

MINI REVIEW

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Monogenic lupus – from gene to targeted therapy

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Abstract

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by loss of tolerance to nuclear antigens. The formation of autoantibodies and the deposition of immune complexes trigger inflammatory tissue damage that can affect any part of the body. In most cases, SLE is a complex disease involving multiple genetic and environmental factors. Despite advances in the treatment of SLE, there is currently no cure for SLE and patients are treated with immunosuppressive drugs with significant side effects. The elucidation of rare monogenic forms of SLE has provided invaluable insights into the molecular mechanisms underlying systemic autoimmunity. Harnessing this knowledge will facilitate the development of more refined and reliable biomarker profiles for diagnosis, therapeutic monitoring, and outcome prediction, and guide the development of novel targeted therapies not only for monogenic lupus, but also for complex SLE.

Keywords SLE, Systemic lupus erythematosus, Cutaneous lupus erythematosus, Nucleic acid immunity, Nucleic acid metabolism, Nucleic acid sensing, Autoimmunity, Genetics, Pathogenesis, Targeted therapy, Type I interferon

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a multifactorial etiology in which the interaction of multiple genes with environmental factors determines disease susceptibility [1]. The clinical spectrum of SLE is very broad, ranging from mild disease, which may be limited to skin and joint involvement, to life-threatening manifestations with renal impairment, severe cytopenias, central nervous system disease, and thromboembolic events. However, these clinically heterogeneous diseases converge on a common phenotype characterized by chronic overproduction of type I interferon (IFN), indicating that inappropriate

activation of antiviral immunity is key to SLE pathogenesis [2]. Type I IFNs (IFN- α , IFN- β), which are induced by the activation of nucleic acid-sensing receptors of the innate immune system, act in an autocrine and paracrine manner by binding to the interferon- α receptor (IFNAR), a cell surface receptor composed of two subunits, IFNAR1 and IFNAR2 (Fig. 1) [3]. Type I IFN signaling activates the Janus kinase (JAK)—signal transducer and activator of transcription (STAT) pathway, leading to transcription of the IFN genes and of IFN-stimulated genes (ISGs). As a result of the ensuing transcriptional program, type I IFNs exert potent immunostimulatory effects promoting inflammation, the loss of B cell self-tolerance, and the formation of autoantibodies, often directed against nuclear self-antigens, including nucleic acids [2]. These antinuclear antibodies form complexes with antigens released from dying cells. Deposition of immune complexes in the capillary bed, followed by local complement and leukocyte activation, leads to destructive tissue inflammation [4]. In addition, these immune complexes provide an important stimulus for increased

