Just Autoimmunity? The Role of the Innate Immune Response in Lupus

Martin A. Rodriguez, MD, MACR and Ana M. Blasini, PhD

Abstract: Systemic lupus erythematosus is considered a prototype of human autoimmune disease based on the appearance of multiple autoantibodies, some of which can have a direct pathogenic effect on tissues. Most therapeutic modalities aim to check the enhanced humoral responses by targeting T and B cells with conventional or biologic drugs. However, in some cases, the clinical response is limited and frequently takes a high toll of toxicity in patients. The last 2 decades have brought up novel discoveries showing profound disturbances of innate immune cell function in systemic lupus erythematosus, including dysregulated NETosis, increased apoptosis, type 1 interferon, and granulopoiesis signatures that are grounded in basic cell biology abnormalities, including response to excessive oxidative stress, mitochondrial dysfunction, and upregulation of the cGAS-STING pathway. Whether the prominent autoimmunity component of lupus patients is sufficient to drive this chronic disease or follows a breakdown of innate immune homeostasis in response to the environmental factors triggering disease is the subject of this revision.

Key Words: SLE, autoimmunity, immune homeostasis, cGAS-STING pathway

(*J Clin Rheumatol* 2025;31: 71–77)

Systemic lupus erythematosus (SLE) is a chronic immune-mediated inflammatory condition with a worldwide distribution affecting predominantly young women. SLE is somewhat a clinical construct to group a phenotypically heterogeneous disease into an entity with common genetic, immunological, and clinical features. It is considered a prototype of human autoimmune disease, based upon the emergence of an ample array of autoantibodies, some of them capable of forming immune complexes (ICs) and activating the complement cascade to promote inflammation in target organs. The presence of some autoantibodies such as anti–double-stranded DNA and anti-Ro antibodies can correlate with damage in specific target organs, such as kidneys and skin, respectively.[1] Similarly, adaptive immune effectors including autoreactive $CD4^+$ T cells can be found in affected organs including renal tissue[2] and skin.[3] Dysregulated T cell responses due to abnormalities in signal transduction from the TCR-CD3 membrane complex receptor to DNA[4] as well as unchecked B cell responses[5] are key components in the immunopathogenesis of the disease. Decreased levels of serum fractions of the complement system such as C3 and C4, triggered by complement-fixing autoantibodies, are traditional markers of the active phase of the disease. Most current remission-inducing treatments seek amelioration of a hyperactive immune response by means of immunosuppressive agents such as cyclophosphamide, azathioprine, or mycophenolate mofetil (MMF), or by biologics including B cell–depleting monoclonal antibodies or inhibitors of B cell–activating factors such as BAFF/BLyS or blockers of CD40 ligand.[6] Frequently, patients with severe clinical activity require large doses of corticosteroids concurrent with immunosuppressive induction therapy, as well as maintenance with antimalarial and stable doses of immunosuppressive drugs.

SLE is a clinically heterogenous disease displaying diverse levels of severity, from cases with mild articular or cutaneous manifestations to those with severe, potentially fatal, multiorgan involvement. The clinical course may be unpredictable, with sudden flares after relatively long periods of remission to stable long periods of quiescency sometimes sustained with minimal drug treatment.[7] Disease flares may occur in response to viral infections, drugs, or sun exposure, among other known environmental factors.[8–12] Also, some lupus patients may evolve with subclinical inflammation and progressive organ damage despite minimal clinical manifestations.[7]

The recent awareness of the role of innate immune mechanisms in the pathogenesis of SLE has opened a new frontier in our understanding of this complex disease. For example, the discovery in 2003 of the interferon type 1 (IFN I)[13,14] and granulopoiesis signatures in SLE[14] set an important landmark. The production of IFN I largely by plasmacytoid dendritic cells (pDCs)[15] can occur after internalization of Fc receptors that have bound IC-containing lupus antibodies.[16] In addition, IC containing nucleic acids and ribonucleoproteins from lupus patients can activate neutrophils in an Fc R-dependent fashion.[17] These mechanisms bridge the innate and adaptive branches in their contribution to the pathogenesis of SLE. NETosis is a form of programmed cell death that occurs as a response of neutrophils when phagocytosis and killing of microbial agents is insufficient to control infection. It may also occur in response to drugs and ultraviolet light. Under these circumstances, they suffer decondensation of chromatin and emit large fibrillar structures to engulf infectious agents and to recruit further innate immune cells to the site of inflammation.[18] A subpopulation of low-density neutrophils with increased propensity to NETosis has been described in patients with SLE.[19,20] In response to signals at inflammation sites, particularly oxygen reactive species, this subpopulation undergoes increased NETOsis, fueling autoimmune responses by the exposure of potential autoantigens, including modified double-stranded DNA and histones, as well as molecules newly citrullinated by the enzyme peptidyl arginine deiminase. Also, LL37, a microbicidal protein expressed in these nets, forms complexes with DNA that stimulate proliferation of pcDC.[20] Histones derived from NETosis can promote capillary necrosis and damage podocytes, thus contributing to increased cardiovascular risk and renal disease of lupus patients.[20] In addition, IFN I can increase NETosis and neutrophil apoptosis closing a pathogenic vicious circle.[21] Phagocytosis of apoptotic debris and NET structures (efferocytosis) by macrophages and other nonprofessional phagocytic cells is a down-regulatory mechanism necessary to curb inflammation and restore immune homeostasis.[22,23] Once phagocytosis occurs resolution molecules,

