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T HELPER 17 (Th17) AND REGULATORY T (Treg) CELLS PROFILE IN TYPE-2 DIABETES MELLITUS (T2DM)

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ABSTRACT

One of the metabolic disorders we are investigating is Type 2 Diabetes mellitus (DM). Our research into the three main metabolic pathways, glycolysis, oxidative phosphorylation, and fatty acid, which provide energy for T cells, has significant implications. The profile of Th17 and Treg cells in type 2 diabetes will be opposite in terms of their populations caused by metabolic disorders in the body. Type 2 diabetes triggers an immunology response with increasing Th17 cells, while Treg cells are lacking. Numerous studies have shown that diabetes mellitus as a metabolic disease affects populations of T helper 17 and regulatory T cells. Glycolysis, the primary energy metabolism, becomes an essential factor that stimulates the proliferation and differentiation of Th17 cells. The energy produced from this metabolism is ATP, which results from glucose synthesis using the Glucose transporter (GLUT). Glucose transporters (GLUT-1) are most dominantly expressed by Th17 and Treg cells. Metabolic disorder causes an imbalance in the population of Th17 cells with Treg cells. This review will provide a comprehensive understanding of the profiles of Th17 and regulatory T cells in Diabetes mellitus and their relationship with metabolism, with significant implications for the understanding and treatment of metabolic disorders.

INTRODUCTION

Diabetes mellitus (DM) is characterized by increased blood glucose levels as a chronic metabolism (WHO, 2019). This can be signed by insulin secretion, insulin resistance, or both. There are two types of diabetes mellitus: type 1 diabetes mellitus

(T1DM) and type 2 diabetes mellitus (T2DM). Of these cases, 90% are type 2 diabetes (T2DM). In T2DM, there is a reduced response to insulin, often referred to as insulin resistance, due to dysfunction of pancreatic beta cells. T2DM is most commonly seen in individuals over 45 years old. However, with lifestyle changes, T2DM is increasingly observed in children, adolescents, and young adults due to decreased physical activity and high-energy diets. The prevalence of T2DM has risen dramatically over the past three decades, affecting 10% of the global population, amounting to 537 million people in 2021. It is projected to increase to 642 million patients by 2040 (International Diabetes Federation, 2021).

The aetiology of DM type 2 involves genetic, environmental and lifestyle factors contributing to disease development. The decreased sensitivity of insulin causes the body to become resistant to the effect of insulin and its response insufficiency to the insulin. As a consequence, blood glucose increases. In addition, genetic factors such as ethnic genetic factors and TCF7L2 polymorphism are convicted as the most potent locus for Type 2 Diabetes. TCF7L2 is a protein that stimulates the Wnt/β catenin signal pathway, negatively regulating adipogenesis. The experiment done by Ari Yuniastuti et al. reported that TCF7L2 gene frequencies are significantly differences in Type 2 Non-obese-DM, and its polymorphism relates to type 2 DM among Javanese ethnic (Ari Yuniastuti, 2023).

In cases of obesity, adipose tissue consists of 40% immune cells. Conversely, research by Cavallari *et al.* (2016) found that a high-fat diet would decrease Th17 cytokines in white adipose tissue while increasing the liver. The inflammatory cells recruited into adipose tissue in obesity are mediated by fatty acids from lipolysis and lipopolysaccharides produced by pathogenic gut microbes such as Firmicutes and Bifidobacterium (Lars, 2018). Other microbiomes, such as *Streptococcaceae* and *Pseudomonas*, are more common in individuals with obesity, while *Ruminococaceae* increases in patients with type 2 diabetes (Dharti, 2022).

These fatty acids and lipopolysaccharides bind to Toll-like receptor 4 (TLR4), triggering abnormal proliferation of innate and adaptive immune cells, such as macrophages and T cells, along with dysfunction of Natural Killer (NK) and B cells, resulting in an inflammatory response. Energy produced from metabolism, such as glycolysis, oxidative phosphorylation, and the Krebs cycle, is required for these immune cells to proliferate and differentiate (Sun L, 2017).

