



Platelets and IgE: Shaping the Innate Immune Response in Systemic Lupus Erythematosus

Benoit Brillard^{1,2,3} • Marc Scherlinger^{4,5,6} • Liliane Khoryati⁷ • Julien Goret³ • Pierre Duffau^{5,6,8} • Estibaliz Lazaro^{5,6,8} • Manon Charrier^{6,8} • Vivien Guillotin^{5,6,8} • Christophe Richez^{4,6,8} • Patrick Blanco^{3,6,8}

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Systemic lupus erythematosus (SLE) is a systemic and potentially fatal autoimmune disease. SLE pathophysiology is complex and involves the interplay between the innate and adaptive immune systems, with a particularly significant role for type I interferons. Recently, the participation of other actors such as platelets and IgE has been described in SLE. On the one hand, platelets activated by different stimuli (antiphospholipid antibodies, immune complexes...) participate in immune dysregulation through direct interactions with immune cells. On the other hand, autoreactive IgE can activate basophils, promoting a Th2 environment and subsequent antibody production by plasma cells. In synergy with IgG, IgE is also able to activate plasmacytoid DCs (pDCs) increasing interferon alpha production. Mirroring the IgG paradox, total nonautoreactive IgE is described as a potential regulator of IFN α production. This review summarizes recent and novel data on innate immunity in SLE pathophysiology with a focus on platelets and IgE, as they represent novel players in immune dysregulation and potential therapeutic targets.

Keywords Systemic lupus erythematosus · Platelets · Microparticles · IgE · Basophils · Type I interferon

Abbreviations

AAV	ANCA-associated vasculitis	DC	Dendritic cell
ADP	Adenosine diphosphate	DNA	Deoxyribonucleic acid
ALPS	Autoimmune lymphoproliferative syndrome	GC	Germinal center
ANCA	Anti-neutrophil cytoplasmic antibody	GM-CSF	Granulocyte/macrophage colony-stimulating factor
BAFF	B-cell-activating factor	HCQ	Hydroxychloroquine
BAK	Bcl-2 homologous antagonist killer	HLA	Human leukocyte antigen
BETs	Basophil extracellular traps	HMGB-1	High-mobility group box 1
CD	Cluster of differentiation	IC	Immune complex
DAMP	Danger-associated molecular pattern	ICAM	Intercellular adhesion molecule

Benoit Brillard and Marc Scherlinger contributed equally to this work.

✉ Patrick Blanco
patrick.blanco@chu-bordeaux.fr

¹ Service de Néphrologie-Dialyse-Transplantation, CHU Angers, 4 rue Larrey, 49100 Angers, France

² Université d'Angers, 40 Rue de Rennes, 49035 Angers, France

³ Laboratoire d'Immunologie et Immunogénétique, FHU ACRONIM, Hôpital Pellegrin, Centre Hospitalier Universitaire, place Amélie Raba Léon, 33076 Bordeaux, France

⁴ Service de Rhumatologie, FHU ACRONIM, Hôpital Pellegrin, Centre Hospitalier Universitaire, place Amélie Raba Léon, 33076 Bordeaux, France

⁵ Service de médecine interne, FHU ACRONIM, Hôpital Saint André, Centre Hospitalier Universitaire, 1 rue Jean Burguet, 33076 Bordeaux, France

⁶ Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France

⁷ Immunology Program, Benaroya Research Institute at Virginia Mason, Seattle, WA 98101, USA

⁸ CNRS-UMR 5164, ImmunoConcept, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France

IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IVIg	Intravenous immunoglobulin
JAK	Janus kinase
KO	Knock-out
MCP-1	Monocyte chemoattractant protein 1
mDC	Myeloid dendritic cell
miRNA	Micro-RNA
mRNA	Messenger RNA
mtDNA	Mitochondrial DNA
NETs	Neutrophil extracellular traps
NLRP3	NOD-like receptor family, pyrin domain containing 3
pDC	Plasmacytoid dendritic cell
PMP	Platelet-derived microparticles
PRR	Pattern recognition receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index
STAT	Signal transducer and activator of transcription
STING	Stimulator of interferon genes
TLR	Toll-like receptor
TXA2	Thromboxane A2

Introduction

Systemic lupus erythematosus (SLE) is a rare albeit potentially severe autoimmune systemic disease. Although the exact etiology of SLE remains unclear, it is now well established that SLE is a complex and multifactorial disease resulting from the interaction of several genetic and environmental factors, eventually characterized by inappropriate activation of the immune system and the development of autoantibodies targeting self-nuclear components [1].

Genetic susceptibility studies have allowed us to gain insights into SLE pathophysiology and, particularly, the involvement of the innate immune system. For example, C1q deficiency leads to a defect in nucleic autoantigen clearance, responsible for reaction against nuclear components such as DNA [2]. Autoantibodies aggregate with circulating autoantigens forming immune complexes (ICs) responsible for both immune system activation (e.g., activation of plasmacytoid dendritic cells (pDCs)) and organ-specific disease (e.g., immune-complex nephritis). Genome-wide association studies have identified many genetic predispositions which often have a cumulative effect on the risk for SLE [3], many of them concerning the immune response or antigen processing (e.g., HLA).

Because anti-nuclear antibodies are a hallmark of SLE, it has long been considered as an adaptive immune system

disorder. Over the past decade, insights into SLE pathophysiology have brought a better comprehension of how the innate and adaptive immune systems interplay in a vicious circle promoting and maintaining autoimmunity. In this complex interplay of immune cells, platelets and immunoglobulin E (IgE) have been recently shown to be new players in modulating the immunopathology of SLE.

Blood platelets are small enucleate cellular fragments derived from megakaryocytes and the second most represented population in the complete blood count. Their role in hemostasis as guardians of vascular integrity has long been known, but as suggested by the fact that their circulating number is far higher than what is needed for this purpose, recent studies have uncovered that platelets play a major role in immunity. Platelets have been reported to be involved in the defense against pathogens [4, 5], as well as in the promotion of autoimmune diseases [6]. Therefore, platelets may be seen as a cellular component of the innate immune system.

In SLE, the role of platelets goes beyond the well-described thrombosis risk. Their activation is increased, leading to the exposure of co-stimulatory proteins (e.g., CD40L) and the release of pro-inflammatory molecules (e.g., damage-associated molecular patterns (DAMPs)). For example, platelets have shown their unique capacity to prime pDCs' immune complex-mediated secretion of interferon alpha (IFN α), a central cytokine in SLE pathophysiology [7]. As an amplification loop, each activated platelet produces many platelet-derived microparticles (PMPs) which can individually expose such pro-inflammatory and prothrombotic factors [8]. This explains how platelets may act as a powerful adjuvant of the immune system activation and thrombosis, which can be further amplified by autoantibodies.

IgE is the least abundant of all circulating immunoglobulins (about 5 times less than IgG). It is involved in the defense against extracellular parasitic organisms, especially helminths and protozoa [9]. In western countries, where parasitic infections became rare due to improved hygiene conditions, these immunoglobulins often react against innocuous antigens, sometimes causing allergic symptoms. The low serum concentration of IgE is to be relativized, since the majority of it is in tissues and bound to Fc ϵ RI (Fc epsilon receptor 1), the high-affinity Fc receptor for IgE. IgE has the shortest half-life of all the Ig isotypes (about 1–5 days versus up to 24 days for IgG1, IgG2, and IgG4) [10], but due to the high affinity of Fc ϵ RI, basophils and mast cells are covered with relatively long-lived Fc ϵ RI–IgE complexes (about 2 weeks after binding).

In SLE, autoreactive IgE has been identified not only as a potent basophil activator but also as a potential trigger for pDC leading to IFN secretion, thereby increasing disease activity [11, 12]. On the contrary, total non-autoreactive IgE has been found to have opposing effects. Consistent with its ability to suppress the inflammation in SLE, its levels negatively

correlate with disease activity [13]. Together, these findings define an emerging concept: the IgE paradox in autoimmunity [14].

The purpose of this review is to summarize recent and novel data on innate immunity in SLE pathophysiology with a focus on platelets and IgE. Indeed, they represent new players in immune dysregulation, and beyond their respective roles in thrombosis and allergies, both may modulate immune (and autoimmune) response and represent potential therapeutic targets.

Noncellular Innate Factors Responsible for SLE Development

Toll-Like Receptors and Other Pattern Recognition Receptors

Toll-like receptors (TLRs) belong to the pattern recognition receptor (PRR) family and are evolutionarily conserved innate immune components. They have the unique capacity to recognize pathogen-associated molecular patterns (PAMPs) while inducing immune system activation and linking innate and adaptive immune responses. TLRs are membrane-bound, and their localization determines the type of ligand they recognize: bacterial or fungal PAMPs for TLRs 1, 2, 4, 5, and 6 which are located on the cell surface; and nucleic acids (single- or double-strand RNA, DNA) for TLRs 3, 7, 8, and 9 located on endosomal membranes (Table 1). In SLE pathogenesis, nucleic acid-sensing TLRs (mainly TLRs 7 and 9) have been strongly implicated since they mediate IFN α production by pDCs upon activation by circulating ICs containing self-nucleic acid components [17].

Platelets have functional TLRs 1, 2, 3, 4, 6, 7, and 9 [15]. The role of platelet TLR-7 in antiviral immunity has recently been demonstrated by Koupenova et al. During viral challenge, TLR-7 is responsible for platelet activation leading to platelet–leukocyte aggregates possibly involved in priming the immune system. In fact, TLR-7 KO mice did not present

such platelet activation and platelet–leukocyte aggregates and had decreased survival after a viral challenge [4]. In SLE, circulating ICs are a major factor responsible for platelet activation and immune system priming, at least via TLR-7.

However, TLR signals can be modulated. In a recent study, total circulating IgE levels were found to be increased in lupus patients in remission compared to active lupus patients suggesting a protective role of IgE in SLE. Mechanistically, the authors demonstrated that nonautoreactive IgE negatively impacted TLR-7 and TLR-9 expression in pDCs [13], therefore negatively regulating IFN α production in response to ICs. A similar mechanism has been described in atopic asthma, where Fc ϵ RI engagement by elevated levels of total IgE was responsible for TLR-7 downregulation and, ultimately, to decreased IFN α production by pDCs in response to influenza infection [18]. On the other hand, another team demonstrated that autoreactive IgE, such as anti-dsDNA IgE, was elevated in SLE patients and elicited an increase in IFN α production by pDCs [19]. Therefore, a tight balance between total and autoreactive IgE seems to be at play for TLR-7/9-mediated IFN α production.

Cytosolic PRRs such as RIG-I, MDA5, and TMEM173/STING have been implicated in SLE pathogenesis through type I interferon production. For example, a gain of function mutation responsible for aberrant STING activation has been described to cause a pediatric lupus-like syndrome called SAVI (STING-associated vasculopathy with onset in infancy) [20]. Of note, baricitinib, a Janus kinase (JAK) inhibitor, is the first drug to allow sustained disease control and corticosteroid tapering in these young patients, demonstrating the importance of the JAK–STAT pathway in IFN-mediated diseases [21].

Damage-Associated Molecular Patterns

DAMPs are endogenous molecules released upon tissue damage capable of activating the immune system and promoting inflammation without the need for foreign antigens. They were initially theorized by Matzinger in 1994 then further described by the same author 10 years later [22, 23]. DAMPs are highly heterogeneous in terms of origin, localization, structure, and function, but all converge at either initiating or promoting the inflammatory response.

Mitochondria and mitochondrial DNA (mtDNA) are potent activators of TLR-9 and STING, therefore inducing IFN α production by pDCs and NETosis of polymorphonuclear cells [24, 25]. mtDNA (as well as whole mitochondria) is released in the extracellular milieu in the case of necrosis, apoptosis, or NETosis [26]. Interestingly, platelets are able to release mitochondria and mtDNA upon activation. Thus, considering their prevalence in the blood, platelets are a major source of mtDNA [27]. Furthermore, inflammation provides a pro-oxidative extracellular milieu with the release of reactive oxygen species (ROS) promoting mtDNA oxidation,

Table 1 Toll-like receptors expressed in platelets

TLRs	Ligands	References
Extracellular localization		
TLR-1	Multiple triacyl lipopeptides	[15]
TLR-2	HMGB-1, lipoteichoic acid	[15, 16]
TLR-4	Lipopolysaccharide (LPS)	[15, 16]
TLR-6	Diacyl lipopeptides	[15]
Intracellular localization		
TLR-3	Double-stranded RNA, poly I:C	[15]
TLR-7	Single-stranded RNA	[4]
TLR-8	Single-stranded RNA	[15]
TLR-9	DNA, HMGB1	[15]

increasing its immunogenicity and its capacity to stimulate IFN production, including in SLE models [28, 29]. In addition to TLR-9 stimulation, oxidized mtDNA also activates the inflammasome, namely nucleotide-binding domain leucine-rich repeat family (NLRP3) to produce IL-1B [30]. Of note, other DAMPs are released by mitochondria such as formyl-peptides which promote sterile inflammation [24, 31].

High-mobility group box 1 (HMGB-1) and S100A8/A9 (also known as calprotectin) are two proteins released in the extracellular milieu upon cell activation, necrosis, or NETosis. Bioavailable HMGB-1 and S100A8/A9 are found to be increased in many autoimmune diseases, including SLE, and correlate with disease activity [16, 32]. Mechanistically, HMGB-1 and S100A8/A9 act via TLR-4 and receptor for advanced glycation endproducts (RAGE) to promote immune system activation and pro-inflammatory cytokine secretion by immune cells [16, 33–35]. Both S100A8/A9 and HMGB-1 were demonstrated to induce activation, chemotaxis, and migration of neutrophils/monocytes [34, 36]. Interestingly, platelets and PMPs are a consequential source of HMGB-1 and/or S100A8/A9, thus not only participating in immune dysregulation but also organ damage such as in cardiovascular diseases by their role in the promotion of thrombosis [37–39].