From the Centro Nacional de Enfermedades Reumáticas, Caracas, Venezuela.
Martin A. Rodriguez, ORCID ID: 0000-0001-6949-9012
The study received funding from Centro Nacional de Enfermedades Reumáticas.
The authors declare no conflict of interest.
Correspondence: Martin A. Rodriguez, MD, MACR, Centro Nacional de Enfermedades Reumáticas, Hospital Universitario de Caracas, Ciudad Universitaria, Los Chaguaramos 1080, Caracas, Venezuela. E-mail: martinalbertove@yahoo.com.

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000002209

such as resolvins and lipoxin A4 are produced, and acts upon monocyte-macrophages to induce apoptosis and a mitigating M2 phenotype, respectively.[22,23] The latter subset secretes anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor β tuning down inflammation. In addition, efferocytosis increases the number of T regulatory cells (Tregs),[23] coupling innate and adaptive immune cells in a homeostatic loop. This down-regulatory mechanism is overwhelmed in SLE by a combination of increased apoptosis,[24] defective clearance of apoptotic debris,[25] and unregulated NETosis.[20] This new body of evidence now places innate immune responses on the front page of SLE immunopathogenesis.

Tolerance to autoantigens is a key protective mechanism, and its breakdown would carry catastrophic consequences for health preservation of the living organism. Loss of tolerance to tissue antigens is definitory of various organ-specific autoimmune diseases in which target organs are affected by the direct effect of autoantibodies and autoreactive T cell clones, such is clearly the case of autoimmune thyroiditis,[26] myasthenia gravis,[27] and bullous pemphigoid,[28] among others. However, despite their clinical utility as diagnostic biomarkers, the pathogenic contribution of most autoantibodies in SLE is not always that clear. Also, loss of tolerance as expressed by the appearance and persistence of autoantibodies can occur in the absence of autoimmune disease. In a cross-sectional study from the National Health and Nutrition Survey (NHANES) in the United States, 13% of the healthy population tested positive for antinuclear antibodies (ANAs).[29] In a Canadian study, 89% of ANA-positive asymptomatic subjects remained healthy after 2 years of follow-up.[30] Stable levels of autoantibodies were observed in a healthy population in Sweden.[31] Antithyroid antibodies[32] and antiphospholipid antibodies[33] can be observed in individuals remaining healthy after several years of follow-up. A proportion of healthy donors serving the US armed forces that tested positive for antinuclear and other autoantibodies evolved to SLE, whereas others remained free of autoimmune disease after several years of follow-up.[34] In addition, first-degree relatives of lupus patients may test positive for autoantibodies without ever developing an immune-mediated disease.[35,36] Thus, the presence of autoimmune serological biomarkers is not necessarily followed by clinical autoimmune disease suggesting that loss of tolerance per se may not be sufficient for disease occurrence. Clearly, loss of tolerance is patent in clinically affected patients with SLE, but whether this event triggers or accompanies the disease during its natural course can be open to discussion.

The preclinical state identified by loss of tolerance and pre-existing autoantibodies can switch abruptly to overt disease in some healthy individuals or also during the typical acute flares occurring after stable periods or remission in lupus patients. Known triggers such as sun exposure, viral infections, pregnancy, or drugs can activate innate immune cells and, through cytokine release, secondarily involve adaptive immune cell responses and expansion of dormant autoreactive clones. For example, IL-23 mainly produced by DCs and monocyte/macrophages (MOs) promote proliferation and expansion of Th17 cell subpopulations; IL-12 produced by DC, neutrophils, and MO contribute to the expansion of the Th1 subset; and BlyS produced by DC stimulates proliferation of B cells. Thus, as in any other inflammatory process, innate immune cells are also primarily involved in response to lupus-triggering environmental factors.

To prevent the expansion of autoreactive clones, several mechanisms must be in order, including central deletion in thymus and bone marrow, peripheral deletion, anergy, and inhibition by Tregs. Mutations of the *FoxP3* gene, affecting the function of the transcription factor driving the phenotype and competence of these cells, cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome,[37] and autoimmune disease quite distinct from the typical lupus clinical phenotype. The role of Treg cells in lupus is at least controversial, with contradictory results in studies assessing both their number and function.[38] So, a main regulatory mechanism preventing autoreactivity by potentially down-regulating autoreactive cell clones can be severely impaired without causing an SLE clinical phenotype. Furthermore, some patients with severe combined immunodeficiency and combined immunodeficiency disorders can present clinical manifestations mimicking systemic autoimmune diseases, including lupus, despite a severe malfunction of the adaptive immune system.[39]

Given the above arguments, several questions may be posed.

