Macêdo *et al. Rare Dis Orphan Drugs J.* 2025;4:17
DOI: 10.20517/rdodj.2025.06

Rare Disease and Orphan Drugs Journal

Review

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Inherently inapt: the role of innate immunity in systemic lupus erythematosus pathogenesis

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How to cite this article: Macêdo MB, Vital E. Inherently inapt: the role of innate immunity in systemic lupus erythematosus pathogenesis. *Rare Dis Orphan Drugs J.* 2025;4:17. https://dx.doi.org/10.20517/rdodj.2025.06

Received: 27 Jan 2025 **First Decision:** 28 May 2025 **Revised:** 12 Jun 2025 **Accepted:** 23 Jun 2025 **Published:** 26 Jun 2025

Academic Editor: Daniel Scherman **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Recent advances in the understanding of the molecular and cellular basis of systemic lupus erythematosus (SLE) have challenged the classical view of SLE as the exemplary B cell and autoantibody-mediated disease. While much emphasis has been given to abnormalities on the humoral side of the immune response as essential to disease development, current findings suggest that mechanisms antedating B cell activation and autoantibody production are at the root of SLE initiation. In this review, we delineate key aspects involved with SLE pathogenesis, with a focus on how disturbances in cell death and metabolism may facilitate disease initiation and progression. We expound the relevance of disrupted cell death by non-programmed pathways, such as NETosis and ferroptosis, and of defective clearance of cellular debris, by complement factor and extracellular endonuclease deficiency, to the generation of damage-associated molecular patterns that will ultimately trigger interferon (IFN) production. We also describe how mitochondrial disturbances leading to reduced respiratory capacity, increased reactive oxygen species, and leakage of mitochondrial nucleic acids into the cytosol, underlie the dysfunctional behavior of multiple cell types involved in the immune response. Lastly, we outline the latest findings on how the IFN signature modulates the disease commencement, suggesting a primordial role of the skin stromal cells in producing several subtypes of IFN that will ultimately shape the behavior of infiltrating immune cells, thus constituting a paradigm shift on regards to the directionality of IFN effects between hematopoietic and non-hematopoietic cells. We advance the proposition that, in SLE, type I IFN plays a central role as an informational influence molecule, i.e., while IFN does not, in itself, act as an effector molecule driving SLE manifestations, it primes multiple cell types and misdirects immune responses, thus enabling autoreactivity.

Keywords: Systemic lupus erythematosus, innate immunity, neutrophils, mitochondria, type I interferon

INTRODUCTION

Systemic lupus erythematosus (SLE) is traditionally recognized as the archetype of an autoimmune condition, with autoantibodies being the hallmark of the disease - accordingly, over two hundred antibodies against self-antigens have been described in SLE individuals, albeit the clinical significance of most of them remains disputable[1,2]. Despite much interest in elucidating which and how autoantibodies play a role in promoting and perpetuating SLE progression, clear pathogenic roles have been demonstrated for only a few of them, such as anti-double-stranded deoxynucleic acid (dsDNA) antibodies in the context of lupus nephritis (LN), and it is noteworthy the absence of a clear-cut correlation of antibodies repertoire or levels with disease manifestations, including a subset of SLE individuals remaining serologically active while clinically quiescent[3-5].

The discovery and eventual incorporation of autoantibodies into clinical practice shaped how SLE classification evolved, with serological tests gaining increasing prominence in disease definition, to the point that current criteria require a positive antinuclear antibody (ANA) test as a mandatory entry criterion. Interestingly, even though the 2019 European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) classification criteria for SLE include 4 autoantibodies, yielding a score of up to 8 points (the cutoff for disease classification being equal to or above 10 points)[6], the very first classification, proposed in 1971 by the then American Rheumatism Association (ARA, presently ACR), did not list any autoantibody among its 14 criteria[7], and still presented an exceedingly good specificity of 98%[8,9]. While this does not imply that autoantibodies are dispensable to either pathogenesis or diagnosis of SLE, it highlights how much, over time, our perception of what makes SLE a distinctive entity has been modified, with a cumulative heightened emphasis on immunoglobulins (and, *per* consequence, on B cells) as fundamental to defining the disease process.

