

Download PDF Download PDF Review Article Open access Published: 17 March 2025 Systemic lupus erythematosus: updated insights on the pathogenesis, diagnosis, prevention and therapeutics Xiaofeng Dai, Yuting Fan & Xing Zhao Signal Transduction and Targeted Therapy volume 10, Article number: 102 (2025) Cite this article Save article View saved research 195k Accesses 268 Citations 91 Altmetric Metricsdetails Abstract Systemic lupus erythematosus (SLE) is a chronic inflammatory illness with heterogeneous clinical manifestations covering multiple organs. Stimulated Th cells activate B cells and contribute to their differentiation through clusters of differentiation 40 ligand (CD40L)/CD40 interactions.³² Activated B cells move to germinal centers (GCs) with the help of Tfh cells and follicular dendritic cells (DCs), where B cells generating antibodies with high antigen affinity are expanded and differentiate into the memory B cells (MBC) and antibody-producing PCs.³³ Over-production of immunoactivating materials Interferons (IFNs) are cytokines with pleiotropic roles in immune regulation that can be categorized into type I, II, and III based on sequence homology.³⁴ Type I IFNs represent the largest IFN family comprised of IFN α , IFN β , IFN γ , IFN δ , and IFN ϵ ; the type II family includes solely IFN γ ; and the type III family contains IFN λ 1, IFN λ 2, IFN λ 3, and IFN λ 4.³⁵ Out of the three families of IFNs, type I IFNs play an immunomodulatory role that bridges the gap between the innate and adaptive immune systems.³⁵ That is, the expression of type I IFNs is activated on the trigger of nucleic acids via intracellular pathways such as Toll-like receptor (TLR)-mediated signaling; the binding of type I IFNs to their receptors activates the intracellular signaling cascade involving the Janus kinase-signal transducer and activator of transcription (JAK/STAT) axis that leads to stimulated effectors of the innate and adaptive systems.^{35,36,37} There has been a well-established positive association between type I IFNs and SLE. Specifically, the blood levels of type I IFNs were documented to be elevated in approximately 50% of SLE patients.³⁸ An even greater percentage of SLE patients were estimated to carry over-represented expression of genes involved in type I IFN-mediated signaling in their peripheral blood cells.^{39,40} Type I IFNs are generated in response to, primarily, the activation of nucleic acid-binding pattern recognition receptors such as the endosomal TLR3/4/7/9, the cytosolic sensor cyclic guanosine monophosphate-adenosine monophosphate (cGMP-AMP) synthase (cGAS), and the ribonucleic acid (RNA)-sensor retinoic acid-inducible gene (RIG) I like receptors (RLRs)-mitochondrial antiviral signaling protein (MAVS).⁴¹ These nucleic-acid sensing pathways are chronically over-activated in many SLE patients, with the pathogenesis roles of TLR7 in SLE being well-established.⁴² For instance, over-activation of the cGAS-stimulator of IFN genes (STING) pathway has been shown to be crucial in autoimmunity and SLE pathogenesis.^{40,43} In addition, events altering nucleic acid metabolism may also trigger type I IFNs production, where the essential roles of cytosolic nucleic acid sensors played in SLE have been well characterized.^{44,45} For instance, ultraviolet (UV) light exposure has been shown capable of enhancing type I IFNs response both locally and systemically, with the evidence being obtained from both the animal model and from the clinics⁴⁶ (Fig. Asian have a lower regional risk of developing SLE than people from the United States,^{21,22} but the prevalence of SLE among people carrying the Chinese background has been reported to be increasing.²³ Such ethnic differences among SLE patients may be explained by their different socioeconomic backgrounds, distinct perceptions on the condition, varied risks of getting infection or developing comorbidities especially cerebrovascular

diseases, imbalanced availability of the medical resources, and non-uniform adherence to the therapeutics.^{3,16,17,24} SLE pathogenesis by mechanisms-of-action SLE is characteristic of increased presentation of autoantibodies such as ANA, anti-Sm, anti-double-stranded DNA (anti-dsDNA) antibody, antiphospholipid (aPL) antibodies, and anti- β 2-glycoprotein (a β 2GPI) antibodies,¹ which even occur years prior to the clinical onset of SLE.²⁵ Being the primary effectors of SLE inflammation and associated damage,²⁶ autoantibodies form immune complexes (ICs) and deposit on multiple organs such as kidney, skin and central nervous system to induce local inflammation.^{26,27} Antibodies are produced by plasma cells (PCs) and plasmablasts, the terminally differentiated B cells.²⁸ As the precursors of PCs and important antigen-presenting cells (APCs),^{29,30} B cells lose tolerance to autoantigens³¹ and may present them to T cells in SLE patients followed by the activation of Th cells.

Adaptive immunity

Rheumatic diseases

Autoimmune Mechanisms in Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE), canonically defined as an autoimmune disorder, can be considered as a chronic inflammatory illness with clinical manifestations encompassing various organs such as the blood vessels, brain, lungs, skin, kidneys and joints due to polymorphic biological alterations.¹ It affects approximately 3.4 million people worldwide, with 400,000 individuals being newly diagnosed each year.^{2,3} It most commonly occurs among women between puberty and menopause,⁴ and individuals of the African origin have a higher risk of developing SLE.^{5,6,7} According to a 2023 global epidemiology study of SLE, Poland, the United States, Barbados, and China showed the highest SLE incidence.² Though still with an unclear disease of origin, the chance of developing SLE is believed to be associated with genetic factors, epigenetic factors, environmental triggers, and hormonal factors.⁸ SLE can be diagnosed from the perspectives of disease onset and disease activity.

The neoclassical period

is characterized by 'SLE manifestations, therapeutics, and identification of the inductive role of some medications on SLE', with representative events being 'documentation of SLE with illustrations as a butterfly rash by Ferdinand Hebra', 'identification of the photosensitive nature of SLE by Jonathon Hutchison', 'definition of the two forms of SLE, i.e., discoid and disseminated SLE by Mariz Kaposi', 'use of quinine by Payne and use of adrenocorticotrophic hormone (ACTH) and cortisone by Philip S. Hency', 'use of hydrocortisone by Sulzberger and Witten', and 'identification of the inductive role of sulfonamides on SLE'. Following the introduction of some basic knowledge of SLE including the history and epidemiology, this review characterized three key determinants of SLE pathogenesis by their mechanisms-of-action, i.e., over-activated immune response, skewed cytokine microenvironment homeostasis, impaired debris clearance machinery; summarized current understandings on SLE diagnosis by disease onset, activity and comorbidity; introduced risk factors predisposing SLE at the genetic, epigenetic, hormonal and intrinsic levels; and classified current SLE preventive strategies and therapeutics by the identified working mechanisms. In summary, we proposed three mechanisms with determinant roles on SLE initiation and progression, i.e., attenuating the immune system, restoring the cytokine microenvironment homeostasis, and rescuing the impaired debris clearance machinery; and provided updated insights on current understandings of SLE regarding its pathogenesis, diagnosis, prevention and therapeutics, which may open an innovative avenue in the fields of SLE management.

Complexities regarding SLE therapeutics

render it essential

and urgent to identify the mechanisms-of-action and pivotal signaling axis driving SLE pathogenesis, and to establish innovative SLE-targeting approaches with desirable therapeutic outcome and safety. Fig. 1 Fig. 1). 1). 1).