Review Article

iMedPub Journals
www.imedpub.com

Journal of Clinical & Experimental Nephrology
ISSN 2472-5056

2024
Vol.9 No.1:232

Molecular and Cellular Mechanisms of Systemic Autoimmune Diseases: Lessons Learned from Human Genetic Studies and Therapies in Systemic Lupus Erythematosus (SLE)

Abstract

Systemic Lupus Erythematosus (SLE) is a prototypical systemic autoimmune disease characterized by a complex interplay of genetic, molecular and cellular factors. It is considered a multifactorial disorder influenced by genetic susceptibility, environmental triggers and dysregulated immune responses. Understanding the molecular and cellular mechanisms driving SLE pathogenesis has been instrumental in developing targeted therapies to manage the disease and improve patient outcomes. In this review, we will delve into the intricate molecular and cellular processes underlying SLE and examine the key lessons learned from human therapies.

Keywords: Systemic Lupus Erythematosus (SLE); Type I interferon response; Transmembrane Activator and CAML Interactor (TACI); B cell Activating Factor (BAFF)

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which the body's dysregulated immune system mistakenly attacks healthy tissue in many parts of the body, resulting in inflammation and damage to multiple organs including the kidney as in Lupus Nephritis (LN) [1].

Perhaps one of the most important breakthrough findings in SLE etiology was the discovery in 1948 by researchers at the Mayo Clinic of the Lupus Erythematosus (LE) cell, which were described as white blood cells containing the nucleus of another cell that was pushing against the white blood cell proper nucleus [2]. The invading nucleus was coated with an antibody (now known as anti-nuclear antibody), that allowed it to be ingested by a phagocytic or scavenger cell. This discovery led to one of the first diagnostic tests as an anti-nuclear antibody for lupus since LE cells are found in approximately 60% of all people diagnosed with lupus [3].

The goal of SLE therapy is to control the symptoms and prevent organ damage. The treatment approach for SLE typically involves a combination of medications [Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or naproxen help relieve mild joint pain, inflammation and fever associated with SLE. Corticosteroids such as prednisone, are often prescribed at high doses for SLE flare-ups to reduce inflammation. Steroids are usually used for short periods due to potential long-term side effects. Antimalarial drugs like hydroxychloroquine (Plaquenil) help control skin rashes, joint inflammation and fatigue and may have a protective effect on organs like the kidneys. For more severe cases of SLE, immunosuppressive medications may be used: Methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide. These medications suppress the immune system to reduce inflammation and prevent organ damage. Most drugs approved for other diseases are used for SLE "off-label", except that hydroxychloroquine was approved by the FDA for lupus in 1955 [5].

Due to the poor therapeutic efficacy and prominent adverse reactions after long-term use of glucocorticoid combined immunosuppressant's, the development of targeted drug use for SLE has been in great need. It's important to note that SLE is a complex condition with multi-organ manifestation and the cellular and molecular mechanisms underlying SLE are not fully understood and are extremely complex. Since the FDA approval of hydroxychloroquine, for the next 56 years, no other drugs were approved for SLE till belimumab (Benlysta, anti- BAFF) was approved by the FDA in 2011 [6]. More recently in 2021, anifrolumab (Saphnelo) (anti-type I interferon) was approved for SLE. Voclosporin (Lupkynis, calcineurin inhibitor) and belimumab (Benlysta) were approved for lupus nephritis (SLE with renal manifestation) [7].

Research undertaken in various murine models shed light on the disease mechanism of SLE leading to potential therapies. On the other hand, given the differences of human and murine immune systems and SLE patient heterogeneity, an important aspect of searching for cure for SLE resides in deeper understanding of human disease data. In addition, analysis of recent clinical trial results provides better understanding of human SLE disease mechanisms and insights in better patient treatment.