1. Is loss of tolerance the event initially triggering the disease?
2. Is autoimmunity the main mechanism leading to disease perpetuation?
3. Is it possible that autoimmune responses result from the expansion of autoreactive cell clones prompted by unregulated innate immune responses triggered by environmental factors?
4. Is it possible that a disrupted immune homeostasis and not autoimmunity be the defining pathogenic mechanism underlying lupus?

We have already discussed the appearance of autoantibodies in healthy people.[29–36] ANA-positive healthy individuals can also display B and T cell and cytokine alterations similar to those seen in lupus patients without developing a clinical disease.[40–42] Regarding the second question, it is evident that a continuous or recurrent inflammatory process in lupus is characterized by innate immune cell abnormalities, such as accelerated NETosis,[19,20] increased apoptosis of MO,[24] saturation of scavenger cells by an excess of apoptotic debris,[25] plasmacytoid DC expansion,[15] and IFN I signature.[13,14] Also, the environmental factors triggering lupus, typically viral infections,[8–12] noninfectious environmental factors,[12] and dysbiosis,[43] do so by inducing activation of innate immune cells in the first place.

CLUES FROM THE IMMUNOBIOLOGY OF LUPUS

The processes underlying a chronic inflammatory condition can ultimately be traced to abnormalities in the regulation of cell biology. In SLE, oxidative stress,[44,45] mitochondrial dysfunction,[46,47] accelerated apoptosis,[24] and altered autophagy, including defective autophagy of oxidized mitochondrial DNA in neutrophils from lupus patients,[48] have been observed (Fig. 1). These abnormalities combined lead to enhanced activation of the cyclic guanosine monophosphate-adenosine synthase (cGAS) stimulator of IFN genes (STING) pathway, the canonical biochemical signaling mechanism of innate immune cells in response to aberrant location of exogenous or endogenous nucleic acids in the cytosol (Fig. 2).[49] In response to oxidative stress mitochondria release DNA that leaks to the cytosol triggering, the cGAS-STING pathway leads to IFN I and proinflammatory gene activation.[50] The mechanism checking this pathway is degradation of c-GAS-STING by inflammophagy, the autophagy mechanism down-regulating inflammation, by which cGAS is ubiquitinated and STING disposed by autophagy after being coupled to p62 protein.[50,51] Interestingly, defects of mitochondrial autophagy in red blood cells related to enhanced clinical activity have been described in children with SLE.[52] The fact that ubiquitous viruses such as Epstein-Barr, cytomegalovirus, parvoviruses, and human endogenous retroviruses[9] are known triggers of SLE opens the unexplored possibility of a dysregulation of the c-GAS-STING pathway in response to exogenous nucleic acids entering the cytosol as a potential mechanism underlying the immunopathology of lupus at a more basic cell biology level. This may be further expanded by the effect of endogenous

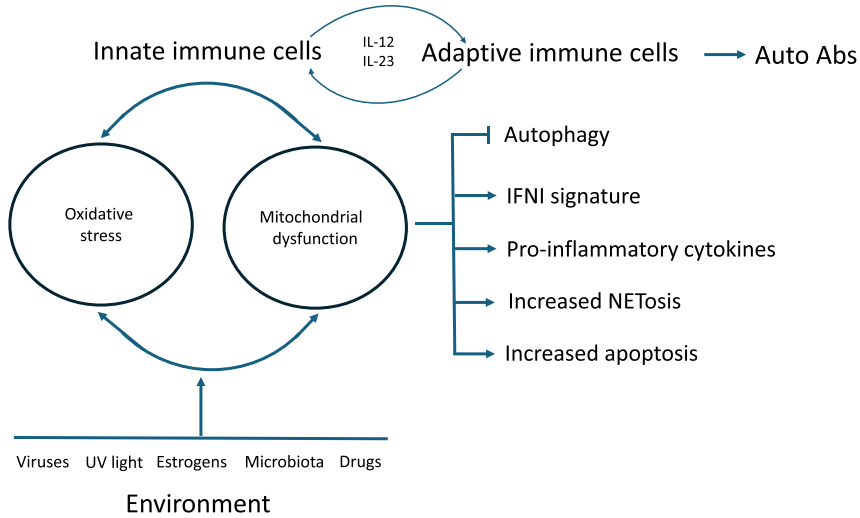

FIGURE 1. Environmental factors trigger a loop of oxidative stress and mitochondrial dysfunction affecting the critical regulatory mechanism of autophagy in innate immune cells, leading to unregulated NETosis, increased apoptosis, and IFN I and proinflammatory cytokine responses. Through enhanced production of IL-12 and IL-23 by innate immune cells, a humoral response ensues with expansion of dormant autoreactive T and B cell clones and production of autoantibodies.