The Complement System

The complement system was originally discovered by a Belgian immunobacteriologist, Jules Bordet, who found evidence of heat-labile plasmatic factors which increased opsonization (bacterial coating facilitating macrophage uptake) and antibody-mediated bacteria death, therefore termed “the complement” [40]. It is composed of more than 30 protein components mostly evolutionarily conserved, which are present in the plasma as soluble factors or bound on the cellular membrane.

Defects in the complement system, such as C1q, C2, or C4 deficiency, have been described as major risk factors for SLE [41]. An increase in apoptosis leading to high levels of circulating apoptotic bodies containing nuclear autoantigens is commonly described. One of the roles of complement and, in particular, C1q is to promote clearance of apoptotic bodies, ICs, and the strongly immunogenic neutrophil extracellular traps (NETs) [42]. The facts that almost all patients with a defect in C1q develop SLE and that patients with severe SLE (e.g., lupus nephritis) very often have anti-C1q autoantibodies underline the importance of this mechanism in regulating the development of autoimmunity [43, 44]. Another role for the complement system is to activate the cellular components of the innate immune system including platelets and to prepare the adaptive immune response.

C4d, a by-product of the classical pathway activation, is found on the platelets of nearly 20% of patients with SLE and is associated with a worse prognosis, more particularly

with a risk of thrombosis [45]. Platelet C4d is a biomarker of classical pathway activation which is both promoted by and a result of platelet activation. Platelets also bind C3b through interaction with P-selectin which is relocated to the platelet surface upon activation [46], leading to alternate pathway activation and a complement amplification loop [47, 48]. Activated platelets upregulate the surface C1q receptor (C1qR) promoting classical pathway activation on their surface. Moreover, cross-linking C1q to C1qR on platelets leads to platelet activation and release of prothrombotic factors [49]. Finally, the terminal complement step produces the membrane attack complex (C5b-9), which activates tissue factor, von Willebrand factor multimers, and prothrombinase (a stimulator of platelet activation) secretion from endothelial cells [50–52]. These mechanisms uniquely place platelets at the interface between the inflammatory response and vessel thrombosis in SLE.

Fas/FasL System

Fas is a transmembrane protein belonging to the TNF receptor superfamily and is expressed on many innate and adaptive immune cells [53]. Its first known action is to mediate apoptosis which is illustrated by the fact that a genetic deficit of Fas is responsible for the autoimmune and lymphoproliferative syndrome (ALPS) which shares autoimmune features with SLE. Fas ligand (FasL)-induced apoptotic cells present increased synthesis of pro-inflammatory cytokines such as IL-6, monocyte chemoattractant protein-1 (MCP-1), and granulocyte/macrophage colony-stimulating factor (GM-CSF) [54]. These cytokines are also responsible for neutrophil/macrophage activation and priming for phagocytosis, which subsequently initiates adaptive immune system activation. However, FasL and, more specifically, its soluble form (sFasL) have demonstrated many nonapoptotic but pro-inflammatory actions, including in SLE [53]. Indeed, sFasL acts as a chemoattractant on neutrophils and Th17 lymphocytes, promoting their migration to inflamed tissues [55, 56]. There is a fine-tuning between the protective and pro-inflammatory roles of the Fas/FasL system. In fact, patients with Fas deficiency fail to eliminate a subgroup of germinal center B cells (GC B cells) called rogue GC B cells which subsequently differentiate into IgG1⁺ and IgE⁺ long-lived plasma cells capable of producing IgG and IgE autoantibodies [57].

Innate Immune Cells in SLE Pathogenesis

Dendritic Cells and IFN Secretion in SLE

Global Picture

Dendritic cells (DCs) are localized in nearly all human tissues and are responsible for immunosurveillance, professional

antigen presentation, and/or innate and adaptive immune system activation.

In humans, we can functionally distinguish two types of DCs, determined by the specific expression of surface molecules [58]:

- *Myeloid (or conventional) DCs (mDCs)*. Immature mDCs residing in tissues have optimal antigen capture (optimal phagocytosis) and minimal presentation properties (low expression of co-stimulatory and antigen-presenting molecules). They undergo a maturation process after encountering foreign antigens under inflammatory conditions, migrate to secondary lymphoid organs such as lymph nodes, and acquire the ability to optimally present antigens to B and T cells, therefore initiating the adaptive immune response [59]. Two subpopulations of mDCs can be identified according to their membranous localization of CD1c (BDCA-1) or CD141 (BDCA-3) [60]. CD1c⁺ mDCs, the predominant subpopulation in blood, tissue, and secondary lymphoid organs, express high levels of PRRs allowing efficient antigen capture and presentation. They have a strong ability to stimulate naive T cells. CD141⁺ mDCs can internalize dead cells, detect viral nucleic acids, and cross-present antigens to CD8⁺ T cells. They have the capacity to produce large amounts of tumor necrosis factor α (TNF α) [61].
- *pDCs* can derive from a myeloid or a lymphoid progenitor [62]. Their main function is to detect foreign nucleic acids via PRR and to secrete large quantities of type I IFN, which is about 1000 times higher than any other cell type [63–65]. Type I IFNs have multiple roles in the immune system: they support monocyte and T-cell function, as well as B-cell activation, proliferation, and differentiation into antibody-producing cells [66]. This massive type I interferon secretion also leads to type II IFN (IFN γ) production by NK cells, which amplify the inflammatory response [66]. pDCs can also produce pro-inflammatory cytokines (IL-1, IL-6, TNF α) thus recruiting and activating other immune cells. By promoting T- and B-cell activation, pDCs serve as a bridge between innate and adaptive immunity.

The role of mDCs in the pathophysiology of SLE was identified when Blanco et al. showed that monocytes from healthy individuals differentiated into mDCs in the presence of serum of lupus patients [67]. Myeloid DCs are then able to phagocytize nuclear material and present self-antigens to naive CD4⁺ T cells [67]. These mDCs can also, just like the previously activated CD4⁺ T cells, activate the cytotoxic functions of CD8⁺ T cells and support the proliferation and differentiation of B cells.

The soluble factor inducing this differentiation to mDC has been identified as type I interferon. This result is particularly

interesting because IFN α is present in large quantities in the serum of lupus patients and its quantity correlates with disease activity. The well-recognized IFN α signature has been identified by showing that many genes overexpressed in SLE are dependent on this cytokine [68]. This signature can be extinguished by steroid bolus, blocking the production of IFN α by pDCs; 95% of children and 50 to 70% of SLE adults have this IFN α signature in their genomic profile [68].

In parallel, the pivotal role of pDC in IFN secretion was underlined [69, 70]. Interferon production by pDCs is mainly mediated by TLRs and CD32 (Fc γ R2). TLR-7 and TLR-9 especially are involved in type I IFN secretion, usually as an antiviral response system. Nucleic acids (bacterial, viral, contained in immune complexes or in apoptotic bodies) after binding to these TLRs lead to the recruitment of an innate immune signal transduction adaptor, MyD88 (myeloid differentiation primary response 88). This latter activates the transcription factors NF- κ B (nuclear factor- κ B) and IRF7 (interferon regulatory factor 7) through the sequential phosphorylation of kinases IRAK4/1 and auto-ubiquitination of TRAF6 [71, 72].

The collaboration of these three actors (DCs, T cells, and B cells) induces the production of autoantibodies targeting nuclear components and ultimately forming ICs. The latter are then recognized by the pDCs (mainly through TLRs) and promote the production of IFN α in a vicious circle (Fig. 1). Many factors such as platelet components and IgE may modulate IFN α production and could therefore have an impact on SLE disease activity.

Platelet-Induced Priming of pDCs and mDCs Through CD154/CD40

Many authors have described how platelets are activated in SLE compared to healthy donors. Many factors interplay in platelet activation: ICs (through Fc γ R2), viruses (through TLRs), or anti-phospholipid antibodies (through direct binding or glycoprotein Ib (GP-Ib)) [73]. Interestingly, IgE, and particularly IgE-ICs, may also activate platelets since they express functional Fc ϵ RI [74].

Upon activation, platelets undergo degranulation and relocalize at their surface proteins which allow deep interaction with the immune system (Table 2). One of these interactions is mediated by CD40 (or TNFRSF5), a stimulatory receptor belonging to the TNF α family expressed by dendritic cells, B cells, and macrophages. Its stimulation by CD154 (CD40L) plays a major role in the adaptive immune response. As an example, the CD40–CD154 interaction was initially described between T follicular helper and B lymphocytes as a major factor promoting class switch, somatic hypermutation, and the development of professional antibody-secreting cells (plasmablasts and plasma cells) in the germinal centers. Interestingly, platelets are the main reservoir of bioavailable

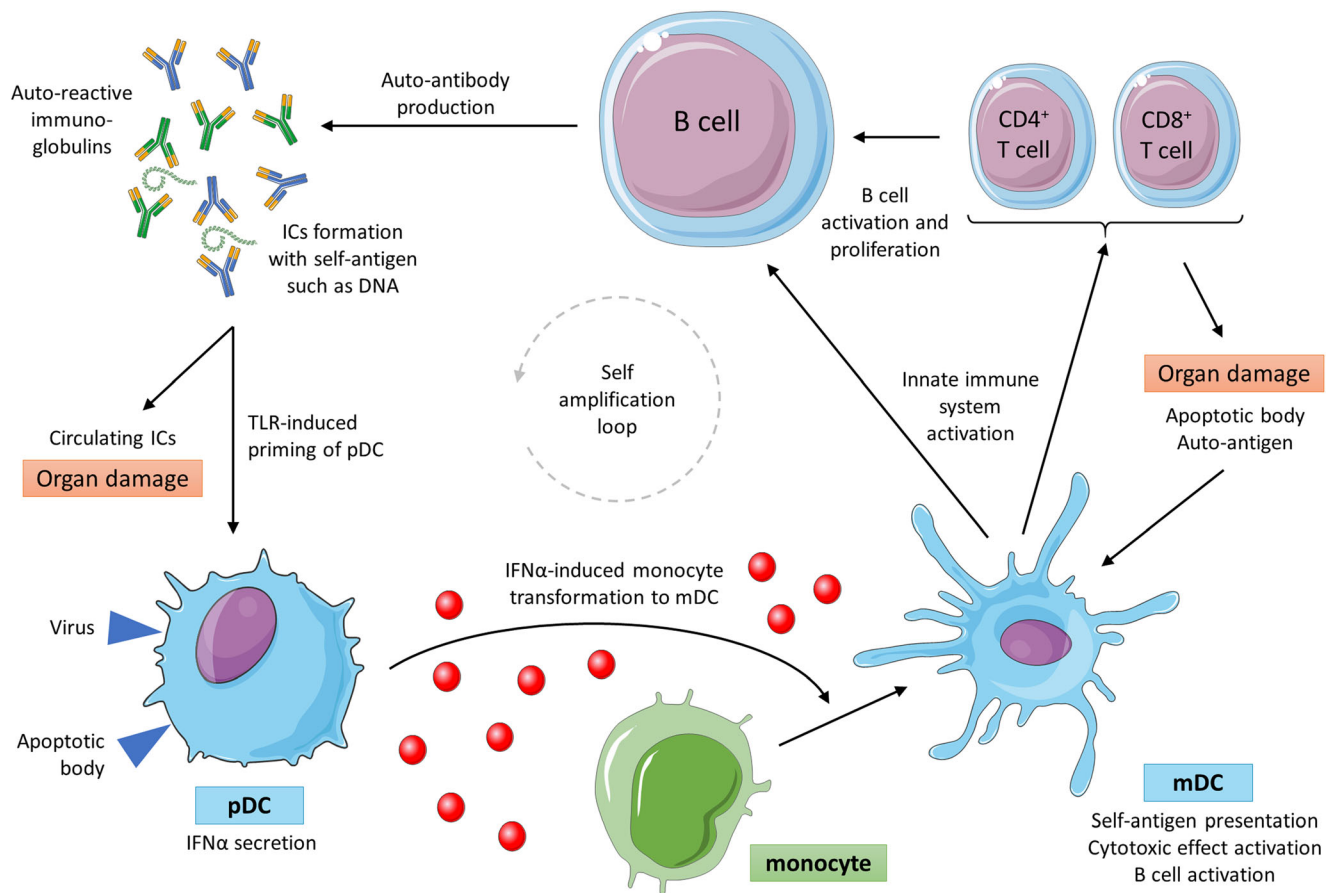


Fig. 1 General overview of DC involvement in SLE pathogenesis. Various environmental triggers, such as viral infection, apoptotic bodies, or circulating immune complexes promote IFN α secretion by plasmacytoid dendritic cells. This type I interferon production induces the transformation of monocytes to myeloid dendritic cells. mDCs are at the interface between innate and adaptive immunity. Indeed, by their antigen presentation skills, they can activate CD4 $^{+}$ T cells. Both mDC

and activated CD4 $^{+}$ T cells will subsequently support the cytotoxic functions of CD8 $^{+}$ T cells. Moreover, mDC will support the proliferation and differentiation of B cells, subsequently enhancing autoantibody production. Such autoantibodies will aggregate with circulating autoantigens therefore forming immune complexes and will perpetuate IFN α production in an amplification loop. IC, immune complex; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell

CD154 which is in part released in a soluble form by activated platelets upon cleavage [80].

Elzey et al. have been the first to demonstrate the platelet role in linking the innate and adaptive immune responses. They showed that platelets could activate mDCs in a CD154/CD40-dependent manner, and increase co-stimulatory molecule

expression (CD80/CD86/ICAM) as well as pro-inflammatory cytokine production (IL-6, IL-12) [81].