In adaptive immune cells, the balance between T helper 17 (Th17) cells and Regulatory T (Treg) cells is regulated by pro-inflammatory cytokines and anti-inflammatory cytokines, as well as several metabolic factors. Th17 cells secrete inflammatory cytokines, while Treg cells secrete inhibitory cytokines that suppress inflammation. Dysregulation of Th17 cells leads to increased production of inflammatory cytokines such as Interleukin-17A (IL-17A), Interleukin-17F (IL-17F), Interleukin-21 (IL-21), and Interleukin-23 (IL-23), mobilizing granulocytes and causing chronic inflammation as seen in T2DM.

A study in rats that blocked IL-17 excretion resulted in greater insulin sensitivity, leading to glucose intolerance, increased serum adiponectin, decreased serum insulin, and lower IL-6 compared to control rats. IL-17 signalling can activate Kupffer cells and hepatic stellate cells, which can exacerbate liver fibrosis in patients with T2DM. The proliferation and differentiation of Th17 and Treg cells originating from naive T cells are influenced by glucose, protein, and lipid metabolism.

Another study by Guzman *et al* (2020). Showed an increase in the population of Th17 cells in DM patients. This research was conducted on patient populations in America and China, revealing that Th17 cells increased in DM patients. This aligns with research by Kiernan (2020), indicating that T2DM patients experience an increase in pro-inflammatory Th17 cytokines compared to obese patients without diabetes. Dysregulation of IL-17 cytokine production results from increased expression of pro-inflammatory cytokines and chronic inflammation caused by insulin resistance. IL-17 cytokines activate the production of pro-inflammatory cytokines such as IL-1β, IL-6, and Tumor necrosis factor-α (TNF-α), which induce insulin resistance and ultimately lead to T2DM.

Conversely, regulatory T cells (Treg) act as anti-inflammatory cells and prevent excessive inflammation. Treg cells are in charge of regulating other T cell responses and stimulating innate immune activity. Their role is very important in maintaining the homeostasis among T lymphocytes.

Qiu *et al.* (2016) conducted a meta-analysis on Treg cells in T2DM patients. They concluded that T2DM patients with complications have decreased immunosuppressive Treg cells, and there is a relationship between immune cells and metabolic homeostasis. Type 2 insulin resistance is characterized by diabetes mellitus, leading to increased blood glucose levels and heightened glucose metabolism, including glycolysis, oxidative

phosphorylation, and lipid metabolism. This increase in metabolism can stimulate inflammatory T cells' production while suppressing anti-inflammatory T cells. The pathogenesis of T2DM culminates in chronic inflammation.

This writing aims to review the profiles of Th17 and Treg cells in T2DM. It is hoped that understanding the regulation of adaptive and innate immunity in diabetes cases can unveil new immunotherapy approaches to modulate metabolic inflammation and insulin resistance.

MATERIALS AND METHODS

The search was conducted using the PubMed search engine (https://pubmed.ncbi.nlm.nih.gov/) on September 5, 2024, with the keywords: "Type 2 DM and Helper-17 T cells". The results obtained were 131 articles. Then, a search filter was used for the "articles published in the last ten years" category, which yielded 114 articles. Then, screening articles were done, and 28 articles were analysed. A systematic literature review was implemented to improve the quality of this study. Approximately 168 articles were organized and examined thoroughly using a reference manager, and 27 articles with the most significant impact and clinical relevance, directly applicable to your work, were selected for this study.

RESULTS AND DISCUSSION

Understanding the differentiation and roles of T helper and regulatory T cells in Type 2 diabetes is crucial. This knowledge forms the foundation for comprehending the metabolic processes that influence the profile of Th17 and Treg cells in Type 2 DM. The source of Th17 and Treg cells, as well as the differentiation and proliferation of T cells in normal and metabolic disorder conditions such as diabetes, will be different.

Origin and Development of T Helper and Regulatory T Cells

Naive T cells undergo maturation and differentiate into various types of T cells. Thus, T cells are also called plastic or flexible cells, transitioning into mature T cells that further differentiate in response to antigens or costimulatory molecules entering the body.

