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Evaluation of ITGAM gene in Systemic Lupus Erythematosus Patients

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Abstract:

Background: The complicated inflammatory illness known as systemic lupus erythematosus (SLE) has a chronic relapsing-remitting history and a wide range of clinical presentations, from very minor symptoms to potentially fatal ones. Several variables, including genetic predispositions, environmental influences, and immunological dysregulation, contribute to the complex pathophysiology of SLE. Immune modulation and inflammatory control in SLE are greatly impacted by the ITGAM gene, which encodes the CD11b protein. This gene is critical for leukocyte adhesion, motility, and phagocytosis. This narrative review seeks to investigate the function of ITGAM and the CD11b protein in the development of systemic lupus erythematosus (SLE), with a particular emphasis on the ways in which variations of this protein cause immunological dysregulation and its consequences, including lupus nephritis. In addition, the analysis delves into possible CD11b treatment approaches for inflammation reduction and better patient outcomes. Approach: We combed through the available literature to find research that looked at the link between SLE and ITGAM variants. This review looked at the function of ITGAM in regulating the immune system, phagocytosis, and inflammation. It also looked at new ways to treat SLE, specifically at how CD11b agonists work to control the condition. In summary, SLE pathogenesis is significantly impacted by ITGAM gene variations, which worsen inflammation and hinder immune complex clearance. Potential novel therapy pathways for controlling this complicated autoimmune illness may be found in CD11b-targeted medicines, such as leukadherin-1, which show promise in modifying immune responses and lowering inflammation in SLE, especially in patients with lupus nephritis.

Keywords: Immune system modulation, inflammation, systemic lupus erythematosus, interferon beta-gamma, and related terms.

Introduction:

Systemic A complicated autoimmune illness, systemic lupus erythematosus (SLE) has a chronic relapsing-remitting history with a broad range of clinical symptoms, from moderate to life-threatening. The condition, which mostly affects women of reproductive age, is the product of a complex interaction between hereditary susceptibility, environmental variables, immunological dysregulation, and hormonal effects. A self-sustaining autoimmune process is driven by a complex immunopathogenesis that includes dysregulated immune responses, chronic tissue inflammation, dysregulated apoptotic clearance, complement activation, and SLE [1].

The activation of autoreactive B-cells, which are not adequately neutralized because of impaired immunological control, is central to the pathogenesis of SLE. Autoimmunity is worsened when these B-cells expose T-cells to self-antigens, setting off a cascade of reciprocal activation. Dysfunction in T-cell subsets, including altered gene transcription and cytokine production, compounds this imbalance in immune control and further contributes to the autoimmune response in SLE [2].

In SLE, the ITGAM gene plays a crucial role since it encodes the CD11b protein. The process of leukocyte adhesion, migration, and phagocytosis in immune cells such as monocytes, macrophages, and neutrophils is mediated by CD11b, which is a part of the macrophage-1 antigen complex (Mac-1 or complement receptor 3). Essential for regulating inflammation and avoiding tissue damage, it is also involved in the clearance of immune complexes and apoptotic cells [3].

Multiple genetic investigations have shown a strong association between ITGAM variations and an elevated risk of systemic lupus erythematosus (SLE), whereas mutations in CD11b decrease its biological activity and contribute to the course of the illness. Lupus nephritis, a serious consequence of systemic lupus erythematosus, is strongly linked to these mutations. Therapeutic targeting of CD11b may be useful since decreased CD11b function results in increased pro-inflammatory signaling [4].

Leukadherin-1 (LA1) and other CD11b agonists have recently emerged as promising new treatment options. By increasing CD11b

activity, LA1 promotes cell adhesion while decreasing inflammation and leukocyte migration. There is hope that this new method may modulate immune responses in SLE, which might help reduce the impact of CD11b mutations linked to illness and provide a tailored approach to treating lupus nephritis and other severe SLE symptoms [5].

This narrative review aims to examine the contributions of the ITGAM gene and its CD11b protein to immunological dysregulation and SLE sequelae such lupus nephritis, as well as the overall pathophysiology of SLE. Potential treatment approaches targeting CD11b to decrease inflammation and enhance outcomes in SLE patients are also examined in the study.

Ulcerative Colitis:

A chronic autoimmune illness known as Systemic Lupus Erythematosus (SLE) causes harm to many organs due to the generation of autoantibodies caused by the immune system losing its tolerance. It mostly impacts women of reproductive age because of a mix of hereditary, environmental, immune, and hormonal variables, and its clinical manifestations range greatly from moderate to hazardous [6].

