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REVIEW ARTICLE

Exploring the Central Role of the Imbalance between T helper 17 (Th17) and Regulatory T (Treg) Cells in Autoimmune Disease Progression: A review

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ABSTRACT (10 PT)

Immune balance is mainly maintained through coordination between effector and regulatory T cells, especially the Th17 and Treg subsets. These two types perform opposite functions—one drives inflammation while the other limits it—to preserve immune tolerance. When this coordination fails, the system drifts toward autoimmunity. Excessive Th17 activity and a shortage of functional Tregs have been reported in many disorders, but the molecular events behind their instability are still being investigated. Researchers have recently focused on therapeutic methods that might restore this disturbed ratio. The flexible nature of T cells makes such control difficult, since each subset can shift its phenotype depending on signals in the environment. Clinical and laboratory findings show altered Th17/Treg proportions in several autoimmune diseases, including type1 diabetes, lupus, multiple sclerosis, and psoriasis. In diabetic patients, a higher percentage of Tregs often coincides with lower HbAIc and reduced insulin demand, while increased Th17 activity predicts more severe disease. Studies of gene expression also reveal specific chromatin patterns that mark pathogenic Th17 cells. In addition, new approaches such as Treg-based treatments and engineered CAR-Treg cells are being explored to regulate these immune pathways. Altogether, current findings highlight that the Th17/Treg disequilibrium is a core element in autoimmune pathology, and restoring this cellular dialogue is a major target for future immunotherapy.

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1- INTRODUCTION

The immune system provides basic protection against pathogenic microorganisms [1]; however, it may also attack autologous tissue [2]. CD4 T cells coordinate diverse immune responses to deal with various pathogens [3]. The naive CD4 T cells are activated when the T cell receptor (TCR) and the catalyst receptor (CD28) bind to the main histological compatibility complex and catalysed peptide (MHC) molecule (B7.1 or B7.2), respectively; the latter is expressed by antigen-presenting cells (APCs) [4].

Activated CD8 T cells differentiate into several subgroups of influential cells that have different functions. These cell types include the adjuvant types ThI, Th2, and Th17, regulatory T cells (Treg), and follicular helper T cells (Th). The ultimate fate is determined primarily by the external environment (such as cytokines) present during

activation [5]. ThI cells stimulate classical macrophages and mediate immune responses to intracellular pathogens, while Th2 cells induce mast cells, eosinophils, and basal cells and mediate immune responses against parasites. Th17 cells stimulate multiple types of cells to recruit neutrophils to sites of infection, mediating immune responses against extracellular bacteria and fungi, while Treg cells inhibit immune responses to maintain immune balance [6]. Among these subgroups, ThI and Th17 cells can cause autoimmune diseases, while Treg cells work to suppress them [7].

Although there is a "central tolerance" mechanism within the thymus gland to restrict immune ammunition, the generation of diverse T cells inevitably produces receptors that can recognise endogenous antigens [8]. As a result, the naive T cells originating from the thymus are able to interact with both foreign antigens and endogenous components. Their maturity is largely influenced by the surrounding physical and chemical microenvironment, which directs them towards the development of effective or regulatory phenotypes, while they usually prevent self-reactive T cells from maturing into influential subgroups and are a necessary process for maintaining tolerance and preventing autoimmune disorders [9]. Experimental studies in mice have shown that naive CD4 T (Thp) auxiliary cells can differentiate into at least four major influencing strains: ThI, Th2, Th17 and regulatory T cells (Treg) [10]. In humans, evidence has been reported for all of these subgroups except Th17 as a distinct entity, although T-cells producing IL-17 are clearly identified. IL-17 plays a pro-inflammatory role and has been associated with several inflammatory and autoimmune conditions, while Treg cells perform anti-inflammatory functions and maintain immune tolerance [11].

The adherence of ratios to naive T cells depends on the nature of the stimulus, the concentration of the antigen, the common stimulus signals, and the cytokine environment [12]. Investigations have shown that IL-4 signals over STAT6 drive Th2 differentiation, while IL-12 through STAT4 promotes ThI development [13]. Each subgroup is defined by its own cytokine profile: IFN-y for ThI, IL-4 for Th2, and IL-17 for Th17, plus T-bet-specific transcription factors for ThI, GATA3 for Th2, FoxP3 for Treg, and RORyt for Th17 [14]. Current evidence confirms that naive T cells in mice may vary along the pathways of Th17 or Treg in a mutually exclusive way, with Th17 cells playing a crucial role in autoimmune inflammation, while Treg cells adjust those responses to maintain immune tolerance [15]. While much of this differentiation knowledge stems from animal research, consistent clinical and pathological observations in humans strongly support the pivotal contribution of Th17/Treg imbalance in the development of immune diseases [16]. Based on these data, the working hypothesis suggests that the deviation of immune responses towards Th17 or ThI and away from Treg lies behind many inflammatory and autoimmune disorders [17]. Conversely, blocking key cytokines such as IL-6 could redirect this polarisation toward the regulatory phenotype, fostering disease remission and restoration of immune homeostasis [18].

