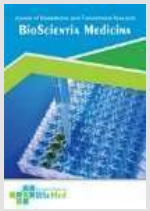
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

T Cell Dysfunction in Systemic Lupus Erythematosus

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ARTICLE INFO

Keywords:
Chemokines
Dysfunction
Leukocytes
Systemic lupus erythematosus
T cells

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i5.988

A B S T R A C T

Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease that can affect many organs in the body with very diverse clinical appearances. The prevalence of SLE in each country varies. The Lupus Foundation of America estimates that around 1.5 million cases occur in America and at least 5 million cases occur worldwide. The pathophysiology of SLE is very complex. The involvement of innate and adaptive immunity in the initiation and pathophysiology of SLE disease shows that there are interactions between leukocytes, cytokines, chemokines and tissue cells. T cells are the main component of the adaptive immune system which can kill infected host cells, activate other immune cells, produce cytokines and regulate immune responses. T cell dysfunction in SLE includes triggering inflammation through the secretion of pro-inflammatory cytokines, helping B cells produce autoantibodies and the accumulation of autoreactive T cells. Aberrations in T cells could be a therapeutic target for development and a potential SLE therapy.

1. Introduction

Systemic lupus erythematosus (SLE), better known as lupus, is a systemic autoimmune inflammatory disease that can affect many organs in the body and have very diverse clinical appearances. The immune system in SLE will experience a loss of the ability to see the difference between the body's own tissue and foreign substances and cells or between "self" and "non-self." In SLE, there is excessive production of antibodies against the body's own tissues (autoantibodies), and they react with "own" antigens to form immune complexes. Immune complexes contained in the tissue will cause inflammation and damage to the tissue.[1-3] The manifestations of SLE are very broad, including involvement of the skin and mucosa, joints, blood, heart, lungs, kidneys, central nervous system, and immune system. SLE disease is often nicknamed by the term "great imitator"/disease of a thousand faces because, from one patient to another, the clinical manifestations are varied and different and often resemble other diseases. Symptoms of SLE can range from mild to severe. Because the manifestations of SLE are very diverse with varying disease courses, there is a high risk of death, so it requires long and lifelong treatment.[1-3]

The prevalence of SLE in each country varies. The Lupus Foundation of America estimates that around 1.5 million cases occurred in America, and at least 5

million cases occurred in the world. Every year, it is estimated that around 16 thousand new cases of Lupus occur. According to Barber et al. (2021), the estimated number of SLE cases in North America ranges from 48-366.6 per 100,000 people; in Europe, it varies between 29-210 per 100,000 people; in England, it is 97 per 100,000 people, and in Greece, it is 123 per 100,000 people.[4] Research conducted by Izmirly et al. (2021) found that the incidence of SLE was 72.8 per 100,000 people per year. The prevalence in women is 9 times higher than men, namely 128.7:14.6 per 100,000 people, with the highest being in black women, namely 230.9 per 100,000 people, white women at 84.7 per 100,000, and Asian women at 84.7 per 100,000 people. 84.4 per 100,000 people.[5] The incidence rate of SLE in Asia, according to Tanaka et al. (2022), ranges from 0.9-8.4 per 100,000 people per year, with a prevalence ranging from 3.7-127 per 100,000 people. The prevalence of SLE in China is 10-70 per 100,000 people; in Hong Kong, it is 58.8 per 100,000 people; in Korea, it is 18.8-21.7 per 100,000 people; and in Japan, it is 3.7-37.7 per 100,000 people.[6] According to Leong et al. (2021), the prevalence of SLE in Taiwan in people aged 10-79 years is increasing year by year, with an overall prevalence ranging from 4.77-8.11 per 10,000 population. The prevalence in women is around 8.56-14.3 per 10,000 population, which is higher than in men, namely ranging from 0.91-1.62 per 10,000 people.[7]

In Indonesia, the exact number of SLE patients is not yet known. According to Hamijoyo et al. (2019), the prevalence of SLE in Indonesia is 0.5% of the total population, with a tendency to increase in the number of incidents every year, and women aged 15-44 years are more frequently affected. Another previous study, conducted from 2008 to 2017, showed that 95.6% of 813 SLE patients were women, and there was a mortality rate of 8.1%. Polyclinic data in several hospitals in Indonesia shows an increase in visits by SLE patients, namely 17.9-27.2% (2015), 18.7-31.5% (2016) and 30.3-58% (2017). The ratio of female to male patients is 15-22:1. The onset of symptoms and signs of SLE generally appears at the age of 9-58 years (the highest age range is 21-30 years), with a peak at 28 years.[2,3,8] Dorner et al. (2019) stated that heredity, race, and ethnicity have a major impact on the manifestation and severity of SLE. The incidence and prevalence of SLE are higher in black, Asian, and Hispanic patients. Early clinical manifestations have more severe disease symptoms with increased disease mortality. About 90% of patients are women and generally of childbearing age. SLE is one of the main causes of death in young women. In research in the United States, it was found that the cause of death for women with SLE was 2.6 times higher than that of the general population due to cardiovascular disease, infection, and kidney disease.[1,4,9]