nucleic acids leaked from mitochondria release DNA to the cytosol, as a result of mitochondrial exhaustion and damage due to oxidative stress (Fig. 2). Despite lack of experimental evidence, it would be tempting to speculate that an increased sensitivity of immune cells to trigger this cascade in response to environmental stimuli or lack of a compensatory down-regulatory control could lead to the unchecked c-GAS-STING pathway seen in SLE.[49,53] In one study, strong IFN I signature predicted disease severity in lupus after 5-year follow-up.[54] Defects in DNA degradation related to DNAse enzyme deficiencies have been described in SLE patients.[55,56] This deficit in DNA disposal may increase the pool of nucleic acids in the cytosol and further contribute to sustained activation of the c-GAS-STING pathway enhancing IFN I and cytokine production. Gain-of-function mutation of STING in humans causes STING-associated vasculopathy with onset in infancy, an inflammatory condition with interstitial lung disease and vasculopathy mimicking some manifestations observed in SLE.[57] The relevance of this metabolic pathway in the pathogenesis of the disease is illustrated by cases of lupus due to a gain-of-function mutation of the stimulator of interferon (*TMEM173*) gene leading to unchecked activation of STING.[58] Further, one case of human lupus has been described in a patient carrying a gain-of-function mutation of the

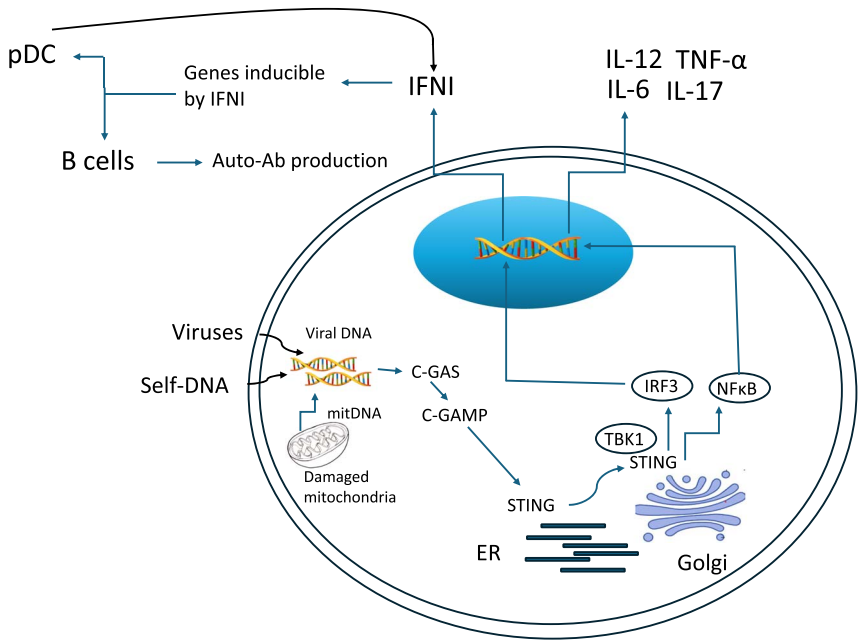

FIGURE 2. The cGAS-STING pathway is triggered by the presence of nucleic acids in the cytosol coming from viruses, extracellular DNA from nonapoptotic dead cells, and from exhausted mitochondria (mit-DNA). IFN I can contribute to expand plasmacytoid dendritic cells (in turn, the main source of IFN I), thus closing a self-sustaining loop. IFN I also contributes to enhance autoantibody (auto Ab) production by B cells.

toll-like receptor 7 (*TLR7*) gene, causing increased sensing to 2′3′ cGMP, the sensor of cytosolic nucleic acids.[59] The increasing number of gene mutations causing inflammatory conditions reminiscent of lupus underscores the relevance of these mechanisms as potential drivers of disease in SLE.

Lupus patients show a myriad of autoantibodies, circulating IC, and enhanced complement activation promoting inflammation in target organs. Whether these events happen primarily, together with, or because of the above-mentioned innate immune mechanisms can be open to discussion. As discussed above, autoantibodies may emerge in individuals that remain healthy, and, on the other hand, autoimmune diseases can be observed in patients with severe deficiency of the adaptive immune function. Nonetheless, abnormal humoral responses are a distinctive feature in SLE, suggesting an important participation of the adaptive immune response. Both branches of the immune system may be bridged once the disease commences. For example, IC containing immunoglobulin G from sera of lupus patients, but not from healthy individuals, can couple to Fc receptors in pDC and the complex internalized to stimulate *TLR-7*, further driving the IFN I response.[16] IFN I can both induce the transformation of MO into pDC and enhance immunoglobulin G production by B cells, setting up an amplifying loop of innate and adaptive immune responses (Fig. 2). The need for events involving primarily innate immune cells can explain the important role of viruses, noninfectious environmental factors, and other environmental factors in the triggering and induction of flares of the disease (Fig. 1).

INFLAMMATION AND IMMUNE HOMEOSTASIS IN LUPUS

Inflammation is the core pathological process occurring in SLE. Immune homeostasis can be defined as a balance of an alerted state to fight a foreign invader through a self-regulated inflammatory response and a repressed state to avoid targeting host antigens. In autoimmune and autoinflammatory diseases, this balance is broken. A homeostatic immune status dictates that inflammation must be commensurate with the needs for defense of the host. One of them is phagocytosis of apoptotic bodies by neutrophils and neutrophil NETS by MO restoring immune homeostasis.[53] In autoinflammatory diseases, several mutations hamper this down-regulatory control, as it has been observed in certain forms of monogenic lupus.[60,61] It is possible that in polygenic SLE, less conspicuous abnormalities affecting the delicate control of proinflammatory and anti-inflammatory responses by innate immune cells may also be playing a role.