IL-17 and Its Immunological Role

Interleukin-17 (IL-17A) represents the first discovered member of the IL-17 cytokine family (IL-17A–F) [19]. It was cloned in 1993 from a murine T-cell cDNA library and initially described as a secretory product of activated $CD4^+$ T cells [20]. Later research broadened this view, showing that IL-17 can also be produced by $CD8^+$ cytotoxic T cells, γδ T cells, and innate immune cells such as neutrophils and macrophages [21]. Within the IL-17 family, IL-17A and IL-17F share the greatest structural homology and frequently function together, either as homo or heterodimers, to mediate overlapping yet distinct immunological responses [22].

Five IL-17 receptors—IL-17RA to IL-17RE—have been identified on many immune and non-immune cells [23]. These receptors assemble as heterodimeric complexes that convey signals through the adaptor protein ACT1 (TRAF3IP2), activating the NF-kappaB and MAPK (ERK, JNK, p38) pathways [24]. Upon activation, these cascades promote the transcription of various pro-inflammatory genes, including chemokines (CXCL1, CXCL2, CXCL8/IL-8, and CCL20) and cytokines (TNF-α, IL-6, G-CSF, and GM-CSF) [25]. Such mediators mobilise neutrophils to inflammatory foci and sustain their activation, thereby bridging innate and adaptive immunity through a continuous feedback loop [26].

From an immunological perspective, IL-17 acts as a link between rapid innate responses and antigen-specific adaptive defence. It reinforces mucosal barriers by stimulating epithelial and stromal cells to produce antimicrobial peptides (such as β-defensins and S100 proteins) and to up-regulate tight-junction molecules that preserve epithelial cohesion. Through these actions, IL-17 enhances resistance to extracellular bacteria and fungi, including Klebsiella pneumoniae, Candida albicans, and Staphylococcus aureus [27]. Yet the same cytokine that protects the host can also cause harm when its production is uncontrolled. Persistent or excessive IL-17 expression drives chronic inflammation, fibrotic remodeling, and autoimmune damage. High serum or tissue levels of IL-17 have been

reported in psoriasis, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease. Animal models mirror these. Findings: IL-17 overexpression induces joint inflammation and cartilage erosion, resembling rheumatoid arthritis, whereas deletion or pharmacologic blockade of the IL-17 pathway ameliorates autoimmune symptoms in experimental arthritis and encephalomyelitis. On a molecular level, IL-17 creates a self-perpetuating "feed-forward" cycle. When epithelial or fibroblast cells encounter IL-17, they release IL-6, IL-8, and G-CSF, which recruit and activate additional neutrophils and macrophages. These cells then produce more cytokines and proteases, maintaining inflammation even after the initial stimulus has faded [28].

IL-17 also cooperates with TNF-α, IL-1β, and IL-22 to boost the expression of adhesion molecules and matrix metalloproteinases, thereby facilitating leukocyte infiltration and tissue degradation. Because of its central position in chronic inflammatory networks, IL-17 has become a major therapeutic target. Neutralising antibodies such as secukinumab (anti-IL-17A), ixekizumab (anti-IL-17A), and brodalumab (anti-IL-17RA) have proven effective in psoriasis and ankylosing spondylitis [29]. Other approaches seek to rebalance the Th17/Treg axis—through low-dose IL-2 therapy or RORgamma t inhibition to restore immune tolerance without weakening host defence. In summary, IL-17 is a dual-natured cytokine: indispensable for protecting against pathogens but damaging when its activity persists [30]. By amplifying local inflammatory signals and engaging multiple immune pathways, IL-17 occupies a pivotal role in autoimmune pathophysiology and represents a strategic node for future targeted immunotherapies that aim to rebalance immune homeostasis rather than suppress it outright [31].

Regulatory T cells (Treg cells)

Different immune-regulating cell types have been described, such as TrI cells producing IL-10, Th3 cells secreting TGF-β, Qa-1-restricted $CD8^+$ cells, $CD28^-$ T cells, $CD8^+CD122^+$ cells, gamma-delta T-cell receptor cells (TCR), natural killer (NK) cells, stem cells, programmed neutrophils, $CD8^+CD28^-$ cells, and $CD3^+CD4^-CD8^-$ cells, in addition to naturally existing $CD4^+CD25^+$ T cells. Both human and mouse models lacking $CD4^+CD25^+$ T cells develop severe autoimmune disorders; therefore, research interest has mainly centred on these cells, known as regulatory T cells (Tregs) [32].

Under in vitro conditions, Tregs can inhibit proliferation and cytokine secretion by $CD4^+CD25^-$ and $CD8^+$ responder T cells after stimulation and can modulate the reactions of $CD8^+$ T cells, NK cells, and $CD4^+$ cells against specific antigens. In vivo, these activities extend beyond maintaining tolerance and preventing autoimmune diseases; they are also involved in controlling allergy, regulating microbial responses, preventing graft rejection, maintaining gastrointestinal tolerance, and maternal tolerance to foetal antigens. Donor-derived Tregs can prevent graft rejection in some experimental models by influencing indirect immune responses. Mutations in Foxp3, a winged-helix transcription factor, lead to the loss of Treg activity in humans and mice. Overexpression of Foxp3 in murine cells produces a Treg phenotype, yet Foxp3 expression alone is not always a definitive marker in humans because it can be transiently induced during TCR activation, similar to CD25 [33,34].