Systemic lupus erythematosus is a multisystemic disease of unknown etiology. Several immunopathogenic pathways play a role in the development of SLE. Hargraves described lupus erythematosus in 1948. Several pathogenic autoantibodies have been identified since then. Genetic, immunological, endocrine, and environmental factors influence the loss of immunological tolerance to self-antigens, which leads to the formation of pathogenic autoantibodies that cause tissue damage. More than 100 gene loci with polymorphisms have been identified to be associated with SLE, which is associated with activation of the immune system in response to foreign antigens, generation of self-antigens, and activation of the innate and adaptive immune systems.[1,10] The pathogenesis of SLE is characterized by loss of tolerance and continued production of autoantibodies. One concept in pathogenesis is the imbalance between the production of apoptotic cells and the removal of apoptotic material. Apoptotic debris containing nucleic acids can stimulate inflammatory responses through the activation of nucleic acid recognition receptors, e.g., Toll-like receptor (TLR). Nucleic acid receptors against endogenous viruses recognize viral pathogens and defend against intracellular bacteria and are associated with type 1 interferon (IFN) production. Disruption of this pathway has an effect on the

pathogenesis of SLE and may increase disease susceptibility.[11] The pathophysiology of SLE is very complex. The involvement of innate and adaptive immunity in the initiation and pathophysiology of SLE disease shows that there are interactions between leukocytes, cytokines, chemokines, and tissue cells. Over the last 2 decades, the role of T cells involved in the pathophysiology of SLE has become increasingly recognized. Production of various SLE-associated autoantibodies by B cells and antibody-forming cells or antibody-forming cells (AFC) indicates the important role of T cells in SLE. In SLE, there is a disruption in the regulatory function of T cells to suppress autoreactive B cells and T cells. In addition, T cells can trigger an inflammatory process through direct contact with other immune cells in primary or secondary lymphoid organs and through the secretion of pro-inflammatory cytokines that have a direct effect. on target organs.[12,13] T cells have a central role in the pathogenesis of SLE. T-cell dysfunction affects peripheral tolerance and activates abnormal B cells. Various types of T cell subsets are involved in the pathogenesis of the disease, namely through excessive production of pro-inflammatory cytokines, increasing the production of autoantibodies, and causing tissue damage through increasing immune cells. In addition to cytokine signals, several other factors influence T-cell dysfunction, such as metabolic and genetic changes. Therefore, in this reference, we discuss SLE, T cells, and disorders that occur in SLE T cells, as well as the molecular and genetic pathways that impact T cell dysfunction. In addition, in this reference, we also discuss the development of therapeutic targets for T cells and their use as a potential SLE therapy.[12-14]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of multiple autoantibodies against many cells, especially nucleic acids and nuclear proteins. Autoantibodies, such as those against double-stranded DNA or double strain (DS), are characteristic of lupus in the presence of cellular and other soluble inflammatory mediators that contribute to end-organ damage. Clinically, SLE can affect many cells, tissues, and organs with varying degrees of severity, and various target organs are affected. Clinical manifestations include inflammation and damage to the skin, joints, kidneys, central nervous system, and cardiovascular and hematological disorders. During its course, SLE disease often recurs (flare) and is unpredictable and difficult to diagnose remissions.[15,16] Research conducted by Izmirly et al. (2021) identified 5,417 cases of SLE from various countries. The prevalence of SLE was found to be 72.8 per 100,000 people per year. The estimated prevalence is 9 times higher among women than among men, namely 128.7:14.6 per 100,000 people, highest among black women, namely 230.9 per 100,000 people, followed by Hispanic women at 120.7 per 100,000 people; women whites were 84.7 per 100,000 people, and Asian Pacific women were 84.4 per 100,000 people. In 2018, an estimated 204,295 individuals in the United States met the ACR classification criteria for the diagnosis of SLE.[5]

Polyclinic data in several hospitals in Indonesia shows an increase in visits by SLE patients, namely 17.9-27.2 (in 2015), 18.7-31.5% (in 2016), and 30.3-58% (in 2017). The ratio of female to male patients is 15-22:1. The onset of symptoms and signs of SLE generally appears at the age of 9-58 years (the highest age range is 21-30 years), with a peak at 28 years. Meanwhile, a national prospective study in 2012-2015 showed that the peak incidence in children was aged 13 years with a female-to-male ratio of 9.5:1. In Indonesia, the most common clinical manifestations of SLE are arthritis (32.9-75.5%), skin and mucosal disorders (13.2-86.3%), lupus nephritis (10.8-65.5%), fatigue (51.1-58.1%), fever (39.3-54.9%). Meanwhile, the most common laboratory manifestations were positive ANA in 98.4%, positive anti-dsDNA in 47%, lymphopenia in 75.4%, and hemolytic anemia in 26.08-34.6%.[3] In recent years, several important steps have been taken to improve understanding of the etiopathogenesis of SLE. The etiopathology of SLE is thought to involve complex and multifactorial

interactions between genetic variations and environmental factors. Several cohort studies identified several new loci and genetic variants associated with SLE. Abnormalities in the phenotype and function of T and B lymphocytes, disturbances in cytokines, and soluble mediators of the adaptive immune system are important factors in the pathophysiology of SLE. Innate immune cells also play a role in disease pathogenesis.[16,10] The genetic elements most studied for their contribution to SLE in humans are the genes of the major histocompatibility complex or major histocompatibility complex (MHC). Population studies show that susceptibility to SLE involves polymorphisms of the human leukocyte antigen (HLA) class II gene. HLA class II genes are also associated with the presence of certain antibodies such as anti-Sm (small nucleas ribonuclearm protein), anti-Ro, anti-La, anti-nRP (nuclear ribonuclear protein) and anti-DNA. HLA class III genes, particularly those encoding complement components C2 and C4, confer a risk of SLE in certain ethnic groups. In addition, many polymorphic non-MHC genes reported to be associated with SLE are genes encoding mannose-binding protein (MBP), TNF-α, T cell receptors, interleukin 6 (IL-6), CR-1, immunoglobulin Gm and Km allotypes, FcγRIIIA and heat shock protein 70 (HSP 70). The genes involved in the development of human SLE are summarized in Table 1.[10,17]