Literature of Review

Genome-wide association studies discovered risk gene alleles

Rate of SLE varies between countries from 20 to 70 per 100,000 [1]. SLE is presumably caused by a genetic susceptibility coupled with an environmental trigger which results in defects in the immune system. SLE is a heterogeneous autoimmune disease with elevated prevalence in women about nine times more often than men [8]. It is also more prevalent in individuals of Asian, African and Hispanic ancestry. Systemic Lupus Erythematosus (SLE), a worldwide autoimmune disease with high heritability, shows differences in prevalence, severity and age of onset among different ancestral groups with estimates of its heritability ranging from 43% to 66% [9,10].

Genetic factors play a crucial role in determining an individual's susceptibility to SLE, even though the cause is not linked to a single gene. More than 90 loci have been shown to be associated with SLE through Genome-Wide Association Studies (GWAS) mostly in European descendants [11]. Variations in genes encoding immune-related molecules, including MHC/HLA alleles, cytokines and complement components, have been shown to be associated with SLE. These genetic variants can have negative Impacts on immune activation and re[illegible] leading to a breakdown of self-tolerance and the de[illegible]opmen of autoimmune diseases.

Recent study in China identified 38 unique lo[illegible]12]. Som[illegible]sk alleles reported from studies on European po[illegible]ations, su[illegible]as those in or near PTPN22, NCF2, SH2B3 [illegible] TNFSF13B, absent in East Asian populations[illegible]13] while a [illegible]ense variant in TYK2 kinase is specific for [illegible]ropean-sp[illegible]ic disease association [14-16]. High level fu[illegible]al annotati[illegible]f these SLE associated loci implicated hematolo[illegible] cells, parti[illegible]arly B and T lymphocytes, cytokine signaling and o[illegible] imm[illegible]ne system pathways. Interestingly, the[illegible]ele in th[illegible]e encoding BAFF is completely ab[illegible]t in C[illegible]ese populations and a missense variant in the [illegible]ne en[illegible]ding [illegible]CI (TNFRSF13B) was found to be specifically [illegible]sso[illegible]ted wit[illegible]SLE in East Asians [12,13]. [illegible]triguing [illegible] these [illegible]erences in genetic backg[illegible]nd mig[illegible]serve as [illegible] indicators of targeted the[illegible]es for SLE.

[illegible]e expre[illegible]evealed patient hetero-gene[illegible]immune dysregulation

In SLE, [illegible] immune system loses its ability to differentiate between self [illegible] foreign antigens, resulting in the production of auto-antibodies [illegible]st nuclear antigens like double-stranded DNA, histones and ribonucleoproteins. B cells are central players in the production of autoantibodies. Aberrant activation and survival of autoreactive B cells, as well as defective clearance mechanisms for apoptotic debris, contribute to the accumulation of immune complexes and sustained inflammation.

Peripheral blood gene expression analyses have shown the heterogeneity of the patient population [17,18]. Studies have shown that patients appear to have a conserved gene signature over time. Even in patients at quiescent phase, clear immune dysregulation persists. One recent study done in longitudinal clinical and transcriptional profil[illegible]g of patients with systemic lupus reveals molecular correla[illegible]of disease activity and progression by clinical and gene trans[illegible]tional profiling of 158 lupus patients up to a period of 4 y[illegible] Neutrophil-related signatures are associated with p[illegible]gression t[illegible]ctive nephritis. Molecular correlates of disease[illegible]ctivity strati[illegible]atients into seven major groups. Clustering [illegible]he inter-indiv[illegible]l Systemic Lupus Erythematosus Disease Activ[illegible]Index (SLE[illegible]) correlation matrix identified seven [illegible]groups[illegible]ch displaying a specific combination[illegible]ive im[illegible]e signatures correlating with the SLEDAI, includ[illegible]g eryth[illegible]poies[illegible] IFN response, myeloid lineage/neutrophils[illegible]plasm[illegible]blasts[illegible]d lymphoid lineage. A preval[illegible] IFN signat[illegible]d plasma[illegible]st signature as the most robust b[illegible]ker. A gr[illegible]l enrich[illegible]nt of neutrophil transcripts during p[illegible]ion to acti[illegible]hritis and distinct signatures in response to tre[illegible]nt in different nephritis subclasses were also obs[illegible]