Our team has demonstrated that in SLE, platelets were activated by ICs via a CD32-dependent mechanism (Fc γ RIIa) leading to the exposure of membrane-bound CD154 [7]. Furthermore, activated platelets were able to interact with pDCs

Table 2 Interaction between dendritic cells and platelets in SLE

Action	Pathway	References
Myeloid dendritic cell (HLA-DR^{+} CD11c^{+} CD123^{-})		
Increase pro-inflammatory cytokine secretion	Platelet CD40L/mDC CD40	[75]
Increase co-stimulation molecule expression	Platelet CD40L/mDC CD40	[75]
Induce tolerogenic phenotype	Platelet-selectin/mDC PSGL-1	[76]
Induce pro-inflammatory phenotype	Platelet serotonin	[77]
Plasmacytoid dendritic cell (HLA-DR^{+} CD11c^{-} CD123^{+})		
IFN secretion in response to ICs	Platelet CD40L/pDC CD40	[7]
Promote IFN secretion	Platelet-released mitochondria/pDC TLR-9	[27, 78]
Promote IFN secretion	Platelet HMGB-1/pDCs RAGE and TLR-9	[79]

via CD154/CD40 and, therefore, increase type I IFN production in response to ICs. Of note, blocking platelet activation with clopidogrel (a platelet receptor P2Y₁₂ blocker) and with it, CD154 exposition and release, increased lupus mouse model survival and lowered anti-dsDNA titers [7]. Another group demonstrated that blocking CD154 with a monoclonal antibody improved survival and prevented nephritis development in the NZBxNZW lupus mouse model [82].

Platelet-derived microparticles may also participate in SLE pathogenesis, at least through an amplification mechanism. In fact, one activated platelet can produce many PMPs, which individually possess pro-inflammatory proteins on their surface (CD40L, P-selectin...) [8]. Interestingly, Cloutier et al. reported that in rheumatoid arthritis, patients' circulating PMPs acted as IgG immune complexes displaying autoantigens such as histones [83]. Recently, another group suggested that MP-immune complexes might also contribute to SLE immune dysregulation, notably by promoting a pro-inflammatory monocyte phenotype [84]. Considering the platelet system hyperactivation in SLE and the fact that PMPs have been found to be elevated in active patients [8], it is very likely that these PMP-ICs participate in pDCs activation and IFN-I production in SLE (Fig. 2).

IgE-Induced Modulation of pDCs' Activation Through FcεRI

IgE autoantibodies were described in SLE and autoimmune diseases for the first time 40 years ago [85]. However, studies focusing on their role in autoimmunity are fairly recent. As for IgGs, autoreactive IgGs have been reported to have multiple antigen targets in SLE [86]: dsDNA, Sm, SS-A, SS-B, ribonucleoprotein (RNP), and nucleosomes. Specific autoantigens recognized by IgE have also been described: APEX, MPG, and CLIP4, especially in lupus nephritis [12].

IgE is recognized by Fc epsilon receptor 1, the high-affinity Fc receptor for IgE. In humans, two forms of FcεRI have been described. The tetrameric receptor ($\alpha\beta\gamma_2$) is composed of one alpha chain binding to IgE, two gamma chains initiating signal transduction, and one beta-chain amplifying the signal [86]. It is expressed mainly on basophils and mast cells, localized in tissues. The trimeric receptor ($\alpha\gamma_2$) is expressed at a lower density on dendritic cells including pDCs, neutrophils, eosinophils, monocytes, Langerhans cells, and certain epithelial cells (bronchial, intestinal cells) [87]. Upon antigen recognition by cell-bound IgE, the signal transduced through FcεRI leads to potent secretion of inflammatory mediators, such as histamine. These mediators are responsible for symptoms associated with allergic rhinitis, asthma, and anaphylaxis [88]. With a thousand times lower affinity, IgE is also recognized by FcεRII (CD23). This second receptor is expressed on monocytes/macrophages, natural killer cells, B lymphocytes, dendritic cells, eosinophils, Langerhans cells, activated epithelial cells, and platelets. FcεRII-IgE interaction leads to the

secretion of mediators of immediate hypersensitivity: pro-inflammatory cytokines and chemokines. It is also involved in antigen capture and presentation, promoting T- and B-cell activation [88].

FcεRI has recently been described for its ability to inhibit the IFN type 1 responses from pDC. Of note, the FcεRI found on pDC lacks the β -chain [9]. Two specific pDC receptors involved in the downregulation of IFN-I production have been described: BDCA2 and ILT7 [89]. Because they lack signaling domains, these two receptors can modulate the pDC IFN-I response only upon association with FcεRI gamma chain homodimer [90, 91]. It has also been shown that the cross-linking of FcεRI on the surface of pDCs inhibits the production of IFN α after stimulation of TLR-9 or TLR-7 [18, 92]. In addition, two different studies showed that FcεRI is strongly expressed on the surface of pDCs in allergic patients, with a direct correlation between its expression and serum total IgE levels [18, 93]. Following stimulation of TLR-7 or TLR-9, pDCs from allergic patients produce significantly lower amounts of IFN α than healthy subjects. Interestingly, the secretion of IFN α in allergic patients is inversely correlated with the expression of FcεRI at the pDC surface and with the levels of total serum IgE. These results support an inhibitory role of FcεRI in the production of IFN-I by pDCs.

Later, two publications supported this important role of IgE in the regulation of IFN α secretion by pDCs (Table 3).

The first team found that self-reactive IgE levels (especially against nuclear antigens) were increased in lupus patients [19]. This finding had already been described earlier in the literature [12]. Indeed, autoreactive IgE could be used as a clinical indicator of disease activity. In this study which included 196 SLE patients, autoreactive IgE were found in 65% of all subjects and in 83% of patients with active disease. Also, the best prediction of disease activity was found to be the presence of both dsDNA-specific IgE and IgG, possibly indicating a role for auto-IgE in SLE [12]. A previous study showed that disease flare rates were higher in SLE patients with demonstrable circulating anti-dsDNA-IgE antibodies than in those without [94]. Furthermore, a role of these IgE in the activation of basophilic polynuclear cells has been elucidated [11] and will be detailed later. The novelty is that autoreactive IgE was shown to enhance IC internalization by pDCs in human SLE. ICs, formed with autoreactive IgGs and nuclear antigens, are recognized by the self-reactive IgE whose Fc fragment will bind to the FcεRs (especially FcεRI) on the pDC surface. This subsequently facilitates the internalization of the complexes and TLR-9 activation, then promotes IRF7 activation leading to IFN α production [19]. Interestingly, DNA-IC with IgG or IgE isotypes induced comparable IFN α amounts, while DNA-IC with both isotypes had a synergistic effect on IFN α production (even when reproducing the unbalanced autoreactive IgE/IgG ratio of SLE serum).

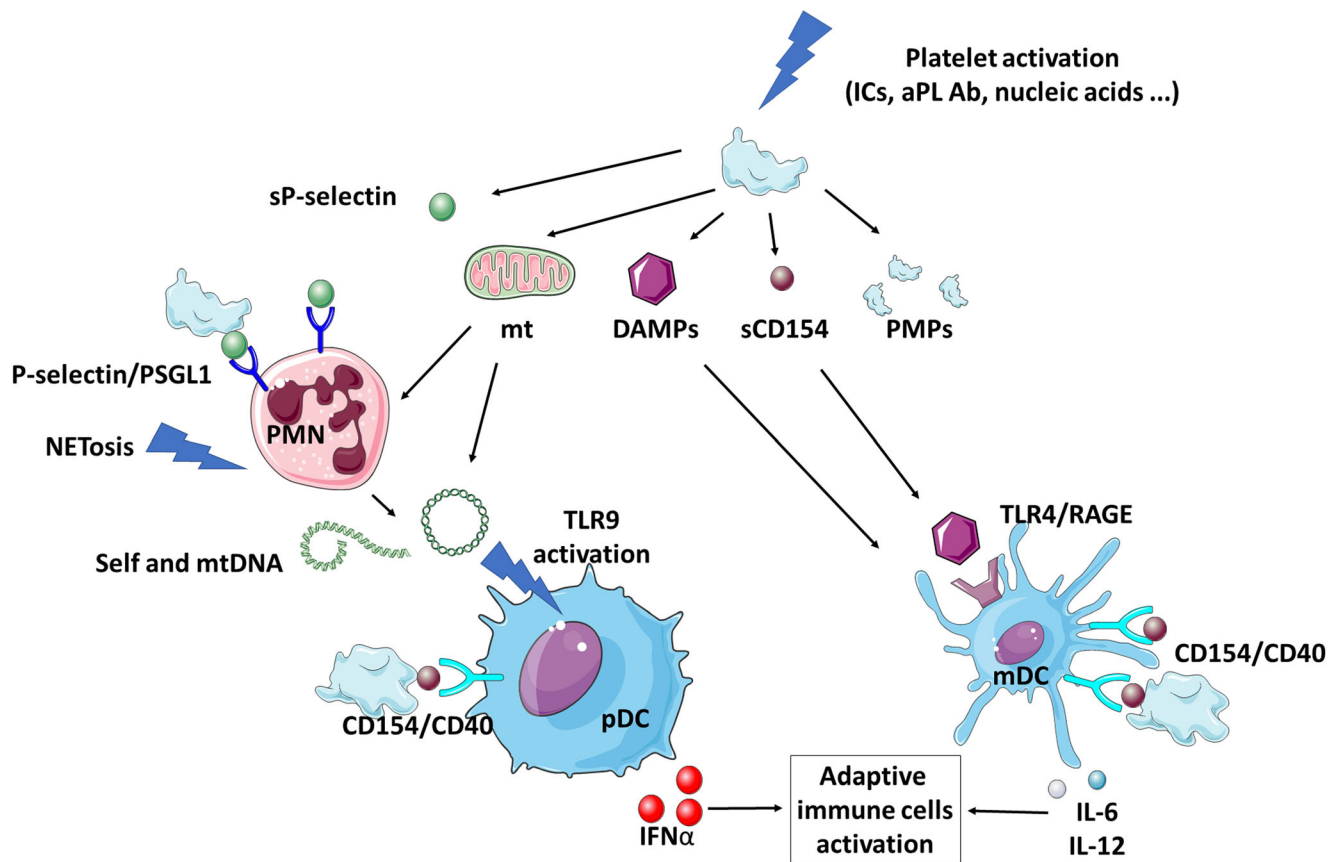


Fig. 2 Interactions between platelets and innate immune cells in SLE. In SLE, platelets are activated in response to several factors: immune complexes, antiphospholipid antibodies, and nucleic acids. Activated platelets relocate these factors to their surface or secrete several molecules which can interact with the immune system (CD154, DAMPs, P-selectin ...). They can also produce many platelet-derived microparticles which amplify platelet actions. Apl Ab, antiphospholipid

antibodies; ICs, immune complexes; IFN α , interferon α ; IL, interleukin; mDC, myeloid dendritic cell; mt, mitochondria; mtDNA, mitochondrial DNA; pDC, plasmacytoid dendritic cell; PMN, polymorphonuclear; PMPs, platelet-derived microparticles; PSGL-1, P-selectin glycoprotein ligand 1; sCD154, soluble CD154; sP-selectin, soluble P-selectin; RAGE, receptor for advanced glycation end products; TLR, toll-like receptor

In the second publication, the authors focused on total IgE (i.e., nonautoreactive IgE) [13]. An inverse correlation between total IgE levels and SLE disease activity (assessed by the SLEDAI) was observed in SLE patients. The engagement of Fc ϵ RI by these nonautoreactive IgE inhibited IFN α production by pDCs stimulated with TLR-7 or TLR-9 ligands [13]. Moreover, monoclonal IgE-primed pDCs secreted less amounts of IFN α in response to SLE-ICs as compared to nonprimed pDCs [13].

Considering that nonautoreactive IgE negatively regulates type I IFN pathways in pDC, the authors suggested a new paradigm describing an IgE protective role in the context of SLE. In fact, their data suggest a paradox with IgE: on the one hand pathogenic self-reactive IgE and on the other hand non-pathogenic and even protective non-self-reactive total IgE (Fig. 3). This echoes the IgG paradox: on one hand, IgG autoantibodies, e.g., found in lupus or rheumatoid arthritis, cause inflammation through various mechanisms [97]. Especially, they can activate Fc γ R and the complement system, promoting the activation of several pro-inflammatory effector

pathways. On the other hand, the perfusion of a large amount of intravenous immunoglobulin (IVIg) acts as an anti-inflammatory agent and is associated with immunomodulatory effects in autoimmune diseases [97]. Moreover, IVIg and the Fc portion of IgG inhibited IFN α produced by pDCs in response to several viruses [98]. Multiple mechanisms have been discussed to explain this paradox [97]: competition for activating Fc γ R, saturation of FcRn (involved in increasing IgG half-life), and induction of inhibitory Fc γ R expression.

We have demonstrated here that DCs play a major role in SLE and that their functions are greatly affected by platelets and IgE. Besides DCs, neutrophils are another major cellular component of the innate immune system involved in SLE.