Table 1. Genes involved in the development of human SLE.[10]

HLA genes	Non-HLA genes
DR2, DR3, DR7, DQw1, DQw2, DQA1, DQB1, B8 (anti-Ro)	Mannose-binding lectin polymorphisms
DR3, DQw2, DQA1, DQB1 (anti-Ro and anti-La)	Tumor necrosis factor α
DR2, DR3, DR7, DQB1 (anti-DNA)	T cell receptor, Interleukin 6, CR1
DR2, DR4, DQw5, DQw8, DQA1, DQB1 (anti-U1 ribonuclear protein)	Immunoglobulins Gm and Km
DR2, DR4, DR7, DQ7, DQw8, DQw9 (anticardiolipin or lupus anticoagulant)	FcgRIIA (IgG Fc receptor)
Complement genes (C2, C4, C1q)	FcgRIIIA (IgG Fc receptor)
	PARP (poly-ADP ribose polymerase)
	Heat shock protein 70 (HSP 70)

SLE is a disease that attacks more women. This is related to the role of the hormone estrogen and genes on the X chromosome. In mammals, females produce a higher antibody response than males. Women exposed to oral contraceptives containing estrogen or hormone replacement have an increased risk of developing SLE. Estradiol binds to receptors on T and B lymphocytes, increasing their activation and survival. These cells are primarily an autoreactive subset, thereby causing a prolonged internal immune response. Several stimuli from the surrounding environment can affect SLE, such as exposure to ultraviolet light flare or recurrence in 70% of SLE patients. Ultraviolet light can increase apoptosis of skin cells or can change intracellular DNA and proteins to become antigenic. Some infections and drugs that trigger lupus can also activate autoreactive T and B cells. The innate immune system interacts with the B and T cells of adaptive immunity to drive an autoimmune response. T lymphocytes can cause metabolic changes (abnormal mitochondrial electron transport, membrane potential, and oxidative stress), increased glucose utilization, increased pyruvate production, mTOR activation, and increased autophagy. T and B cells are more easily activated and undergo apoptosis than normal cells due to autoantibodies binding to them. Abnormal signaling causes low IL2 production for the survival of T cells. B cells present antigens and secrete IL6 and IL10, resulting in autoreactive B cells, which are also supported. by estrogen.[18] Phagocytic cells in lupus have reduced capacity to eliminate immune complexes, apoptotic cells, DNA/RNA/Ro/La apoptotic cells, and blebs containing phospholipids. This causes large amounts of autoantigens and autoantibodies with an increase in the number of

activated B cells, plasma cells, and autoreactive T cells, resulting in an increase in the number and function of Th1, T17, and Tfh cells, all of which increase autoantibody production and cause tissue damage. The autoantibodies involved can be seen in Table 2.[10,18]

Table 2. Pathogenic autoantibodies in SLE.[10]

Specific antigen	Prevalence (%)	Main clinical effects
Anti-dsDNA	70-80	Kidney disorders, skin
Nucleosome	60-90	Kidney disorders, skin
Ro	30-40	Kidney disorders, skin disorders, fetal heart problems
La	15-20	Fetal heart problems
Sm	10-30	Kidney disorders
Phospholipids	20-30	Thrombosis, abortion

Skin involvement in SLE occurs in nearly 90% of patients and includes specific lupus-like manifestations: acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous lupus (discoid lupus, lupus profundus). Arthralgia and synovitis occur very often in SLE, namely almost 90%. Typically, arthralgia presents as symmetric polyarthritis involving the metacarpophalangeal, proximal interphalangeal, and knee joints. Kidney involvement occurs in approximately 50% of lupus patients, especially in certain ethnic groups, namely African-Americans (70%). Delay in diagnosing lupus nephritis will be a risk factor for end-stage kidney disease. Kidney disease is suspected if proteinuria is present. However, lupus nephritis (classes III, IV, and V) can occur in 25% of SLE patients without clinical symptoms of kidney disease. Urine protein levels above 500 mg/24 hours are related to histopathological lupus nephritis and require immediate renal biopsy. Various neuropsychiatric manifestations are also associated with SLE, including seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state.[3,19] T cells, also called T lymphocytes, are the main component of the adaptive immune system that responds to pathogens, allergens, and tumors. The role of T cells is to directly kill infected host cells, activate other immune cells, produce cytokines, and regulate the immune response. T cells can control and maintain immune homeostasis.[20] All lymphocytes originate from common lymphoid precursor cells (common lymphoid precursor) in the bone marrow. T lymphocytes mature in an organ called the thymus. The places where mature lymphocytes are produced are called generative (or central) lymphoid organs. Mature lymphocytes leave the generative lymphoid organs, entering the circulation and peripheral (secondary) lymphoid organs, which are the main sites of the immune response where lymphocytes encounter antigens and are activated. When naive lymphocytes recognize microbial antigens and also receive additional microbial-induced signals, antigen-specific lymphocytes proliferate and differentiate into effector cells and memory cells.[21] Naive T cells recognize antigens in peripheral (secondary) lymphoid organs, which initiates the proliferation of T cells and their differentiation into effector cells and memory cells, and effector cells perform their function when activated by the same antigens in peripheral tissues or lymphoid organs. Naive $CD4^+$ T cells and $CD8^+$ T cells recognize peptides derived from protein antigens and presented by dendritic cells or dendritic cells (DC) in peripheral lymphoid organs. Some activated $CD4^+$ T cells remain in the lymph nodes, migrate into the follicles, and help the B cells produce antibodies. $CD4^+$ T cells recruit and activate phagocytes to destroy microbes, while $CD8^+$ or cytotoxic T cells cytotoxic T lymphocyte (CTL) kill infected cells.[21]

