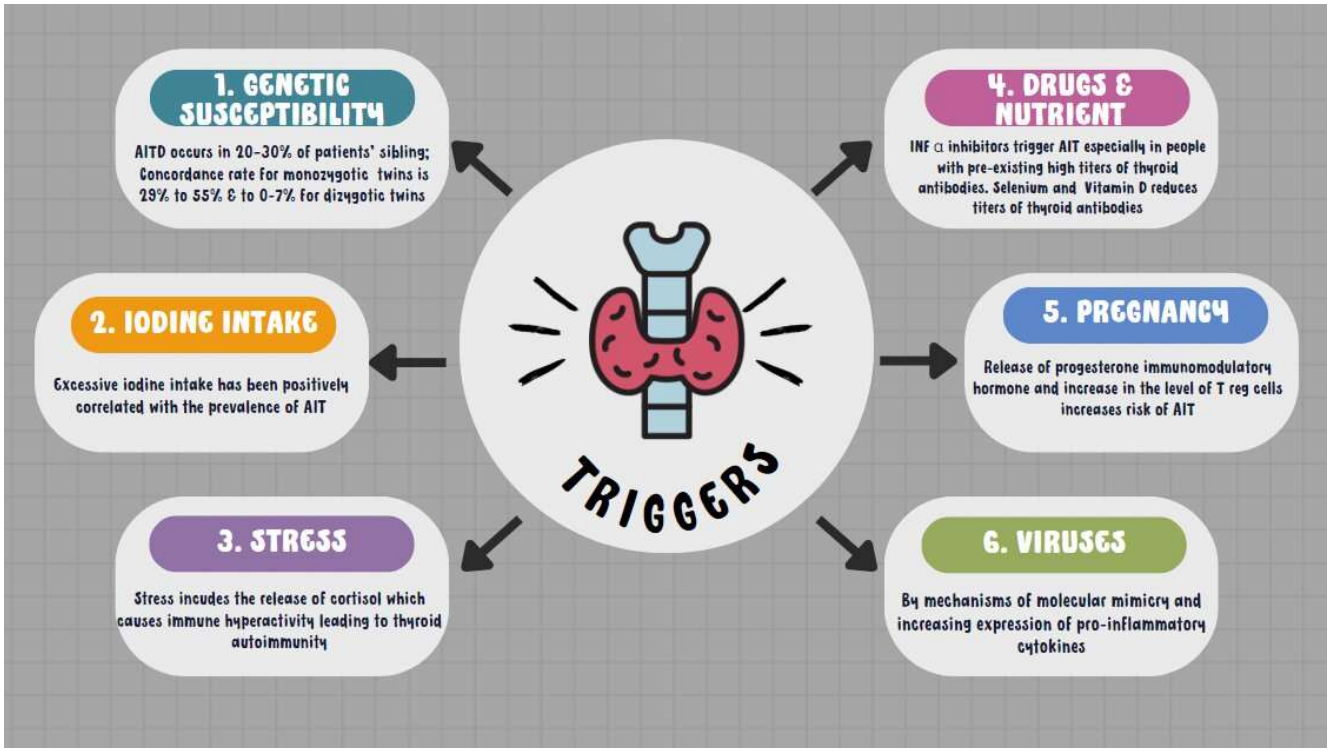
Description: The above figure shows the steps to activate helper T cells 1. Recognition of the antigen; 2. Clonal selection; 3. Secretion of ILs