Thus, we could propose the following sequence of events. Environmental factors may initially trigger the disease by involving innate immune cells and promoting inflammation. Consequently, adaptive immune responses follow, and autoimmune features may emerge in those individuals with genetic susceptibility for autoimmunity. If the response to the environmental agent is balanced in the axis inflammation versus repair (immune homeostasis), no chronic inflammation ensues, although autoantibodies may appear in those individuals with susceptibility genes for autoimmunity (Fig. 3). If immune homeostasis is disrupted, disease proceeds until immune homeostasis is reestablished, as may occur in rare cases spontaneously or in response to treatment (Fig. 3). Neutrophils further support the restoration of immune homeostasis by clearing potentially proinflammatory debris through efferocytosis.[22,23] Also, to the purpose of restoring immune homeostasis, low-dose IL-2 has been used in various clinical trials aiming to enhance Treg activity,[62] based on the known regulatory effect of this T cell subpopulation on both innate and adaptive immune cells.[63] However, the study of Treg numbers and function in SLE patients have yielded contradictory results. This has been confirmed in a recent meta-analysis that only showed a negative correlation with disease activity.[64]

WHAT TREATMENT OPTIONS INFORM US ABOUT THE PATHOGENESIS OF THE DISEASE?

Since autoimmunity has been the defining mechanism of SLE, most treatment modalities have been focused on checking adaptive immune responses by immunosuppressive therapy. Conventional immunosuppressive drugs or biologics have been the mainstay of treatment with significant but often variable degrees of success and unfortunately with a toll of sometimes serious adverse effects. Specific adaptive immune targeting modalities such as anti-CD20 and anti-BAFF (BlyS) monoclonal antibodies ameliorate disease activity but have not always been effective in controlling visceral disease.[6,65] The recent still experimental alternative, CAR-T cells targeting the CD19+ B cells, has shown impressive results after at least 1 year,[66] but the intense lymphodepletion regimes required previously to CAR-T cell infusion can have effects on other bone marrow cell lineages including myeloid lineage progenitor cells, as shown by prolonged neutropenia in some cases, making the relevant mechanism of action less clear. Unquestionably, cyclophosphamide and MMF are effective treatments of renal and other affected organs in lupus. Both drugs have an effect in fundamental cell biology processes. Cyclophosphamide is an alkylating agent inducing cell DNA damage and is used in cancer, prevention of transplant rejection, and autoimmune diseases. It is an approved treatment for severe visceral lupus, but its high potential for nonimmune cell damage limits its utility. MMF inhibits de novo purine

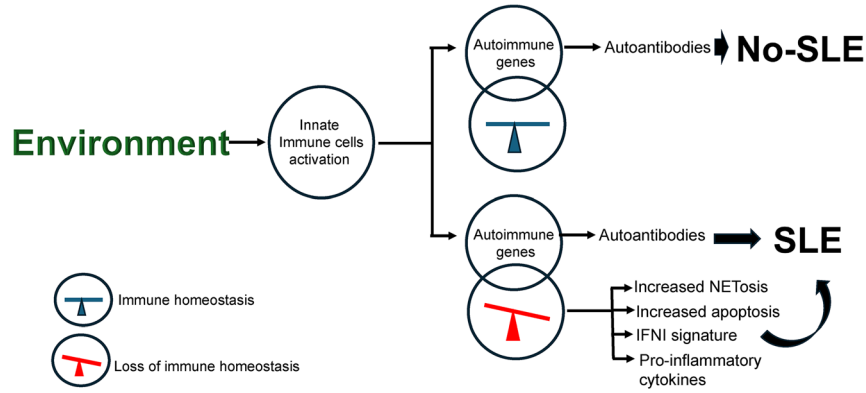

FIGURE 3. The integrity of immune homeostasis is necessary to avert the progression to disease in individuals exposed to environmental factors.

synthesis predominantly in proliferating T and B cells but also in monocytes,[67] DC,[67–69] and renal podocytes,[70] thus targeting a combined cell population. Hydroxychloroquine (HCQ) is a key drug in the treatment of lupus patients. This drug acts by increasing lysosomal pH and inhibiting lysosomal enzyme activity, thus diminishing autophagy of internalized molecules, internal traffic of cytosol molecules, and blocking activation of intracellular toll-like receptors.[71] HCQ binds to cytosolic nucleic acids and prevents activation of the c-GAS-STING cascade, the main pathway responsible for IFN I and proinflammatory cytokine production. It needs to be proven that these cell biology effects are the basis for the therapeutic efficacy of this drug. The long-term benefit of continuous treatment with HCQ in the prevention of flares,[72] prolonging survival[73] and even curtailing the progress of disease in patients with incomplete lupus,[74] with a drug lacking a potent immunosuppressive or anti-inflammatory effect, makes this hypothesis worth to consider.