Therefore, not all $CD4^+CD25^+Foxp3^+$ induced cells are functionally suppressive. Recent findings indicate that CD127 (IL-7 receptor) serves as a useful biomarker for human Tregs; the $CD4^+CD25^+CD127$^low subset in peripheral blood shows strong suppressive ability and high Foxp3 levels [35]. Tregs can function independently of antigen-presenting cells (APCs) and without antigen specificity, although they can proliferate in response to their own antigens in vivo. Their suppressive function largely depends on cell-to-cell contact, since experiments show that separation of Tregs from effector T cells by a semi-permeable membrane abolishes suppression. Signalling through the T-cell receptor is also essential for maintaining this activity. In vivo data highlight the importance of TGF-β and IL-10 as mediators of Treg activity but do not rule out the involvement of soluble factors acting over very short distances or attached to the cell surface. While direct contact is frequently required, some of the regulatory effects may also proceed through other immune cells such as NKT cells or mast cells [36].

Their influence on target T cells includes suppression of cell-cycle progression through IL-2 signal interruption. Moreover, IFN-γ has been linked to Treg regulation, as antigen-reactive Tregs show IFN-γ mRNA upregulation after antigen exposure, and neutralisation of IFN-γ disrupts skin-graft tolerance. Tregs express CTLA-4 (cytotoxic T-lymphocyte antigen-4) and signalling via this molecule appears important since antibody interaction with CTLA-4 can interfere with Treg-mediated suppression. Because CTLA-4 is also induced on $CD4^+CD25^-$ effector cells, some early experimental inconsistencies in mice and humans might be explained by effects on non-regulatory cells rather than on Tregs themselves. Since both Th17 and Treg cells arise from naïve $CD4^+$ precursors under opposing cytokine conditions, their interplay determines immune tolerance or pathology [37].

Th17/Treg Balance and Crosstalk

Th17 cells and Treg regulatory cells share a common signalling pathway based on the transformer growth factor β (TGF-β). However, signs supporting inflammation during cell activation determine the fate of each of these two types in a mutual manner. When interleukin-6 (IL-6) or interleukin-21 (IL-21) is present with TGF-β, the naive CD4+ T cells are differentiated to Th17 cells, while the absence of inflammatory cytokines allows TGF-β to be pushed towards Treg cells [38]. Th17 cells secrete cytokines IL-17, IL-22, and IL-23, resulting in neutrophil recruitment and promoting inflammation at the site of infection. In contrast, Treg cells produce anti-inflammatory cytokines such as IL-10 and TGF-β, inhibiting the activity of multiple types of immune cells, limiting the inflammatory response. Thus, the two cells perform opposite functions during immune and inflammatory responses [39].

Th17 cells are a major factor in autoimmune diseases such as psoriasis, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and multiple sclerosis (MS). The STAT3 protein is activated when the T cell receptor (TCR) is stimulated in parallel with the TGF-β and IL-6 signals, stimulating the expression of the RORgammat transcription factor that guides the cells towards the Th17 pattern. In contrast, Treg cells inhibit autoimmune responses. These cells originate either in the thymus gland during development (tTreg) or in the periphery (pTreg) as a result of activation of naive CD4+ T cells [40].

Treg cells are formed when a strong signal is received via TCR from endogenous MHC complexes in antigen-presenting cells (APCs) in the thymus gland, resulting in the expression of the Foxp3 factor. pTreg cells are formed in peripheral tissues of CD4+ T cells under the influence of TGF-β and IL-2 and are spread especially in the intestine and placenta, where they maintain tolerance for food antigens, symbiotic bacteria and the foetus [41]. TGF-β stimulates activation of SMAD2 and SMAD3 proteins within naive T cells, activating Foxp3 and pushing cells towards the pTreg pattern. IL-2 also stimulates the STAT5 protein, which in turn enhances Foxp3. Foxp3-positive Treg cells can also be generated in vitro using TGF-β and IL-2, known as iTreg cells [42].

Other inhibitive patterns include TGF-β-positive Th3 cells, TrI cells that secrete IL-10 and lack Foxp3, as well as GITRsp cells that show high expression of the GITR receptor with low CD25 and produce large amounts of IL-10 and TGF-β. The crosstalk between Th17 and Treg cells plays a pivotal role in autoimmune control. Maintaining this balance depends on multiple factors such as TCR signalling, stimulator signals, cytokines, Foxp3 stability, metabolic regulation, and the effect of microbes. Understanding these factors and their mechanisms contributes to explaining how autoimmune diseases develop and identifying possible future treatment goals [43].

Mechanistic Pathways Regulating Th17/Treg Balance

The immune balance between the Th17 and Treg groups acts as a central checkpoint that controls inflammation and general immune stability. With different signalling of cytokines and metabolic environments, naive CD4+ T cells may convert to different auxiliary phenotypes such as ThI, Th2, and Th17, or into regulatory T cells. Since their identification in 2005, Th17 cells have been recognised by their RORγt transcription factor and by secreting cytokines, including IL-17, IL-17F, IL-21, and IL-22. Together, these media work to recruit neutrophils and phages and intensify localised inflammatory responses [44].