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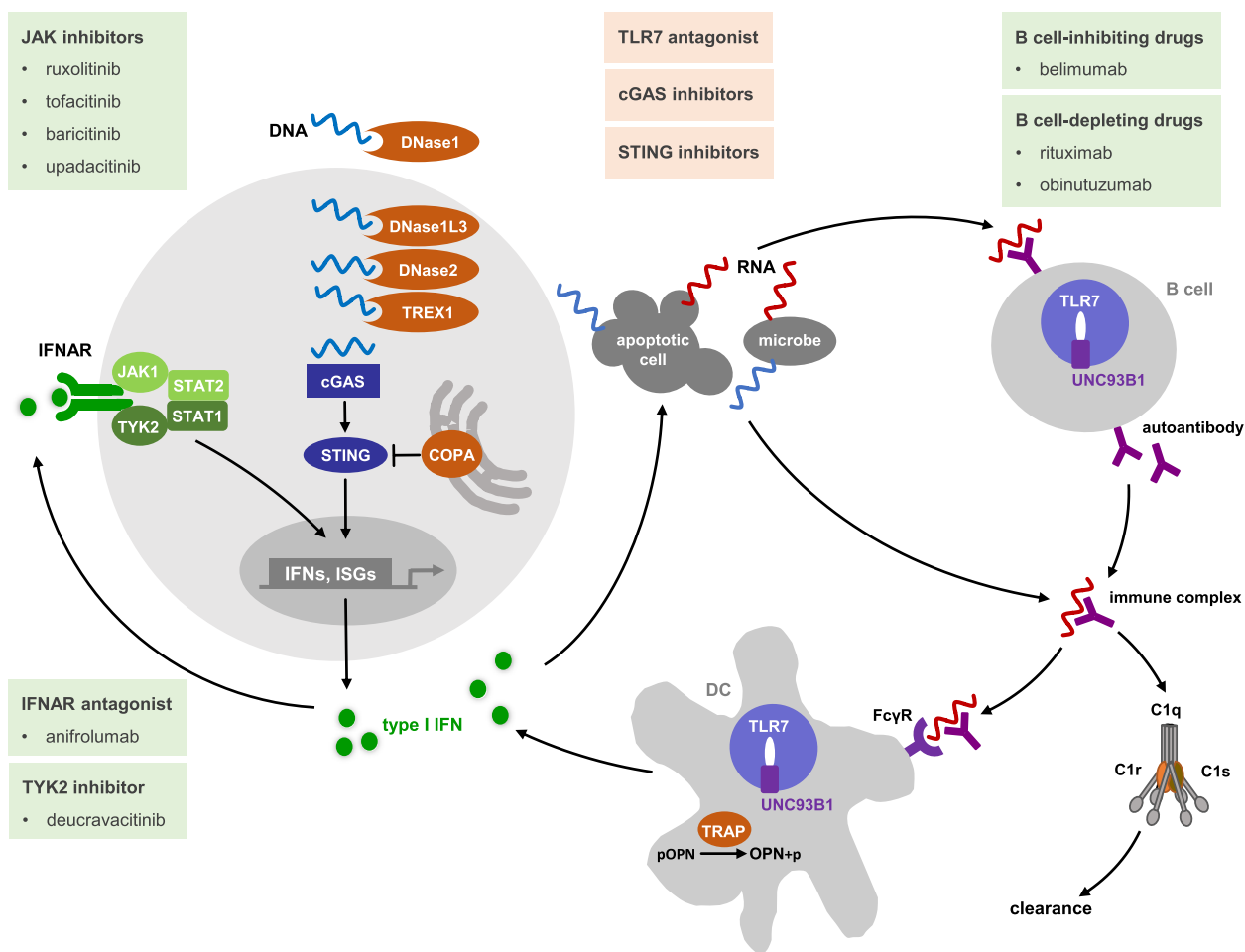


Fig. 1 Pathogenetic principles of monogenic forms of lupus and therapeutic targets. Nucleases clear the extracellular space (DNase I) or the cytosol (DNase1L3, DNase2, TREX1) of DNA derived from pathogens or damaged cells or emanating from various metabolic processes to prevent aberrant immune recognition of self-DNA by the DNA sensor cGAS. Ligand binding of cGAS triggers activation of the STING signaling adaptor, resulting in transcriptional induction of type I IFN and IFN-stimulated genes (ISGs). Secreted type I IFN binds to the IFN receptor (IFNAR) which induces JAK/STAT signaling resulting in activation of IFN and ISG transcription. STING trafficking via COPI vesicles to the endoplasmic reticulum or into the autophagy pathway is required for termination of STING signaling. Gain-of-function mutations in STING or loss-of-function mutations in COPA result in ligand-independent cGAS activation with uncontrolled type I IFN activation. Gain-of-function mutations in the single-stranded RNA sensor TLR7 or its chaperone UNC93B1 result in constitutive type I IFN signaling and promote the proliferation of autoreactive B cells. Secreted autoantibodies form immune complexes that are cleared by complement activation. Loss-of-function mutations in the subunits encoding complement component 1 impair clearance of RNA autoantigen-containing immune complexes, which subsequently stimulate increased type I IFN production by dendritic cells (DC) after Fc gamma receptor (FcγR)-mediated internalization in a TLR7-dependent manner. TRAP dephosphorylates and thereby inactivates osteopontin (OPN), which promotes type I IFN production in plasmacytoid dendritic cells. Loss-of-function mutations in TRAP result in constitutively active OPN. Drugs that target specific molecules or pathways are shown in boxes. Green boxes indicate approved drugs, orange boxes indicate drugs in preclinical development or clinical trials

type I IFN production by dendritic cells, further fueling the autoimmune response (Fig. 1) [2].