A female-to-male ratio of up to thirteen to one indicates that SLE mostly affects women of reproductive age; the worldwide incidence rate is 5.14 per one hundred thousand person-years. The most prevalent age group for SLE is 15–44 years old, although it may also affect children and the elderly; the symptoms in youngsters tend to be more severe, while in adults it can develop more slowly. Higher rates in African American, Hispanic, and Asian populations are generally linked to more severe clinical characteristics [7], and the prevalence varies by ethnicity, ranging from 40 to 200 per 100,000.

Multiple variables, including genetics, epigenetics, hormones, and the environment, contribute to the aetiology of SLE. There are more than 100 gene loci linked to polygenic SLE, which lends credence to a significant hereditary propensity, as do high concordance rates in identical twins and family aggregation. Apoptotic debris clearing, the activity of interferon-alpha (INF-α), and intracellular signaling in T and B lymphocytes are all regulated by important genes that are associated with immune system activation [8].

Important epigenetic alterations include microRNA regulation, DNA methylation, and histone modifications. These alterations have the ability to influence gene expression without changing the DNA sequence, which might establish a connection between hereditary predisposition and environmental factors [9].

The role of environmental variables in the development and exacerbation of SLE is well-established. Infections such as Epstein-Barr virus (EBV), exposure to certain medicines, smoking, and ultraviolet radiation are among the known causes. DNA methylation alterations and the activation of pro-inflammatory cytokines are two mechanisms by which exposure to UVB worsens illness [10].

The increased frequency of SLE in women, particularly during menstruation, is likely due to hormonal changes. One reason why men and women experience SLE symptoms differently is because estrogen boosts immunological responses while androgens decrease them [11].

Both the innate and adaptive immune systems are involved in the intricate immunopathogenesis of SLE. The development of autoantibodies occurs as a result of persistent immunological stimulation, faulty clearance of apoptotic cells, and dysregulation of T and B cell signaling. Tissue deposition of immune complexes containing these autoantibodies causes organ damage and inflammation. A deterioration in immunological tolerance, prompted by both hereditary predisposition and environmental variables, causes systemic lupus erythematosus (SLE) and the involvement of many organs [12].

Characteristics of Patients:

SLE is an autoimmune illness that affects several systems; the disease's clinical manifestations may range from quite minor to potentially fatal, and it can affect more than one organ. Common constitutional symptoms include lethargy, fever, anorexia, and weight loss, and it has a relapsing-remitting course. Joint involvement, including arthritis and arthralgia, is seen in more than 90% of patients, whereas 70% of patients have mucocutaneous symptoms include baldness, photosensitivity, and malar rash. Also prevalent are symptoms involving the muscles and joints, such as myalgia, serositis, and pleuritis [13].

Any number of organ systems may be impacted by SLE. Myocarditis, pericarditis, and accelerated atherosclerosis are cardiovascular problems; pneumonitis, pulmonary fibrosis, and pulmonary hypertension are respiratory symptoms. A worse prognosis is associated with neuropsychiatric symptoms such psychosis, convulsions, cognitive impairment, and renal involvement (especially nephritis). Disease

care is already challenging when hematologic abnormalities, such as anemia, thrombocytopenia, or lymphopenia, add to the mix [14].

Different Kinds & Varieties:

The sun's rays may set off one of three kinds of cutaneous lupus erythematosus (CLE): acute (ACLE), subacute (SCLE), or chronic (CCLE). Of these, 75% are chronic instances. Idiopathic systemic lupus erythematosus (SLE) may manifest with fever, polyarthritis, and serositis; however, the brain, kidneys, and oral mucosa are spared in drug-induced lupus erythematosus (DILE), which happens as a result of certain medicines such as hydralazine and procainamide. Anti-histone antibodies are connected with DILE, which disappears after the triggering medicine is discontinued. Congenital heart block, rash, cytopenia, and liver abnormalities are symptoms of neonatal lupus, which develops in babies born to mothers with lupus, primarily as a result of maternal anti-Ro or anti-La antibodies [15].

While most women with SLE do not have problems with fertility, there are a number of hazards that might rise during pregnancy, such as the possibility of a premature delivery, hypertensive issues such as preeclampsia, intrauterine growth restriction, fetal AV block, and miscarriage. Lupus anticoagulant, anticardiolipin, anti-Ro/SSA, anti-La/SSB, and maternal anti-Ro/SSA antibodies are tested for during pregnancy for diagnosis. Although the presence of antiphospholipid antibodies increases the chance of miscarriage [16], a positive result is more probable for women who get the right therapy and do not have serious heart or renal problems.

Classification of systemic lupus erythematosus (SLE) according to the 2019 EULAR/ACR criteria begins with a positive anaphylaxis (ANA) and continues with seven clinical domains (constitutional, haematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and three immunological domains (antiphospholipid antibodies, complement proteins, SLE-specific antibodies). Individuals diagnosed with SLE have a point total of 10 or above. In order to differentiate between infections and SLE flares, some serological tests may be performed in the lab. These tests include total blood counts, ESR, CRP, complement levels, and anti-dsDNA and anti-Ro/La antibodies. (Fig. (1) [17].