Neutrophils

Global Picture

Neutrophil involvement in SLE pathogenesis has long been known since the lupus erythematosus (LE) cell was described

Table 3 Autoreactive IgE interaction with innate immune cells involved in SLE pathogenesis

Immune cells	Action of autoreactive IgE on immune cells	Consequences of interaction	References
Basophils	Activation and degranulation	B cell interaction: - Auto-reactive B cell proliferation and maturation - Class switch (towards IgG, IgA and IgE) - Humoral memory response - Plasma cell survival and autoantibody production T cell interaction: - T cell activation - IL-3 secretion: sustaining basophil activation and survival - Th17 polarization - Th2 polarization	Charles et al. 2010 [11], Sanjuan et al. 2016 [86], Pellefigues and Charles 2013 [94], Rodriguez Gomez et al. 2010 [95]
	Migration to lymph nodes and spleen		
	Membrane expression of BAFF, APRIL, CD40L		
	IL-4, -5, -6, -13 secretion		
	Surface expression of CD40 and MHC-II		
plasmacytoid Dendritic Cells	IL-6 and histamine secretion	Induction of IFN α secretion: - DC maturation, monocyte differentiation to DC - T and B cell activation and proliferation - IFNγ production by NK cells Pro-inflammatory cytokines secretion (IL-6, IL-8, TNF α): - Recruitment and activation of other immune cells - Endothelial activation - Neutrophils recruitment and NETosis	Dema et al. 2014 [12], Henault et al. 2016 [19], Hanaoka et al. 2012[96]
	IL-4, TSLP, IL-25 and RA secretion		
	pDC maturation and migration		
	Antigen presentation to T-cells		
	Induction of IFN α and pro-inflammatory cytokines secretion		

IL, interleukin; *BAFF*, B-cell-activating factor; *APRIL*, a proliferation-inducing ligand; *TSLP*, thymic stromal lymphopoietin; *RA*, retinoic acid; *MHC*, major histocompatibility complex; *pDC*, plasmacytoid dendritic cell; *IFN*, interferon

in 1948. This cell is a mature neutrophil in the bone marrow that has phagocytized the nucleus of another cell, thus containing a large amount of nuclear material. This LE cell, also called Hargraves cell, was initially used as a reference diagnostic test for SLE [99].

Besides phagocytosis, neutrophils are able to undergo a specialized cell death called NETosis, during which they release NETs allowing the NETs to bind pathogenic material. NETs are extracellular structures composed of chromatin studded with antimicrobial proteins, and DAMPs, such as histones, myeloperoxidase, and ROS [100]. While NETosis is probably an evolutionary conserved innate defense mechanism, it is also responsible for autoantigen release participating in the loss of tolerance against self-nuclear antigens [101]. This is exemplified by the fact that antibodies targeting histones, DNA, or myeloperoxidase are often found in autoimmune diseases such as SLE and anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis. NETs then interact with pDCs, facilitating the internalization and delivery of DNA fragments to endosomal TLRs, while protecting this DNA from nuclease degradation. Those NETs are part of immune complexes capable of (i) stimulating pDCs via TLR-9 and (ii) eliciting an autoimmune response with the production of anti-DNA and anti-microbial peptide antibodies. In turn, these

autoantibodies present in the serum of lupus patients are able, like ANCAs, to stimulate NETosis [102], demonstrating a vicious circle.

There is a self-sustaining circle between neutrophils and pDCs, IFN α promoting NET production, itself supporting the secretion of IFN α [102, 103]. Furthermore, NETs are deleterious to endothelial cells [104] and found in excess in the skin and kidney of lupus patients [105].

NETosis relies on ROS for its induction as well as for its antibacterial activities [29, 101]. Two recently published studies have highlighted the importance of oxidative stress in lupus, with a major role played by oxidized mtDNA [28, 29]. In SLE patients, neutrophils undergo NETosis in response to RNP ICs, leading to the production of ROS, the oxidation of mtDNA, and its release in the extracellular milieu. This oxidized mtDNA is highly immunogenic and promotes type I IFN production by the cGAS-STING pathway [29]. Interestingly, mitochondrial ROS produced during NETosis can induce NETosis in SLE patients' low-density granulocytes, showing another pro-inflammatory activation loop [29].

Promoting immune system activation in a vicious circle, NETs are likely to be the link between the interferon and neutrophilic signatures often found in SLE patients [68]. Several factors may modulate neutrophils and NETosis in SLE, therefore affecting disease activity.

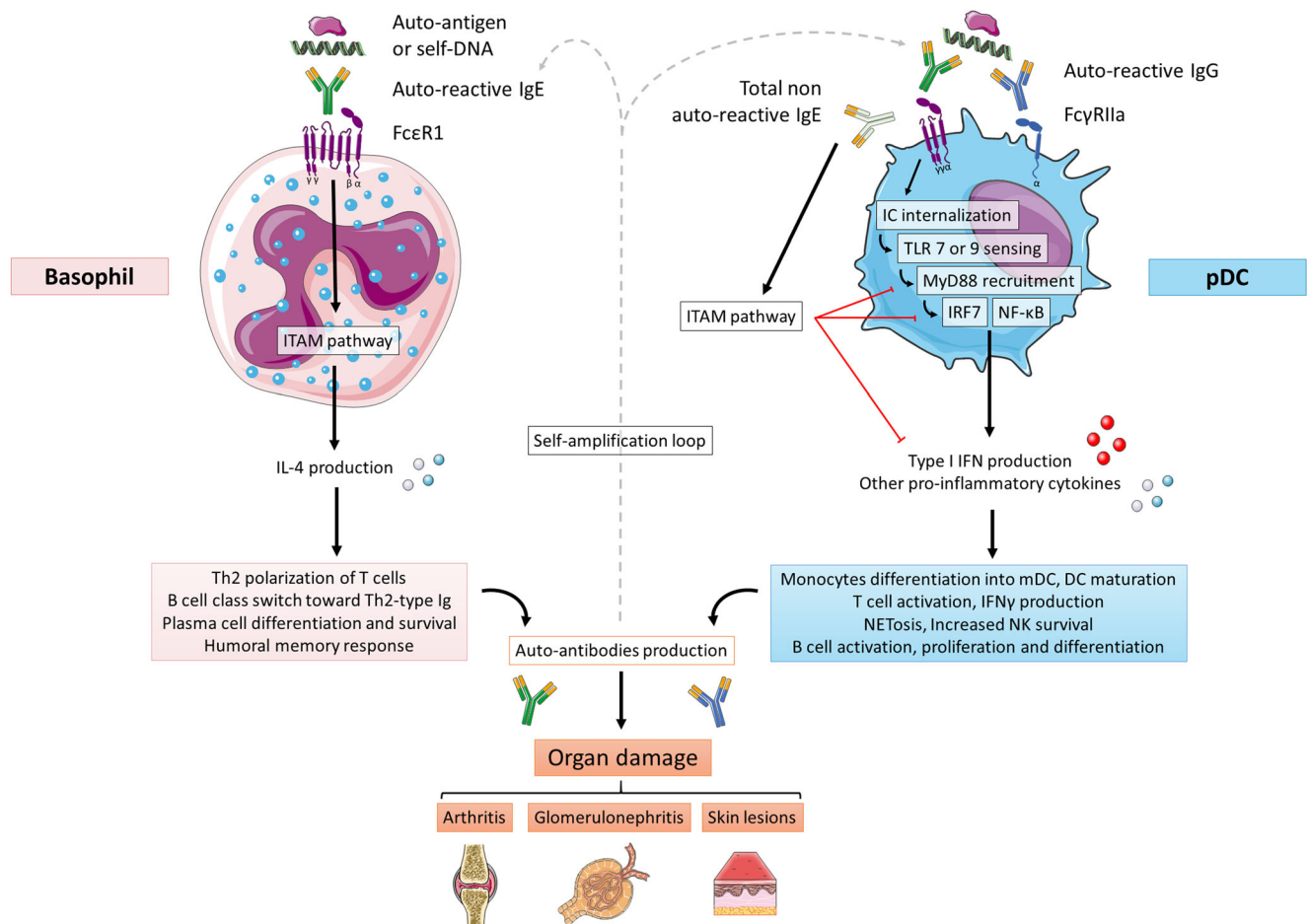


Fig. 3 IgE involvement in SLE pathophysiology. Left panel. Autoreactive IgE bind to self-DNA or another autoantigen forming circulating immune complexes (ICs). The latter induces cross-linking of FcεRI and engagement of ITAM-mediated signaling on basophils. This leads to synthesis and secretion of IL-4 by basophils. Right panel. Circulating ICs including autoreactive IgE and IgG act in synergy and bind, respectively, to FcεRI (lacking β-chain) and FcγRIIa on plasmacytoid dendritic cells (pDCs). After internalization, ICs, recognized by TLR-7 or TLR-9, induce MyD88 recruitment and

phosphorylation of transcription factors such as IRF7 and NF-κB. Eventually, large amounts of type I interferon (IFN-I) and other inflammatory cytokines are produced. FcεRI activation induced by nonautoreactive IgE inhibits expression of TLR-9 and IRF7 through an ITAM-mediated pathway. This leads to downregulation of type I IFN secretion. ICs, immune complexes; IFN, interferon; IL, interleukin; IRF7, interferon regulatory factor 7; NF-κB, nuclear factor-kappa B; pDC, plasmacytoid dendritic cell; TLR, toll-like receptor

Platelet-Induced Neutrophils Modulation of Inflammatory Activity

Another vicious circle promoting innate immune system dysregulation in SLE pathogenesis is exemplified by platelet–neutrophil interactions. As described earlier, NETosis induces the release of immunogenic components such as histones and oxidized mtDNA, both of which are potent platelet activators through their TLRs and other PRRs (see “Toll-Like Receptors and Other Pattern Recognition Receptors” section). Upon activation, platelets promote NETosis in a number of ways. On the one hand, activated platelets relocate and release mitochondria and mtDNA in the extracellular milieu, promoting local inflammation and NETosis [27]. On the other hand, P-selectin (CD62P), a membrane glycoprotein exposed on activated platelets, has been shown to induce NETosis, either directly by its interaction with its P-selectin

glycoprotein ligand-1 (PSGL-1 or CD162) or by the priming of neutrophils for NETosis by other stimuli [106]. Originally, P-selectin (as well as E-selectin) was described as a cellular-adhesion molecule responsible for neutrophil migration to the site of inflammation, also called diapedesis [107]. It is therefore seductive to hypothesize that upon encountering inflammatory conditions, platelets (and endothelial cells) exposing P-selectin locally promote inflammation by priming neutrophil inflammatory functions (ROS production, NETosis...).

Outside of direct and well-described platelet–neutrophil interactions, platelet-derived microparticles may contain nuclear information (mRNA, miRNA) as well as pro-inflammatory organelles (e.g., mitochondria). Recently, active transfer of nuclear information from PMPs to neutrophils was demonstrated, as well as its relevance in an in vivo model of autoimmune arthritis [108].

IgE-Induced Neutrophil Activation

Neutrophils appear to express very low levels of Fc γ RI and IgE does not appear to induce an Fc γ RI-mediated signal in them. However, Mac-2/CD15, a protein of the S-type lectin family expressed by neutrophils, has been described as a receptor for IgE [109]. Interestingly, polyclonal and monoclonal IgE can induce a respiratory burst (ROS) in neutrophils and therefore a pro-inflammatory phenotype [109].

Some authors have described IgE-containing ICs as activators of neutrophils [110], but these results have been challenged by others [111].

Basophil Activation

Global Picture

Although they have been neglected until recently because of their similarity with tissue-resident mast cells, basophils are potent effector cells of the innate immune system. They are characterized by their ability to release histamine. They also produce IL-4 and other cytokines for Th2 polarization, while their antigen presentation ability is still a matter of debate [94, 112]. They also have the potency to induce a switch of B cells toward Th2-type immunoglobulins (IgG1, IgG2b, and IgE), plasma cell differentiation, and survival while supporting humoral memory response. They also promote differentiation of monocytes into M2 macrophages, the anti-inflammatory and pro-fibrotic subtype of macrophages [94]. Basophils can have beneficial and detrimental functions for the host. While they play an important role in protection against infections with parasites, including ticks and helminths, they can be deleterious for the host by promoting pro-inflammatory responses to allergens [113].

Recently, the deleterious role of basophils has been highlighted in SLE patients. This is not only linked to autoreactive IgE included in ICs but also to other factors dysregulated in SLE, which could influence the basophil activation status and their recruitment to secondary lymphoid organs [94].

Platelet-Induced Basophil Activation

It has been shown that platelet-derived supernatants can induce, in vitro, histamine release from human mixed leukocytes containing basophils [114]. However, histamine release was found only when using supernatants from activated platelets. Thus, upon activation, platelets can produce a soluble substance which can initiate basophil-mediated reactions, suggesting that platelets may enhance inflammatory and allergic reactions through its action on basophils [114].

Autoreactive IgE-Induced Basophil Activation

The role of basophils and Th2-type response have been demonstrated in a murine model of lupus nephritis [11]. IgE activate basophils which promote a Th2 environment with, subsequently, production of autoantibodies by plasma cells (Table 3). In this lupus nephritis model using *Lyn*^{-/-} mice, depletion of basophils or the absence of IL-4 or IgE caused a marked reduction in autoantibody production and preserved kidney function.

In individuals with SLE, self-reactive IgE levels are associated with active disease and active lupus nephritis. A more marked activation (HLA-DR⁺) of their basophils was found. Despite a low patient number, it was shown that these basophils were found in the secondary lymphoid tissues where they may influence T- and B-cell functions [11]. Here, they act as amplifiers of the humoral immune response, inducing the upregulation of CD62L, MHC-II, and the B-cell-activating factor BAFF [11] enhancing B-cell proliferation and increased IgG1 and IgE production. Furthermore, by producing IL-4 and IL-6, they promote a Th2 environment with an increase of IL-4 producing activated T-helper cells [11, 115] (Fig. 3).

In a cohort of 48 newly diagnosed patients with SLE, a decreased number and an increased activation state of peripheral basophils were found to correlate with increased autoantibody production and disease activity [116]. Autoreactive IgE activate basophils, resulting in an amplification of autoantibody production but also IL-17 secretion, thereby contributing to the SLE pathogenesis [116].