Genome-wide association studies have provided important insights into the genetic architecture of SLE and identified numerous risk loci [5]. However, the causative disease genes at many loci remain unclear, limiting the translation of such genetic discoveries into novel therapeutic concepts. Recent advances in human genetics have led to the identification of rare monogenic causes

of lupus, providing a unique opportunity to study the functional consequences of single gene mutations and to distinguish primary pathophysiological from secondary adaptive processes in SLE. In addition, unlike common complex SLE, which primarily affects women of child-bearing age, monogenic lupus typically affects children of both sexes equally and is associated with a more severe disease phenotype, reflecting the strong genetic contribution. In particular, mutations in genes involved in nucleic

acid metabolism, nucleic acid sensing, and type I IFN signaling have emerged as important causes of monogenic lupus, highlighting the central role of innate immunity in disease pathogenesis. Thus, by studying these rare Mendelian forms of SLE, it is possible to trace the pleiotropic effects of a single gene and apply mechanistic insights to common forms of SLE. This review focuses on monogenic forms of lupus sensu stricto. Other inborn errors of immunity, in which immune dysregulation may be associated with lupus-like features, are not the subject of this review.

Complement activation

Activation of complement component C1, consisting of C1q, C1r, and C1s, initiates the classical complement pathway. This occurs by binding of C1q to immune complexes, apoptotic bodies, or pathogens, leading to autocatalytic activation of C1r and subsequent cleavage of the zymogen C1s [6]. The classical complement pathway is involved in pathogen recognition,

antibody-mediated cytotoxicity, and clearance of immune complexes and apoptotic debris (Fig. 1) [6]. The clearance of extracellular waste by the complement system is an important aspect of immune homeostasis, as reduced complement activity promotes presentation of autoantigens to the immune system in the context of inflammatory injury.

Deficiencies in the subcomponents of complement 1 (Table 1) result in early-onset SLE with prominent cutaneous disease, renal, and neurological symptoms [7, 8]. This is in contrast to deficiencies in other Mendelian forms of complement deficiency, in which systemic autoimmunity is associated with increased susceptibility to bacterial infection. In patients with complete C1 deficiency, autoimmunity is induced by increased neutrophil extracellular trap formation and enhanced activity of endosomal Toll-like receptor (TLR) 7 and TLR9, which sense RNA and DNA, respectively, upon Fc gamma receptor (FcγR)-mediated uptake of nucleic acid-containing immune complexes (Fig. 1) [7, 8]. This

Table 1 Monogenic forms of lupus. The table shows Mendelian diseases in which systemic or cutaneous lupus is the main clinical feature, with the exception of COPA, which is associated with interstitial lung disease, and SPENCD, which is associated with skeletal dysplasia. AR: autosomal recessive; AD: autosomal dominant; XD: X-linked dominant

Disease	Main clinical findings	Age of onset	Gene / Protein	Mode of inheritance	References
C1 complement deficiency	SLE	< 5 years	<i>C1R</i> (complement component C1r) <i>C1QA</i> (complement component C1q, A chain) <i>C1QB</i> (complement component C1q, B chain) <i>C1QC</i> (complement component C1q, C chain) <i>C1S</i> (complement component C1s)	AR	[7, 8]
DNase I deficiency	SLE	< 10 years, variable	<i>DNASE1</i> (deoxyribonuclease I)	AD	[10]
DNase I-like 3 deficiency	SLE	< 10 years, variable	<i>DNASE1L3</i> (deoxyribonuclease I-like 3)	AR	[13]
Autoinflammatory-pancytopenia syndrome (AIPCS)	anemia, thrombocytopenia, arthritis, dermatitis, hepatosplenomegaly, glomerulonephritis, fever	< 5 years	<i>DNASE2</i> (deoxyribonuclease II, lysosomal)	AR	[14]
Familial chilblain lupus (CHBL)	Chilblain lesions, arthralgia	< 5 years	<i>TREX1</i> (three prime repair exonuclease 1) <i>STING</i> (stimulator of interferon genes protein)	AD AD	[17, 18, 27]
TLR7 gain-of-function	SLE, autoimmune cytopenia, autoimmune encephalitis	< 5 years	<i>TLR7</i> (Toll-like receptor 7)	XD	[31, 32]
UNC93B1 gain-of-function	SLE, autoimmune cytopenias	< 5 years	<i>UNC93B1</i> (UNC93 homolog B1)	AD, AR	[33–37]
Autoimmune interstitial lung joint, kidney disease (AILJK)	interstitial lung disease, pulmonary hemorrhage, arthritis, nephritis	< 10 years	<i>COPA</i> (coatamer protein complex, subunit alpha)	AD	[28]
Spondyloenchondrodysplasia (SPENCD)	spondylometaphyseal dysplasia, arthritis, thrombocytopenia, basal ganglia calcification, spasticity	< 5 years, variable	<i>ACP5</i> (tartrate-resistant acid phosphatase, type 5)	AR	[38]