Recent developments in single cell RNA sequencing (RNAseq) gav[illegible]more granularity of dysregulated immune p[illegible]ways. SLE [illegible]ses exhibited differences in both the co[illegible]sition a[illegible] state of PBMCs. Analysis of lymphocyte compo[illegible]vealed a reduction in naïve $CD4^+$ T cells and an [illegible]crease in repertoire restricted $GZMH^+CD8^+$ T cells. Analysis of t[illegible]scriptomic profiles across eight cell types revealed that cla[illegible]monocytes expressed the highest levels of both pan-cell ty[illegible] and myeloid-specific type 1 Interferon Stimulated Genes ([illegible]s). The expression of ISGs in monocytes was inversely [illegible]orrelated with naïve $CD4^+$ T cell abundance.

Lessons learned from human therapies

According to clinicaltrial.gov, the SLE drug development landscape is booming with over 40 drugs in the clinic. The LN development landscape also has 13 drugs in active development toward US/EU approval, with four active phase III trials anticipated to complete dosing by 2027. The current research and development strategies being pursued are diverse including many novel mechanisms of action. We will focus on a few major clinical breakthrough treatments in connection with related findings from research, in particular large scale genetic studies discussed above.

B cell targeting therapy: BAFF, TACI: Since B-cells play a significant role in the pathogenesis of SLE, these molecules like BAFF and TACI, are considered a prime target for therapeutic benefit [19,20]. BAFF (TNFSF13B) and its receptors, one of which is TACI (Transmembrane Activator and CAML Interactor, TNFRSF13B), play essential roles in B cell survival and differentiation. Belimumab (Benlysta), a drug that is currently approved for SLE and LN, causes inhibition of B-cell survival factors BAFF [21].

An important feature about BAFF and TACI shown previously in genetic studies is that SLE risk allele in the gene encoding BAFF is completely absent in Chinese populations and a missense variant in the gene encoding TACI (TNFRSF13B) was found to be specifically associated with SLE in East Asians [12]. A

natural question to ask is whether these genetic differences would lead to differences in response to targeted drugs. Although Belimumab has shown huge success, other molecules that present similar MOA as belimumab, such as Anthera Pharmaceuticals' blisibimod, did not show significant improvements in the composite endpoint, SLE Responder Index (SRI), for patients with SLE [22]. Patient genetic background may very well play a significant role influencing on efficacy in different clinical trials.

Previously, atacicept (a TACI fusion protein by MERCK, binds to and neutralizes the activity of two B cell-signaling molecules, BAFF and APRIL, thereby suppressing the development and survival of plasma cells and mature B cells) treatment showed evidence of efficacy in SLE, particularly in HDA and serologically active patients [23]. Reductions in disease activity and severe flare were observed with Atacicept treatment, with an acceptable safety profile. Unfortunately, it was not pursued further by MERCK until recently out-licensed to Veera therapeutics, which again deprioritized its trial in SLE/LN recently.

Interestingly, Telitacicept (Tai'ai®), a TACI fusion protein similar to atacicept, received its first approval in China for the treatment of patients with active SLE [24]. In humans, TACI is expressed at very low levels in new-borns prior to exposure to pathogens [25]. TACI blockers might give better response to SLE in patients of Asian ancestry. In addition, the variant found in TNFRSF13B may be a useful prognostic genetic marker for the treatment efficacy of BAFF and TACI blockers. Multiple follow-up trials of telitacicept will further understand the mechanism of action and find predictive biomarkers for potential response to the drug [26].

Interferon blockade therapy: Type I interferon gene signature was indicated as one of most robust biomarkers by previous gene profiling studies in SLE patients. An estimate of 50%-70% of adult and pediatric SLE patients have an up-regulated IFN signature that correlates with disease activity and severity [27]. These cytokines are essential for antiviral responses but can also trigger autoimmune reactions when dysregulated *via* upregulation of pro-inflammatory genes.