In the same study, Pan et al. used another murine model of lupus, the MRL/lpr mouse, to confirm observations from *Lyn*^{-/-} mice. Basophil-depleted MRL/lpr mice exhibited a prolonged survival, a decreased level of serum anti-nuclear IgG and IgE, a reduction of kidney injury due to a lesser deposition of IgG and IgE immune complexes in the glomeruli, and a reduction of IL-17 production [116].

Of note, basophils activated by IgE or complement may produce basophil extracellular traps (BETs) [117]. BETs are similar to NETs and induce the release of DAMPs such as mitochondrial DNA, ROS, and antibacterial nuclear components such as histones and DNA [118].

Mastocyte Activation

Mastocytes are myeloid-derived cells well known for their role in allergy and anaphylaxis. These innate immune cells are characterized by a large repartition in all epithelia, the high expression of Fc γ RI, and the fact that they possess many vesicles loaded with vasoactive hormones such as histamine. The mastocyte's role in SLE has been suggested by the identification of mastocyte infiltrates in different organs affected by lupus, such as the skin and kidneys [119, 120].

Recently, a new subset of T-helper cells characterized by IL-9 secretion (named Th9 cells) has been described [121]. Interleukin-9, found to be elevated in SLE [122], has the ability to mediate mastocyte migration into organs where it can subsequently exert a pro-inflammatory or anti-inflammatory effect based on other signals from the microenvironment [123]. Among their pro-inflammatory effects, mastocytes may present autoantigens to T cells through HLA I or II [124], promote immunoglobulin production through CD40L, or express the co-stimulatory factor OX40L which has been shown to promote T follicular helper functions [125] and alter Treg immunosuppressive activity (paper in press).

Outside of their activation by IgE, mastocytes possess Fc γ RI and Fc γ RIII and may therefore be stimulated by IgG and IgE ICs found in SLE. In summary, mast cells are found in SLE lesions and may participate in the immune dysregulation and organ disease in several ways, including the promotion of autoantibody production and alteration of the IgE imbalance (see IgE paradox “[Dendritic Cells and IFN Secretion in SLE](#)” section).

Platelets as Innate Immune Cells

Although their small size and their lack of a nucleus, platelets can be seen as a unique component of the innate immune system. In fact, platelets constitute the second most prevalent blood component and might play a major role in the case of bacteremia (presence of bacteria in the bloodstream).

Firstly, platelets have the capacity to recognize pathogens through their pathogen recognition receptors such as TLRs (see “[Toll-Like Receptors and Other Pattern Recognition Receptors](#)” section). Upon recognition, platelets acquire an activated phenotype (e.g., exposition of tissue factor and P-selectin) and alter their shape by remodeling their cytoskeleton. Gaertner et al. have beautifully demonstrated how platelets could act as mechano-scavengers, binding bacteria and trapping them on their surface [5]. Furthermore, platelet–bacteria bundles facilitate phagocytosis by neutrophils as well as NETosis [5]. As discussed in the “[Neutrophils](#)” section, NETs promote platelet activation (e.g., by the release of mitochondria) as well as aggregation and thrombosis [126].

Secondly, pathogen-activated and NET-activated platelets promote thrombosis in a phenomenon called immunothrombosis [126]. This evolutionarily conserved immune mechanism is used to limit the dissemination of a pathogen via the bloodstream. Immunothrombosis explains why some pathogens produce thrombolytic proteins as an escape mechanism (e.g., streptokinase from *Streptococcus*) and why severe infection can lead to disseminated thrombosis (called disseminated intravascular coagulation). Therefore, we can consider that in SLE, platelets play a central role as innate immune cells, as well as effectors of thrombosis.

Therapeutic Opportunities

Until a few years ago, SLE patients were treated with empiric immunosuppressive therapies at the cost of severe adverse effects such as infection and atherosclerosis which are nowadays the major causes of mortality in SLE [127].

Recent research providing new insights into SLE pathogenesis has opened a huge window of opportunities for targeted therapies. In fact, a recent meta-analysis by Felten et al. identified 74 targeted therapies under development illustrating the dynamics of SLE research considering that its pharmacopeia has little changed outside the recent marketing of belimumab, an anti-BAFF agent [128]. We will describe here the therapies that have potent action on the innate immune system with a particular focus on platelets and IgE.

Nonspecific Therapies Acting Against Innate Immunity

Corticosteroids have revolutionized the treatment of autoimmune diseases including SLE since their first use in 1948 to treat a 29-year-old woman hospitalized for severe rheumatoid arthritis [129]. However, the current paradigm is to avoid their long-term use as they have been consistently linked to dose- and time-dependent increased risk of infection as well as with accelerated atherosclerosis and global damage accrual in SLE [130, 131]. In fact, novel therapeutic protocols try to limit or even avoid the use of corticosteroids [132]. Corticosteroids affect nearly all immune cells, lowering their activation state, pro-inflammatory cytokine production, and co-stimulatory molecule expression. Of note, although intravenous corticosteroids extinguish the IFN signature in SLE patients, they induce an increase in the neutrophil count and do not alter the neutrophilic signature, suggesting that some pathophysiological pathways might not be affected by corticosteroids [68].

Hydroxychloroquine (HCQ) is an antimalarial drug considered as the mainstay of SLE treatment. Hydroxychloroquine use in SLE has demonstrated its ability to decrease damage accrual, corticosteroid cumulative use, flare-ups but also infection risks and thrombosis [133]. Its mechanisms of action are multiple and still incompletely understood. One of them is to decrease or inhibit endosomal and lysosomal acidification, lower TLR activation in response to nucleic acids, and decrease IFN production by pDCs. Interestingly, platelets treated with HCQ present lower activation by different stimuli, with a synergistic effect with aspirin [134]. Furthermore, HCQ decreases antiphospholipid antibody-mediated platelet activation along with thrombotic events in SLE [135], suggesting an anti-platelet mechanism of action of HCQ [136].

Molecules targeting IFN have been developed since the description of the role of IFN in SLE pathophysiology and of an IFN signature in roughly two thirds of adult SLE patients [137]. Different approaches have been used: monoclonal

antibody (mAb) targeting IFN subtypes (e.g., rontalizumab [138] and sifalimumab [139]), mAb targeting IFN receptor (e.g., anifrolumab), or IFN-kinoid which induces a transient polyclonal humoral response against self-IFN [132]. So far, the results have been inconsistent, even in the phase III trial of anifrolumab which has the advantage of blocking most IFN by blocking IFN receptor [140, 141]. Intuitively, patients with a positive IFN signature benefit more from these treatments. Another strategy in trials is to target directly pDCs using an anti-BDCA2 antibody (e.g., BIIB059), and is currently in phase II trial (NCT02847598). However, considering the multiple and redundant mechanisms involved in SLE pathogenesis, the blockade of a single cytokine might not be enough to provide long-lasting disease improvement.

The Janus kinase inhibitor (JAKi) therapeutic class might fill this gap. Janus kinases are a group of tyrosine kinases which are responsible for signal transduction for numerous cytokines and growth factors, including but not limited to: IFN α , IFN γ , IL-2, IL-6, and GM-CSF. Consequently, JAKi could have increased effect by blocking several signaling pathways which are at play in complex inflammatory diseases such as SLE. Moreover, the ubiquitous JAK expression makes JAKi affect nearly all cells, including platelets, neutrophils, and mastocytes [142–144] whose roles in SLE have been detailed previously in this paper. Of note, baricitinib, a JAK-2 inhibitor, has shown its efficacy in some pediatric lupus-like IFN α -mediated diseases such as SAVI [20]. It also showed a decrease of arthritis or rash symptoms (as defined by the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) in adults with nonsevere SLE at the higher dose tested (4 mg/day) [145]. This promising study led to two ongoing phase III trials of baricitinib (BRAVE studies, NCT03616912 and NCT03616964).

Blocking complement activation might also be an interesting strategy in SLE. Recently, an anti-C5a monoclonal antibody (NNC 0151-0000-0000) has completed phase I, but to date, the results are not yet available.

The Interest in Blocking Platelet Activation in SLE

Blocking platelet activation or products of their activation (e.g., CD40L) might be an interesting strategy in SLE.

Aspirin is an irreversible inhibitor of cyclooxygenase I, blocking platelet production of thromboxane A₂ (TXA₂). It has been demonstrated that TXA₂ was increased in SLE and that its level correlated with disease activity [146]. While aspirin could decrease TXA₂ levels in healthy donors, its effect was attenuated in patients with SLE, suggesting a strong and multimodal platelet activation that would benefit from a combination therapy [146].

Clopidogrel is an oral inhibitor of P2Y₁₂, a receptor responsible for platelet activation in response to adenosine diphosphate (ADP). It is widely prescribed in patients with the

most severe cardiovascular disease. In a recent paper, our group demonstrated that in a model of lupus-prone mice, treatment with clopidogrel could decrease several markers of disease activity such as anti-dsDNA antibodies and proteinuria [7]. The clopidogrel effect in SLE may be multimodal: blocking CD40L exposure [147], PMP production [148], and the release of pro-inflammatory factors such as serotonin. These data have led our group to set up a trial of clopidogrel in SLE (CLOPUS, NCT02320357).

CD40L blockade using a monoclonal antibody appears to be an interesting target in SLE. To note, a full-sized monoclonal antibody targeting CD40L was under trial in 2003, but its further development was stopped early after several episodes of thrombosis in the treatment group [149]. Indeed, CD40L-bearing platelets were activated by the Fc fragment of this therapeutic antibody, therefore inducing severe episodes of thrombosis (e.g., myocardial infarction). This gap has been bridged by replacing the Fc fragment by a polyethylene glycol chain as in dapirolizumab, a recombinant humanized monoclonal antibody targeting CD40L. If dapirolizumab showed interesting preliminary results in SLE and Sjogren's disease [150], it failed to meet its primary endpoint (dose responses at 24 weeks on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA)) in a phase II trial [151].

Metformin is a biguanide drug widely used in type 2 diabetes. Its interest in SLE has been raised by a recent report demonstrating its effect on platelet activation and its potency to inhibit platelet release of mtDNA [152]. A proof of concept brought promising data for the use of metformin in SLE as it improved two major clinical endpoints: prednisone exposure and flare incidence [153]. This very cheap and safe drug could be used as an add-on therapy in SLE but more data are needed.

Therapies Targeting Directly IgE and Basophils

As previously detailed, autoreactive IgE and IC containing IgE are involved in basophil and pDC activation. Moreover, IgE deposits with pDC infiltration have been found in kidneys from lupus patients suggesting a contribution to local inflammatory processes [19]. Therefore, IgE might be a promising target in SLE.

Omalizumab, a humanized anti-IgE monoclonal antibody, acts by neutralizing free IgE and inhibiting IgE production by B cells [154]. Other effects have been reported such as a potentially beneficial effect of IgE–anti-IgE immune complexes, playing the role of antigen traps in the blood and in the extravascular compartment and downregulation of Fc ϵ RI on basophils and mast cells [154]. Omalizumab is not able to bind to IgE-bound Fc ϵ RI, thus preventing receptor cross-linking on basophils or pDCs. Omalizumab has been successfully used for patients with moderate to severe or corticoid-resistant asthma [155, 156] and chronic urticaria [157]. This anti-IgE

therapy also showed effectiveness in allergic rhinitis and non-allergic asthma and a fair evidence of efficacy in atopic dermatitis, physical urticaria, mast cell activation disorders, and food allergies. Omalizumab was used to successfully treat patients with bullous pemphigoid, another autoimmune disorder associated with the development of autoreactive IgE directed against BP180 [157].

A phase I clinical trial recently proved the safety of omalizumab for patients with lupus [158]. The efficacy of anti-IgE in these patients remains to be evaluated.

However, it is interesting to note that SLE appeared in patients treated with omalizumab (XOLAIR®) for a moderate to severe asthma or chronic urticaria. Two cases evolved favorably after treatment discontinuation, and one other case relapsed after reintroduction of treatment. Nevertheless, a causal link between SLE and omalizumab could not be formally identified [159].

Targeting FcεRI by using specific inhibitory compounds could be another approach. The pro-apoptotic molecule BCL-2 antagonist/killer (BAK) and the IgE Cε3 domain have been engineered to form a fusion molecule. In vitro, this fusion molecule can efficiently deplete FcεRI-expressing cells [160]. Basophil and pDC depletion has also been achieved with a cytotoxic anti-IL-3Rα antibody, with efficient in vitro results, notably inhibiting TLR-9-induced IFN-inducible gene expression [161].

Because pDCs and basophils predominantly express the inhibitory FcγRIIb in opposition to other activating Fcγ receptors, tandem molecules of Fcγ–Fcε have been engineered. It has been shown that these molecules could suppress FcεRI signaling by co-engaging FcεRI and FcγRIIb receptors on mast cells [162]. Thus, this could be an efficient way to inhibit autoreactive IgE action on pDCs [163].

Helminth therapy. As suggested earlier [13], total IgE could have a protective role in lupus. An inverse association was found between autoimmune diseases and certain helminth infections [164]. Helminth excretory/secretory (ES) products polarize the immune system toward a Th2 response with increased IgE production and prevent Th1 or Th17 immune response, highly involved in SLE pathogenesis. Furthermore, helminth ES products favor an M2 anti-inflammatory macrophage phenotype, decrease DC synthesis of pro-inflammatory cytokines (such as IFNγ or TNFα), and promote the production of immunosuppressive cytokines such as IL-10 or TGFβ thus promoting regulatory T cells. The ability of parasitic worms to skew the immune response from Th1/Th17 to Th2/Tregs has led to a new therapeutic approach: the helminth-based immunotherapy. More precisely, research focused on helminth secretions in order to use them as immunomodulatory drugs.