In contrast, regulatory T cells (CD4+CD25+FoxP3+) perform the opposite but complementary task. These cells inhibit excessive immune activation and maintain self-tolerance by releasing anti-inflammatory cytokines such as IL-10 and TGF-β1. There are two main types: tTregs, which originate from the thymus, and pTregs, which develop in peripheral tissues. Both are essential to prevent autoimmune activity and maintain immune balance. These two types of cells act as a counterweight within the immune network – Th17 cells promote inflammation, while regulatory cells restore balance and decay [45].

Its differentiation depends on the surrounding cytokine environment. TGF-β plays a dual role: when it acts alone, it activates SMAD2/3 signalling to stimulate FoxP3 and promote Treg production; However, in the presence of inflammatory cytokines such as IL-6, IL-21 or IL-23, it stimulates STAT3, leading to RORgammat expression and differentiation towards the Th17 strain [46]. Thus, the mutual inhibition between FoxP3 and RORgammat ensures that each subgroup maintains its identity and function. Metabolic regulation provides another level of control. The mTOR-HIF-1α axon promotes glucose hydrolysis and new lipid synthesis, fuelling Th17 activity, while AMPK in turn works by inhibiting mTOR and promoting oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) – two key features of T regulatory cell metabolism. Th17 cells mainly rely on glycolysis. and lipid synthesis (through ACCI), while Treg cells rely on OXPHOS and FAO to produce ATP efficiently. Furthermore, GLSI-mediated glycolysis supports the vital energy of Th17, but its inhibition shifts the differentiation towards the

dominance of T-regulatory cells. Supragenereconfiguration of this balance further improves [47, 48]. Histone acetyl at the RORC catalyst enhances the transcription of Th17, while the demethylation in FoxP3's demethylated region (TSDR) of FoxP3 maintains the stability of the Treg's identity, even under inflammatory pressure. Environmental influences also play a role. Short-Chain fatty acids (SCFAs), such as butyrates and propionates, promote Treg differentiation.by increasing the FoxP3 acetyl, while segmented filamentous bacteria (SFB) catalyse the growth of Th17 through IL-23-dependent mucous pathways [49].

As shown in Figure (1), the balance between Th17 and Treg cells plays a crucial role in maintaining immune balance and preventing excessive subjective responses.

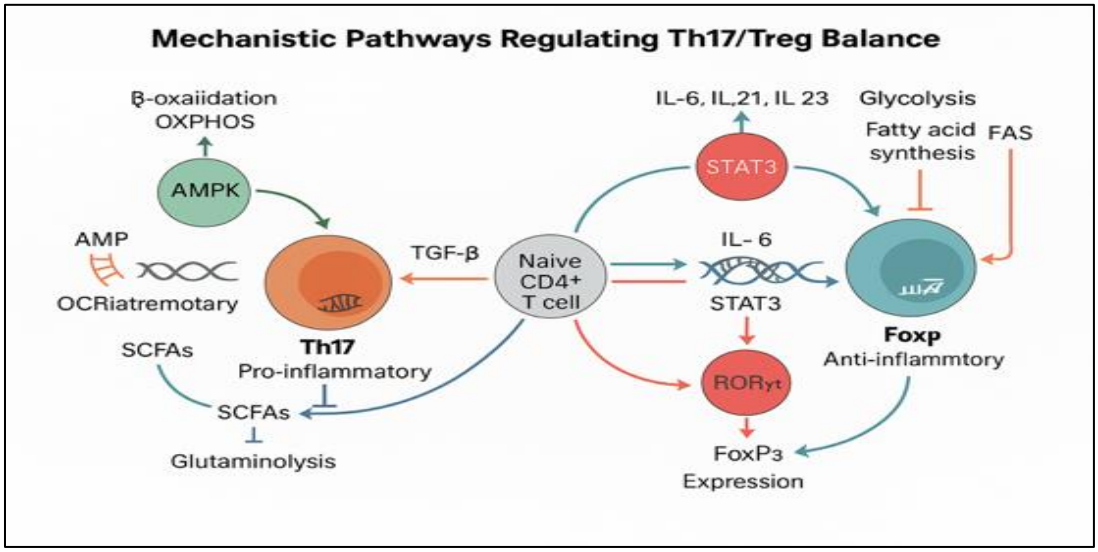

Fig (1): A schematic representation of the balance of Th17 and Treg cells and its role in maintaining immune balance. The imbalance of this axis leads to the development of autoimmune diseases

Emerging discussion and perspectives

The balance between Th17 and Treg cells is a pivotal regulatory point that controls the stability of the immune system and determines whether the immune response will end with the going of inflammation or develop towards an autoimmune condition. This mutual interaction between the two groups gives flexibility in response, but at the same time it shows an aspect of weakness; any minor disorder in cytokine signalling or metabolic pathways can lead to chronic inflammation. Several studies have shown that the ratio of Th17/Treg varies depending on diseases, such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, reflecting the severity of the disease and the extent of response to treatment [50].

While IL-17 is the cytokine-chaser of Th17 cells, its role extends beyond inflammation to include tissue repair modification and epithelial septum integrity. Similarly, Treg cells not only suppress self-reactive lymphocytes but also participate in tissue regeneration through the secretion of amphigulin. The interaction between STAT3 and STAT5 signals remains a key determinant of the ratio obligation, IL-6 and IL-21 drive the activation of STAT3 and promote Th17 differentiation, while IL-2 activates STAT5 to stabilise the FoxP3 expression and maintain the Treg function [51].