CONCLUDING REMARKS

The basic tenet in SLE of autoimmunity as the main pathogenetic mechanism has driven the development drugs focused on ameliorating humoral responses to the detriment of developing alternative target options. Most current treatment modalities are of limited efficacy to curtail severe visceral disease and also add a high toxicity toll. The recent understanding of the critical role of abnormalities in key cell biology processes involving innate immune cell mechanisms opens a gate for the future development of new therapeutic modalities acting at earlier and perhaps more fundamental stages of the disease. For example, the blockade of the STING pathway increased survival[75] and ameliorated renal and lung disease[76] in Three-prime Repair EXonuclease 1 (TREX-1) *TREX*-mutant lupus mice models. Several small molecule compounds interfering at specific steps of the cGAS-STING are under rapid development.[73] The experience with HCQ, an old but conceptually rejuvenated drug, is an incentive for intervention at key cell biological processes that precede the breakdown of immune homeostasis. Clearly, this requires redirecting the focus from the classical view of SLE as solely an autoimmune disease to SLE as a chronic inflammatory disease with a significant autoimmune component. Future research should also provide biomarkers that allow the prediction for future disease in those individuals with preclinical serological markers of autoimmunity.

ACKNOWLEDGMENTS

We greatly appreciate the critical revision of this manuscript by George S. Tsokos, MD, Beth Israel Deaconess Medical Center, Boston, MA.

REFERENCES

1. Rekvig OP. The dsDNA, anti-dsDNA antibody, and lupus nephritis: what we agree on, what must be done, and what the best strategy forward could be. *Front Immunol*. 2019;10:1104. doi:10.3389/fimmu.2019.01104.
2. Abdirama D, Tesch S, Grießbach AS, et al. Nuclear antigen–reactive $CD4^+$ T cells expand in active systemic lupus erythematosus, produce effector cytokines, and invade the kidneys. *Kidney Int*. 2021;99:238–246.
3. Dunlap GS, Billi AC, Xing X, et al. Single-cell transcriptomics reveals distinct effector profiles of infiltrating T cells in lupus skin and kidney. *JCI Insight*. 2022;7:e156341. doi:10.1172/jci.insight.156341.
4. Moulton VR, Tsokos GC. T cell signaling abnormalities contribute to aberrant immune cell function and autoimmunity. *J Clin Invest*. 2015;125:220–227.
5. Dörner T, Giesecke C, Lipsky PE. Mechanisms of B cell autoimmunity in SLE. *Arthritis Res Ther*. 2011;13:243. doi:10.1186/ar3433.
6. Murphy G, Isenberg DA. Biologic therapies for systemic lupus erythematosus: where are we now? *Curr Opin Rheumatol*. 2020;32:597–608.
7. Lim LSH, Pullenayegum E, Feldman BM. From childhood to adulthood: disease activity trajectories in childhood-onset systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2018;70:750–757.
8. Jog NR, Young KA, Munroe ME, et al. Association of Epstein-Barr virus serological reactivation with transitioning to systemic lupus erythematosus in at-risk individuals. *Ann Rheum Dis*. 2019;78:1235–1241.
9. Quaglia M, Merlotti G, de Andrea M, et al. Viral infections and systemic lupus erythematosus: new players in an old story. *Viruses*. 2021;13:277. doi:10.3390/v13020277.
10. Parks CG, de Souza Espindola Santos A, Barbhaiya M, et al. Understanding the role of environmental factors in the development of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2017;31:306–320.
11. Sharma C, Bayry J. High risk of autoimmune diseases after COVID-19. *Nat Rev Rheumatol*. 2023;19:399–400.
12. Liu JL, Woo JMP, Parks CG, et al. Systemic lupus erythematosus risk: the role of environmental factors. *Rheum Dis Clin North Am*. 2022;48:827–843.
13. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci U S A*. 2003;100:2610–2615.
14. Bennett L, Palucka AK, Arce E, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med*. 2003;197:711–723.
15. Fitzgerald-Bocarsly P, Dai J, Singh S. Plasmacytoid dendritic cells and type I IFN: 50 years of convergent history. *Cytokine Growth Factor Rev*. 2008;19:3–19.
16. Bave U, Magnusson M, Eloranta ML, et al. Fc gamma RIIa is expressed on natural IFN-alpha-producing cells (plasmacytoid dendritic cells) and is required for the IFN-alpha production induced by apoptotic cells combined with lupus IgG. *J Immunol*. 2003;171:3296–3302.
17. Bonegio RG, Lin JD, Beaudette-Zlatanova B, et al. Lupus-associated immune complexes activate human neutrophils in an FcγRIIA-dependent but TLR-independent response. *J Immunol*. 2019;202:675–683.
18. Othman A, Sekheri M, Filep JG. Roles of neutrophil granule proteins in orchestrating inflammation and immunity. *FEBS J*. 2022;289:3932–3953.
19. Kaplan MJ. Neutrophils in the pathogenesis and manifestations of SLE. *Nat Rev Rheumatol*. 2011;7:691–699.
20. Wang M, Ishikawa T, Lai Y, et al. Diverse roles of NETosis in the pathogenesis of lupus. *Front Immunol*. 2022;13:895216. doi:10.3389/fimmu.2022.895216.
21. Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med*. 2011;3:73ra20. doi:10.1126/scitranslmed.3001201.
22. Lee M, Lee SY, Bae YS. Emerging roles of neutrophils in immune homeostasis. *BMB Rep*. 2022;55:473–480.
23. Doran AC, Yurdagul A Jr., Tabas I. Efferocytosis in health and disease. *Nat Rev Immunol*. 2020;20:254–267.
24. Denny MF, Chandaroy P, Killen PD, et al. Accelerated macrophage apoptosis induces autoantibody formation and organ damage in systemic lupus erythematosus. *J Immunol*. 2006;176:2095–2104.
25. Shao WH, Cohen PL. Disturbances of apoptotic cell clearance in systemic lupus erythematosus. *Arthritis Res Ther*. 2011;13:202. doi:10.1186/ar3206.
26. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. *Front Immunol*. 2017;8:521. doi:10.3389/fimmu.2017.00521.