Type I IFNs are a family of cytokines binding to a common receptor, IFN-α receptor (IFNAR) initiating immune responses to antiviral infection [28]. IFN-α is produced mostly by plasmacytoid Dendritic cells (pDCs) and less by myeloid DCs, monocytes and macrophages [29], genome wide association studies in SLE patients has demonstrated Single Nucleotide Polymorphisms (SNPs) in loci near IFN related genes [11].

Given the significance of type I IFN signaling in SLE pathogenesis, therapies targeting the IFN pathway have emerged as promising candidates. Anifrolumab, a monoclonal antibody that blocks the IFN receptor, has shown positive results in clinical trials and is approved by the FDA [30]. By inhibiting the IFN pathway, anifrolumab can potentially reduce inflammation and disease activity in SLE patients.

An alternative way of inhibiting inflammation is *via* type I interferon receptor associated kinases. While prior genetic studies indicated TYK2 allele with a European-specific disease association [14-16]. IFNAR is a transmembrane receptor consisting of IFNAR1 and IFNAR2 that interact with a group of kinases called Janus Activated Kinases (JAKs) in the cytoplasm. IFNAR1 constitutively associates with Tyrosine Kinase 2 (TYK2) whereas IFNAR2 associates with JAK1 [31,32]. These JAKs can then activate a group of transcription factors called Signal Transducer and Activator of Transcription (STAT). Binding of IFN-α/β to the IFNAR results in auto-phosphorylation and activation of the IFNAR-associated JAKs, which in turn phosphorylate and activate STATs. The phosphorylated STATs form heterodimers or homodimers that translocate to the nucleus to induce transcription of IFN Stimulated Genes (ISGs). Deucravacitinib (Sotyktu), a medication by BMS used for the treatment of moderate-to-severe plaque psoriasis, has demonstrated impressive efficacy in SLE/LN [33,34].

Targeting complement activation: Genetic analysis clearly indicates strong association with complement system components with the development of SLE: ITGAM, C1q and MBL [11]. The complement system is an integral part of the innate immune response, contributing to the clearance of immune complexes. Complement dysfunction results in impaired ability in clearing apoptotic cell debris that may stimulate autoantibody production in Systemic Lupus Erythematosus (SLE).

In SLE complement components, particularly C3 and C4, become dysregulated, leading to impaired immune complex clearance and increased inflammation [35,36]. This contributes to tissue damage and organ involvement, especially in the kidneys, known as lupus nephritis. In addition to the contribution of lymphocytes, deposition of Immune Complexes (ICs) and activation of the complement system are well-established processes involved in the pathogenesis of LN. In most tissue injury scenarios complement is activated through three well established major pathways: Classical, lectin and alternative, which merge into C3 and then C5 activation. C3 and C5. Both C3a and C5a are strong Chemoattractants for phagocytes which upon engagement discharge their stored proteases, Reactive Oxygen Species (ROS) and chemokines/ cytokines to intervene local tissue injury.

Anti-C5 monoclonal antibody Eculizumab/Soliris showed renal function improvements in SLE patients [37]. More recently, Avacopan, previously developed by Chemocentryx and approved for Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA)-associated vasculitis, is an orally administered small-molecule C5a Receptor (C5aR) antagonist that selectively blocks the effects of C5a through the C5aR, being tested in lupus [38].

Discussion

Diagnosis and treatment of SLE has great clinical challenges due to its complex pathogenesis involving a large array of genetic, molecular and cellular factors. Recent multi-omics technology development has enabled deeper understanding of the molecular and cellular mechanisms of SLE. Several experimental drugs have shown efficacy in patient trials. There are many lessons we can learn. Firstly, understanding patient heterogeneity may be the key to SLE treatment. For example, GWAS studies clearly showed that certain risk alleles (e.g., BAFF)

are present in one ethnic group but are absent in another ethnic group. This is likely linked to efficacy variability within and among trials in the patient population consisting of different ethnic groups. This should be considered in future clinical designs and specification of Intent-To-Treat (ITT) patient population. Secondly, targeted therapies in SLE have shown a lot of promise in improving current treatment. Potential combination therapy may further improve efficacy. Thirdly, advanced technology may translate to fast and precise diagnosis of SLE, where patient genetic signature will be included to assist rheumatologists to make treatment decisions.