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

§Additional criteria items within the same domain will not be counted. *In an assay with at least 90% specificit against relevant disease controls. Anti-β2GPI, anti-β2-glycoprotein I.
Reproduced from Aringer et al. (2019).[2]

Fig. (1) The 2019 EULAR/ACR criteria for SLE categorization are as follows: [17].

The diagnosis and monitoring of SLE rely heavily on serological markers such as ANA, anti-dsDNA, and ENAs. Anti-dsDNA antibodies are often linked to disease activity. An increase in anti-dsDNA and a decrease in complement levels are common symptoms of flares. With points given for issues like renal failure, pulmonary hypertension, cardiovascular disease, and neuropsychiatric impairment, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR) provides a comprehensive tool for long-term disease management [18].

Medical care:

Disease remission, organ preservation, pharmacological side effect minimization, and quality of life enhancement are the long-term goals of SLE therapy. Avoiding direct sunlight, applying sunscreen, and urging patients to quit smoking are all part of the general care plan. It is possible to manage CLE with topical medicines including retinoids, calcineurin inhibitors, and corticosteroids; but, depending on the severity of the condition, systemic treatments like hydroxychloroquine, glucocorticoids, and immunosuppressive drugs may be used. In situations when conventional treatments have failed, biologic medicines such as rituximab and belimumab are reserved [19].

A more tailored approach to controlling SLE is being achieved via the use of personalized medicine, which integrates genetic and molecular data to adapt medications to unique patient profiles. Reducing illness exacerbations and progression requires preventive interventions such as early diagnosis, lifestyle adjustments, and treatment of comorbidities. Individuals at high risk of developing SLE are the primary target of primary prevention efforts, whereas patients diagnosed with the illness and its consequences are the focus of secondary and tertiary preventive efforts, with the goal of improving disease management and patient outcomes overall [20].

Other issues:

The illness or its treatment medicines may both cause SLE complications. Cardiovascular problems such as pericarditis, myocarditis, and Libman-Sacks verrucous endocarditis, which impact the heart valves, are common consequences, as are chronic renal disease and accelerated atherosclerosis. Lupus pneumonia and pleural effusion are pulmonary consequences. Lupus and immunosuppressive medications greatly increase the risk of infections and cause pancytopenia. Premature menopause is a potential side effect of immunosuppressants and long-term usage of corticosteroids may cause osteonecrosis, osteoporosis, cataracts, and secondary diabetes. An important consequence that raises the risk of blood clots and pregnancy problems is anti-phospholipid syndrome (APS) [21].

Lupus nephritis and other forms of renal involvement of SLE significantly impact prognosis, increasing the risk of kidney failure and the need for dialysis. It is defined by the accumulation of immunological complexes in kidney tissue, which may be seen as proteinuria, hematuria, or glomerulonephritis. Treatment options, such as corticosteroids and cytotoxic medications like mycophenolate mofetil or cyclophosphamide, are dependent on the severity of the condition and are determined by kidney biopsy results. A higher chance of malignancies, including haematological, cervical, breast, and lung cancers, as well as gastrointestinal problems such mesenteric vasculitis, stroke, and thrombotic events, are additional consequences.

In order to diagnose and track systemic lupus erythematosus (SLE), serological markers such as anti-dsDNA antibodies, ENAs, and ANA are essential. Elevated anti-dsDNA and decreased complement levels are common hallmarks of flares. One comprehensive tool for long-term disease management is the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR), which assigns points for issues like renal failure, pulmonary hypertension, cardiovascular disease, and neuropsychiatric impairment, among others, to measure irreversible damage in different organ systems [18].

Medical care:

Remission of illness, protection of organs, reduction of medication side effects, and improvement of quality of life are the goals of SLE therapy with an eye on improving long-term patient outcomes. Sunscreen use, avoiding direct sunlight, and smoking cessation are all part of the general treatment plan. If the condition is severe enough, systemic medicines such as hydroxychloroquine, glucocorticoids, and immunosuppressive drugs may be used to manage CLE; however, topical therapy including retinoids, calcineurin inhibitors, and corticosteroids are usually sufficient. When conventional treatments fail, doctors may prescribe biologic medicines such rituximab and belimumab [19].

To better manage SLE, personalized medicine is being utilized more and more to customize

medicines to specific patient profiles by combining genetic and molecular data. To lessen the severity of symptoms and slow the course of the illness, preventative measures are essential. These include getting a diagnosis early, making lifestyle changes, and dealing with co-occurring conditions. Aiming to improve overall disease management and patient outcomes, tertiary and secondary prevention work to treat patients who have been diagnosed with SLE and avoid complications, while primary prevention targets persons at high risk of getting the condition [20].