27. Koneczny I, Herbst R. Myasthenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. *Cells*. 2019;8:671. doi.org/10.3390/cells8070671.
28. Moro F, Fania L, Sinagra JLM, et al. Bullous pemphigoid: trigger and predisposing factors. *Biomolecules*. 2020;10:1432. doi:10.3390/biom10101432.
29. Satoh M, Chan EKL, Ho LA, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. *Arthritis Rheum*. 2012;64:2319–2327.
30. Johnson SR, Alahmari H, Bonilla D, et al. Evaluation of progression from preclinical to systemic autoimmune rheumatic disease: novel use of the European Alliance of Associations for Rheumatology/American College of Rheumatology Systemic Lupus Erythematosus Classification Criteria as an outcome measure. *ACR Open Rheumatol*. 2024;6:871–877. doi:10.1002/acr2.11723.
31. Neiman M, Hellström C, Just D, et al. Individual and stable autoantibody repertoires in healthy individuals. *Autoimmunity*. 2019;52:1–11.
32. Kohno Y, Yamaguchi F, Saito K, et al. Anti-thyroid peroxidase antibodies in sera from healthy subjects and from patients with chronic thyroiditis: differences in the ability to inhibit thyroid peroxidase activities. *Clin Exp Immunol*. 1991;85:459–463.
33. Ceccarelli F, Natalucci F, Olivieri G, et al. Development of systemic autoimmune diseases in healthy subjects persistently positive for antiphospholipid antibodies: long-term follow-up study. *Biomolecules*. 2022;12:1088. doi:10.3390/biom12081088.
34. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*. 2003;349:1526–1533.
35. Penev B, Vasilev G, Todorova EI, et al. First-degree relatives of patients with systemic lupus erythematosus: autoreactivity but not autoimmunity? *Int J Rheum Dis*. 2023;13:907–916. doi:10.1111/1756-185X.14669.
36. Munroe ME, Young KA, Kamen DL, et al. Discerning risk of disease transition in relatives of systemic lupus erythematosus patients utilizing soluble mediators and clinical features. *Arthritis Rheumatol*. 2017;69:630–642.
37. Ben-Skowronek I. IPEX syndrome: genetics and treatment options. *Genes (Basel)*. 2021;12:323. doi:10.3390/genes12030323.
38. Ohl K, Tenbrock K. Regulatory T cells in systemic lupus erythematosus. *Eur J Immunol*. 2015;45:344–355.
39. Costagliola G, Cappelli S, Consolini R. Autoimmunity in primary immunodeficiency disorders: an updated review on pathogenic and clinical implications. *J Clin Med*. 2021;10:4729. doi:10.3390/jcm10204729.
40. Baglaenko Y, Chang NH, Johnson SR, et al. The presence of anti-nuclear antibodies alone is associated with changes in B cell activation and T follicular helper cells similar to those in systemic autoimmune rheumatic disease. *Arthritis Res Ther*. 2018;20:264.
41. Gupta R, Vanlieshout E, Manion K, et al. Altered balance of pro-inflammatory immune cells to T regulatory cells differentiates symptomatic from asymptomatic individuals with anti-nuclear antibodies. *Front Immunol*. 2022;13:886442. doi:10.3389/fimmu.2022.886442.
42. Slight-Webb S, Lu R, Ritterhouse LL, et al. Autoantibody-positive healthy individuals display unique immune profiles that may regulate autoimmunity. *Arthritis Rheumatol*. 2016;68:2492–2502.
43. Ma L, Morel L. Loss of gut barrier integrity in lupus. *Front Immunol*. 2022;13:919792. doi:10.3389/fimmu.2022.919792.
44. Quintero-Gonzalez DC, Muñoz-Urbano M, Vásquez G. Mitochondria as a key player in systemic lupus erythematosus. *Autoimmunity*. 2022;55:497–505.
45. Liu L, de Leeuw K, Arends S, et al. Biomarkers of oxidative stress in systemic lupus erythematosus patients with active nephritis. *Antioxidants (Basel)*. 2023;12:1627. doi:10.3390/antiox12081627.
46. Gergely P Jr., Grossman C, Niland B, et al. Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2002;46:175–190.
47. Halfon M, Tankeu AT, Ribi C. Mitochondrial dysfunction in systemic lupus erythematosus with a focus on lupus nephritis. *Int J Mol Sci*. 2024;25:6162. doi:10.3390/ijms25116162.
48. Xu Y, Shen J, Ran Z. Emerging views of mitophagy in immunity and autoimmune diseases. *Autophagy*. 2020;16:3–17.
49. Liu Y, Pu F. Updated roles of cGAS-STING signaling in autoimmune diseases. *Front Immunol*. 2023;14:1254915. doi:10.3389/fimmu.2023.1254915.
50. Kim J, Kim HS, Chung JH. Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. *Exp Mol Med*. 2023;55:510–519.
51. Chauhan S, Jena KK, Mehto S, et al. Innate immunity and inflammophagy: balancing the defence and immune homeostasis. *FEBS J*. 2022;289:4112–4131.
52. Kaplan MJ. Mitochondrial dysfunction in the erythroid compartment. *Nat Immunol*. 2021;22:1354–1355.
53. An J, Durcan L, Karr RM, et al. Expression of cyclic GMP-AMP synthase in patients with systemic lupus erythematosus. *Arthritis Rheumatol*. 2017;69:800–807.
54. Mai L, Asaduzzaman A, Noamani B, et al. The baseline interferon signature predicts disease severity over the subsequent 5 years in systemic lupus erythematosus. *Arthritis Res Ther*. 2021;23:29. doi:doi.org/10.1186/s13075-021-02414-0.
55. Meas R, Burak MJ, Sweasy JB. DNA repair and systemic lupus erythematosus. *DNA Repair (Amst)*. 2017;56:174–182.
56. Mireles-Canales MP, González-Chávez SA, Quiñonez-Flores CM, et al. DNA damage and deficiencies in the mechanisms of its repair: implications in the pathogenesis of systemic lupus erythematosus. *J Immunol Res*. 2018;2018:8214379.
57. Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med*. 2014;371:507–518.
58. Jeremiah N, Neven B, Gentili M, et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *J Clin Invest*. 2014;124:5516–5520.
59. Brown GJ, Cañete PF, Wang H, et al. *TLR7* gain-of-function genetic variation causes human lupus. *Nature*. 2022;605:349–356.
60. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. *Nat Rev Immunol*. 2015;15:429–440.
61. Alperin JM, Ortiz-Fernandez L, Sawalha AH. Monogenic lupus: a developing paradigm of disease. *Front Immunol*. 2018;9:2496. doi:10.3389/fimmu.2018.02496.
62. Tsokos GC. The immunology of systemic lupus erythematosus. *Nat Immunol*. 2024;25:1332–1343.
63. Grover P, Goel PN, Greene MI. Regulatory T cells: regulation of identity and function. *Front Immunol*. 2021;12:750542. doi:10.3389/fimmu.2021.750542.
64. Li W, Deng C, Yang H, et al. The regulatory T cell in active systemic lupus erythematosus patients: a systemic review and meta-analysis. *Front Immunol*. 2019;10:159. doi:10.3389/fimmu.2019.00159.
65. Lee DSW, Rojas OL, Gommerman JL. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nat Rev Drug Discov*. 2021;20:179–199.
66. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-cell therapy in autoimmune disease—a case series with follow-up. *N Engl J Med*. 2024;390:687–700.
67. Allison AC, Eugui EM. Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. *Transplantation*. 2005;80:S181–S190.