Recent investigations have revealed a strong metabolic component of this balance. Th17 cells rely on sugar metabolism and fatty acid synthesis, which are regulated by HIF-1α and mTORCI, while Tregs favour oxidative phosphorylation and fatty acid oxidation driven by AMPK activity. Therefore, pharmacological or dietary modification of these pathways may restore immune balance. Furthermore, the intestinal microorganisms and their metabolites, especially short-chain fatty acids such as butyrate, promote acetyl FoxP3 and promote peripheral Treg generation [52]. This suggests that environmental and nutritional factors can reshape the immune landscape towards tolerance. Despite these ideas, questions remain about the durability and reflexivity of Th17/Treg polarisation in human autoimmune diseases. Future research should focus on the longitudinal monitoring of these cell groups and cytokine signatures during treatment, using single-cell transcription and immune system approaches to determine the patient's immune fingerprints [53].

Therapeutic targeting of the Th17/Treg axis

The therapeutic modification of the Th17/Treg axis has become a promising strategy for restoring immune balance in autoimmune diseases and chronic inflammatory diseases. Given that excessive activity of Th17 contributes to tissue inflammation while poor Treg function limits tolerance, modern approaches aim to rebalance rather than suppress immunity. Inhibition of the IL-17 pathway has been the most successful clinical strategy to date. Monoclonal antibodies that target IL-17A or its receptors such as Secukinumab, Ixekizumab, and Brodalumab have shown significant efficacy in psoriasis, ankylosing spondylitis, and psoriatic arthritis [54]. This biology neutralises IL-17 signaling, thereby reducing cytokine-driven inflammation and tissue destruction while maintaining adequate immune defense. Another promising approach is the treatment of low-dose IL-2, which selectively expands Treg cells without activating large-scale affected T cells. Clinical studies have shown improved immune regulation and decreased disease activity in systemic lupus erythematosus, graft vs. host disease, and type 1 diabetes. By engaging STATS signalling, IL-2 enhances FoxP stabilisation and supports Long-term Treg maintenance. RORyt inhibitors represent a newer class of small molecules designed to suppress Th17 differentiation at the transcriptial level. RORgammat prevention interferes with the production of IL-17A and IL-22, effectively relieving inflammation. In parallel, targeting metabolic checkpoints such as mTOR and HIF-la can modify the fate of the ratios diverting glucose-lyted Thl7 cells towards oxidative and regulatory phenotypes supported by AMPK activation [55].

In addition to pharmacological modification, microbiome-based interventions provide a physiological pathway to restore the Th17/Treg balance. Short-chain fatty acids (SCFAs), such as butyrates and propionates – contribute to the process of histone acetylation at the FoxP3 gene site, supporting the formation of Treg regulatory cells in peripheral tissues. In contrast, the imbalance of the intestinal microbiome (dysbiosis) or a decrease in the number of some beneficial bacteria such as Clostridia and Bifidobacteria leads to the activation of inflammation associated with Th17 cells [56]. From this point of view, probiotic supplements, increasing the intake of dietary fibre, and the cultivation of microorganisms (microbiota) are means of helping to support natural immune regulation.Together, these therapeutic strategies suggest that the modification of the Th17/Treg axis is not only aimed at curbing inflammation but also at restoring the physiological balance of immunity, providing a basis for the development of accurate and targeted immune treatments for inflammatory and autoimmune diseases [57]. As shown in Figure (2), the balance between Th17 and Treg cells depends on cytokine signalling and genetic regulation pathways, while plate (B) shows the therapeutic mechanisms that can restore this balance in inflammation or autoimmune situations.