This selective attention to the adaptive side of immunity in SLE may be related to the fact that it is much more feasible to standardize and automate tests based on antibody or other soluble molecules assessment, compared to tests of cell function (e.g., chemotaxis, phagocytosis)[10-12]. This may create a skewed view in which other cells, such as those pertaining to the innate side of immunity, or stromal cells in affected tissues (e.g., skin, kidney), are overlooked due to technical exigencies related to assessing how they function and interact, both in healthy and diseased states. Nonetheless, for SLE to manifest itself, more than the mere expression of autoantibodies is necessary, as it is well-known that otherwise healthy individuals may have measurable autoantibodies in circulation without ever developing a symptomatic autoimmune disease[13,14]. Therefore, SLE pathogenesis involves much more than a classical "break of tolerance against the self"; it also includes multi-level perturbations of the relationship of both innate and adaptive immune cells with parenchymal cells[15,16]. Notably, this implies that SLE could not be cured by strategies that aim to eliminate specific clones of B cells, even though these may lead to good time-limited responses.

In this review, we aim to raise awareness of the essential role of innate elements of immunity in initiating and facilitating SLE development.

LUPUS: A DISEASE DEFYING DEFINITIVE DEFINITIONS

Dead but not gone: disrupted cell death at the crux of systemic lupus erythematosus pathogenesis

A historical perspective on how SLE was at first diagnosed and classified may broaden our understanding of how several cells and molecules interplay to create a chronic, self-perpetuating, and dysfunctional inflammatory *milieu* beyond a B-cell-centric or antibody-centric standpoint. Looking back to the 1971 ARA criteria, the main laboratory evidence suggestive of SLE was the lupus erythematosus (LE) cell, described

some two decades previously by Hargraves *et al.* in the bone marrow[17], and then by Sundberg *et al.* in the blood of SLE individuals[18]. LE cells have long since fallen into obsolescence as a diagnostic test, but they still represent a fair starting point for understanding SLE etiopathogenesis. In fact, LE cells are neutrophils exhibiting aberrant morphology due to the phagocytosis of nuclear remnants from apoptotic cells[19]. Thus, they encompass one essential mechanistic process that is, *per* definition, disrupted in SLE: mismanagement of how cellular debris, in particular of nuclear origin, are disposed of, rather than autoantibody production specifically. It has even been hypothesized that autoimmunity in SLE may derive from a failed attempt of the immune system to compensate for the defective clearance of intracellular material after cell death[20,21].

Supporting this hypothesis is the observation that genetic mutations resulting in deficient complement C1q levels manifest as lupus or a lupus-like syndrome[22,23]. *In vitro* and murine models showed that C1q assists in the elimination of apoptotic bodies by coating autoantigens, thus signaling them for removal by macrophages[24]. Likewise, in SLE patients, anti-C1q autoantibodies have been demonstrated to impair opsonization of immune complexes composed of DNA and anti-DNA antibodies, which are eventually filtered and deposited in the glomerulus, thus constituting a strong risk factor for proliferative LN[25].

While deficiency of components of the C1 complex is exceedingly rare, with less than a hundred reported cases, the reverse situation is more common: the presence of polymorphisms in the C1q gene may confer protection against SLE by influencing transcript abundance and, therefore, increasing serum levels of C1q. The single nucleotide polymorphism (SNP) rs653286 has been associated with a 25% decreased risk of SLE, and SLE individuals who carry this SNP present with lower anti-dsDNA titres[26].

Further evidence favoring the compromised clearance hypothesis is that accumulation of free DNA in circulation, secondary to reduced activity of an extracellular enzyme responsible for its degradation, is a well-established cause of monogenic SLE[27]. Null mutations in the gene of deoxyribonuclease1-like 3 (DNASE1L3) manifest as a clear SLE phenotype, with the residual amount of the secreted functional endonuclease determining the age of onset of the disease (i.e., complete absence resulting in SLE presentation already in infancy)[28]. A mechanism has been proposed based on a mouse model in which full knockout of Dnase1/3 results in extracellular DNA being recognized by toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells, which, in turn, aid the differentiation of antibody-forming cells outside germinal centers (GCs), thereby enabling the thriving of autoreactive B cells responsible for the generation of autoantibodies[29].

Similar to inherited C1 deficiency, loss-of-function variants in Dnase1L3 are very infrequent in the population. However, neutralizing anti-Dnase1L3 antibodies have been detected in a third of SLE individuals[30] and in up to half of those affected by LN[31], highlighting that decreased nuclease function may also be a significant mechanism in common polygenic SLE.

Metabolism fostering inflammation: unbalanced oxidative phosphorylation foments immune deregulation in SLE

Not only DNA from nucleic origin is central to triggering immune activation in SLE. Oxidized mitochondrial DNA (mtDNA), when recognized by the cytosolic DNA sensor stimulator of interferon genes (STING), can induce a type I interferon (IFN) signature in peripheral blood mononuclear cells (PBMCs)[32]. Interestingly, mtDNA copy numbers in SLE plasma were found to be elevated, as compared to healthy controls' plasma, and to correlate with disease activity[33]. mtDNA is particularly sensitive to oxidative stress due both to the lack of protection by histones and to its proximity to the oxidative phosphorylation (OXPHOS) multiprotein complex[34,35].