68. Čolič M, Stojič-Vukanič Z, Pavlovič B, et al. Mycophenolate mofetil inhibits differentiation, maturation and allostimulatory function of human monocyte-derived dendritic cells. *Clin Exp Immunol*. 2003;134:63–69.
69. Shigesaka M, Ito T, Inaba M, et al. Mycophenolic acid, the active form of mycophenolate mofetil, interferes with IRF7 nuclear translocation and type I IFN production by plasmacytoid dendritic cells. *Arthritis Res Ther*. 2020; 22:264. doi:10.1186/s13075-020-02356-z.
70. Hackl A, Nüsken E, Voggel J, et al. The effect of mycophenolate mofetil on podocytes in nephrotoxic serum nephritis. *Sci Rep*. 2023;13:14167. doi:10.1038/s41598-023-41222-1.
71. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. 2020;16:155–166.
72. Almeida-Brasil CC, Hanly JG, Urowitz M, et al. Flares after hydroxychloroquine reduction or discontinuation: results from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. *Ann Rheum Dis*. 2022;81:370–378.
73. Dima A, Jurcut C, Chasset F, et al. Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. *Ther Adv Musculoskelet Dis*. 2022;14:1759720X211073001. doi:10.1177/1759720X211073001.
74. Lambers WM, Westra J, Bootsma H, et al. Hydroxychloroquine suppresses interferon-inducible genes and B cell activating factor in patients with incomplete and new-onset systemic lupus erythematosus. *J Rheumatol*. 2021;48:847–851.
75. Vejvisithsakul PP, Thumarat C, Leelahavanichkul A, et al. Elucidating the function of STING in systemic lupus erythematosus through the STING Goldenticket mouse mutant. *Sci Rep*. 2024;14:13968. doi:10.1038/s41598-024-64495-6.
76. Xiao N, Wei J, Xu S, et al. cGAS activation causes lupus-like autoimmune disorders in a TREX1 mutant mouse model. *J Autoimmun*. 2019;100:84–94.