More than that:

Both the illness and its treatment drugs carry the risk of SLE complications. Conditions affecting the heart valves, such as pericarditis, myocarditis, and Libman-Sacks verrucous endocarditis, as well as chronic renal disease and accelerated atherosclerosis, are common side effects. Lupus pneumonia and pleural effusion are pulmonary consequences. Lupus and immunosuppressive therapy can lead to pancytopenia and an increased risk of infections. Immunosuppressants have the potential to cause menopause to occur earlier than expected, and long-term use of corticosteroids has the potential to cause osteonecrosis, osteoporosis, cataracts, and secondary diabetes. Notable risks include anti-phospholipid syndrome (APS), which raises the risk of blood clots and problems during pregnancy [21].

An important component of SLE prognosis is renal involvement, especially lupus nephritis, which may cause kidney failure and need dialysis. Proteinuria, hematuria, or glomerulonephritis are symptoms of immune complex accumulation in kidney tissue, which characterizes this condition. Treatment options include cytotoxic medications such as mycophenolate mofetil or cyclophosphamide, as well as corticosteroids, based on the results of a kidney biopsy. The list of potential side effects is long and includes gastrointestinal problems such mesenteric vasculitis, cardiovascular problems like stroke and thrombotic events, and malignancies including haematological, cervical, breast, and lung cancers, among others.

Table (1) ISN/RPS Lupus nephritis classification [22].

Class	Type
I	Minimal mesangial lupus nephritis
II	Mesangial proliferative nephritis
III	Focal proliferative nephritis
IV	Diffuse proliferative nephritis,
V	Membranous nephritis
VI	Sclerotic nephritis

Prognosis

The Important serological indicators for SLE diagnosis and surveillance include ENAs, anti-dsDNA antibodies, and ANAs. Anti-dsDNA antibodies are often linked to disease activity. The levels of anti-dsDNA and complement drop during flares. Renal failure, pulmonary hypertension, cardiovascular disease, and neuropsychiatric impairment are some of the organ systems that can be irreversibly damaged by systemic lupus. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR) is a comprehensive tool for managing the disease over the long term [18].

Medical care:

St. Louis encephalomyelitis (SLE) therapy goals include achieving illness remission, avoiding organ damage, reducing medication side effects, and increasing quality of life for patients. As a general rule, patients should try to limit their time in the sun, use sunscreen, and get rid of their smoking habits. When it comes to controlling CLE, topical medicines like retinoids, calcineurin inhibitors, and corticosteroids work well. Systemic treatments like hydroxychloroquine, glucocorticoids, and immunosuppressive drugs are used based on the severity of the condition. Reserving biologic medicines like rituximab and belimumab for situations when conventional treatments have failed is the recommended practice [19].

Tailoring medicines to unique patient profiles, personalized medicine integrates genetic and molecular data, enabling a more tailored approach to controlling SLE. Important steps in preventing worsening of symptoms and further illness development include getting a diagnosis early, making lifestyle changes, and dealing with co-occurring conditions. When it comes to systemic lupus erythematosus (SLE), primary prevention targets those most likely to get the condition, while secondary and tertiary preventive work to treat those who have been diagnosed and head off any problems they may have [20].

Possible difficulties:

Neither the illness nor the drugs used to treat SLE may cause complications. Libman-Sacks verrucous endocarditis, myocarditis,

pericarditis, and chronic renal disease are common consequences. Accelerated atherosclerosis and chronic renal disease are other common cardiovascular concerns. Pulmonary issues may manifest as pleural effusion or lupus pneumonia, and the illness and its immunosuppressive therapies often lead to pancytopenia and an elevated risk of infections. Some side effects of immunosuppressants include early menopause and osteonecrosis, osteoporosis, cataracts, and secondary diabetes if used for an extended period of time. One serious issue that may arise during pregnancy is anti-phospholipid syndrome (APS), which raises the likelihood of blood clots and other problems [21].

Lupus nephritis and other forms of renal involvement are important predictors of kidney failure and the need for dialysis in sickle cell disease (SLE) patients. Clues include proteinuria, hematuria, or glomerulonephritis, which are symptoms of immune complex accumulation in kidney tissue. Depending on the severity, patients may be prescribed cytotoxic medications such as cyclophosphamide or mycophenolate mofetil or corticosteroids after undergoing a kidney biopsy for diagnosis and categorization. Mesenteric vasculitis, stroke, thrombotic events, and an increased risk of malignancies (including haematological, cervical, breast, and lung cancers) are among the other consequences.

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