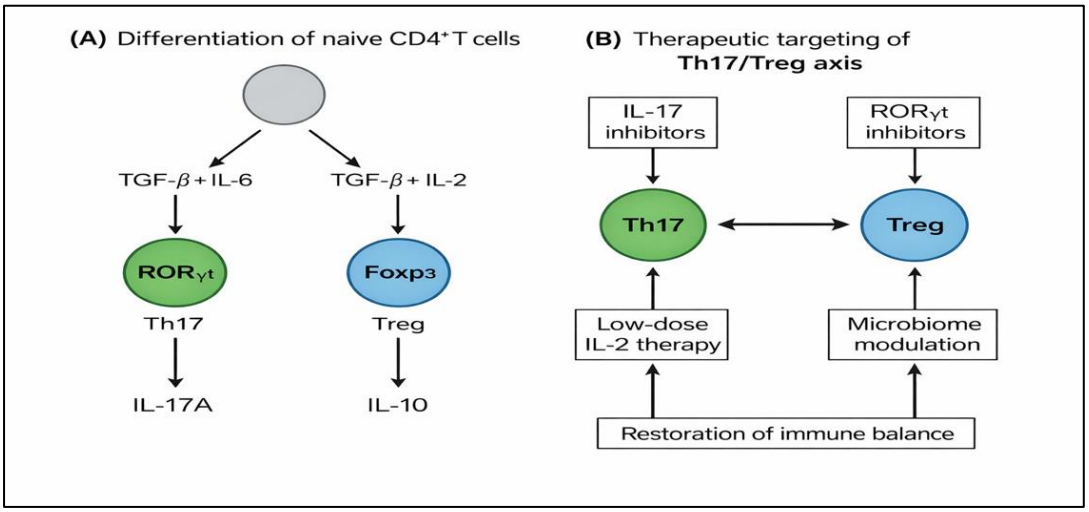

Fig (2): A Differentiation pathway of naïve CD4⁺ T cells into Th17 or regulatory T (Treg) cells. In the presence of TGF-β and IL-6, naïve CD4⁺ T cells differentiate into Th17 cells through the activation of the transcription factor RORγt, leading to IL-17A production. In contrast, stimulation with TGF-β and IL-2 promotes Treg differentiation via Foxp3 expression, resulting in anti-inflammatory cytokine production such as IL-10.B Therapeutic targeting of the Th17/Treg axis, including IL-17 and RORγt inhibitors, low-dose IL-2 therapy, and microbiome modulation, aiming to restore immune balance.

2- CONCLUSION

The delicate balance between Th17 cells and Treg cells forms an essential regulatory centre in the immune system, deciding whether the immune response will contribute to ending the inflammation or will deviate towards the subjective state. This adaptive flexibility provides some kind of important ability, but at the same time it opens the door to dysfunction. A small disturbance in the signalling of cytokines or metabolic pathways can lead to a state of chronic inflammation.Research has shown that the ratio of Th17/Treg varies in immune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, as these changes reflect the severity of the disease and the body's response to treatment.Recent studies suggest that therapeutic interventions aimed at curbing interleukin-17 activity (IL-17) or to stimulate regulatory T-cell dilation (Treg) have shown encouraging results in several clinical trials. It is understood that the main goal is not to extinguise the entire immune system, but to restore the functional balance within the immune network. Rapid developments in the fields of metabolic immunity, modification of the intestinal microbiome, and cytokine-directed therapies are also expected to enhance the ability to reset this balance and achieve a long-term immune calm in autologous diseases.

REFERENCES

[1] Abbas, A. K., Lichtman, A. H., & Pillai, S. (2021). *Cellular and molecular immunology* (10th ed.). Elsevier.

[2] Matzinger, P. (1994). Tolerance, danger, and the extended family. *Annual Review of Immunology, 12*, 991–1045. https://doi.org/10.1146/annurev.iy.12.040194.005015

[3] Zhu, J., & Paul, W. E. (2008). CD4 T cells: Fates, functions, and faults. *Blood, 112*(5), 1557–1569. https://doi.org/10.1182/blood-2008-05-078154

[4] Chen, L., & Flies, D. B. (2013). Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nature Reviews Immunology, 13*(4), 227–242. https://doi.org/10.1038/nri3405

[5] Sharpe, A. H. (2009). Mechanisms of costimulation. *Immunity, 30*(3), 229–232. https://doi.org/10.1016/j.immuni.2009.02.002

[6] Kaech, S. M., & Cui, W. (2012). Transcriptional control of effector and memory $CD8^+$ T cell differentiation. *Nature Reviews Immunology, 12*(11), 749–761. https://doi.org/10.1038/nri3307

[7] O'Shea, J. J., & Paul, W. E. (2010). Mechanisms underlying lineage commitment and plasticity of helper $CD4^+$ T cells. *Science, 327*(5969), 1098–1102. https://doi.org/10.1126/science.1178334

[8] Curtsinger, J. M., & Mescher, M. F. (2010). Inflammatory cytokines as a third signal for T cell activation. *Current Opinion in Immunology, 22*(3), 333–340. https://doi.org/10.1016/j.coi.2010.02.013

[9] Szabo, S. J., Sullivan, B. M., Peng, S. L., & Glimcher, L. H. (2003). Molecular mechanisms regulating Th1 immune responses. *Annual Review of Immunology, 21*, 713–758. https://doi.org/10.1146/annurev.immunol.21.120601.141138

[10] Paul, W. E., & Zhu, J. (2010). How are T(H)2-type immune responses initiated and amplified? *Nature Reviews Immunology, 10*(4), 225–235. https://doi.org/10.1038/nri2735

[11] Korn, T., Bettelli, E., Oukka, M., & Kuchroo, V. K. (2009). IL-17 and Th17 cells. *Annual Review of Immunology, 27*, 485–517. https://doi.org/10.1146/annurev.immunol.021908.132710

[12] Sakaguchi, S., Yamaguchi, T., Nomura, T., & Ono, M. (2008). Regulatory T cells and immune tolerance. *Cell, 133*(5), 775–787. https://doi.org/10.1016/j.cell.2008.05.009

[13] Noack, M., & Miossec, P. (2014). Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. *Autoimmunity Reviews, 13*(6), 668–677. https://doi.org/10.1016/j.autrev.2013.12.004

[14] Klein, L., Kyewski, B., Allen, P. M., & Hogquist, K. A. (2014). Positive and negative selection of the T cell repertoire. *Nature Reviews Immunology, 14*(6), 377–391. https://doi.org/10.1038/nri3667

[15] Huseby, E. S., Crawford, F., White, J., Marrack, P., & Kappler, J. W. (2005). How the T cell repertoire becomes peptide and MHC specific. *Cell*, *122*(2), 247–260. https://doi.org/10.1016/j.cell.2005.06.021