Intensive studies by Sun L. *et al.*(2017) have shown that complex environmental factors, cytokines, and transcription factors influence *Cluster Differentiation* 4 (CD4+) T cells in differentiation and can function as activators or suppressors of immune responses. Treg cells represent one form of differentiation of CD4+ T cells, having functions opposite to those of Th17 cells, acting to modify immune responses as inhibitors or suppressors. Autoimmune disease can be prevented by Treg cells, which maintain immune tolerance to self. Generally, Treg cells are categorized into two subsets: natural Treg (nTreg) and induced Treg (iTreg). Natural Treg cells are produced in the thymus, while induced Treg cells can be found in peripheral tissues. Treg cells can be expressed on the cell surface by CD4+ and CD25+ (Wawman *et al.*, 2018). The primary markers for Treg cell expression in mice are CD4+, CD25+, and Forkhead box P3 (FOXP3).

Although Th17 and Treg cells have similar signal pathways for development under certain conditions, they can also switch into one another. If exogenous conditions lead to higher concentrations of cytokines in Th17 cells, they can convert the market of Treg cells, which is FOXP3, into cells capable of secreting IL-17. Treg cells may lose FOXP3 expression and thus secrete inflammatory cytokines. Several studies have shown the presence of intermediate cells in transforming Th17 cells into trans-differentiated Treg cells (Figure 1).

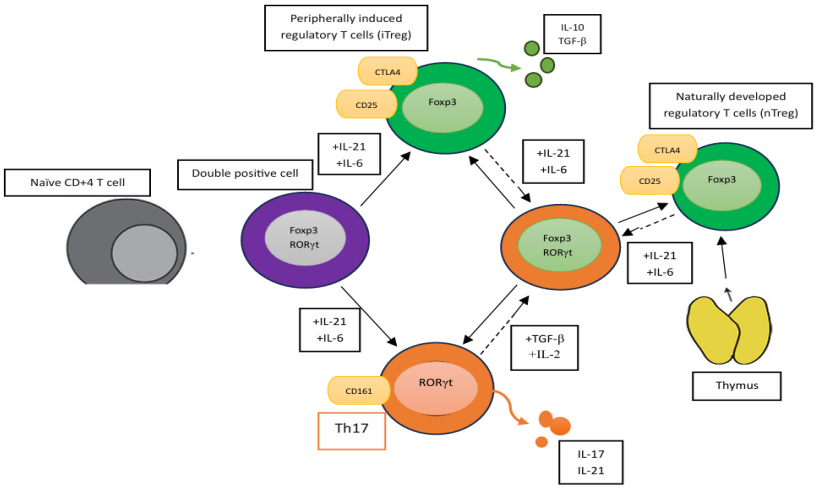

Figure 1. Differentiation Th17 and regulatory T cells from naive T cell (Sun L *et al.*, 2017)

FOXP3, a transcription factor, is expressed in Treg cells and other T cells, such as helper T cells, in humans. Despite its presence in different T cells, its primary function remains the same-to express T cells that suppress the immune system. The reduction of

Treg cells can lead to autoimmune diseases, while a high ratio of Treg to Th17 cells can be correlated with cancer incidence.

Signalling pathways play a crucial role in influencing the differentiation of T cell subsets from naïve T cells. The activation of different signalling pathways leads to the formation of different T-cell variants. For instance, th17 cells result from CD4+ T cell differentiation through the RORγt/STAT1 pathway, while Treg cells result from CD4+ T cell differentiation through the FOXP3/STAT5 pathway. Once CD4+ T cells are activated, they undergo clonal expansion and distribute to lymphoid organs via the bloodstream (Neshat *et al.*, 2021).

The role of T helper, TH 17 and Treg in type 2 diabetes mellitus

Type 2 diabetes (T2D) is characterized characterized by insulin resistance. Insulin resistance has increased significantly in metabolic diseases due to improved living standards associated with lifestyle change. Moreover, the prevalence of insulin resistance increases in the younger population.