$CD8^+$ T cells use most of the same molecules, except that the TCR recognizes MHC class I peptide complexes and the coreceptor is CD8, which

recognizes MHC class I. CD3 consists of three polypeptide chains, δ, ε, and γ, arranged in two pairs (δε and γε). The role of CTLA-4 and PD-1 or programmed death-1 plays a role in stopping the T cell response.[21] The biochemical signals that cause T cell activation are triggered by a series of TCR-associated proteins that are part of the TCR complex and by the CD4 or CD8 coreceptors. The TCR is associated with a complex of transmembrane signaling proteins, including three CD3 proteins and a protein called the ζ chain. The TCR, CD3, and ζ chains form the TCR complex. TCR signaling function was the same in all clones, and CD3 and ζ proteins did not change between different T cells. Complete T cell activation depends on the recognition of costimulators on APCs other than antigens. Costimulators are molecules that can provide stimulation to T cells, which function together with stimulation by antigen and are considered the second signal for T cell activation. The best-known T cell costimulators are two homologous proteins called B7-1 (CD80) and B7-2 (CD86), both of which are expressed when APC encounters microbes. This B7 protein is recognized by a receptor called CD28, which is expressed in most T cells. Antigen-presenting cells (APC) that have not been exposed to microbes can present peptide antigens, but if they do not express costimulators, they cannot activate naive T cells.[21]

Table 3. Types of T cells and their functions.[21]

Class	Function	Antigen receptors and specificity	Phenotypic markers
T cells helper $CD4^+$	B cell activation, macrophage activation, inflammatory stimulation	Specificity varies for MHC class II peptide complexes	$CD3^+$, $CD4^+$, $CD8^-$
T cells $CD8^+$	Kills cells infected with intracellular microbes, tumor cells	Specificity varies for MHC class I peptide complexes	$CD3^+$, $CD4^-$ $CD8^+$
T cells regulator	Suppresses other T cell functions (regulation of immune response, maintenance of self-tolerance)	Specific for self-antigens and some foreign antigens (MHC class II peptide complexes)	$CD3^+$, $CD4^+$ $CD25^+$, $FoxP3^+$ (most common)

All lymphocytes are morphologically similar and do not differ in appearance, but lymphocytes are very heterogeneous in their origin, function, and phenotype and are capable of complex biological responses. These cells are often distinguished by surface proteins identified using a panel of monoclonal antibodies. The standard nomenclature for these surface proteins is a cluster of differentiation (CD) marked with a number, which is used to determine surface proteins that indicate a specific cell or cell differentiation stage and are recognized by a group of antibodies. Each T cell has a specific CD, which can be seen in Table 3.[21,22] T cells helper $CD4^+$, which has various effector functions and can differentiate into different subtypes. These cells are not differentiated by their surface molecules but by the cytokines they secrete. The first two known subsets are called T cells helper type 1 (Th1) and T cells helper type 2 (Th2); the third group, called Th17 cells because their typical cytokine is interleukin (IL)-17; a fourth group of T cells that help B lymphocytes, called follicular T cells helper (Tfh).[21,23,24]

Th2 cells are important in fighting worm infections. These T cells produce IL-4, IL-5, and IL-13, which activate and expand the cells' mast and eosinophils to eradicate parasitic infections. Macrophages are also activated by these cells to begin clearing cellular debris and inflammation caused by large parasites. Th2 cells also play a role in allergies. Th2 cells are cells that secrete cytokines that act on B cells to differentiate into plasma cells that produce antibodies. Th17 cells are essential in mucosal immunity and are involved in fighting extracellular bacteria and fungi. Th17 cells produce IL-17, IL-22. These cytokines activate neutrophils and monocytes and promote increased

inflammation. Proinflammatory functions play a role in the development of autoimmune inflammatory disorders.[23,24] $CD8^+$ T cells activated by antigen and other signals differentiate into cytotoxic T lymphocytes (CTL) by recognizing the MHC class I peptide complex so that it is able to kill infected cells. Because all nucleated cells express MHC class I and differentiated CTLs do not require costimulation or T cell assistance for activation, CTLs can be active and kill infected cells in any tissue. Target cells are killed by CTLs through the delivery of granule proteins into the target cells. Two types of granule proteins important for killing are granzymes (granule enzymes) and perforin. Perforin damages the integrity of target cell plasma membranes and endosomal membranes, thereby facilitating the delivery of granzymes into the cytosol. The granzyme breaks down and activates the caspase enzyme contained in the cytosol of the target cell and induces apoptosis.

