Review

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

Siriust Ling * and R. Andrea Fan *

Posted Date: 4 January 2024

doi: 10.20944/preprints202401.0359.v1

Keywords: Systemic Lupus Erythematosus (SLE); type I interferon response; TACI; BAFF

Review

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

Siriust Ling [1,*] and R. Andrea Fan [1,*]

[1] Kezar Life Sciences, Inc., South San Francisco, CA 94080, USA
* Correspondence: siriust.ling@gmail.com, afan@kezarbio.com

Abstract: A 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 essay, 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; TACI; BAFF

1. 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 LE cell (the lupus erythematosus cell), which were described as white blood cells contained the nucleus of another cell that was pushing against the white blood cell proper nucleus[2]. The invading nucleus was coated with 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 definitive tests as 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[4]. Nonsteroidal 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 dose 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 immunosuppressants, 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

 doi:10.20944/preprints202401.0359.v1

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 lights 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 mechanism and insights in better patient treatment.

2. Results

2.1. 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 regulation, leading to a breakdown of self-tolerance and the development of autoimmune diseases.

Recent study in China identified 38 unique loci [12]. Some risk alleles reported from studies on European populations, such as those in or near PTPN22, NCF2, SH2B3, and TNFSF13B, are absent in East Asian populations [13] while a missense variant in TYK2 kinase is specific for a European-specific disease association [14–16] High level functional annotation of these SLE associated loci implicated hematological cells, particularly B and T lymphocytes, cytokine signaling and other immune system pathways. Interestingly, the 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. It is intriguing how these differences in genetic background might serve as prognostic indicators of targeted therapies for SLE.

2.2. Gene expression analysis revealed patient heterogeneity in Immune dysregulation:

In SLE, the immune system loses its ability to differentiate between self and foreign antigens, resulting in the production of autoantibodies against 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 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 profiling of patients with systemic lupus reveals molecular correlates of disease activity and progression by clinical and gene transcriptional profiling of 158 lupus patients up to a period of 4 years [17]. Neutrophil-related signatures associate with progression

 doi:10.20944/preprints202401.0359.v1

to active nephritis. Molecular correlates of disease activity stratify patients into seven major groups. Clustering of the interindividual SLEDAI correlation matrix identified seven patient groups (PG1–7), each displaying a specific combination of five immune signatures correlating with the SLEDAI, including erythropoiesis, IFN response, myeloid lineage/neutrophils, plasmablasts, and lymphoid lineage. A prevalent IFN signature and plasmablast signature as the most robust biomarker. A gradual enrichment of neutrophil transcripts during progression to active nephritis and distinct signatures in response to treatment in different nephritis subclasses were also observed.

Recent developments in single cell RNA sequencing (scRNAseq) gave more granularity of dysregulated immune pathways. SLE cases exhibited differences in both the composition and state of PBMCs. Analysis of lymphocyte composition revealed a reduction in naïve CD4+T cells and an increase in repertoire restricted GZMH+CD8+T cells. Analysis of transcriptomic profiles across eight cell types revealed that classical monocytes ex-pressed the highest levels of both pan–cell type and myeloid-specific type 1 interferon–stimulated genes (ISGs). The expression of ISGs in monocytes was inversely correlated with naïve CD4+T cell abundance.

2.3. Lessons Learned from Human Therapies:

According to Clinicaltrial.gov, 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.

2.3.1. B cell targeting therapy: BAFF, TACI

Since B-cells play a significant role in the pathogenesis of SLE, these molecules like BAF and TACI, are considered a prime target for therapeutic benefit. BAFF (TNFSF13B) and its receptors, one of which is TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor, TNFRSF13B), play essential roles in B cell survival and differentiation. Belimumab (Benlysta), a drug that is currently approved for SLE and LN, cause inhibition of B-cell survival factors BAFF.

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 [19]. 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 [20]. 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 [21]. In human, TACI is expressed at very low levels in new-borns prior to exposure to pathogens [22]. TACI blockers might give better responses 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. Multiomics follow-up trial of Telitacicept will further understand the mechanism of action and finding predictive biomarkers for potential response to the drug [23].

 doi:10.20944/preprints202401.0359.v1

2.3.2. 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 [24]. 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) mediating immune responses to antiviral infection[25]. IFN-α is produced mostly by plasmacytoid dendritic cell (pDCs) and less by myeloid DCs, monocytes and macrophages [26,27], 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 approved by FDA. 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 [27,28]. 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 demonstrate impressive efficacy for SLE/LN. [29,30].

2.3.3. Target Complement Activation:

Genetic analysis clearly indicate the association of compliment system components with the development of SLE: ITGAM, C1q, MBL [11].The complement system, an integral part of the innate immune response, contributes 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 [31,32]. 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 (IC) 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 chemoattracts 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 [33]. More recently, Avacopan, previously 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 [34].