Numerous studies have shown that insulin resistance will initiate the inflammatory response. Secretion of cytokine inflammation such as TNF-α, IL-6 and C-reactive Protein (CRP) is important in the pathophysiological process. A family of T cells has been shown to be involved in the development and progression of inflammation. T helper is proven to secrete inflammatory cytokines, such as T helper 1 (Th1), which secretes TNF-α. Moreover, T helper 17 (Th17) has been discovered recently in the progression of inflammation.

Insulin resistance drives the secretion of inflammation factors. The level of inflammation factors will increase the lipolysis in peripheral free fatty acids. Inflammatory cytokines will be regulated by a T cell subpopulation, namely regulatory T cells. These Tregs will keep the body balanced and stay in homeostasis.

During insulin resistance, RORγt and IL-17 expression, which are markers of Th17, were increased. Meanwhile, markers of Treg, such as Foxp3 and CD4+CD25+Tregs, were decreased (Tao L *et al.*2019). This is how the pathogenesis of T2D is clearly illustrated: it starts from insulin resistance, which causes inflammation, and progresses because the function of Treg is impaired.

Metabolic Pathways in the Activation, Differentiation, and Polarization of T helper 17 (Th17) and Regulatory T (Treg) Cells

Cytokine IL-17A is produced in excess in tissues in type 2 diabetes compared to non-diabetic individuals, supporting insulin resistance development. The mechanisms extensively researched regarding the increase in cytokine levels are related to lipid and protein metabolism. In type 2 diabetes, excess glucose and lipids lead to changes in T cells due to the AMP-Activated Protein Kinase (AMPK) protein pathway and increased circulation of lipid metabolism, specifically C-acylcarnitine. Both pathways cause transformation in T cell metabolism and function. The synthesis of fatty acids is known to produce acetyl-CoA carboxylase 1 (ACC1), which is important in developing Th17 cells. Fatty acid oxidation independently optimally activates Th17 cells.

Th17 cytokines were first discovered in experiments on encephalomyelitis in mice in 2003, where levels of IL-23 were found to be higher than Th1 cells and cytokine IL-12. Many studies, which were validated by Genome-Wide Association Studies (GWAS), found that IL-23 production promotes the secretion of IL-17 cytokines (Mc Geachy *et al.*, 2019). It was not until a new lineage of CD4+ T cells was successfully identified as Th17 in 2005 (Sun L. *et al.*, 2017). IL-17 serves as a factor that can identify Th17 cells. IL-23 is a cytokine that promotes the proliferation and differentiation of IL-17. The relationship between IL-23 and IL-17 depends on the presence of *Transforming Growth Factors*-β (TGF-β) and IL-6, as IL-23 alone is insufficient to drive naïve CD4+ T cells to differentiate into TH17 cells.

TGF-β1 is necessary for differentiating T cells into both Th17 and Treg cells, indicating that the formation of these two T cell subsets is interconnected. The expression of ROR-γt and FOXP3 increases when the TGF-β1 signal is activated. However, the polarization of naïve T cells into Th17 or Treg phenotypes depends on the microenvironment or immune environment, a cell circumstance where cytokines and growth factors influence the cells. For example, when activation of the TGF-β signalling pathway, it will express RORγt and Foxp3, so does regulatory T cell differentiation and Th17 differentiation is inhibited; meanwhile, the second e of IL-6, TGF-β will inhibit the formation of Treg from T naïve cells. The presence of IL-6 is crucial for this polarisation polarisation. Interleukin-6 has the most significant influence on the differentiation of Th17 cells. In addition, Th17 polarization polarization is affected by ROR-γt, the main

transcription factor, by which the genes-specific TH17 cells expression is regulated, such as C-*Chemokine Receptor* type 6 (CCR6), CD161, IL-17A, IL-17F, and IL-23R. (Sun L. *et al.* 2017).

The role of IL-6 in the differentiation of Th17 cells is significant. The synergistic action of TGF-β and IL-6 greatly influences the Th17 cell differentiation. Without the presence of IL-6, TH17 differentiation does not occur. TGF-β can induce the proliferation of regulatory T cells. Th17 and Treg cells operate antagonistically. When the body is stable without inflammation, TGF-β inhibits effector T cells and induces FOXP3 in Treg cells, thus establishing a tolerant immune system mechanism. In contrast, during inflammation, a large amount of IL-6 is produced by Toll-like receptors (TLRs). This cytokine has the function of inhibiting Treg cell proliferation but inducing T lymphocytes to form Th17 cells.