A secreted compound of the parasitic worm *Acanthocheilonema viteae*, ES-62, was evaluated in a model of lupus prone mice (MRL/Lpr) [165]. Known to inhibit T- and B-cell activation [166, 167], it was successfully used to prevent

lupus nephritis. Indeed, it decreased proteinuria and cellular infiltration of the kidney. It also inhibited plasmablast differentiation with a consequent reduction in antinuclear antibody production, IC, and complement deposition in the kidneys. It also reduced IL-22 production, a cytokine recently found to be involved in lupus pathophysiology [168, 169].

Conclusions

Recent advances in the comprehension of SLE pathogenesis have underlined the implication of the innate immune system in the disease. We have focused our review on the recent data describing the role of platelets and IgE in SLE, which are at the interface between the innate and adaptive immune systems. This study allows a better understanding of systemic lupus as well as the discovery of novel and promising therapeutic targets. In fact, considering that thrombosis and cardiovascular diseases are nowadays the primary cause of mortality in SLE, it is inciting to consider development of therapies targeting both platelet-induced immune dysregulation and thrombosis. Moreover, a better comprehension of the interplay between total and autoreactive IgE (the IgE paradox) might allow us to develop novel and synergistic therapeutic regimens.

Acknowledgments Servier Medical is thanked for providing free art for the figures.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

References

1. Tsokos GC (2011) Systemic lupus erythematosus. *N Engl J Med* 365:2110–2121. <https://doi.org/10.1056/NEJMr1100359>
2. Manderson AP, Botto M, Walport MJ (2004) The role of complement in the development of systemic lupus erythematosus. *Annu Rev Immunol* 22:431–456. <https://doi.org/10.1146/annurev.immunol.22.012703.104549>
3. Jeong DY, Lee SW, Park YH et al (2018) Genetic variation and systemic lupus erythematosus: a field synopsis and systematic meta-analysis. *Autoimmun Rev* 17:553–566. <https://doi.org/10.1016/j.autrev.2017.12.011>
4. Koupenova M, Vitseva O, MacKay CR et al (2014) Platelet-TLR7 mediates host survival and platelet count during viral infection in the absence of platelet-dependent thrombosis. *Blood* 124:791–802. <https://doi.org/10.1182/blood-2013-11-536003>

5. Gaertner F, Ahmad Z, Rosenberger G et al (2017) Migrating platelets are mechano-scavengers that collect and bundle bacteria. *Cell* 171:1368–1382.e23. <https://doi.org/10.1016/j.cell.2017.11.001>
6. Linge P, Fortin PR, Lood C et al (2018) The non-haemostatic role of platelets in systemic lupus erythematosus. *Nat Rev Rheumatol* 14:195–213. <https://doi.org/10.1038/nrrheum.2018.38>
7. Duffau P, Seneschal J, Nicco C et al (2010) Platelet CD154 potentiates interferon- secretion by plasmacytoid dendritic cells in systemic lupus erythematosus. *Sci Transl Med* 2:47ra63–47ra63. <https://doi.org/10.1126/scitranslmed.3001001>
8. Mobarrez F, Vikersfors A, Gustafsson JT et al (2016) Microparticles in the blood of patients with systemic lupus erythematosus (SLE): phenotypic characterization and clinical associations. *Sci Rep* 6:36025. <https://doi.org/10.1038/srep36025>
9. Wu LC, Zarrin AA (2014) The production and regulation of IgE by the immune system. *Nat Rev Immunol* 14:247–259. <https://doi.org/10.1038/nri3632>
10. Dullaers M, De Bruyne R, Ramadani F et al (2012) The who, where, and when of IgE in allergic airway disease. *J Allergy Clin Immunol* 129:635–645. <https://doi.org/10.1016/j.jaci.2011.10.029>
11. Charles N, Hardwick D, Daugas E et al (2010) Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nat Med* 16:701–707. <https://doi.org/10.1038/nm.2159>
12. Dema B, Pellefigues C, Hasni S et al (2014) Autoreactive IgE is prevalent in systemic lupus erythematosus and is associated with increased disease activity and nephritis. *PLoS One* 9:e90424. <https://doi.org/10.1371/journal.pone.0090424>
13. Khoryati L, Augusto J-F, Shipley E, et al (2016) IgE Inhibits Toll-like Receptor 7- and Toll-like Receptor 9-Mediated Expression of Interferon- α by Plasmacytoid Dendritic Cells in Patients With Systemic Lupus Erythematosus. *Arthritis Rheumatol* 68:2221–2231. <https://doi.org/10.1002/art.39679>
14. Augusto J-F, Truchetet M-E, Charles N et al (2018) IgE in lupus pathogenesis: friends or foes? *Autoimmun Rev* 17:361–365. <https://doi.org/10.1016/j.autrev.2017.11.027>
15. Cognasse F (2015) The inflammatory role of platelets via their TLRs and Siglec receptors. *Front Immunol* 6. <https://doi.org/10.3389/fimmu.2015.00083>
16. Lu M, Yu S, Xu W et al (2015) HMGB1 promotes systemic lupus erythematosus by enhancing macrophage inflammatory response. *J Immunol Res* 2015:946748. <https://doi.org/10.1155/2015/946748>
17. Crow MK (2014) Type I interferon in the pathogenesis of lupus. *J Immunol* 192:5459–5468. <https://doi.org/10.4049/jimmunol.1002795>
18. Gill MA, Bajwa G, George TA et al (2010) Counterregulation between the Tcep50RI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol* 184:5999–6006. <https://doi.org/10.4049/jimmunol.0901194>
19. Henault J, Riggs JM, Karnell JL et al (2016) Self-reactive IgE exacerbates interferon responses associated with autoimmunity. *Nat Immunol* 17:196–203. <https://doi.org/10.1038/ni.3326>
20. Liu Y, Jesus AA, Marrero B et al (2014) Activated STING in a vascular and pulmonary syndrome. *N Engl J Med* 371:507–518. <https://doi.org/10.1056/NEJMoa1312625>
21. Sanchez GAM, Reinhardt A, Ramsey S et al (2018) JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. <https://doi.org/10.1172/JCI98814>
22. Matzinger P Tolerance, Danger, and the extended family. *Annu Rev Immunol* 55
23. Seong S-Y, Matzinger P (2004) Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol* 4:469–478. <https://doi.org/10.1038/nri1372>
24. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ (2010) Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464:104–107. <https://doi.org/10.1038/nature08780>
25. White MJ, McArthur K, Metcalf D et al (2014) Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. *Cell* 159:1549–1562. <https://doi.org/10.1016/j.cell.2014.11.036>
26. West AP, Shadel GS (2017) Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nat Rev Immunol* 17:363–375. <https://doi.org/10.1038/nri.2017.21>
27. Boudreau LH, Duchez A-C, Cloutier N et al (2014) Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A2 to promote inflammation. *Blood* 124: 2173–2183. <https://doi.org/10.1182/blood-2014-05-573543>
28. Caielli S, Athale S, Domic B, Murat E, Chandra M, Banchemareau R, Baisch J, Phelps K, Clayton S, Gong M, Wright T, Punaro M, Palucka K, Guiducci C, Banchemareau J, Pascual V (2016) Oxidized mitochondrial nucleoids released by neutrophils drive type I interferon production in human lupus. *J Exp Med* 213: 697–713. <https://doi.org/10.1084/jem.20151876>
29. Lood C, Blanco LP, Purmalek MM et al (2016) Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat Med* 22: 146–153. <https://doi.org/10.1038/nm.4027>
30. Shimada K, Crother TR, Karlin J et al (2012) Oxidized mitochondrial DNA activates the NLRP3 Inflammasome during apoptosis. *Immunity* 36:401–414. <https://doi.org/10.1016/j.immuni.2012.01.009>
31. Dorward DA, Lucas CD, Doherty MK, Chapman GB, Scholefield EJ, Conway Morris A, Felton JM, Kipari T, Humphries DC, Robb CT, Simpson AJ, Whitfield PD, Haslett C, Dhaliwal K, Rossi AG (2017) Novel role for endogenous mitochondrial formylated peptide-driven formyl peptide receptor 1 signalling in acute respiratory distress syndrome. *Thorax* 72:928–936. <https://doi.org/10.1136/thoraxjnl-2017-210030>
32. Soyfoo MS, Roth J, Vogl T et al (2009) Phagocyte-specific S100A8/A9 protein levels during disease exacerbations and infections in systemic lupus erythematosus. *J Rheumatol* 36:2190–2194. <https://doi.org/10.3899/jrheum.081302>
33. Yang H, Hreggvidsdottir HS, Palmblad K et al (2010) A critical cysteine is required for HMGB1 binding to Toll-like receptor 4 and activation of macrophage cytokine release. *Proc Natl Acad Sci* 107:11942–11947. <https://doi.org/10.1073/pnas.1003893107>
34. Ryckman C, Vandal K, Rouleau P et al (2003) Proinflammatory Activities of S100: Proteins S100A8, S100A9, and S100A8/A9 Induce Neutrophil Chemotaxis and Adhesion. *J Immunol* 170: 3233–3242
35. Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, Avila C, Kambham N, Bierhaus A, Nawroth P, Neurath MF, Slattery T, Beach D, McClary J, Nagashima M, Morser J, Stern D, Schmidt AM (1999) RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 97:889–901
36. Schiraldi M, Raucci A, Muñoz LM, Livoti E, Celona B, Venereau E, Apuzzo T, de Marchis F, Pedotti M, Bachi A, Thelen M, Varani L, Mellado M, Proudfoot A, Bianchi ME, Uguccioni M (2012) HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4. *J Exp Med* 209:551–563. <https://doi.org/10.1084/jem.20111739>
37. Maugeri N, Franchini S, Campana L et al (2012) Circulating platelets as a source of the damage-associated molecular pattern HMGB1 in patients with systemic sclerosis. *Autoimmunity* 45: 584–587. <https://doi.org/10.3109/08916934.2012.719946>