Neutrophil extracellular traps (NETs) have been shown to be markedly enriched in mtDNA, being probably the main source of oxidized mtDNA in circulation[36]. Additionally, despite having been first described as the end product of a form of cell death (suicidal NETosis), NETs can be released by living neutrophils that remain viable even after their extrusion (vital NETosis), in which situation the NETs' nucleic acid contents are exclusively comprised of mtDNA[37]. Retention of NETs has been linked to LN, and at least a third of SLE patients have a reduced ability to eliminate circulating NETs[38]. Those patients were shown to present anti-NET antibodies hindering the cleavage of NETs by DNase I, the main enzyme responsible for NET degradation[38].

Increased reactive oxygen species (ROS) have been detected in multiple biospecimens (e.g., serum, plasma, urine) from SLE individuals[39], suggesting that abnormal redox homeostasis may predispose to a dysfunctional inflammatory response, ultimately leading to organ damage in SLE[40,41]. A major knowledge gap, though, is the absence of studies exploring mitochondrial disturbances in *ex vivo* human tissue (e.g., synovium, skin, or kidney), and it should be pondered that molecules evaluated in body fluids might not be faithfully reflective of the redox status of tissues.

However, recent findings have challenged the concept that oxidative stress is necessarily harmful. An animal model has been described in which, contrariwise, reduced production of ROS enabled SLE development[42]. A decrease in ROS production in granulocytes has been linked to enhanced susceptibility to SLE[43], implying that ROS generation may have disparate consequences, depending on the cell type or, even within the same cell, on its metabolic state[44]. Mechanistically, ROS mediates several pathways of cell death, from programmed, well-regulated apoptosis to non-programmed, uncontrolled necroptosis, and the instigation of a specific pathway depends on the associated factors implicated in ROS production and scavenging[45,46].

A leading counterregulatory molecule involved in detoxifying peroxides and preventing them from reacting with cell membrane lipids is glutathione[47]. Several studies revealed reduced levels of glutathione and its enzymes in the blood of SLE individuals, presumably due to enhanced consumption superseding their replenishing capacity[48-50]. Depletion of intracellular glutathione is key to the initiation of ferroptosis, a cell death triggered by lipid peroxidation[51]. Recently, a seminal study demonstrated that suppression of glutathione peroxidase 4, the main enzyme regulating ferroptosis, in mouse neutrophils was sufficient to induce a lupus-like phenotype[52]. In this same study, the authors showed that ferroptosis is the main cause of cell death in SLE neutrophils, likely explaining the neutropenia commonly observed in active disease[52].

More than the provenance of ROS: mitochondria as wealthy wellsprings of damage-associated molecular patterns (DAMPs)

Given the bacterial ancestry of mitochondria, it is, perhaps, not surprising that exposure to free, circulating mitochondria may induce a strong immunogenic response[53]. While mtDNA is the mitochondrial component with better evidence regarding activation of several pro-inflammatory pathways, from cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-STING to TLR9[54,55], mitochondrial proteins as a potential antigenic source should not be neglected, as more than half of the mitochondria proteome has no correlate in eukaryotic cells[56,57].

Accordingly, antibodies against the outer membrane protein mitofusin 1 have been detected in SLE serum samples, but not in samples from individuals with either primary biliary cholangitis or antiphospholipid syndrome, the better-known examples of diseases characterized by autoantibodies targeting mitochondria components (M2 antigen and cardiolipin, respectively)[58]. However, this is only an incipient field, and the role (if any, except as biomarkers) of those antibodies remains to be elucidated.

Intriguingly, recent studies showcased that the permanence of mitochondria in red blood cells (RBCs) may activate type I IFN signaling in SLE[59,60]. During their normal maturation, RBCs undergo mitophagy, a process controlled upstream by hypoxia-inducible factor 2 alpha (HIF-2α). In SLE, stabilization of HIF-2α prevents mitochondria degradation, enabling RBCs to retain mitochondria during their entire life cycle. When they are eventually cleared by reticuloendothelial macrophages, RBCs with retained mitochondria serve as potent inducers of IFN, as engulfed mtDNA activates cGAS-STING[59]. The same research group further extended this study and showed that mitochondrial ribonucleic acid (mtRNA) from phagocytized RBCs is recognized by retinoic acid-inducible gene I-like receptors (RLRs), and induces interleukin-1beta (IL-1β) in monocytes. Additionally, mtRNA from RBCs acts synergistically with mtDNA from monocytes to activate NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome[60].