In research by Tao *et al*. (2019), RORγt, IL-17, and FOXP3 proteins expressed in adipose tissue varied among different research groups. The groups were divided into four: standard control, standard control with IL-6 blocked, insulin-resistant (IR), and insulin-resistant with IL-6 blocked. The standard control with IL-6 blocked has no significant difference. However, the expression of FOXP3 was higher in the IR group with IL-6 blocked compared to the non-IR group. Meanwhile, the expression levels of RORγt and IL-17 were lower in the IR group with IL-6 blockade.

Although the development of Th17 and Treg cells are similar in the signalling pathways, a transition between these two cell types can occur under certain conditions. Cytokines that can convert FOXP3-expressing Treg cells to secrete IL-17 instead are produced by Th17 exogenously. Conversely, Treg cells that lose FOXP3 expression will adopt inflammatory functions—biomarkers from RORγt and FOXP3 as transcription factors, indicating the progression of infectious and autoimmune diseases.

Metabolic Pathways Affecting of T helper 17 (Th17) and Regulatory T (Treg) Cells Development

Immune response dysregulation due to changes in Th17 cell function in metabolic diseases such as diabetes mellitus (DM) strongly correlates with glucose and lipid metabolism. Disruptions in glucose and lipid metabolism can lead to chronic inflammation. Type 2 DM is closely associated with glycolysis, which is linked to the

Th17 cell profile. Differences in cytokine profiles between Type 2 DM and non-DM conditions are minimised under glucose-deficient conditions.

Aerobic glycolysis is essential for polarising T cells into T helper 17 cells. In this process, glucose will be converted into pyruvic acid; then, it will be converted into ATP by Acetyl Co-A to help in TCA. The energy produced from ATP will stimulate CD4 T cells to differentiate and polarize into Th17 cells. In this pathway, acetyl-CoA conversion from pyruvate can enter the Tricarboxylic Acid Cycle (TCA), where NADH and FADH2 are produced and resulting ATP forms through oxidative phosphorylation. One glucose molecule produces two ATP molecules (Sun L. *et al*., 2017).

The glycolysis process and the TCA cycle generate energy and other metabolic pathways, such as lactate dehydrogenase, which produces pseudo-pyruvic acid from the conversion of lactic acid in the cytosol. Pyruvic acid is converted from lactic acid under low oxygen conditions, but often, even in sufficient oxygen conditions, cells will convert glucose into lactic acid, a process called the Warburg effect or glycolysis in aerobics. The unusual phenomena have been reported in tumour cells and T cells.

The main energy-producing pathways that influence T cell functionality are the metabolism of glycolysis, glutaminolysis, and fatty acid. T-cell activation from cellular biosynthesis is achieved by reprogramming metabolism through increased glycolysis. Th17 cells function as an effector and as cells of the inflammation population. They have a short lifespan dependent on glycolysis rather than other metabolic pathways.

Glycolysis is an enzymatic reaction that catalyses the conversion of pyruvate, lactate, oxygen, and energy from glucose in the cytosol. Subsequently, the pyruvate, lactate, and pentose sugar metabolic pathways enhance Th17 cells. For further reactions in glycolysis, pyruvate kinase M2 is essential for T cell differentiation, particularly fatty acid synthesis (FAS) mediated for T cells to undergo polarization polarization.

Glucose metabolism, in this case, glycolysis, significantly affects the differentiation of T cells into TH17 cells because, for differentiation, T cells require energy from ATP, which is the final product of glycolysis. The activation of naïve T cells alters both the size and functionality of T cells. T cells' enlargement and functional development occur rapidly and require significant energy, transforming naïve T cells into Th17 cells or other T cell forms. This high energy demand is met through glycolysis, which can produce 100 times more ATP than *Oxidative phosphorylation* (OXPHOS).