38. Lood C, Tydén H, Gullstrand B et al (2016) Platelet-derived S100A8/A9 and cardiovascular disease in systemic lupus erythematosus. *Arthritis Rheum* 68:1970–1980. <https://doi.org/10.1002/art.39656>
39. Vogel S, Bodenstein R, Chen Q et al (2015) Platelet-derived HMGB1 is a critical mediator of thrombosis. *J Clin Invest* 125:4638–4654. <https://doi.org/10.1172/JCI81660>
40. Murphy K, Travers P, Walport M, Janeway C Janeway's immunobiology, 8th edition. Garland Science, New York ©2012
41. Truedsson L, Bengtsson AA, Sturfelt G (2007) Complement deficiencies and systemic lupus erythematosus. *Autoimmunity* 40:560–566. <https://doi.org/10.1080/08916930701510673>
42. Farrera C, Fadeel B (2013) Macrophage Clearance of Neutrophil Extracellular Traps Is a Silent Process. *J Immunol* 191:2647–2656. <https://doi.org/10.4049/jimmunol.1300436>
43. Leffler J, Bengtsson AA, Blom AM (2014) The complement system in systemic lupus erythematosus: an update. *Ann Rheum Dis* 73:1601–1606. <https://doi.org/10.1136/annrheumdis-2014-205287>
44. Potlukova E, Kralikova P (2008) Complement component C1q and anti-C1q antibodies in theory and in clinical practice. *Scand J Immunol* 67:423–430. <https://doi.org/10.1111/j.1365-3083.2008.02089.x>
45. Kao AH, McBurney CA, Sattar A et al (2014) Relation of platelet C4d with all-cause mortality and ischemic stroke in patients with systemic lupus erythematosus. *Transl Stroke Res* 5:510–518. <https://doi.org/10.1007/s12975-013-0295-9>
46. Del Conde I, Cruz MA, Zhang H et al (2005) Platelet activation leads to activation and propagation of the complement system. *J Exp Med* 201:871–879. <https://doi.org/10.1084/jem.20041497>
47. Lood C, Tydén H, Gullstrand B, Sturfelt G, Jönsen A, Truedsson L, Bengtsson AA (2014) Platelet activation and anti-phospholipid antibodies collaborate in the activation of the complement system on platelets in systemic lupus erythematosus. *PLoS One* 9:e99386. <https://doi.org/10.1371/journal.pone.0099386>
48. Hamad OA, Ekdahl KN, Nilsson PH et al (2008) Complement activation triggered by chondroitin sulfate released by thrombin receptor-activated platelets. *J Thromb Haemost* 6:1413–1421. <https://doi.org/10.1111/j.1538-7836.2008.03034.x>
49. Ghebrehiwet B, Lim BL, Kumar R et al (2001) gC1q-R/p33, a member of a new class of multifunctional and multicompartmental cellular proteins, is involved in inflammation and infection. *Immunol Rev* 180:65–77
50. Hamilton KK, Hattori R, Esmon CT, Sims PJ (1990) Complement proteins C5b-9 induce vesiculation of the endothelial plasma membrane and expose catalytic surface for assembly of the prothrombinase enzyme complex. *J Biol Chem* 265:3809–3814
51. Saadi S (1995) Complement-mediated regulation of tissue factor activity in endothelium. *J Exp Med* 182:1807–1814. <https://doi.org/10.1084/jem.182.6.1807>
52. Kilgore KS, Shen JP, Miller BF et al (1995) Enhancement by the complement membrane attack complex of tumor necrosis factor-alpha-induced endothelial cell expression of E-selectin and ICAM-1. *J Immunol* 155:1434–1441
53. Guégan J-P, Legembre P (2018) Nonapoptotic functions of Fas/CD95 in the immune response. *FEBS J* 285:809–827. <https://doi.org/10.1111/febs.14292>
54. Cullen SP, Henry CM, Kearney CJ et al (2013) Fas/CD95-induced chemokines can serve as “find-me” signals for apoptotic cells. *Mol Cell* 49:1034–1048. <https://doi.org/10.1016/j.molcel.2013.01.025>
55. Dupont PJ, Warrens AN (2007) Fas ligand exerts its pro-inflammatory effects via neutrophil recruitment but not activation. *Immunology* 120:133–139. <https://doi.org/10.1111/j.1365-2567.2006.02504.x>
56. Poissonnier A, Guégan J-P, Nguyen HT et al (2018) Disrupting the CD95–PLCγ1 interaction prevents Th17-driven inflammation. *Nat Chem Biol*. <https://doi.org/10.1038/s41589-018-0162-9>
57. Butt D, Chan TD, Bourme K, Hermes JR, Nguyen A, Statham A, O'Reilly LA, Strasser A, Price S, Schofield P, Christ D, Basten A, Ma CS, Tangye SG, Phan TG, Rao VK, Brink R (2015) FAS inactivation releases unconventional germinal center B cells that escape antigen control and drive IgE and autoantibody production. *Immunity* 42:890–902. <https://doi.org/10.1016/j.immuni.2015.04.010>
58. Collin M, Bigley V, Haniffa M, Hambleton S (2011) Human dendritic cell deficiency: the missing ID? *Nat Rev Immunol* 11:575–583. <https://doi.org/10.1038/nri3046>
59. Banchereau J, Steinman RM (1998) Dendritic cells and the control of immunity. *Nature* 392:245–252. <https://doi.org/10.1038/32588>
60. Haniffa M, Collin M, Ginhoux F (2013) Ontogeny and functional specialization of dendritic cells in human and mouse. In: *Adv Immunol Elsevier*, pp 1–49
61. Schäkel K, Kannagi R, Kniep B, Goto Y, Mitsuoka C, Zwirner J, Soruri A, von Kietzell M, Rieber EP (2002) 6-Sulfo LacNAc, a novel carbohydrate modification of PSGL-1, defines an inflammatory type of human dendritic cells. *Immunity* 17:289–301
62. Onai N, Kurabayashi K, Hosoi-Amaike M et al (2013) A clonogenic progenitor with prominent plasmacytoid dendritic cell developmental potential. *Immunity* 38:943–957. <https://doi.org/10.1016/j.immuni.2013.04.006>
63. Siegal FP, Kadowaki N, Shodell M et al (1999) The nature of the principal type 1 interferon-producing cells in human blood. *Science* 284:1835–1837
64. Cella M, Jarrossay D, Facchetti F, Alebardi O, Nakajima H, Lanzavecchia A, Colonna M (1999) Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat Med* 5:919–923. <https://doi.org/10.1038/11360>
65. Reizis B, Bunin A, Ghosh HS et al (2011) Plasmacytoid dendritic cells: recent progress and open questions. *Annu Rev Immunol* 29:163–183. <https://doi.org/10.1146/annurev-immunol-031210-101345>
66. McNab F, Mayer-Barber K, Sher A et al (2015) Type I interferons in infectious disease. *Nat Rev Immunol* 15:87–103. <https://doi.org/10.1038/nri3787>
67. Blanco P, Palucka AK, Gill M et al (2001) Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. *Science* 294:1540–1543. <https://doi.org/10.1126/science.1064890>
68. Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, Pascual V (2003) Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med* 197:711–723. <https://doi.org/10.1084/jem.20021553>
69. Rönnblom L, Alm GV (2001) An etiopathogenic role for the type I IFN system in SLE. *Trends Immunol* 22:427–431
70. Rönnblom L, Alm GV (2001) A pivotal role for the natural interferon alpha-producing cells (plasmacytoid dendritic cells) in the pathogenesis of lupus. *J Exp Med* 194:F59–F63
71. Honda K, Takaoka A, Taniguchi T (2006) Type I interferon [corrected] gene induction by the interferon regulatory factor family of transcription factors. *Immunity* 25:349–360. <https://doi.org/10.1016/j.immuni.2006.08.009>
72. Kawai T, Akira S (2007) Signaling to NF-kappaB by Toll-like receptors. *Trends Mol Med* 13:460–469. <https://doi.org/10.1016/j.molmed.2007.09.002>
73. Scherlinger M, Guillotin V, Truchetet M-E, Contin-Bordes C, Sisirak V, Duffau P, Lazaro E, Richez C, Blanco P (2018) Systemic lupus erythematosus and systemic sclerosis: all roads lead to platelets. *Autoimmun Rev* 17:625–635. <https://doi.org/10.1016/j.autrev.2018.01.012>

74. Amison RT, Cleary SJ, Riffó-Vasquez Y et al (2018) Platelets play a central role in sensitization to allergen. *Am J Respir Cell Mol Biol* 59:96–103. <https://doi.org/10.1165/rcmb.2017-0401OC>
75. Elzey BD, Tian J, Jensen RJ et al (2003) Platelet-mediated modulation of adaptive immunity: a communication link between innate and adaptive immune compartments. *Immunity* 19:9–19
76. Urzainqui A, Martínez del Hoyo G, Lamana A et al (2007) Functional role of P-selectin glycoprotein ligand 1/P-selectin interaction in the generation of tolerogenic dendritic cells. *J Immunol Baltim Md 1950* 179:7457–7465
77. Li N, Ghia J-E, Wang H et al (2011) Serotonin activates dendritic cell function in the context of gut inflammation. *Am J Pathol* 178: 662–671. <https://doi.org/10.1016/j.ajpath.2010.10.028>
78. Ries M, Schuster P, Thomann S et al (2013) Identification of novel oligonucleotides from mitochondrial DNA that spontaneously induce plasmacytoid dendritic cell activation. *J Leukoc Biol* 94: 123–135. <https://doi.org/10.1189/jlb.0612278>
79. Tian J, Avalos AM, Mao S-Y et al (2007) Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nat Immunol* 8:487–496. <https://doi.org/10.1038/nri1457>
80. Viallard J-F, Solanilla A, Gauthier B et al (2002) Increased soluble and platelet-associated CD40 ligand in essential thrombocythemia and reactive thrombocytosis. *Blood* 99:2612–2614. <https://doi.org/10.1182/blood.V99.7.2612>
81. Elzey BD, Tian J, Jensen RJ et al (2003) Platelet-mediated modulation of adaptive immunity. *Immunity* 19:9–19. [https://doi.org/10.1016/S1074-7613\(03\)00177-8](https://doi.org/10.1016/S1074-7613(03)00177-8)
82. Early GS, Zhao W, Burns CM (1996) Anti-CD40 ligand antibody treatment prevents the development of lupus-like nephritis in a subset of New Zealand black x New Zealand white mice. Response correlates with the absence of an anti-antibody response. *J Immunol Baltim Md 1950* 157:3159–3164
83. Cloutier N, Tan S, Boudreau LH et al (2013) The exposure of autoantigens by microparticles underlies the formation of potent inflammatory components: the microparticle-associated immune complexes: immune complexes contain microparticles. *EMBO Mol Med* 5:235–249. <https://doi.org/10.1002/emmm.201201846>
84. Burbano C, Villar-Vesga J, Orejuela J, et al (2018) Potential involvement of platelet-derived microparticles and microparticles forming immune complexes during monocyte activation in patients with systemic lupus erythematosus. *Front Immunol* 9. <https://doi.org/10.3389/fimmu.2018.00322>
85. Permin H, Wiik A (1978) The prevalence of IgE antinuclear antibodies in rheumatoid arthritis and systemic lupus erythematosus. *Acta Pathol Microbiol Scand [C]* 86C:245–249
86. Sanjuan MA, Sagar D, Kolbeck R (2016) Role of IgE in autoimmunity. *J Allergy Clin Immunol* 137:1651–1661. <https://doi.org/10.1016/j.jaci.2016.04.007>
87. van der Kleij H, Charles N, Karimi K, Mao YK, Foster J, Janssen L, Chang Yang P, Kunze W, Rivera J, Bienenstock J (2010) Evidence for neuronal expression of functional Fc (epsilon and gamma) receptors. *J Allergy Clin Immunol* 125:757–760. <https://doi.org/10.1016/j.jaci.2009.10.054>
88. Paul WE (2013) *Fundamental immunology*, 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia
89. Gilliet M, Cao W, Liu Y-J (2008) Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. *Nat Rev Immunol* 8:594–606. <https://doi.org/10.1038/nri2358>
90. Cao W, Rosen DB, Ito T et al (2006) Plasmacytoid dendritic cell-specific receptor ILT7-Fc epsilonRI gamma inhibits Toll-like receptor-induced interferon production. *J Exp Med* 203:1399–1405. <https://doi.org/10.1084/jem.20052454>
91. Cao W, Zhang L, Rosen DB, Bover L, Watanabe G, Bao M, Lanier LL, Liu YJ (2007) BDCA2/Fc epsilonRI gamma complex signals through a novel BCR-like pathway in human plasmacytoid dendritic cells. *PLoS Biol* 5:e248. <https://doi.org/10.1371/journal.pbio.0050248>
92. Schroeder JT, Bieneman AP, Xiao H et al (2005) TLR9- and Fc epsilonRI-mediated responses oppose one another in plasmacytoid dendritic cells by down-regulating receptor expression. *J Immunol* 175:5724–5731
93. Tversky JR, Le TV, Bieneman AP et al (2008) Human blood dendritic cells from allergic subjects have impaired capacity to produce interferon-alpha via Toll-like receptor 9. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 38:781–788. <https://doi.org/10.1111/j.1365-2222.2008.02954.x>
94. Pellefigues C, Charles N (2013) The deleterious role of basophils in systemic lupus erythematosus. *Curr Opin Immunol* 25:704–711. <https://doi.org/10.1016/j.coi.2013.10.003>
95. Rodriguez Gomez M, Talke Y, Goebel N et al (2010) Basophils support the survival of plasma cells in mice. *J Immunol Baltim Md 1950* 185:7180–7185. <https://doi.org/10.4049/jimmunol.1002319>
96. Hanaoka H, Okazaki Y, Satoh T et al (2012) Circulating anti-double-stranded DNA antibody-secreting cells in patients with systemic lupus erythematosus: a novel biomarker for disease activity. *Lupus* 21:1284–1293. <https://doi.org/10.1177/0961203312453191>
97. Nimmerjahn F, Ravetch JV (2007) The antiinflammatory activity of IgG: the intravenous IgG paradox. *J Exp Med* 204:11–15. <https://doi.org/10.1084/jem.20061788>
98. Green DS, Lum T, Green JA (2004) IgG-derived Fc down-regulates virus-induced plasmacytoid dendritic cell (pDC) IFNalpha production. *Cytokine* 26:209–216. <https://doi.org/10.1016/j.cyto.2004.02.012>
99. Haserick JR, Sundberg RD (1948) The bone marrow as a diagnostic aid in acute disseminated lupus erythematosus; report on the Hargraves' L. E. cell. *J Invest Dermatol* 11:209–213
100. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A (2004) Neutrophil extracellular traps kill bacteria. *Science* 303:1532–1535. <https://doi.org/10.1126/science.1092385>
101. Berthelot J-M, Le Goff B, Neel A et al (2017) NETosis: at the crossroads of rheumatoid arthritis, lupus, and vasculitis. *Joint Bone Spine* 84:255–262. <https://doi.org/10.1016/j.jbspin.2016.05.013>
102. Lande R, Ganguly D, Facchinetti V, Frasca L, Conrad C, Gregorio J, Meller S, Chamilos G, Sebasigari R, Riccieri V, Bassett R, Amuro H, Fukuhara S, Ito T, Liu YJ, Gilliet M (2011) Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Sci Transl Med* 3:73ra19. <https://doi.org/10.1126/scitranslmed.3001180>
103. Garcia-Romo GS, Caielli S, Vega B et al (2011) Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med* 3:73ra20. <https://doi.org/10.1126/scitranslmed.3001201>
104. Villanueva E, Yalavarthi S, Berthier CC et al (2011) Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. *J Immunol Baltim Md 1950* 187:538–552. <https://doi.org/10.4049/jimmunol.1100450>
105. Hakkim A, Fümrohr BG, Amann K et al (2010) Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc Natl Acad Sci U S A* 107:9813–9818. <https://doi.org/10.1073/pnas.0909927107>
106. Panicker SR, Mehta-D'souza P, Zhang N et al (2017) Circulating soluble P-selectin must dimerize to promote inflammation and coagulation in mice. *Blood* 130:181–191. <https://doi.org/10.1182/blood-2017-02-770479>
107. Lam FW, Burns AR, Smith CW, Rumbaut RE (2011) Platelets enhance neutrophil transendothelial migration via P-selectin