One of the extraordinary properties of the normal immune system is that it can react to a wide variety of microbes but not to self-antigens (self). This unresponsiveness to self-antigens is called immunological tolerance. Immunologic tolerance is the absence of a response to an antigen that is triggered by exposure of lymphocytes to that antigen. Immunologic tolerance to different self-antigens can be induced when developing lymphocytes encounter these antigens in generative (central) lymphoid organs, which is called central tolerance, whereas when mature lymphocytes are exposed to self-antigens in peripheral (secondary) lymphoid organs, it is called peripheral tolerance.[21] Autoimmunity is defined as an immune response to self-antigens (autologous) antigens. Autoimmunity is not a simple process to develop. There are several pathological mechanisms that are still not understood, leading to autoimmunity and autoimmune diseases. Autoimmune diseases are caused by an adaptive immune response involving T cells and B cells.[22,25] Autoantibodies are antibodies produced by the immune system against one or more of the body's own proteins. Autoantibodies attack healthy cells, tissues, and/or the body's own organs, causing inflammation and damage. Autoantibodies can be found several years before a diagnosis of autoimmune diseases such as SLE, rheumatoid arthritis, antiphospholipid syndrome, and type 1 DM can be made. The presence of autoantibodies is evidence of an autoimmune disease that is mediated by autoantibodies. Several criteria are met to prove the existence of autoimmunity, namely (1) autoantibodies and autoreactive T cells with the specificity of the affected person; (2) autoantibodies and autoreactive T cells are found in injured tissues; (3) the threshold of autoantibody or T cell response reflects disease activity; (4) reduction of autoimmune response provides disease amelioration.[22]

Systemic lupus erythematosus is a complex autoimmune disease characterized by the presence of autoantibodies against cell nuclei and involving many organ systems in the body. The exact immunological events that trigger the clinical manifestations of SLE are not yet known with certainty. Various pro- and anti-inflammatory cytokines such as TGF-β, IL-10, BAFF, IL-6, IFN-α, IFN-γ, IL-17, and IL-23 play important pathogenic roles. Autoantibodies produced by B cells and the deposition of immune complexes in organs contribute to tissue damage. T cells play a major role in the pathogenesis of SLE because they can trigger inflammation through the secretion of proinflammatory cytokines, helping B cells produce autoantibodies and the accumulation of autoreactive T cells.[10,27] T cells develop in the thymus and undergo a rigorous selection process through the central tolerance process. Some MHC-interacting cells that do not have a high affinity for self-antigens exit the thymus. This shows that autoreactive T cells are very rare. However, this process does not occur in SLE because a number of autoreactive T cells are found in the peripheral blood. In addition, there are many deviations in T cell expression and function associated with SLE T cell activation. This also leads to a lowered TCR activation threshold and reduced peripheral tolerance.[27,28] T cells helper $CD4^+$, which can help B cells produce antibodies. Without the help of T cells, most protein antigens cause a weak antibody response

or no immune response. T cells helper, which recognize antigens presented by B cells using CD40 ligand (CD40L) and secrete cytokines to activate antigen-specific B cells. CD40L expressed on T cells helper Activated ones bind to CD40 on B lymphocytes. Binding of CD40 produces a signal in B cells, then stimulates the proliferation, synthesis, and secretion of antibodies.[21,29]

Events in the development of a complete antibody response occur in germinal centers that form in lymphoid follicles and require T cells helper special type. Some helper-activated T cells express many of the chemokine receptors CXCR5, which attracts these cells into adjacent follicles. $CD4^+$ T cells that migrate into B cell-rich follicles are called T cells helper follicular (Tfh). The formation and function of Tfh cells depend on the so-called CD28 family receptors inducible ostimulator (ICOS). Tfh cells can secrete cytokines, such as interferon (IFN)-γ, interleukin (IL)-4, and IL-17, which are typical for Th1, Th2, and Th17 subsets. Most Tfh cells also secrete the cytokine IL-21.[21,29] According to Suarez et al. (2019), the response to autoantigens and the development of autoantibodies cannot yet be understood in SLE patients. However, it is most likely because the IgG antibody has a somatic gene mutation in the germinal center. The presence of activated B cell subsets in the peripheral blood of SLE patients is associated with increased expression of CD40L on T cells or OX40L on central terminal dendritic cells.[29] According to Rodriguez et al. (2016), in experimental animal models, Tfh is associated with the development of autoimmunity, such as SLE, due to dysregulation of the germinal center, which can lead to failure of tolerance. If there is a deficiency in ICOS, which is required for the development of Tfh, its protective role in lupus-susceptible rats is impaired. In addition, it was reported that Tfh-like CD4+ cell subsets were frequently found in the peripheral blood of patients with SLE. This shows that there is a relationship between the amount of Tfh and lupus activity. Tfh cells were also found in the kidneys of SLE patients in association with B cells, suggesting that their pathogenic capacity extends to nonlymphoid organs. Therefore, Tfh cells are increasingly recognized as major contributors to SLE by assisting in the formation of autoantibodies and assisting in the formation and maintenance of follicles.[28] Autoreactive B cells undergo tolerance and are eliminated through a process of deletion, anergy, changes in receptor specificity (receptor editing), or its activation is suppressed by binding to an inhibitory receptor. Central tolerance to immature B cells occurs in the thymus, while peripheral tolerance to mature B cells occurs in the lymphoid. It is estimated that in healthy people, autoreactive B cells are reduced from 50-75% to 5-20%. In SLE patients, peripheral tolerance is impaired so that the number of autoreactive mature B cells is greater, namely 5-20%. This shows that $CD4^+$ T cells play an important role in self-tolerance, and if there is a disruption in T cell regulation, it causes an autoimmune response in SLE patients. The characteristics of autoantibodies found in SLE patients further support that $CD4^+$ T cells are involved in the formation of high-affinity antibodies and class switching and carry somatic mutations in their receptors.[28]