Conclusion

Systemic Lupus Erythematosus (SLE) is a complex systemic autoimmune disease with complicated molecular and cellular mechanisms. Genetic studies reveal significant differences in SLE risk alleles among different patient populations. Gene expression analysis revealed patient heterogeneity in immune dysregulation which may be used to stratify patients for therapy. Through human therapies, valuable lessons have been learned about how to target specific components of the immune system to manage the disease effectively. However, more research is needed to develop personalized and safer therapies to improve the lives of SLE patients. Ongoing research, along with advancements in precision medicine, holds promise for brighter future in the management of SLE and other systemic autoimmune diseases.

Acknowledgements

Authors thanks for helpful discussions and inputs from colleagues and fellow scientists.

References

1. Danchenko N, Satia JA, A MS (2006) iology of systemic lupus erythe tosus: omparison of worldwide disease burden. Lup 15: 308 8.
2. Carr RI (1986) Lup ematos A handbook for phy tients, eir famil 2nd edition, Lupus F dation merica In 15
3. illips RH (2) Coping with Lupus: A practical guide to alleviating of systemic lupus erythematosus. th editi enguin G New York, USA, p: 24.
4. kis A, Kostopoulou M, Alunno A, Aringer M, Baje et al. (2019) 2019 update of the EULAR recomm tions for the management of systemic lupus erythemato Ann Rheum Dis 78: 736-745.
5. Vasudevan AR, Ginzler EM (2009) Established and novel treatments for lupus. J Musculoskelet Med 26: 291-296.
6. Vincent FB, Morand EF, Mackay F (2012) BAFF and innate immunity: New therapeutic targets for systemic lupus erythematosus. Immunol Cell Biol 90: 293-303.
7. US Food and Drug Administration (2021) Advancing health through innovation: New drug therapy approvals 2021.
8. Lisnevskaia L, Murphy G, Isenberg D (2014) Systemic lupus erythematosus. Lancet 384: 1878-1888.
9. Lawrence JS, Martins CL, Drake GL (1987) A family survey of lupus erythematosus. 1. tability. J Rheumatol 14: 913-921.
10. Wang J, Yang S, Chen JJ, Zhou SM, et al. (2007) Systemic lupus erythemato A ge epidemiology study of 695 patients from ina. Arch De tol Res 298: 485-491.
11. Kuo CF, Grainge MJ, Valdes AM, LC, Luo et al. (2015) Familial aggregati emic hematosus and coaggregation utoimm diseases in affected families. JAMA Intern M 175: 1 -15
12. W ng YF, Zhan , Zhang , Wang TU, et al. (2021) Id tion 8 novel oci for systemic lupus eryth tosus a heterogeneity between ancestral ps. Nat Commun 12: 772.
13. YF, Lau (2019) Genetic studies on systemic lupus erythemat in East Asia point to population differences disease susceptibility. Am J Med Genet C Semin Med net 181: 262-268.
14. aham DS Morris DL, Bhangale TR, Criswell LA, Syvänen A 011) Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. PLoS Genet 7: 1002341.
15. LH, Chang YK, Shek KW, Lau YL (2011) Lack of association of TYK2 gene polymorphisms in Chinese patients with systemic lupus erythematosus. J Rheumatol 38: 177-178.
16. Kyogoku C, Morinobu A, Nishimura K, Sugiyama D, Hashimoto H, et al. (2009) Lack of association between Tyrosine Kinase 2 (TYK2) gene polymorphisms and susceptibility to SLE in a Japanese population. Mod Rheumatol 19: 401-406.
17. Banchereau R, Hong S, Cantarel B, Baldwin N, Baisch J, et al. (2016) Personalized Immunomonitoring uncovers molecular networks that stratify lupus patients. Cell 165: 551-565.
18. Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, et al. (2008) A modular analysis framework for blood genomics studies: Application to systemic lupus erythematosus. Immunity 29: 150-164.
19. Perez RK, Gordon MG, Subramaniam M, Kim MC, Hartoularos GC, et al. (2022) Single-cell RNA-seq reveals cell type-specific molecular and genetic associations to lupus. Science 376: eabf1970.
20. Bossen C, Schneider P (2006) BAFF, APRIL and their receptors: Structure, function and signaling. Semin Immunol 18: 263-275.
21. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, et al. (2011) Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: A randomised, placebo-controlled, phase 3 trial. Lancet 377: 721-731.
22. Merrill JT, Shanahan WR, Scheinberg M, Kalunian KC, Wofsy D, et al. (2018) Phase III trial results with blisibimod, a