Glycolysis correlates with the predisposition of naïve T cells to proliferate into inflammatory T cells, such as Th17 cells. T-cell differentiation can occur via the Phosphatidyl-Inositol-3 Kinase (PI3K) pathway, which promotes glucose transporter (GLUT) entry into the cell membrane. When GLUT expression increases, PI3K regulates GLUT traffic into the cell membrane. The PI3K pathway is used by insulin to regulate glucose metabolism in the blood.

Both Th17 and Treg cells express glycolytic enzymes, specifically Hexokinase 1 (HK1), which Treg cells express. Meanwhile, HK2 and HK3 are expressed by Th17 cells. This expression occurs through glucose transporter (GLUT) usage, where Treg cells express only GLUT1, while Th17 cells express GLUT1 and GLUT3, with GLUT1 being the dominant transporter. Glucose transporters are vital for Th17 cells, and in the absence of GLUT, Th17 cell development is impaired. Incomplete glycolysis results in poor differentiation of Th17 cells, such as glycolysis blockade, leading to inhibition of cytokine production and Th17 cell proliferation.

Glycolysis also initiates metabolic pathways for protein, nucleic acid, and fat synthesis during T helper cell development. Metabolic pathways can also influence the epigenetic mechanisms of Th17 and Treg cells. Th17 cell differentiation can shift to Treg cells if the formation of Glutamate Oxaloacetate Transaminase 1 (GOT1) is inhibited. GOT1 is an enzyme that promotes glycolytic metabolism programming in T lymphocytes.

T helper cell differentiation requires a substantial amount of energy, which is correlated to a glycolysis enzyme, GAPDH (Glyceraldehyde-3-Phosphate-Dehydrogenase). Suppose glycolysis is interrupted due to the absence of a substrate. In that case, GAPDH disrupts the 3' UTR IFN-γ mRNA's translation process, causing instability in the T helper cells' translation process. Aerobic glycolysis metabolism can regulate GAPDH or other enzymes that inhibit T-cell development.

Another essential component for T cell differentiation through glycolysis is NAD+, which can convert Treg cells into Th17 cells via P2RX4 and P2RX7, the purinergic receptors. Systemically, NAD+ increases the production of CD4+ IL-10 T cells and decreases Treg cells.

In addition, Tcellïve T cell's differentiation is influenced by glycolytic metabolism and is also affected by lipid metabolism, which plays an important role in potentially modulating immune cells. Th17 and Treg cell differentiation are influenced by FAS

(Fatty Acid Synthesis) and FAO (Fatty Acid Oxidation). The formation of pyruvate analogues through aerobic glycolysis occurs in the presence of FAS (Fatty Acid Synthesis) or the simultaneous synthesis of fatty acids and cholesterol. The final product of FAS metabolism is palmitic acid, which can further be utilized to produce other fatty acids or lipoproteins. Fatty acid synthesis (FAS) is an anaerobic metabolic process that generates energy. In contrast, fatty acid oxidation (FAO) is an aerobic metabolism process that converts fatty acids into acetyl-CoA, a molecule that produces the energy necessary for cell proliferation and activation.

Aerobic glycolysis, FAS, and FAO modulate the activation and differentiation of T lymphocytes, particularly Treg cells. As mentioned earlier, Th17 cells heavily depend on glycolysis. In contrast, Treg cell activation is more dependent on FAO metabolism and the ability of AMP-Activated Protein Kinase (AMPK) to modulate metabolism for balance. This protein complex is more widely expressed and active in induced Treg cells (iTreg). AMPK activation can direct the naïve T cell differentiation into Treg cells both in vitro and in vivo. However, if AMPK function is impaired, it increases mTOR activity and enhances glycolysis (Figure 2).