T cells in patients with SLE experience impaired function, which is characterized by the production of pro-inflammatory cytokines and adhesion molecules. $CD4^+$ T cells contribute to inflammation in SLE patients by producing various cytokines such as IL-17 and IFN-γ. Th17 cells are a subset of CD4 T cells that are activated in the presence of TGF-β and certain proinflammatory cytokines such as IL-1β, IL-6, and IL-21. Th17 cells produce IL-17A, IL-17F, and IL-22, which trigger the inflammatory process and act on epithelial, endothelial, and hematopoietic cells. SLE patients have high levels of IL-17 in serum and an increase in the number of T cells that produce IL-17. In addition, increased IL-17 in patients with SLE correlates with disease activity. IL-17-producing T cells are also found in kidney cells in lupus nephritis patients. Although it is not fully explained why IL-17 is increased in SLE, there are several contributing factors, namely disturbances in TCR signaling and T

cell metabolism, which cause a cytokine imbalance.[14,28,29] In SLE, low production of IL-2 is also found, which causes the differentiation of effector T cells into a pro-inflammatory subset that releases cytokines that strengthen the autoimmune response. IFN-γ is a proinflammatory cytokine produced by Th1 cells, CD8 T cells, and several other cells. IFN-γ-producing cells are sometimes found in the glomeruli of kidneys with lupus nephritis. In SLE, there is an increase in the number of autoreactive $CD8^+$ T cells and the enzymes perforin and granzyme B. In addition, there is an increase in IFN-γ production, and this directly causes tissue damage with the presence of perivascular and interstitial infiltrates in the kidneys.[27-29]

Regulatory T cells (Treg) have the function of suppressing the immune response. SLE disease is associated with a reduction in the number and quality of regulatory T cells. Treg cells express a transcription factor called FoxP3, which is necessary for cell development and function. $CD4^+$ $FoxP3^+$ regulatory T cells are selected in the thymus and confer suppressive properties on these cells. This is supported by experiments on NZB/WF1 rats and lupus rats; when the number of Treg cells is increased, it will reduce autoantibody production and improve disease. However, the low number of Treg cells and the impaired suppressive properties of Treg cells contribute directly to SLE, and the mechanisms are still unknown.[28] Treg dysfunction can cause direct organ damage or cause germinal center reactions to become uncontrolled, thereby triggering an autoimmune response by producing autoantibodies. Treg absolute deficiency causes immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), whose phenotype is very different from SLE. This shows that Treg dysfunction is not the main cause of SLE but rather is one of the factors that contribute to causing damage.[27,28] Antigen recognition by T cells induces the onset of initial signals, which include tyrosine phosphorylation of T cell receptor (TCR) complex molecules and recruitment of adapter proteins to the T cell antigen recognition site. These initial events lead to the activation of several biochemical intermediates, which in turn activate transcription factors that stimulate transcription of genes whose products mediate T cell responses. These signaling pathways are described as unrelated to each other but maybe interrelated in a more complex network.[21,30]

The cytoplasmic portion of the CD4 and CD8 coreceptors has a constantly attached protein tyrosine kinase called Lck. Several transmembrane signal proteins are associated with the TCR, including CD3 and ζ chains. CD3 and ζ contain motifs, each with two tyrosine residues called tyrosine-based immunoreceptor activation motifs/immunoreceptor tyrosine-based activation motifs (ITAM), which is important for signaling. Lck, which is brought into close proximity to the TCR complex by CD4 or CD8 molecules, phosphorylates tyrosine residues contained in the ITAMs of CD3 and ζ proteins and causes signal transduction in T cells. The phosphorylated ITAMs of the ζ chain become binding sites for a tyrosine kinase called ZAP -70 (zeta-related protein 70 kD), which is also phosphorylated by Lck to become an active enzyme.[21,30] The main signaling pathways related to TCR complex activation are the NFAT–calcium pathway, the Ras/Rac–MAP kinase pathway, the PKCθ–NF-κB pathway, and the PI-3 kinase pathway. The activated T cell nuclear factor or nuclear factor of activated T cells (NFAT) is a transcription factor that exists in an inactive phosphorylated form in the cytoplasm of resting T cells. NFAT activation and its nuclear translocation depend on the concentration of calcium ions (Ca^{2+}) in the cytosol. This signaling pathway is initiated by phosphorylation mediated by activation of the enzyme phospholipase Cγ (PLCγ) by the kinase, Itk, attached to one of the adapter proteins in the signaling complex. Activated PLCγ catalyzes the hydrolysis of a plasma membrane phospholipid called phosphatidylinositol 4,5-bisphosphate (PIP2). One of the products of the PLCγ-mediated breakdown of PIP2, called inositol 1,4,5-triphosphate (IP3), binds to IP3 receptors on the membranes of the endoplasmic reticulum and

mitochondria and stimulates the release of Ca^{2+} into the cytosol. An increase in cytosolic Ca^{2+} causes the activation of a phosphatase called calcineurin. This enzyme releases phosphate from cytoplasmic NFAT, allowing the transcription factor to migrate into the nucleus, where it binds to and activates the promoters of several genes, including the gene encoding IL-2.[21,30]

