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Review Article: Is there a relationship between Systemic Lupus Erythematosus and the Mannose Binding Lectin gene?

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Abstract:

Our review article discusses the relationship between systemic lupus erythematosus and the mannose-binding lectin gene. The complex trait of systemic lupus erythematosus (SLE), which manifests as a variety of clinical phenotypes and the production of several autoantibodies, is SLE. SLE patients experience a wide range of clinical phenotypes, such as skin rash, and neuropsychiatric, and musculoskeletal symptoms, some of which can progress to lupus nephritis. Abnormal complement activation causes inflammation, which damages multiple organs' tissue. About 50% of systemic lupus erythematosus patients, a chronic inflammatory disease, experience kidney damage. Despite effective anti-inflammatory and immunosuppressive therapies, lupus nephritis still results in end-stage kidney impairment (ESRD) or chronic kidney disorder (CKD) for an excessive number of patients. It represents a significant risk factor regarding mortality and morbidity in SLE. The family of C-type lectins of collectins includes the mannose-binding lectin (MBL), whose portion in the pre-immune first line of defense seems to involve pattern recognition. MBL can identify carbohydrate modes that abound on the surfaces of numerous pathogenic bacterial, viral, protozoal, and fungal microorganisms. The complement system's lectin pathway is activated when MBL binds to a microorganism. Numerous studies have linked MBL polymorphism, SLE, and lupus nephritis.

Keywords: Systemic lupus erythematosus (SLE), Lupus nephritis, Mannose-binding lectin (MBL).

Introduction

A chronic inflammatory condition called systemic lupus erythematosus (SLE) is defined by an autoantibody response to cytoplasmic and nuclear antigens. It progresses in an occurring, relapsing situation fashion. Greater than ninety percent of SLE patients involve women, and they typically begin while they are of childbearing age.[(1)] The development is thought to be influenced by both environmental and hereditary influences.[(2)] These environmental and hereditary influences lead to immune system flaws.[(3)] SLE risk factors include exposure to the

sun, smoking, deficiency of vitamin D, and particular infections in addition to female sex hormones.[2]

Epidemiology

In the US, there are 20–150 cases of Systemic Lupus Erythematous (SLE) per 100,000 people.[4-7] Rates of prevalence per 100,000 women vary from 164 in white people to 406 in African Americans.[4] At the end of the twenty-eth century, regarding 40 years occurre-nces nearly tripled as a result of better identification of mild diseases.[8] About 1 and 25 cases per 100,000 people occur in the Americas, Latin America, Europe, and Asia.[5, 9-11]

The prevalence of SLE, as well as the pattern and seriousness of medical conditions and diagnostic studies, are influenced by geographic presentation and race:

- The disease is more widely spread in cities than in rural areas.[4,12] Compared to White people, SLE is more common in Asian, African, American, Caribbean, and Hispanic American populations. [5,9,10,12] SLE is a rare occurrence in Africa. [5, 13]
- Patients with Northern European ancestry experience photosensitivity and discoid skin lesions more frequently than patients Many with Southern European ancestry are less likely to have anticardiolipin and anti-double-stranded DNA (anti-dsDNA) antibodies than those with Northern European ancestry.[14]

Pathogenesis

Apoptosis seems to be important for maintaining during both homeostasis, growth, and aging. cells in apoptosis are normally consumed by using phagoc-ytes, lysosomes and eliminated in this manner; no inflammation is involved.[15] When NETosis occurs, neutro-phil extracellular traps (NETs) are distributed as a controlled form of neutrophil cell death, aiding the host's defense against infections.[16] According to numerous studies, SLE is caused by a faulty removal of NETs and apoptotic remains from the tissues and blood. [17, 18, 19, 20] Consequently, it is commonly believed that SLE begins to show symptoms when the elimination of dead cells is compromised. There must be sufficient molecules that promote the removal of damaged cells by phagocytes from dying cells, which requires several ligands and receptors.[21] Understanding this intricate mechanism offers therapeutic potential, particularly for the early detection and treatment of SLE.[22] Upon losing an unbroken cell membrane, dying cells that are not removed go through secondary necrosis rapidly and effectively, and then erupt, releasing nuclear material. [23] The failure of phagocytes to recognize apoptotic cells in SLE is caused by one of three factors: either the phagocytes are smaller,[24] have weakened and delayed phagocytic activity,[25] or differentiate less readily from CD34-positive hematopoietic stem cells. [20,26,27]