results in a self-perpetuating feedback loop that stimulates type I IFN activation and proliferation of autoreactive B cells.

Nucleic acid metabolism

Nucleolytic degradation of endogenous nucleic acids plays an important role in protecting against inappropriate and pathogenic activation of innate sensors by self-nucleic acids [9]. Heterozygous loss-of-function mutations in *DNASE1*, which encodes the major serum DNA-degrading enzyme, cause SLE associated with high levels of autoantibodies to nucleosomal antigens (Table 1) [10]. The DNA substrate for DNase I can come from a variety of sources, including extracellular DNA waste derived from dying cells or immune complexes and oxidized mitochondrial DNA contained in neutrophil extracellular traps [11]. While perturbations in the removal of extracellular nucleic acid waste primarily trigger type I IFN signaling through non-cell autonomous pathways, intracellular nucleic acids can also elicit antiviral immune responses in a cell-intrinsic manner. The host organism has therefore evolved several mechanisms to prevent harmful immune recognition of self-nucleic acids produced during physiological metabolic processes.

For example, biallelic loss-of-function mutations in *DNASE1L3*, which encodes an intracellular DNase involved in chromatin degradation during apoptosis, have been reported to cause familial SLE with renal involvement (Table 1) [12, 13]. Complete deficiency of DNase II, which is essential for endolysosomal degradation of DNA in macrophages, is associated with systemic and multi-organ autoimmunity (Table 1) [14]. Interestingly, type I IFN activation in DNase II deficiency is initiated by the DNA sensor, cyclic GMP-AMP synthase (cGAS), which recognizes undegraded lysosomal DNA released into the cytosol [15]. Mutations in the intracellular DNase TREX1 cause a spectrum of inflammatory phenotypes characterized by autoimmunity, including Aicardi-Goutières syndrome, a neuroinflammatory interferonopathy and familial chilblain lupus, a monogenic form of cutaneous lupus characterized by bluish-red, partially ulcerating, skin lesions at acral location (Table 1) [16–18]. Furthermore, rare *TREX1* variants contribute to the genetic risk of complex SLE [19, 20]. TREX1 is an outer nuclear membrane-anchored cytosolic DNase that degrades DNA metabolites resulting from DNA damage repair or from reverse transcribed retroelements to prevent cGAS-dependent innate immune activation (Fig. 1) [21–23]. Taken together, these findings have revealed novel cell-intrinsic mechanisms for the initiation of autoimmunity.

Nucleic acid sensing and type I IFN signaling

cGAS acts as a central sensor of cytosolic DNA derived from pathogens or cellular stress. Upon DNA binding, cGAS catalyzes the synthesis of the second messenger, cyclic GMP-AMP (cGAMP), which binds and activates the adapter molecule stimulator of interferon genes (STING) localized at the endoplasmic reticulum membrane (Fig. 1) [24]. STING is then incorporated into coatamer protein complex II (COPII) vesicles and passes through the Golgi network, where it ultimately activates IFN regulatory factor 3 (IRF3), which induces gene expression of type I IFN, ISGs, and other proinflammatory cytokines. Termination of STING signaling occurs via autophagy-associated degradation of STING in the lysosome [24].