Various transcription factors that are induced or activated in T cells, including NFAT, AP-1, and NF-κB, stimulate transcription and production of cytokines, cytokine receptors, cell cycle stimulants, and effector molecules such as CD40L. All of these signals start from antigen recognition and binding of the TCR and coreceptors to the peptide-MHC complex required to bring together important enzymes and substrates in T cells.[21] According to Suarez et al. (2019), T-cell activation is impaired in SLE patients. The disturbances caused could be due to changes in the signaling pathway of the TCR, causing disruption in the expression of genes that control T cell function. According to Katsuyama et al. (2018), the expression of the CD3ζ chain decreased significantly in the T cells of SLE patients, but there was an increased response to TCR stimulation. This is caused by the TCR-CD3 complex undergoing substitution by a homologous chain of the Fc receptor gamma subunit (FcRγ). CD3ζ and FcRγ are structurally and functionally homologous. FcRγ pairs with spleen tyrosine kinase (Syk), not with ZAP70. The FcRγ–Syk interaction was stronger than the CD3ζ–ZAP-70 interaction. This leads to disproportionately high PLC-γ phosphorylation and calcium influx into T cells. In rats with CD3ζ deficiency, it causes inflammation in multiorgan tissues. Therefore, reduced CD3ζ expression leads to impaired T-cell signaling.[29,30]

TCR-CD3 binding to antigen induces ITAM phosphorylation by Lck. According to Katsuyama et al. (2018), Lck expression decreases in the T cells of SLE patients. The lipid network in the plasma membrane of SL T is rich in cholesterol, sphingomyelin, and glycosphingolipids, which play an important role in TCR signaling. Lck resides on the lipid network, and accumulation of the lipid network induces increased phosphorylation and signal transduction. SLE T cells express higher levels of cholesterol, a major component of the lipid network. Atorvastatin, which can reduce cholesterol synthesis, restored Lck expression and lipid raft-related aberrant signaling in vitro in T cells from patients with SLE. Atorvastatin also reduces the production of IL-10 and IL-6 by activated T cells.[30,31] Spleen tyrosine kinase (Syk) plays a role in T cell signaling and is also an important molecule for B cell receptors. Syk expression levels of B cells from active SLE patients were increased compared with controls. Therefore, Syk inhibitors are a promising therapy. Fostamatinib, known as R788, is the active molecule of R406, which selectively inhibits Syk. Inhibition of Syk by fostamatinib prevented skin and renal involvement in MRL/lpr and BAK/BAX lupus-prone rats. Administration of fostamatinib improves kidney damage in lupus-prone rats. New Zealand black/white (NZB/NZW). Further research is needed to assess the effectiveness of Syk inhibitor in patients with SLE.[30]

Increased T cell signaling and increased calcium levels lead to increased calcineurin activation. Calcineurin dephosphorylated the cytoplasm inactive nuclear factor of activated T cells (NFAT) and dephosphorylated NFAT undergoes translocation to the nucleus. NFAT was increased in the nuclei of activated T cells of SLE patients after undergoing CD3 stimulation compared with those from controls. Apart from that, it also binds and activates the promoter of the CD154 gene (CD40L) and the IL2 gene. CD40-CD40L signaling is also important for Th17 cell differentiation. NFAT expression was increased in lupus-susceptible MRL/lpr rats. Dipyridamole, an inhibitor of the calcineurin-NFAT pathway, can reduce CD154 expression and improve nephritis in MRL/lpr rats. Calcineurin inhibitors such as cyclosporine and tacrolimus are now widely used for the treatment of SLE. This drug is effective in the treatment of lupus nephritis.[29,30] Signaling in T cells of SLE patients experiences various disorders and deviations, including decreased CD3ζ, activation of the PI3K-Akt-mTORC1 pathway, Rho-associated protein kinase

(ROCK), calcium/calmodulin kinase IV (CaMKIV), and protein phosphatase 2A (PP2A). This causes abnormal T cell differentiation, production of pro-inflammatory cytokines such as IL-17, and decreased production of important cytokines such as IL-2. Molecules that are abnormally increased or decreased in SLE are shown in red and blue boxes, and molecules that are potential therapeutic targets are shown in green circles.[30]

CD44 is a cell surface glycoprotein involved in the activation, adhesion, and migration of T cells. Research genome-wide association studies (GWAS) have now identified CD44 as a gene associated with SLE. It was reported that CD44 expression levels were increased in T cells from SLE patients and correlated with disease activity in SLE patients. The ezrin/radixin/moesin (ERM) proteins are important in linking plasma membrane proteins to actin filaments. The interaction of ERM proteins with CD44 is associated with cell adhesion and migration functions. T cells predominantly express ezrin and moesin. Moesin-deficient rats show systemic autoimmune features such as glomerulonephritis, decreased regulatory T cells, impaired activation signal transducer, and activator of transcription (STAT) 5 by IL-15, which is known to regulate the development of CD8 Treg cells. In SLE T cells, ERM phosphorylation increases, causing increased adhesion and migration of SLE T cells.[29,30] Rho-associated protein kinase (ROCK) is a serine/threonine kinase that phosphorylates ERM. ROCK has two families of serine-threonine kinases, namely ROCK1 and ROCK2. ROCK plays an important role in T cell migration, activation, and differentiation and regulates the activity of cytoskeletal components such as ERM and cell migration. ROCK2 plays a role in Th17 cell differentiation, production of IL-17 and IL-21, and induction of Tfh cells. Patients with SLE showed higher levels of ROCK activity compared with healthy controls. Therefore, ROCK inhibitors are candidates to be used for the treatment of SLE patients. KD025 is a selective ROCK2 inhibitor, while simvastatin is a non-selective ROCK inhibitor. Oral administration of KD025 to healthy individuals in a randomized phase I clinical trial reduced IL-17 and IL-21 production and reduced Tfh cell numbers and autoantibody production in MRL/lpr rats.[29,30] The Mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that regulates various cellular processes, including cell survival, proliferation, differentiation, and cellular metabolism. mTOR consists of two different complexes, namely the mTORC1 and mTORC2 complexes. mTORC1 induces glycolysis genes in which the glycolysis process is increased in CD4+ T cells from lupus-prone rats (B6.Sle1.Sle2.Sle3 rats and B6.lpr rats), and SLE patients. mTORC1 also regulates autophagy and mitophagy which are important in maintaining mitochondrial function. T cells from SLE patients show increased mitochondrial mass and mitochondrial dysfunction characterized by increased mitochondrial transmembrane potential. Increased mitochondrial metabolism in SLE T cells may disrupt T cell function. The role of mTOR in Treg cell differentiation is complex. Disrupted mTORC1 signaling in Treg cells results in profound loss of Treg suppressors.[30,32]