Laboratory tests

The two mainstays of serologic testing for SLE are anti-extractable nuclear antigen (anti-ENA) and antinuclear antibody (ANA) testing. There are numerous methods for finding ANAs. The technique that is most frequently utilized in medicine is indirect immunefluorescence (IF). The kind of antibody serum of the subjects is shown by the fl-uorescence pattern. Immunoglobulin and complement protein deposits in human skin can be found via direct immunofluorescence. A positive direct IF test (also known as the "lupus band test") on skin that has

not been exposed to the sun is indicative of systemic lupus erythema-atosus.[28] Antinuclear antibody testing is positive for many autoimmune diseas-es and connective tissue disorders, and it can also happen in healthy people. Anti-Smith, anti-dsDNA (related to SLE), antihistone, and antibodies against double-stranded DNA (dsDNA) are examples of subtypes of antibodies to nucleic acids (which are linked to drug-induced lupus). In people without SLE, only 0.5% have anti-dsDNA antibodies, even though they are present in 70% of instances of SLE.[29] Anti-U1- Rib nucleoprotein (Anti-U1- RNP), which also manifests in systemic sclerosis and mixed connective tissue disease, SS-A and SS-B (all of which are more prevalent in Sjögren's syndrome), and newborn lupus-specific risk for cardiac conduction block are other ANA that may be present in patients with SLE.[30] Other common tests for S-LE include liver enzymes, complete blood count, electrolytes and renal function (disturbed if the kidney is affected), complement system levels (low levels signal immune system consumption), and electrolytes. [31]

Diagnostic criteria

The systemic lupus erythematosus (SLE) cell test, once widely utilized for diagnosis, is no longer employed because only 50–75% of SLE cases exhibit LE cells, and other instances of rheumatoid arthritis, scleroderma, and drug sensitivity also exhibit LE cells. As a result, the LE cell test is currently only occasionally conducted and only has historical importance .[32] The right combination of clinical symptoms and laboratory data must support the diagnosis of SLE. Clinical professionals can identify SLE and subclassify this complicated disease depending focused on the target organ's symptoms with the support of familiarity with the diagnostic criteria.[33]

The criteria established in 1982 the characteristics necessary to distinguish SLE were listed by the American College of Rheumatology (ACR).[34] This list's most recent revision was made in 1997. The presence of 4 out of the 11 criteria results in a sensitivity of 85% and a specificity of 95% for SLE (Table 1).

The Systemic Lupus International Collaborating Clinics (SLICC) group modified and confirmed the ACR SLE classification criteria in 2012. Acco-rding to the revision, an indivi-dual is diagnosed with SLE if they have biopsy-proven lupus nephritis and ANA or anti-dsDNA antibodies, as well as 4 of the criteria, into at least 1 clinical and 1 immunologic standard, [35] (**Table (2)**).

Table (1) lists the Systemic lupus erythematosus classification criteria that were updated in 1997 from the 1982 edition published by the American College of Rheumatology. [34]

Criterion	Definition
Malar rash	The nasolabial folds and the malar eminences are spared by fixed erythema, whether it is flat or raised.
Discoid rash	An atrophic scarring, erythematous raised patches with adherent keratotic scale, and follicular plugging may appear in older legions.
Photosensitivity	Skin rash brought on by unusual sun exposure, according to the patient's medical history or a doctor's observation.
Oral ulcers	A doctor may diagnose oral or nasopharyngeal ulceration, which is typically painless.
Arthritis	Non-erosive arthritis is characterized by tenderness, swelling, or effusion in two or more peripheral joints.
Serositis	Pleuritis symptoms include pleuritic pain or rub, or pleural effusion. Pericarditis can be seen through an ECG, rub, or pericardial effusion.
Renal disorder	Persistent proteinuria greater than 0.5 grams per day OR cellular casts (RBC, granular, mixed).
Neurologic disorder	seizures not caused by drug use or other factors; OR psychosis not caused by drug use
Hematologic disorder	Hemolytic anemia with reticulocytosis, leukopenia 4000/mm, lymphopenia 1500/mm, or thrombocytopenia 100,000/mm are all potential diagnoses.
Immunologic Disorder	Results of tests that are positive for antiphospholipid, anti-Sm, or anti-DNA antibodies.
Positive ANA	Enzyme-linked immunosorbent assay or immunofluorescence.