De novo gain-of-function mutations in *STING* underlie STING-associated vasculopathy (SAVI), an autoinflammatory interferonopathy characterized by acral vasculitis, recurrent fever, and interstitial lung disease due to constitutive type I IFN signaling even in the absence of cGAMP stimulation [25]. While patients with SAVI show no signs of autoimmunity, dominant *STING* mutations can also cause SLE-like disease and familial chilblain lupus (Table 1) [26, 27]. Heterozygous mutations in *COPA*, which encodes the alpha subunit of the COPI complex, cause COPA syndrome, an interferonopathy characterized by interstitial lung disease, arthritis, and immune complex-mediated glomerulonephritis [28]. The COPI complex regulates the sorting of molecules between Golgi cisternae and their transport from the Golgi to the endoplasmic reticulum. *COPA* mutations impair trafficking of STING-containing COPI vesicles to the endoplasmic reticulum and within the Golgi network, thereby promoting ligand-independent STING activation or preventing STING signaling termination [29, 30].

Unlike cGAS, which recognizes DNA in the cytosol, TLR7 senses endocytosed RNA in the endosomal compartment and triggers type I IFN activation via myeloid differentiation primary response gene 88 (MyD88) (Fig. 1). Gain-of-function mutations in *TLR7* have recently been shown to cause SLE due to constitutive type I IFN signaling (Table 1) [31, 32]. Similarly, mutations in *UNC93B1*, a chaperone that controls the trafficking and positioning of TLR7 within the endosomal membrane, have also been shown to cause early-onset SLE (Table 1) [33–37]. Indeed, these discoveries have shown that *UNC93B1* controls ligand recognition, signaling initiation and signaling termination of the TLR7 pathway [33, 34]. Both, *TLR7* and *UNC93B1* mutations are associated with proliferation of autoreactive B cells, resulting in high levels of antinuclear antibodies.

SLE-like features are also seen in spondyloenchondrodysplasia (SPENCD), a skeletal dysplasia caused by

biallelic mutations in *ACP5*, which encodes tartrate-resistant acid phosphatase (TRAP) [38]. In fact, patients may present with lupus while the bone changes may be subtle. TRAP dephosphorylates and inactivates osteopontin, a cytokine that has been shown to be essential for TLR9-dependent IFN- α production in plasmacytoid dendritic cells [39].

In summary, these findings have advanced our understanding of the multiple levels of both positive and negative regulatory control that govern type I IFN signaling during immune activation.

Translational aspects – on the way to precision medicine for lupus

The genetic dissection of rare monogenic forms of lupus has provided unprecedented insight into the molecular basis of autoimmunity. Indeed, SLE is a heterogeneous group of diseases, not only clinically but also molecularly. As we continue to understand each pathway of the complex regulatory network that controls and fine-tunes the initiation, execution, and termination of immune responses, we will be able to apply this knowledge to the development of improved and more precise therapeutic concepts. The current arsenal of biologic disease-modifying antirheumatic drugs already provides a number of drugs such as JAK inhibitors, the IFNAR antagonist anifrolumab or B-cell targeting drugs that allow pathway-specific intervention (Fig. 1). Ongoing efforts to develop novel compounds targeting other molecules or pathways along the type I IFN signaling axis, such as cGAS/STING or TLR7, will undoubtedly broaden the prospects for targeted therapies. These efforts will be greatly aided by the definition of molecular profiles that will help predict who is at risk of complications and who is likely to respond to a given treatment. In addition, such molecular profiles will allow patient stratification for much-needed clinical trials based on mechanistic insights.

Abbreviations

cGAS	Cyclic GMP-AMP synthase
COPA	Coatomer protein complex, subunit alpha
COP1/II	Coatomer protein complex I/II
cGAMP	Cyclic GMP-AMP
DNA/RNA	Deoxyribonucleic acid / ribonucleic acid
DNase	DNA-degrading nuclease
Fc γ R	Fc gamma receptor
IFN	Interferon
IFNAR	IFN- α/β receptor
IRF3	IFN regulatory factor 3
ISG	IFN-stimulated gene
JAK1	Janus kinase 1
MyD88	Myeloid differentiation primary response gene 88
OPN	Osteopontin
STAT1/2	Signal transducer and activator of transcription 1/2
STING	Stimulator of interferon genes
TLR7/9	Toll-like receptor 7/9
TRAP	Tartrate-resistant acid phosphatase
TYK2	Tyrosine kinase 2

UNC93B1 UNC93 homolog B1, TLR signaling regulator

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M.L.-K. drafted the manuscript. K.M., K.N., N.J., and C.W. edited and approved the final manuscript.

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Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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