selective inhibitor of B-cell activating factor, in subjects with Systemic Lupus Erythematosus (SLE): Results from a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 77: 883-889.

23. Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA, et al. (2018) Efficacy and safety of atacicept in patients with systemic lupus erythematosus: Results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. Arthritis Rheumatol 70: 266-276.

24. Akkoyunlu M (2012) TACI expression is low both in human and mouse newborns. Scand J Immunol 75: 368.

25. Kanswal S, Katsenelson N, Selvapandiyan A, Bram RJ, Akkoyunlu M (2008) Deficient TACI expression on B lymphocytes of newborn mice leads to defective Ig secretion in response to BAFF or APRIL. J Immunol 181: 976-990.

26. Li F (2022) Multi-omics studies on the efficacy of telitacicept in Chinese SLE patients.

27. Wahadat MJ, Bodewes ILA, Maria NI, van Helden-Meeuwsen CG, van Dijk-Hummelman A, et al. (2018) Type I IFN signature in childhood-onset systemic lupus erythematosus: A conspiracy of DNA- and RNA-sensing receptors? Arthritis Res Ther 20: 4.

28. Isaacs A, Lindenmann J (1957) Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 147: 258-26

29. Cella M, Jarrossay D, Facchetti F, Alebardi Nakajima et al. (1999) Plasmacytoid monocytes mig te to infla d lymph nodes and produce large a nts of type interferon. Nat Med 5: 919-

30. Morand EF, Furie R, Tanaka Y, Ruce IN, Askanase AD, et al. (2020) Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 382: 211-221.

31. Velazquez L, Fellous M, St GR, Pellegrini S (1992) A protein tyrosine kinase in interferon alpha/beta signaling pathway. Cell 70: 313-322

32. Domanski P, Witte M, Kellum I, Rubin M, Hackett R, et al. (1995) Cloning and ex ession of a form of the beta subunit of the interfe alpha beta r tor that is required for signaling. J Biol C 270: 2160 21611.

33. Hoy SM (2022) D itinib: oval. Drugs 82: 1671-1679.

34. Morand E, Pik M, Me JT, v Vollenhoven R, Werth VP, et al. (2023) De ay tinib, a t osine kinase 2 inhibitor, in sy upus ematosu A phase II, randomized, doub nd, place ed trial. Arthritis Rheumatol 75: 242-2

35. tein A, an RV, Zack DJ (2021) A review of complement activ n in SLE. Curr Rheumatol Rep 23: 16.

Cook HT, to M (2006) Mechanisms of disease: The complemen ystem and the pathogenesis of systemic pus eryth atosus. Nat Clin Pract Rheumatol 2: 330-337.

37. Scia S, Radin M, Yazdany J, Tektonidou M, Cecchi I, et al. (2017) Expanding the therapeutic options for renal volvement in lupus: Eculizumab, available evidence. Rheumatol Int 37: 1249-1255.

3 Lee A (2022) Avacopan: First approval. Drugs 82: 79-85.