According to Oaks et al. (2016), activation of the mTOR pathway plays an important role in the pathogenesis of autoimmune diseases, including SLE. In SLE T cells, mTORC1 activity was increased while mTORC2 was reduced compared with T cells in healthy individuals. In addition, mTORC1 activation causes severe SLE disease activity. Therefore, according to Morel (2017), mTOR has become a therapeutic target in SLE. Rapamycin is the most well-known mTOR inhibitor. Recent studies revealed that the effects of rapamycin led to the suppression of IL-17 expression in $CD4^+$ T cells from SLE patients, and the effect of Treg cells was enhanced. SLE Treg cells showed increased mTORC1 and mTORC2, and IL21 stimulated mTORC1 and mTORC2 and blocked Treg cell differentiation. Rapamycin reduces the activation of STAT3 and IL-17-producing cells in patients with SLE, thereby reducing the severity of lupus nephritis and prolonging survival in MRL/lpr rats. N-acetylcysteine (NAC), a glutathione precursor, is also an mTOR inhibitor. A study assessing the effectiveness

and safety of NAC in SLE patients showed that 2.4 and 4.8 grams of NAC daily could reduce disease activity and mTOR activity. There are other reports showing the efficacy of NAC in SLE patients with lupus nephritis.[30,32,33] Phosphoinositide-3 kinase (PI3K) plays an important role in T cell differentiation. PI3K activity in T cells is increased in lupus-prone rats and in SLE patient T cells. According to Suarez et al. (2019), PI3K inhibitors can improve lupus disease in MRL/lpr rats. Through activation of the AKT-mTOR pathway, PI3K can increase Th17 cell activity and reduce regulatory T cell function. CaMK4, a kinase whose activity is increased in SLE, can activate AKT and mTOR. CaMK4 inhibitor drugs can improve disease in rats with lupus by influencing Th17 differentiation and increasing the formation and function of Treg cells.[29,30] O'Shea et al. (2015) stated that cytokines play an important role in the proliferation, activation, differentiation, and function of T cells. Signaling pathways Janus kinase- signal transducer and activator of transcription (JAK-STAT) is the most important pathway after cytokine receptor activation. In humans, seven STATs have been identified (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). Different cytokines can activate specific STATs, and STATs regulate the transcription of various genes. Numerous studies have shown that STAT signaling plays an important role in autoimmune diseases, including SLE.[30,34]

Bengtsson et al. (2017) stated that Interferon (IFN) plays an important role in the pathogenesis of lupus. IFN-activated STAT1 phosphorylation is increased in lupus-prone MRL/lpr rats. Th17 cells produce the cytokines IL-17, IL-17A, and IL-17F. Koga et al. (2017) stated that increased numbers of Th17 cells and increased levels of IL-17 were found in SLE patients and in lupus-prone rats. IL-17-producing cells have been found in kidney biopsies of patients with lupus nephritis and in the kidneys and spleens of MRL/lpr lupus-prone rats. IL-17 correlates with SLE disease activity.[35,36] According to Zickert et al (2015) serum IL-23 levels increase in SLE patients with severe disease activity. IL-23 induces STAT3 activation, and STAT3 directly binds the IL-17A and IL-17F promoters. In lupus-prone rats, there was an increase and activation of STAT3 and in SLE patient T cells. In addition to its role in Th17 differentiation, STAT3 is also important for assisting the development of Tfh cells that induce the differentiation of germinal center B cells into memory cells and antibody-secreting cells. Tfh cells became more numerous in SLE patients and lupus-prone rats. STAT3 also plays a role in the production of other cytokines, including IL-10, which promotes B cell proliferation and antibody production and is elevated in the serum and kidneys of SLE patients. Therefore, STAT3 inhibitors may be promising therapeutic candidates for treating SLE patients.[30,37] Clinical manifestations, symptoms, severity, and clinical response vary greatly in SLE patients. This suggests that there is no single mediator or pathway to explain the complexity of pathogenesis in SLE. For example, CD3ζ expression levels were found to be decreased in SLE but not in all cases. However, each aberration has the potential to be a promising therapeutic target. In addition, analysis of molecular diversity may contribute to the development of more personalized therapies in the treatment of SLE.[30]

2. Conclusion

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multi-organ system involvement. The pathogenesis of SLE involves genetic, immunological, and environmental factors that influence the loss of immunological tolerance to self-antigens, leading to the formation of pathogenic autoantibodies and tissue damage. T cells are the main component of the adaptive immune system, which can kill infected host cells, activate other immune cells, produce cytokines, and regulate immune responses. T cell dysfunction in SLE includes triggering inflammation through the secretion of pro-inflammatory cytokines, helping B cells produce autoantibodies, and the accumulation of autoreactive T cells. Aberrations in T cells could be a therapeutic target for development and a potential SLE therapy.

3. References

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