- glycoprotein ligand-1. *Am J Physiol Heart Circ Physiol* 300: H468–H475. <https://doi.org/10.1152/ajpheart.00491.2010>
108. Duche A-C, Boudreau LH, Naika GS et al (2015) Platelet microparticles are internalized in neutrophils via the concerted activity of 12-lipoxygenase and secreted phospholipase A₂-IIA. *Proc Natl Acad Sci* 112:E3564–E3573. <https://doi.org/10.1073/pnas.1507905112>
 109. Truong MJ, Gruart V, Kusnierz JP et al (1993) Human neutrophils express immunoglobulin E (IgE)-binding proteins (Mac-2/epsilon BP) of the S-type lectin family: role in IgE-dependent activation. *J Exp Med* 177:243–248
 110. De Clerck LS, Gigase PL, Bridts CH, Stevens WJ (1988) Neutrophil activation by IgE-containing circulating immune complexes of patients with connective tissue diseases. *J Allergy Clin Immunol* 81:95–99
 111. Zhang W, Voice J, Lachmann PJ (1995) A systematic study of neutrophil degranulation and respiratory burst in vitro by defined immune complexes. *Clin Exp Immunol* 101:507–514
 112. Karasuyama H, Yamanishi Y (2014) Basophils have emerged as a key player in immunity. *Curr Opin Immunol* 31:1–7. <https://doi.org/10.1016/j.coi.2014.07.004>
 113. Voehringer D (2013) Protective and pathological roles of mast cells and basophils. *Nat Rev Immunol* 13:362–375. <https://doi.org/10.1038/nri3427>
 114. Orchard MA, Kagey-Sobotka A, Proud D, Lichtenstein LM (1986) Basophil histamine release induced by a substance from stimulated human platelets. *J Immunol Baltim Md* 136: 2240–2244
 115. Karasuyama H, Mukai K, Obata K et al (2011) Nonredundant roles of basophils in immunity. *Annu Rev Immunol* 29:45–69. <https://doi.org/10.1146/annurev-immunol-031210-101257>
 116. Pan Q, Gong L, Xiao H et al (2017) Basophil activation-dependent autoantibody and interleukin-17 production exacerbate systemic lupus erythematosus. *Front Immunol* 8. <https://doi.org/10.3389/fimmu.2017.00348>
 117. Morshed M, Hlushchuk R, Simon D et al (2014) NADPH oxidase-independent formation of extracellular DNA traps by basophils. *J Immunol Baltim Md* 192:5314–5323. <https://doi.org/10.4049/jimmunol.1303418>
 118. Yousefi S, Morshed M, Amini P et al (2015) Basophils exhibit antibacterial activity through extracellular trap formation. *Allergy* 70:1184–1188. <https://doi.org/10.1111/all.12662>
 119. Kaczmarczyk-Sekuła K, Dyduch G, Kostański M, Wielowieyska-Szybińska D, Szpor J, Białas M, Okoń K (2016) Mast cells in systemic and cutaneous lupus erythematosus. *Pol J Pathol* 66: 397–402. <https://doi.org/10.5114/pjp.2015.57253>
 120. Kaczmarczyk K, Musiał J, Soja J et al (2015) Renal interstitial mast cell count is significantly higher in membranoproliferative glomerulonephritis than in class IV lupus nephritis. *Pol J Pathol Off J Pol Soc Pathol* 66:149–153
 121. Veldhoen M, Uytendhoe C, van Snick J, Helmby H, Westendorf A, Buer J, Martin B, Wilhelm C, Stockinger B (2008) Transforming growth factor-beta “reprograms” the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. *Nat Immunol* 9:1341–1346. <https://doi.org/10.1038/ni.1659>
 122. Yanaba K, Yoshizaki A, Asano Y et al (2011) Serum interleukin 9 levels are increased in patients with systemic sclerosis: association with lower frequency and severity of pulmonary fibrosis. *J Rheumatol* 38:2193–2197. <https://doi.org/10.3899/jrheum.110268>
 123. Galli SJ, Grimaldeston M, Tsai M (2008) Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. *Nat Rev Immunol* 8:478–486. <https://doi.org/10.1038/nri2327>
 124. Galli SJ, Nakae S, Tsai M (2005) Mast cells in the development of adaptive immune responses. *Nat Immunol* 6:135–142. <https://doi.org/10.1038/nri1158>
 125. Jacquemin C, Schmitt N, Contin-Bordes C et al (2015) OX40 ligand contributes to human lupus pathogenesis by promoting T follicular helper response. *Immunity* 42:1159–1170. <https://doi.org/10.1016/j.immuni.2015.05.012>
 126. Gaertner F, Massberg S (2016) Blood coagulation in immunothrombosis—at the frontline of intravascular immunity. *Semin Immunol* 28:561–569. <https://doi.org/10.1016/j.smim.2016.10.010>
 127. Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA (2014) Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies: mortality in SLE. *Arthritis Care Res* 66:608–616. <https://doi.org/10.1002/acr.22173>
 128. Felten R, Dervovic E, Chasset F et al (2018) The 2018 pipeline of targeted therapies under clinical development for Systemic Lupus Erythematosus: a systematic review of trials. *Autoimmun Rev* 17: 781–790. <https://doi.org/10.1016/j.autrev.2018.02.011>
 129. Benedek TG (2011) History of the development of corticosteroid therapy. *Clin Exp Rheumatol* 29:S–5–12
 130. Yang S-C, Lai Y-Y, Huang M-C, et al (2018) Corticosteroid dose and the risk of opportunistic infection in a national systemic lupus erythematosus cohort. *Lupus* 961203318792352. <https://doi.org/10.1177/0961203318792352>
 131. Bruce IN, O’Keeffe AG, Farewell V et al (2015) Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. *Ann Rheum Dis* 74:1706–1713. <https://doi.org/10.1136/annrheumdis-2013-205171>
 132. Lazaro E, Scherlinger M, Truchetet M-E et al (2017) Biotherapies in systemic lupus erythematosus: new targets. *Joint Bone Spine* 84:267–274. <https://doi.org/10.1016/j.jbspin.2016.07.004>
 133. Costedoat-Chalumeau N, Dunogué B, Morel N, le Guern V, Guettrot-Imbert G (2014) Hydroxychloroquine: a multifaceted treatment in lupus. *Presse Med* 43:e167–e180. <https://doi.org/10.1016/j.lpm.2014.03.007>
 134. Achuthan S, Ahluwalia J, Shafiq N, Bhalla A, Pareek A, Chandurkar N, Malhotra S (2015) Hydroxychloroquine’s efficacy as an antiplatelet agent study in healthy volunteers: a proof of concept study. *J Cardiovasc Pharmacol Ther* 20:174–180. <https://doi.org/10.1177/1074248414546324>
 135. Espinola RG, Pierangeli SS, Gharavi AE et al (2002) Hydroxychloroquine reverses platelet activation induced by human IgG antiphospholipid antibodies. *Thromb Haemost* 87:518–522
 136. Belizna C (2015) Hydroxychloroquine as an anti-thrombotic in antiphospholipid syndrome. *Autoimmun Rev* 14:358–362. <https://doi.org/10.1016/j.autrev.2014.12.006>
 137. Becker AM, Dao KH, Han BK et al (2013) SLE peripheral blood B cell, T cell and myeloid cell transcriptomes display unique profiles and each subset contributes to the interferon signature. *PLoS One* 8:e67003. <https://doi.org/10.1371/journal.pone.0067003>
 138. Kalunian KC, Merrill JT, Maciuga R et al (2016) A phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). *Ann Rheum Dis* 75:196–202. <https://doi.org/10.1136/annrheumdis-2014-206090>
 139. Khamashta M, Merrill JT, Werth VP et al (2016) Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 75:1909–1916. <https://doi.org/10.1136/annrheumdis-2015-208562>
 140. Furie R, Khamashta M, Merrill JT et al (2017) Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheum* 69:376–386. <https://doi.org/10.1002/art.39962>

141. AstraZeneca (2018) Update on TULIP 1 phase III trial for anifrolumab in systemic lupus erythematosus. <https://www.astrazeneca.com/media-centre/pressreleases/2018/update-on-tulip-1-phase-iii-trial-for-anifrolumab-in-systemic-lupus-erythematosus-31082018.html> (Accessed 18 Sept 2018)
142. Lu W-J, Lin K-C, Huang S-Y, Thomas PA, Wu YH, Wu HC, Lin KH, Sheu JR (2014) Role of a Janus kinase 2-dependent signaling pathway in platelet activation. *Thromb Res* 133:1088–1096. <https://doi.org/10.1016/j.thromres.2014.03.042>
143. Futosi K, Fodor S, Mócsai A (2013) Neutrophil cell surface receptors and their intracellular signal transduction pathways. *Int Immunopharmacol* 17:638–650. <https://doi.org/10.1016/j.intimp.2013.06.034>
144. Tanimoto A, Ogawa Y, Oki C et al (2015) Pharmacological properties of JTE-052: a novel potent JAK inhibitor that suppresses various inflammatory responses in vitro and in vivo. *Inflamm Res* 64:41–51. <https://doi.org/10.1007/s00011-014-0782-9>
145. Wallace DJ, Furie RA, Tanaka Y et al (2018) Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Lond Engl* 392:222–231. [https://doi.org/10.1016/S0140-6736\(18\)31363-1](https://doi.org/10.1016/S0140-6736(18)31363-1)
146. Avalos I, Chung CP, Oeser A et al (2007) Aspirin therapy and thromboxane biosynthesis in systemic lupus erythematosus. *Lupus* 16:981–986. <https://doi.org/10.1177/0961203307083313>
147. Hermann A, Rauch BH, Braun M et al (2001) Platelet CD40 ligand (CD40L)—subcellular localization, regulation of expression, and inhibition by clopidogrel. *Platelets* 12:74–82
148. França CN, Pinheiro LFM, Izar MCO et al (2012) Endothelial progenitor cell mobilization and platelet microparticle release are influenced by clopidogrel plasma levels in stable coronary artery disease. *Circ J Off J Jpn Circ Soc* 76:729–736
149. Boumpas DT, Furie R, Manzi S et al (2003) A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. *Arthritis Rheum* 48:719–727. <https://doi.org/10.1002/art.10856>
150. Chamberlain C, Colman PJ, Ranger AM et al (2017) Repeated administration of dapirolizumab pegol in a randomised phase I study is well tolerated and accompanied by improvements in several composite measures of systemic lupus erythematosus disease activity and changes in whole blood transcriptomic profiles. *Ann Rheum Dis* 76:1837–1844. <https://doi.org/10.1136/annrheumdis-2017-211388>
151. UCB, Biogen (2018) UCB and Biogen announce topline results from a phase 2b study of dapirolizumab pegol in systemic lupus erythematosus. <https://www.ucb.com/stories-media/Press-Releases/article/UCB-and-Biogen-Announce-Topline-Results-from-a-Phase-2b-Study-of-Dapirolizumab-Pegol-in-Systemic-Lupus-Erythematosus> (Accessed 23 Oct 2018)
152. Xin G, Wei Z, Ji C, et al (2016) Metformin Uniquely Prevents Thrombosis by Inhibiting Platelet Activation and mtDNA Release. *Sci Rep* 6:. <https://doi.org/10.1038/srep36222>
153. Wang H, Li T, Chen S et al (2015) Neutrophil extracellular trap mitochondrial DNA and its autoantibody in systemic lupus erythematosus and a proof-of-concept trial of metformin. *Arthritis Rheum* 67:3190–3200. <https://doi.org/10.1002/art.39296>
154. Chang TW (2000) The pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 18:157–162. <https://doi.org/10.1038/72601>
155. Busse W, Corren J, Lanier BQ et al (2001) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 108:184–190. <https://doi.org/10.1067/mai.2001.117880>
156. Holgate ST, Chuchalin AG, Hébert J et al (2004) Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 34:632–638. <https://doi.org/10.1111/j.1365-2222.2004.1916.x>
157. Chia JC, Mydlarski PR (2017) Dermatologic uses of omalizumab. *J Dermatol Treat* 28:332–337. <https://doi.org/10.1080/09546634.2016.1249819>
158. Hasni S, Gupta S, Davis M et al (2018) Safety and tolerability of omalizumab, a randomized clinical trial of humanized anti-IgE monoclonal antibody in systemic lupus erythematosus (STOP LUPUS). *Arthritis Rheumatol Hoboken NJ*. <https://doi.org/10.1002/art.40828>
159. European Medicines Agency (2016) Procedure no. EMEA/H/C/PSUSA/00002214/201512. Committee for Medicinal Products for Human Use (CHMP)
160. Kraft S, Kinet J-P (2007) New developments in FcεpsilonRI regulation, function and inhibition. *Nat Rev Immunol* 7:365–378. <https://doi.org/10.1038/nri2072>
161. Oon S, Huynh H, Tai TY et al (2016) A cytotoxic anti-IL-3Rα antibody targets key cells and cytokines implicated in systemic lupus erythematosus. *JCI Insight* 1:e86131. <https://doi.org/10.1172/jci.insight.86131>
162. Cemerski S, Chu SY, Moore GL, Muchhal US, Desjarlais JR, Szymkowski DE (2012) Suppression of mast cell degranulation through a dual-targeting tandem IgE–IgG Fc domain biologic engineered to bind with high affinity to FcγRIIb. *Immunol Lett* 143:34–43. <https://doi.org/10.1016/j.imlet.2012.01.008>
163. Williams M, Bruhns P, Saeys Y et al (2014) The function of Fcγ receptors in dendritic cells and macrophages. *Nat Rev Immunol* 14:94–108. <https://doi.org/10.1038/nri3582>
164. Rook GAW (2012) Hygiene hypothesis and autoimmune diseases. *Clin Rev Allergy Immunol* 42:5–15. <https://doi.org/10.1007/s12016-011-8285-8>
165. Rodgers DT, McGrath MA, Pineda MA et al (2015) The parasitic worm product ES-62 targets myeloid differentiation factor 88-dependent effector mechanisms to suppress antinuclear antibody production and proteinuria in MRL/lpr mice. *Arthritis Rheumatol Hoboken NJ* 67:1023–1035. <https://doi.org/10.1002/art.39004>
166. Harnett W, Harnett MM (1993) Inhibition of murine B cell proliferation and down-regulation of protein kinase C levels by a phosphorylcholine-containing filarial excretory-secretory product. *J Immunol Baltim Md* 150:4829–4837
167. Harnett MM, Deehan MR, Williams DM, Harnett W (1998) Induction of signalling anergy via the T-cell receptor in cultured Jurkat T cells by pre-exposure to a filarial nematode secreted product. *Parasite Immunol* 20:551–563
168. Yang X, Wang H, Zhao X et al (2013) Th22, but not Th17 might be a good index to predict the tissue involvement of systemic lupus erythematosus. *J Clin Immunol* 33:767–774. <https://doi.org/10.1007/s10875-013-9878-1>
169. Pan H-F, Li X-P, Zheng SG, Ye D-Q (2013) Emerging role of interleukin-22 in autoimmune diseases. *Cytokine Growth Factor Rev* 24:51–57. <https://doi.org/10.1016/j.cytofr.2012.07.002>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.