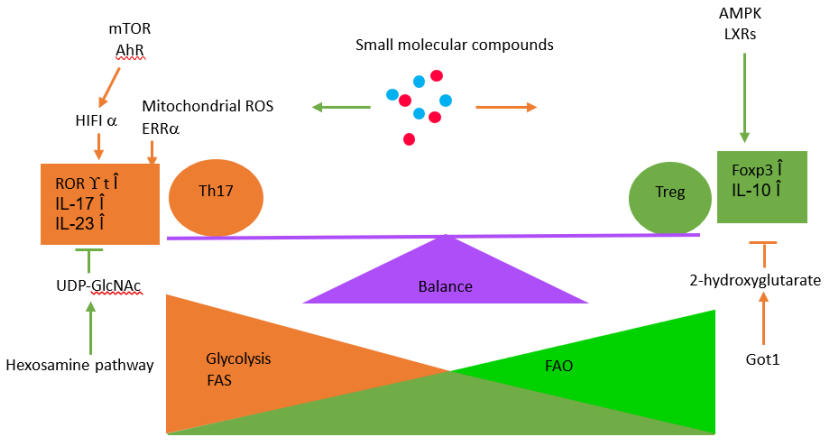

Figure 2. Glycolysis, FAS and FAO influence Activation of Th17 and Treg. Metabolism of glycolysis or FAS will activate Th17 cells, while FAO metabolisme will activate Treg (Sun L. *et al.*2017).

Metabolic Pathways in Th17 and Treg Imbalance that Influence Type 2 Diabetes Mellitus

T cell activation requires metabolic reprogramming and the differing metabolic profiles that arise influence Th17 and Treg cell balancing. Th17 cells typically exhibit high levels of pyruvate and moderate lactate levels, while Treg cells show intermediate

levels in the TCA cycle. Fatty acid oxidation (FAO) is higher in Treg cells than in Th17 cells, indicating that fatty acids are the primary energy source for Treg cells. In contrast, glycolysis is the key driver for forming Th17 cells. Therefore, insufficient or impaired glycolysis disrupts Th17 cell differentiation and blocks glycolysis, inhibiting the proliferation of Th17 cells and cytokine IL-17 production.

Several research hypotheses suggest glycolysis is a critical metabolic process that bridges other metabolic pathways, such as protein, lipid, and nucleic acid metabolism, in forming Th17 cells. Type 2 diabetes mellitus (T2DM) is a condition of hyperglycemia or hyperlipidemia, where blood glucose, cholesterol, and triglyceride levels increase, potentially leading to abnormal protein, lipid, and nucleic acid metabolism.

The experiment by Araujo L *et al.*, cited by Sun L *et al.* (2017), reported that the glucose nucleotide Uridine Diphosphate N-acetylglucosamine (UDP-GicNAc) can affect the Th17/Treg cell ratio balance. This metabolism stimulates naïve T cells' differentiation into Treg cells. In Th17 cells, increased glycolysis and glutaminolysis lead to competition between fructose-6-phosphate and glutamine in the hexosamine pathway, a key metabolic process that regulates N-glycan branching. If GicNAc branching is blocked, Treg cell differentiation shifts towards Th17 cells.

Other studies by *Zhang et al.*(2021) have indicated that metabolism influences epigenetic mechanisms, further affecting Th17 and Treg cell balancing. Metabolism of lipids is an essential element in the T helper cell formation. Lipids are the main structure of cell membranes that provide energy and participate in signalling cells. Numerous studies have shown that lipid metabolism is crucial for forming regulatory T cells (Tregs).

ACC1, a potential therapeutic target for Th17-related diseases, has been a focus of research. The study by Cluxton et al. (2019) has shown that ACC1-mediated fatty acid synthesis (FAS) is crucial for Th17 cells that produce phospholipids for cell membranes. In contrast, Treg cells rely on fatty acids for extracellular processes. Incomplete ACC1 function decreases FAS and glycolysis levels in Th17 cells, leading to a shift in differentiation from Th17 to Treg cells. Furthermore, ACC1 blockade reduces FAS but increases FAO, promoting the development of Treg cells, as their growth relies heavily on FAO for energy. The potential of ACC1 as a therapeutic target offers hope for the future of Th17-related disease treatment.