[16] Zehn, D., King, C., Bevan, M. J., & Palmer, E. (2012). TCR signaling requirements for activating T cells and for generating memory. *Cellular and Molecular Life Sciences*, *69*(10), 1565–1575. https://doi.org/10.1007/s00018-012-0965-4

[17] Van der Windt, G. J. W., & Pearce, E. L. (2012). Metabolic switching and fuel choice during T-cell differentiation and memory development. *Immunological Reviews*, *249*(1), 27–42. https://doi.org/10.1111/j.1600-065X.2012.01150.x

[18] Goodnow, C. C., Sprent, J., Fazekas de St Groth, B., & Vinuesa, C. G. (2005). Cellular and genetic mechanisms of self-tolerance and autoimmunity. *Nature*, *435*(7042), 590–597. https://doi.org/10.1038/nature03724

[19] Abd, I.S. (2025). Association of Vitamin D and IL-7 Levels in Severity of COVID-19. Dijlah Journal of Medical Sciences, 1(3):77-83.

[20] Fossiez, F., Djossou, O., Chomarat, P., et al. (1996). T cell interleukin 17 induces stromal cells to produce pro-inflammatory and hematopoietic cytokines. *Journal of Experimental Medicine*, *183*(6), 2593–2603. https://doi.org/10.1084/jem.183.6.2593

[21] Cua, D. J., & Tato, C. M. (2010). Innate IL-17–producing cells: The sentinels of the immune system. *Nature Reviews Immunology*, *10*(7), 479–489. https://doi.org/10.1038/nri2800

[22] Wright, J. F., et al. (2007). Identification of an interleukin 17F/17A heterodimer. *Journal of Biological Chemistry*, *282*(18), 13447–13455. https://doi.org/10.1074/jbc.M700499200

[23] Gaffen, S. L. (2009). Structure and signalling in the IL-17 receptor family. *Nature Reviews Immunology*, *9*(8), 556–567. https://doi.org/10.1038/nri2586

[24] Qian, Y., Liu, C., Hartupee, J., et al. (2007). The adaptor Act1 is required for interleukin 17–dependent signaling. *Nature Immunology*, *8*(3), 247–256. https://doi.org/10.1038/ni1439

[25] Onishi, R. M., & Gaffen, S. L. (2010). Interleukin-17 and its target genes: Mechanisms of IL-17 function in disease. *Immunology*, *129*(3), 311–321. https://doi.org/10.1111/j.1365-2567.2009.03240.x

[26] Kolls, J. K., & Linden, A. (2004). Interleukin-17 family members and inflammation. *Immunity*, *21*(4), 467–476. https://doi.org/10.1016/j.immuni.2004.08.018

[27] Kao, C. Y., Chen, Y., Thai, P., et al. (2004). IL-17 markedly up-regulates human β-defensin-2 in airway epithelium via NF-kappaB and JAK pathways. *Journal of Immunology*, *173*(5), 3482–3491. https://doi.org/10.4049/jimmunol.173.5.3482

[28] Park, H., Li, Z., Yang, X. O., et al. (2005). A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nature Immunology*, *6*(11), 1133–1141. https://doi.org/10.1038/ni1261

[29] Bettelli, E., Carrier, Y., Gao, W., et al. (2006). Reciprocal developmental pathways for the generation of pathogenic Th17 and regulatory T cells. *Nature*, *441*(7090), 235–238. https://doi.org/10.1038/nature04753

[30] Read, S., Greenwald, R., Izcue, A., et al. (2006). Blockade of CTLA-4 on $CD4^+CD25^+$ regulatory T cells abrogates their function in vivo. *Journal of Experimental Medicine*, *203*(4), 769–777. https://doi.org/10.1084/jem.20051359

[31] Wing, K., Onishi, Y., Prieto-Martin, P., et al. (2008). CTLA-4 control over $Foxp3^+$ Treg function. *Science*, *322*(5899), 271–275. https://doi.org/10.1126/science.1160062

[32] Huber, M., Heink, S., Grothe, H., et al. (2009). A Th17-like developmental process leads to $CD8^+$ Tc17 cells with reduced cytotoxic activity. *European Journal of Immunology*, *39*(7), 1716–1725. https://doi.org/10.1002/eji.200939412

[33] Ivanov, I. I., McKenzie, B. S., Zhou, L., et al. (2006). The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory IL-17$^+$ T helper cells. *Cell, 126*(6), 1121–1133. https://doi.org/10.1016/j.cell.2006.07.035

[34] Veldhoen, M., Hocking, R. J., Atkins, C. J., Locksley, R. M., & Stockinger, B. (2006). TGF beta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17–producing T cells. *Immunity, 24*(2), 179–189. https://doi.org/10.1016/j.immuni.2006.01.001

[35] Zhou, L., Chong, M. M., & Littman, D. R. (2009). Plasticity of CD4$^+$ T cell lineage differentiation. *Immunity, 30*(5), 646–655. https://doi.org/10.1016/j.immuni.2009.05.001

[36] Berod, L., Friedrich, C., Nandan, A., et al. (2014). De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. *Nature Medicine, 20*(11), 1327–1333. https://doi.org/10.1038/nm.3704