3. Conclusions

Systemic Lupus Erythematosus is a complex systemic autoimmune disease with complicated molecular and cellular mechanisms. Genetic studies reveal significant difference 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 a brighter future in the management of SLE and other systemic autoimmune diseases.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Danchenko N, Satia JA, Anthony MS (2006). "Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden". Lupus. 15 (5): 308-318.
2. Carr RI (1986). Lupus Erythematosus: A Handbook for Physicians, Patients, and Their Families (2nd ed.). Lupus Foundation of America Inc. p. 15.
3. Phillips RH (2012). Coping with Lupus: A Practical Guide to Alleviating the Challenges of Systemic Lupus Erythematosus (4th ed.). New York, NY: The Penguin Group. p. 24. ISBN 978-1-58333-445-4.
4. Fanouriakis A, Kostopoulou M, Alunno A, et al
5. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus
6. Annals of the Rheumatic Diseases 2019;78:736-745.
7. FDA. Advancing Health Through Innovation: New Drug Therapy Approvals 2021
8. Lisnevskaia L, Murphy G, Isenberg D (November 2014). "Systemic lupus erythematosus". The Lancet. 384 (9957): 1878-1888.
9. Lawrence, J. S., Martins, C. L. & Drake, G. L. A family survey of lupus-erythematosus .1. heritability. J. Rheumatol. 14, 913-921 (1987).
10. Wang, J. et al. Systemic lupus erythematosus: a genetic epidemiology study of 695 patients from China. Arch. Dermatol. Res. 298, 485-491 (2007).
11. Kuo, C. F. et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern. Med. 175, 1518-1526 (2015).
12. Wang, YF., Zhang, Y., Lin, Z. et al. Identification of 38 novel loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. Nat Commun 12, 772 (2021).
13. Wang, Y. F., Lau, Y. L. & Yang, W. Genetic studies on systemic lupus erythematosus in East Asia point to population differences in disease susceptibility. Am. J. Med. Genet. C Semin. Med. Genet
14. .Cunninghame Graham, D. S. et al. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. PLoS Genet. 7, e1002341 (2011).
15. Li, P., Chang, Y. K., Shek, K. W. & Lau, Y. L. Lack of association of TYK2 gene polymorphisms in Chinese patients with systemic lupus erythematosus. J. Rheumatol. 38, 177-178 (2011).
16. Kyogoku, C. et al. Lack of association between tyrosine kinase 2 (TYK2) gene polymorphisms and susceptibility to SLE in a Japanese population. Mod. Rheumatol. 19, 401-406 (2009).
17. Banchereau R, Hong S, Cantarel B, Baldwin N, Baisch J, Edens M, Cepika AM, Acs P, Turner J, Anguiano E, Vinod P, Kahn S, Obermoser G, Blankenship D, Wakeland E, Nassi L, Gotte A, Punaro M, Liu YJ, Banchereau J, Rossello-Urgell J, Wright T, Pascual V. Personalized Immunomonitoring Uncovers Molecular Networks that Stratify Lupus Patients. Cell. 2016 Apr 21;165(3):551-65
18. Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, Baldwin N, Stichweh D, Blankenship D, Li L, Munagala I, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. Immunity. 2008;29:150-164. [PMC free article] [PubMed] [Google Scholar]
19. Merrill JT, Shanahan WR, Scheinberg M, Kalunian KC, Wofsy D, Martin RS. 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. 2018 Jun;77(6):883-889.
20. Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA, Chang P, Isenberg D; ADDRESS II Investigators. 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. 2018 Feb;70(2):266-276
21. Akkoyunlu, M. TACI expression is low both in human and mouse newborns. Scand. J. Immunol. 75, 368 (2012).

22. Kanswal, S., Katsenelson, N., Selvapandiyan, A., Bram, R. J. & Akkoyunlu, M. 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 (2008).
23. Multi-omics Studies on the Efficacy of Telitacicept in Chinese SLE Patients https://classic.clinicaltrials.gov/ct2/show/NCT05666336
24. Wahadat M. J., Bodewes I. L. A., Maria N. I., van Helden-Meeuwsen C. G., van Dijk-Hummelman A., Steenwijk E. C., 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 (1), 4. 10.1186/s13075-017-1501-z
25. Isaacs A., Lindenmann J. (1957). Virus interference. I. The interferon. Proc. R. Soc. Lond. B Biol. Sci. 147 (927), 258-267. 10.1098/rspb.1957.0048
26. Cella M., Jarrossay D., Facchetti F., Alebardi O., Nakajima H., Lanzavecchia A., et al. (1999). Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nat. Med. 5 (8), 919-923. 10.1038/11360
27. Velazquez L., Fellous M., Stark G. R., Pellegrini S. (1992). A protein tyrosine kinase in the interferon alpha/beta signaling pathway. Cell 70 (2), 313-322.
28. Domanski P., Witte M., Kellum M., Rubinstein M., Hackett R., Pitha P., et al. (1995). Cloning and expression of a long form of the beta subunit of the interferon alpha beta receptor that is required for signaling. J. Biol. Chem. 270 (37), 21606-21611.
29. Hoy, Sheridan M. (2022). "Deucravacitinib: First Approval". Drugs. 82 (17): 1671-1679.
30. Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, Delev N, Shah V, Sharkey B, Wegman T, Catlett I, Banerjee S, Singhal S. Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol. 2023 Feb;75(2):242-252
31. Weinstein A, Alexander RV, Zack DJ. A Review of Complement Activation in SLE. Curr Rheumatol Rep. 2021 Feb 10;23(3):16.
32. Cook, H., Botto, M. Mechanisms of Disease: the complement system and the pathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2, 330–337 (2006).
33. Sciascia, S., Radin, M., Yazdany, J. et al. Expanding the therapeutic options for renal involvement in lupus: eculizumab, available evidence. Rheumatol Int 37, 1249–1255 (2017)
34. Lee A. Avacopan: First Approval. Drugs. 2022 Jan;82(1):79-85.