A study conducted by Jie Wen *et al.* (2021) examined Th17 and Treg cell expression in T2DM patients. Participants were divided into two groups: T2DM patients and non-DM individuals, selected in a cross-sectional, masked study. White blood cell samples were collected from peripheral blood vessels, and immunofluorescence staining and flow cytometry tests were conducted. The results showed that the white blood cells increased in T2DM patients stacked up in the non-DM group. Additionally, population and neutrophil percentages were sharply higher in the peripheral blood of T2DM patients, while lymphocyte percentages decreased, leading to a shift in immune cell subpopulations. This is consistent with studies conducted on monkeys, where neutrophil counts were elevated in T2DM samples and increased polymorphonuclear leukocytes in the monkey retina.

The human study by Lee WI *et al.* (2020) showed a significant decline in the expression of CD4+CD25hi T cells, which is analysed. The confirmation that these T cells were Tregs, further analysis of FOXP3 and CD127 expression and specific markers of Tregs were conducted. The findings revealed that T2DM patients, compared to healthy individuals, had significantly lower CD4+CD25hiCD127 Tregs. The function of Tregs was then assessed by isolating CD4+CD25hi Tregs from both groups and subjecting them to an immunosuppressive assay. Results showed that the indicator function of CD4+CD25hi Tregs in the peripheral blood of T2DM patients was significantly impaired if cell proliferation was inhibited.

The study also measured levels of Th-1 and Th17 cells through IL17+CD4+ and IFN-γ+CD4+ expression in the peripheral blood, which were significantly elevated in T2DM patients compared to healthy controls. The ratio of IL17+CD4+ and IFN-γ+CD4+ cells was the same in both groups. However, the ratio of CD4+CD25hiCD127 Tregs to IL17+CD4+ cells and CD4+CD25hiCD127 Tregs to IFN-γ+CD4+ cells was significantly reduced in T2DM patients. Likewise, the ratio of CD4+CD25hiFOXP3 Tregs to IL17+CD4+ cells and CD4+CD25hiFOXP3 Tregs to IFN-γ+CD4+ cells was lower in T2DM patients.

The findings of these studies strongly suggest a significant imbalance in the CD4+ T cell subsets in T2DM patients. The drastic reduction in the CD4+CD25hi Treg/TH17 or Th-1 ratio contributes to immune cell activation and inflammation in diabetes

complications. This imbalance underscores the urgent need to address the immune system dysregulation in T2DM patients to prevent potential cell death.

Over the past decade, many studies have examined the role of Th17 cells, producing pro-inflammatory cytokines in almost all body tissues. It is also exploring the relationship between Th17 and Treg cells. The balance between these two cell types is not just critical for immune responses, especially in cases of liver damage or abnormalities due to diabetes complications, but it is also fundamental to maintaining immune homeostasis. This underscores the significance of your research in understanding and restoring immune homeostasis.

Th17 cells become important in combating exogenous bacteria like salmonella and cholera that can infect our bodies. These cells produce pro-inflammatory cytokines that are effective in fighting off such infections. On the other hand, if the immune response is uncontrolled and Tregs fail to function as suppressors, it can lead to harmful outcomes for the body. In a homeostatic State's, the balance between these two cell types is tightly regulated to ensure an effective immune response and prevent tissue damage.

CONCLUSION

Type 2 Diabetes mellitus is a metabolic disorder classified by increased blood glucose levels, hyperglycemia, elevated cholesterol, and triglycerides. It leads to insulin resistance and imbalances between Th17 and Treg cells. The disorder begins with metabolic disruptions caused by glycolysis, oxidative phosphorylation, and fatty acid metabolism, which influence the proliferation and differentiation of T cells into Th17 or Treg cells.

T helper 17 and regulatory T cells have distinct but complementary roles in the immune system. Th17 cells compete with the pathogens and promote inflammation. Then, Treg cells, with their unique ability to suppress inflammation, play a key role in restoring normal conditions once the immune response has been achieved. This potential for recovery is a testament to the power of the immune system. Ideally, these two cell types should maintain a homeostatic environment. The nearest relationship of Th17 and Treg cells means that maintaining a balance between them is crucial to ensure an effective immune response and prevent tissue damage from excessive inflammation.

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