Table (2) lists the standards of the Systemic Lupus International Collaborating Clinics (SLICC). [35]

clinical guidelines	Immunologic guidelines
1. Primarily, acute cutaneous lupus	1. ANA antibody
2. long-lasting cutaneous lupus	2. anti-ds DNA antibody
3. Mucous membrane lupus	3. Positive direct Coombs' test result in absence of hemolytic anemia
4. Alopecia without scarring	4. Antiphospholipid antibody
5. Neurologic impairment	5. Low complement levels
6. Serositis	6. Anti-smooth muscle
7. kidney affection	
8. Hemolytic anemia	
9. leucopenia	
10. Decrease in platelets number (< 100,000/ mm3)	
11. Arthritis	

Mannose-binding lectin gene affection:

Our review article discusses the relationship between systemic lupus erythematosus and the mannose binding lectin gene. The serum protein known as mannose- Mannose-binding lectin (MBL), also referred to as Mannose-binding protein (MBP) originated in the hepatic system. It's a lectin that works through the lectin pathway like an immunomodulator in innate immunity.[36,37] MBL is made up of polypeptide chains with three 30-base pair peptide chains that are almost clearly identical and has an oligomeric structure (400–700 kDa). Even though MBL can take on a variety of There are indicators that dimers and trimers exist in isomeric forms that lack biological activity like opsonins and that minimum a tetramer form is required for complement stimulation.[38]

Polymorphisms and genes

The MBL2 gene for humans is found on chromosome 10q11.2-q21.[39] The MBL2 gene, which is located on chromosome 10, controls the production of MBL, and polymorphisms in the gene's structural regions or its promoter have been linked to relative or absolute serum MBL deficiencies. [40]

The MBL2 gene has three known mutations in exon 1: codon 52 (rs5030737; C>T; Arg>Cys), known as the D variant; codon 54 (rs1800450; G>A; Gly>Asp), known as the B variant; and codon 57 (rs1800451; G>A; Gly>Glu), known as the C variant. The wild-type is A, and the variants B, C, and D are collectively referred to as O. Wild-type genotype (A/A) individuals typically have high MBL levels, whereas heterozygotes (A/O) have 10% or less of the wild-type MBL serum concentrations and homozygotes (O/O) have very low or nonexistent MBL levels. [41]

The connection between systemic lupus erythematosus (SLE) and MBL gene polymorphism:

Numerous studies have examined the relationship between MBL expression and/or concentrations in body fluids and clinical presentation as a result of mounting evidence in recent years that the MBL is essential for the innate immune response. Blood MBL levels rise in response to infections, just like the proteins of the acute phase of inflammation. The sugar moieties on the surface of bacteria, viruses, fungi, and parasites are recognized by MBL and bound to them. Through MBL-associated proteases, MBL binding causes these microorganisms to agglutinate and enables phagocytic clearance of pathogens as well as activ-ation of the lectin-complement pathway. [42]

While non-genetic factors are also important, genetic factors account for a sizable portion of the concentration of functional MBL. [43] The functional MBL2 gene for humans is highly polymorphic. [44] In addition to promoter polymerphism, the collagenous region of MBL is altered by three independent single point mutations (SNPs) at codons 52 (Arg-/Cys, allele D), 54 (Gly/Asp, allele B), and 57 (Gly/Glu, allele C).[45] The protein's collagenous structure is broken down, which lowers the percentage of higher-order oligomers in circulation and sharply lowers serum MBL concentrateions. Increased MBL causes enhanced complement activation and tissue damage, while its absence has been linked to the ineffective removal of apoptotic cells, which acts as a catalyst for the production of autoantibodies[46]. Additionally, MBL deficiency is assoc-iated with a higher risk of developing secondary

infections, which is thought to play a role in the develop-ent of SLE. [47]