[37] Furusawa, Y., Obata, Y., Fukuda, S., et al. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature, 504*(7480), 446–450. https://doi.org/10.1038/nature12721

[38] Ivanov, I. I., & Littman, D. R. (2011). Segmented filamentous bacteria and the fate of the Th17 lineage. *Current Opinion in Immunology, 23*(2), 161–167. https://doi.org/10.1016/j.coi.2011.01.002

[39] McGeachy, M. J., Bak-Jensen, K. S., Chen, Y., et al. (2007). TGF-β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain Th17 cell–mediated pathology. *Nature Immunology, 8*(12), 1390–1397. https://doi.org/10.1038/ni1539

[40] Noack, M., & Miossec, P. (2017). Regulation of Th17 and Treg cell balance in autoimmune and inflammatory diseases. *Cytokine, 101*, 76–85. https://doi.org/10.1016/j.cyto.2016.08.011

[41] Gratz, I. K., Truong, H. A., Yang, S. H., et al. (2013). Cutting edge: Memory regulatory T cells require IL-7 and not IL-2 for their maintenance in peripheral tissues. *Journal of Immunology, 190*(9), 4483–4487. https://doi.org/10.4049/jimmunol.1300212

[42] Quintana, F. J., Basso, A. S., Iglesias, A. H., et al. (2008). Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature, 453*(7191), 65–71. https://doi.org/10.1038/nature06880

[43] Ueno, H., Banchereau, J., & Vinuesa, C. G. (2015). Pathophysiology of T follicular helper (Tfh) cells in humans and mice. *Nature Immunology, 16*(2), 142–152. https://doi.org/10.1038/ni.3054

[44] Weaver, C. T., Elson, C. O., Fouser, L. A., & Kolls, J. K. (2013). The Th17 pathway and inflammatory diseases of the intestines, lungs and skin. *Annual Review of Pathology, 8*, 477–512. https://doi.org/10.1146/annurev-pathol-011110-130318

[45] Yang, J., Chu, Y., Yang, X., et al. (2009). Th17 and natural Treg cell population dynamics in systemic lupus erythematosus. *Arthritis & Rheumatism, 60*(5), 1472–1483. https://doi.org/10.1002/art.24499

[46] Wu, Y., Wang, Q., Li, Z., et al. (2018). Th17/Treg imbalance and associated cytokines in peripheral blood of patients with psoriasis. *Journal of Dermatological Science, 89*(2), 123–130. https://doi.org/10.1016/j.jdermsci.2017.10.007

[47] Yu, A., Snowhite, I. V., Vendrame, F., et al. (2021). Selective IL-2 responsiveness of regulatory T cells through IL-2 receptor β versus γ chain. *Frontiers in Immunology, 12*, 636827. https://doi.org/10.3389/fimmu.2021.636827

[48] Liao, W., Lin, J. X., & Leonard, W. J. (2013). Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. *Immunity, 38*(1), 13–25. https://doi.org/10.1016/j.immuni.2013.01.004

[49] Chi, H. (2022). Metabolic regulation of T cells in immunity and autoimmunity. *Cellular & Molecular Immunology, 19*(3), 388–399. https://doi.org/10.1038/s41423-021-00822-7

[50] Esensten, J. H., Helou, Y. A., Chopra, G., Weiss, A., & Bluestone, J. A. (2016). CD28 costimulation: From mechanism to therapy. *Immunity, 44*(5), 973–988. https://doi.org/10.1016/j.immuni.2016.04.020

[51] Ahern, P. P., Izcue, A., Maloy, K. J., & Powrie, F. (2008). The interleukin-23 axis in intestinal inflammation. *Immunological Reviews*, *226*(1), 147–159. https://doi.org/10.1111/j.1600-065X.2008.00700.x

[52] Belkaid, Y., & Harrison, O. J. (2017). Homeostatic immunity and the microbiota. *Immunity*, *46*(4), 562–576. https://doi.org/10.1016/j.immuni.2017.04.008

[53] Gaur, P., Singh, A. K., Shukla, N. K., et al. (2021). Therapeutic targeting of the Th17/Treg axis in autoimmune diseases. *Frontiers in Immunology*, *12*, 661601. https://doi.org/10.3389/fimmu.2021.661601

[54] Hueber, W., et al. (2014). Effects of secukinumab in patients with moderate to severe psoriasis. *New England Journal of Medicine*, *371*(4), 326–338. https://doi.org/10.1056/NEJMoa1314258

[55] Brunkow, M. E., Jeffery, E. W., Hjerrild, K. A., et al. (2001). Disruption of a new forkhead/winged-helix protein results in fatal lymphoproliferative disorder in the scurfy mouse. *Nature Genetics*, *27*(1), 68–73. https://doi.org/10.1038/83784

[56] Bennett, C. L., Christie, J., Ramsdell, F., et al. (2001). The immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome caused by mutations of FOXP3. *Nature Genetics*, *27*(1), 20–21. https://doi.org/10.1038/83713

[57] Sakaguchi, S., Vignali, D. A. A., Rudensky, A. Y., Niec, R. E., & Waldmann, H. (2013). The plasticity and stability of regulatory T cells. *Nature Reviews Immunology*, *13*(6), 461–467. https://doi.org/10.1038/nri3464