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

10.3 Appendix C: Picture of Hashimoto's Risk Factors

Diagram 3: Most common triggers for Hashimoto's thyroiditis



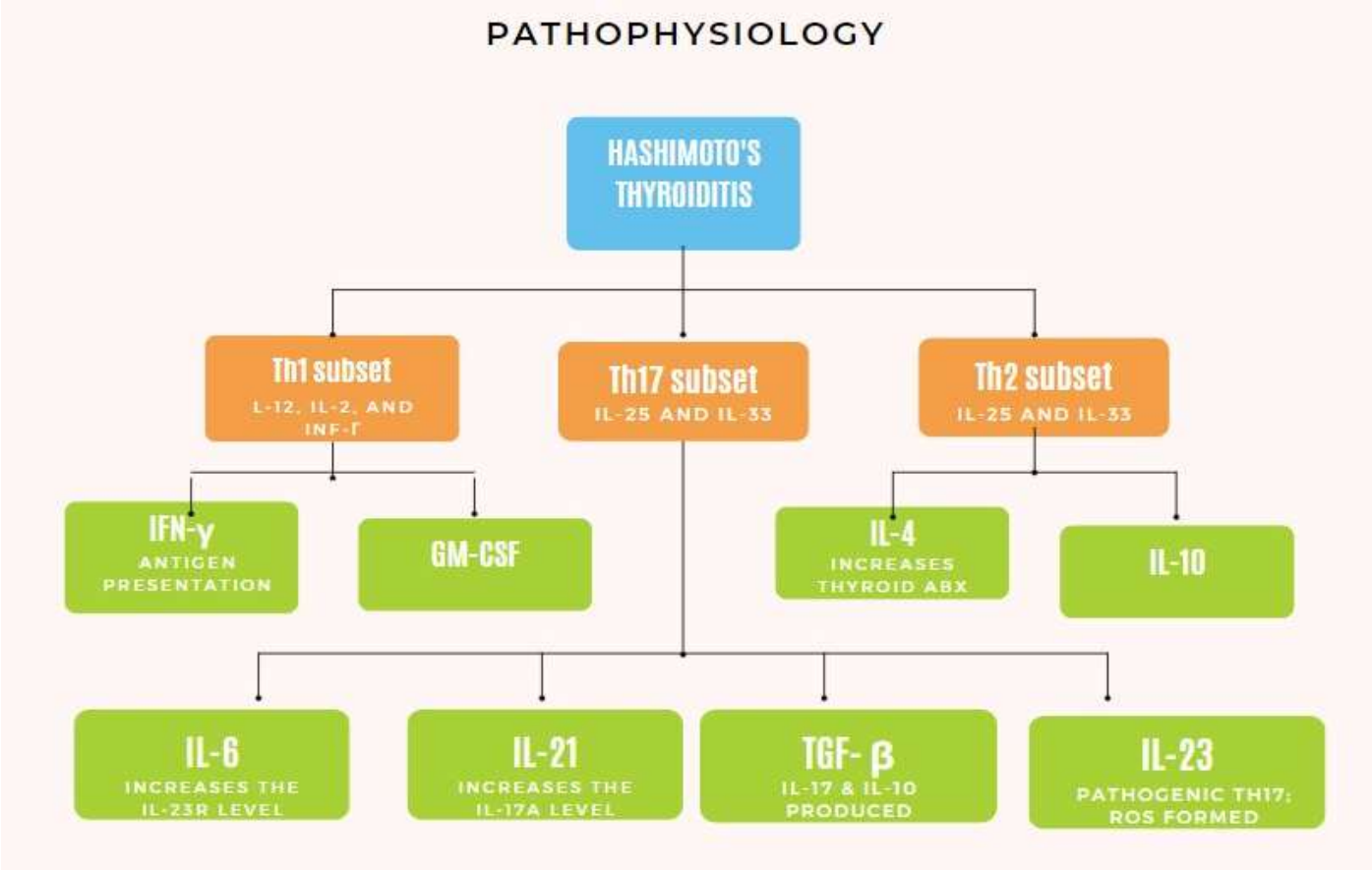
Description: This picture lists the several risk factors for HT and provides reasons for them

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 46 No. 1 August 2024, pp. 384-397

10.4 Appendix D: Flow chart on Hashimoto's thyroiditis pathophysiology

Diagram 4: Differentiation of the three subsets of C4+ cells



Description: The picture lists each step and the various cytokines involved in causing HT

DISCLOSE

The authors have nothing to disclose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As this study did not involve human participants, animal subjects, or clinical data, ethical approval was not required.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The author declares no competing interests.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

All the authors collaborated to conceptualize the study, perform the data analysis, and write the manuscript. The authors read and approved the final manuscript.