References

1. **Bartels CM. and Muller D** Systemic Lupus Erythematosus (SLE), Drugs & Diseases > Rheumatology 2020**.**
2. **Henderson, LA; Loring, SH; Gill, RR; Liao, KP; Ishizawar, R; Kim, S; Perlmutter- Goldenson, R; Rothman, D; Son, MB; Stoll, ML; Zemel, LS; Sandborg, C; Dellaripa, PF; Nigrovic, PA.** "Shrinking lung syndrome as a manifestation of pleuritis: a new model based on pulmonary physiological studies". The Journal of Rheumatology. 2013; 40 (3): 273–81.
3. **Lisnevskaia, L; Murphy, G; Isenberg, D**. "Systemic lupus erythematosus". Lancet. 2014;384 (9957): 1878–88.
4. **Chakravarty EF, Bush TM, Manzi S.** Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis Rheum 2007; 56:2092.
5. P**ons-Estel GJ, Alarcón GS, Scofield L, et al.** Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum2010; 39:257.
6. P**ons-Estel GJ, Alarcón GS, Scofield L, et al.** Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum2010; 39:257.
7. **Izmir PM, Parton H, Wang L, et al (2021):** Prevalence of Systemic Lupus Erythematosus in the United States: estimates from a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis Rheumatol 2021; 73:991.
8. **Stojan G, Petri M.** Epidemiology of systemic lupus erythematosus: an update. Curr Opin Rheumatol 2018; 30:144.
9. **Uramoto KM, Michet CJ Jr, Thumboo J, et al**. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. Arthritis Rheum1999; 42:46.
10. **Danchenko N, Satia JA, Anthony MS.** Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15:308.
11. **Rus V, Maury EE, Hochberg MC**. The epidemiology of systemic lupus erythematosus. In: Dubois' Lupus Erythematosus, Wallace DJ, Hahn BH (Eds), Lippincott Williams and Wilkins, Philadelphia 2002.
12. **Peschken CA, Esdaile JM.** Rheumatic diseases in North America's indigenous peoples. Semin Arthritis Rheum 1999; 28:368.
13. **Petri M.** Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2002; 16:847.
14. **Symmons DP (1995):** Frequency of lupus in people of African origin. Lupus 1995; 4:176.
15. **Chung SA, Tian C, Taylor KE, et al.** European population substructure is associated with mucocutaneous manifestations and autoantibody production in systemic lupus erythematosus. Arthritis Rheum 2009; 60:2448.
16. **Biermann M, Maueroder C, Brauner JM, Chaurio R, Janko C, Herrmann Ml.** Surface code –biophysical signals for apoptotic cell clearance. Phys Biol. 2013; 10:065007.
17. **De Bont CM, Boelens WC, Pruijn GJM.** NETosis, complement, and coagulation: a triangular relationship.

Cellular & Molecular Immunology journal (16)2009; 19–27.

18. **Elliott M, Ravichandran K**. Clearance of apoptotic cells: implications in health and disease. J Cell Biol.2010; 189:1059–70.

19. **Fadeel B, Xue D, Kagan V**. Programmed cell clearance: molecular regulation of the elimination of apoptotic cell corpses and its role in the resolution of inflammation. Biochem Biophys Res Commun.2010; 396:7–10.

20. **Muñoz L, Lauber K, Schiller M, Manfredi A, Herrmann M.** The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol. 2010; 6:280–9.

21. **Muñoz L, Peter C, Herrmann M, Wesselborg S, Lauber K**. Scent of dying cells: the role of attraction signals in the clearance of apoptotic cells and its immunological consequences. Autoimmun 2010; 9:425–30.

22. **Munoz LE, Frey B, Appelt U, Janko C, Carter K, Voll R.** Peripheral blood stem cells of patients with systemic lupus erythematosus show altered differentiation into macrophages. Open Autoimmun J 2010; 2:11–6.

23. **Shao W, Cohen P.** Disturbances of apoptotic cell clearance in systemic lupus erythematosus. Arthur Res Ther.2010; 13:202.

24. **Rahman Z, Shao W, Khan T, Zhen Y, Cohen P**. Impaired apoptotic cell clearance in the germinal center by deficient tingible body macrophages leads to enhanced antibody-forming cell and germinal center responses. J Immunol. 2010; 185:5859–68.

25. **Poon I, Lucas C, Rossi A, Ravichandran K**. Apoptotic cell clearance: basic biology and therapeutic potential. Nat Rev Immunol. 2014; 14:166–80.

26. **Röszer T.** Transcriptional control of apoptotic cell clearance by macrophage nuclear receptors. Apoptosis.2016; 22:284–94.

27. **Mahajan A, Herrmann M, Muñoz L**. Clearance deficiency and cell death pathways: a model for the pathogenesis of SLE. Front Immunol. 2016; 7:35.

28. **Gail US, Munoz LE, Grossmayer G, Lauber K, Franz S, Carter K.** Clearance deficiency and systemic lupus erythematosus (SLE). J Autoimmun. 2007; 28:114–21.

29. **Szondy Z, Garabuczi Ã, JoÃs G, Tsay G, Sarang Z**. Impaired clearance of apoptotic cells in chronic inflammatory diseases: therapeutic implications. Front Immunol. 2014; 5:1–8.

30. **Bradley SJ, Suarez-Fueyo A, Moss D, Kyttaris V, Tsokos G**. T cell transcriptomes describe patient subtypes in systemic lupus erythematosus 2015. 10(11): e0141171.

31. **Honczarenko K, Budzianowska A, Ostanek L.** "Neurological syndromes in systemic lupus erythematosus and their association with antiphospholipid syndrome". Neurol. Neurochir. Pol. 2008; 42 (6): 513–7.

32. **D'Cruz DP**. "Systemic lupus erythematosus". BMJ.2006; 332(7546): 890–4.

33. **Jump RL, Robinson ME, Armstrong AE, Barnes EV, Kilbourn KM, Richards HB**. "Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support". J. Rheumatol.2005; 32 (9): 1699–705.

34. **Hochberg MC.** Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum1997; 40(9):1725.

35. **Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman**

R, Smolen JS, Wofsy D, Boumpas DT, Kamen DL, Jayne D, Cervera R, Costedoat-Chalumeau N, Diamond B, Gladman DD, Hahn B, Hiepe F, Jacobsen S, Khanna D, Lerstrøm K, Massarotti E, McCune J, Ruiz-Irastorza G, Sanchez-Guerrero J, Schneider M, Urowitz M, Bertsias G, Hoyer BF, Leuchten N, Tani C, Tedeschi SK, Touma Z, Schmajuk G, Anic B, Assan F, Chan TM, Clarke AE, Crow MK, Czirják L, Doria A, Graninger W, Halda-Kiss B, Hasni S, Izmirly PM, Jung M, Kumánovics G, Mariette X, Padjen I, Pego-Reigosa JM, Romero-Diaz J, Rúa- Figueroa FernándezÍ, Seror R, Stummvoll GH, Tanaka Y, Tektonidou MG, Vasconcelos C, Vital EM, Wallace DJ, Yavuz S, Meroni PL, Fritzler MJ, Naden R, Dörner T, Johnson SR. European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. Journal 2019; 78(9):1151.

36. **Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sánchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG Jr, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G Jr, Magder LS.** Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. Journal 2012; 64(8):2677-86.

37. **Fraser IP, Koziel H, Ezekowitz RA**. "The serum mannose-binding protein and the macrophage mannose receptor are pattern recognition molecules that link innate and adaptive immunity". Semin. Immunol.1998; 10 (5): 363–72.

38. **Worthley DL, Bardy PG, Mullighan CG**. "Mannose-binding lectin: biology and clinical implications". Internal Medicine Journal.2005; 35 (9): 548–55.

39. **Auriti c, Giusi Prencipe, Maria Moriondo, Iliana Bersani, Chiara Bertaina, Vito Mondì, and Rita Inglese**. (2017): Mannose-Binding Lectin: Biologic Characteristics and Role in the Susceptibility to Infections and Ischemia-Reperfusion Related Injury in Critically Ill Neonates. Journal of Immunology Research Volume 2017, Article ID 7045630, 11 pages.

40. **Sastry K, Herman GA, Day L, Deignan E, Bruns G, Morton CC, Ezekowitz RA**. "The human mannose-binding protein gene. Exon structure reveals its evolutionary relationship to a human pulmonary surfactant gene and localization to chromosome 10". J. Exp. Med. 1989;170 (4): 1175–1189.

41. **Monticielo OA, Mucenic T, Xavier RM, João Carlos Tavares Brenol & José Artur Bogo Chies.** The role of mannose-binding lectin in systemic lupus erythematosus. Clinical Rheumatology 2008; 27: 413–419.

42. **Garred, P, Larsen, F, Madsen, HO.** Mannose-binding lectin deficiency revisited. Molecular Immunology 2003; 40: 73–80.

43. **Lau Y. L., Chan S. Y., Turner M. W., Fong J., Karlberg J.** Mannose-binding protein in preterm infants: developmental profile and clinical significance. Clinical and Experimental Immunology.1995; 102(3):649–654.

44. **Sorensen CM, Hansen TK, Steffensen R, Jensenius JC, Thiel S**. Hormonal regulation of mannan-binding lectin

synthesis in hepatocytes. Clin Exp Immunol.2006; 145:173-82.

45. **Messias Reason LJ, Schafranski MD, Jensenius JC, Steffensen R**. The association between mannose-binding lectin gene polymorphism and rheumatic heart disease. Hum Immunol. 2006; 67:991-8.

46. **Ivanova M, Ruiqing J, Matsushita M, Ogawa T, Kawai S, Ochiai N, Shivarov V, Maruya E, Saji H.** MBL2 single nucleotide polymorphism diversity among four ethnic groups as revealed by a bead-based liquid array profiling. Hum Immunol. 2008; 69:877-84.

47. **Stuart LM, Takahashi K, Shi L, Savill J, Ezekowitz RA.** "Mannose-binding lectin-deficient mice display defective apoptotic cell clearance but no autoimmune phenotype". J. Immunol 2005; 174 (6): 3220–6.

48. **Bouwman LH, Roep BO, Roos A**. Mannose-binding lectin: clinical implications for infection, transplantation, and autoimmunity. Hum Immunol2006; 67: 247–256.