Mitochondrion dysfunction in SLE, though, may be even more complex than either disturbance in OXPHOS causing an increase in ROS, or the mishandling of its nucleic acids provoking type I IFN activation. A new field that has sparked interest lately is that of mitokines, molecules released by mitochondria overwhelmed by metabolic demand, with the intention of signaling to mitochondria from neighboring cells that a stressful situation is in course[61,62]. Among candidate mitokines with a possible role in SLE is growth and differentiation factor 15 (GDF 15). Plasma GDF 15 was initially shown to be increased in humans with miscellaneous infectious conditions, and then demonstrated to be a critical immunomodulatory molecule for the resolution of inflammation, functioning as a break to inappropriate escalation of inflammatory responses, as in sepsis, or in cardiomyocyte death after myocardial infarction[63,64].

Serum levels of GDF 15 were described to be elevated in SLE individuals, and to correlate positively with disease activity[65], implying a failure in counteracting inflammation despite its augmented production, while its expression in the kidneys of individuals suffering from LN has been shown to be decreased, either due to insufficient tissue production or accelerated local consumption[66]. In line with such a protective role, the knockout of GDF 15 in lupus-prone mice intensified disease severity, with GDF15-deficient mice presenting stronger type I IFN signature and anti-dsDNA antibodies[66]. Further, in a pristane-induced lupus mouse model, intraperitoneal injection of GDF 15 resulted in decreased inflammatory cytokines in serum and lessened renal involvement[65]. Finally, in a study that compared GDF 15 polymorphisms across several autoimmune conditions, the SNP rs1054564 was associated with a 30% decrease in the risk of developing SLE[67].

Meticulously disordered: how disarray in metabolism modulates immune dysfunction in SLE

In order to produce energy and preserve cell viability, strict regulation of the mitochondrial transmembrane potential must be maintained at all times, with an inadequately low or high charge of the mitochondria inner membrane making the cell susceptible to apoptosis[68]. Hyperpolarized mitochondria have been described both in T cells[69,70] and B cells[71] from SLE individuals, and in the latter to correlate with disease activity levels.

Aberrant respiratory function has also been noted in SLE monocytes, with a recent study evidencing that treatment of healthy monocytes with IFNα replicated the OXPHOS abnormalities seen in SLE, inducing a significant drop in adenosine triphosphate (ATP) generation, together with an increase in ROS[72]. Curiously, this unbalanced ROS-to-ATP ratio is linked to alterations of lysosomal pH, which, in turn, impairs the capacity of lysosomes to clear damaged mitochondria, thus creating a self-feeding cycle of ineffective bioenergetics[72].

Much is still unknown about the intricate relationship between IFN and mitochondria metabolism, with several metabolites and receptors involved in their communication shown to be inappropriately regulated in SLE[73,74]. One metabolite with immunomodulatory properties, whose participation in autoimmune disorders has attracted attention lately, is itaconate[75]. Reduced serum levels of itaconate were found in SLE individuals[76]. Correspondingly, in an SLE murine model, treatment with an itaconate derivative ameliorated several aspects of the disease, such as proteinuria, thrombocytopenia, and levels of anti-ribonucleoprotein antibody[77]. Splenocytes from treated mice showed a decrease in type I IFN gene expression and, at the same time, an upregulation of genes related to Treg cell differentiation[77]. The reason behind the shift from a pro- to an anti-inflammatory cytokine profile seemed to be related to a reduction of mitochondrial antiviral signaling protein (MAVS) oligomerization. MAVS oligomers assemble when cells face a surcharge of ROS, after which they function as adaptors for melanoma differentiation-associated protein 5 (MDA-5) and retinoic acid-inducible gene 1 (RIG-1)[77].

Counterintuitively, another study demonstrated that itaconate drives IFNβ production by macrophages, through induction of the pore-forming voltage-dependent anion-selective channel 1 (VDAC-1) on mitochondria outer membrane, enabling passage of mtRNA into the cytosol, which is then sensed by MDA-5 and RIG-1[78]. The effect of itaconate in different IFN subtypes production, and in different cell lineages, remains an open field.

As a last addition to the link between IFN and faulty mitochondria performance, aberrant mitochondria were seen in CD8+ T cells from selected SLE individuals displaying a high IFN signature. Enlarged mitochondria with reduced spare respiratory capacity were more prominent in the effector memory CD8+ T cells subpopulation, while no abnormalities were detected in mitochondria from CD4+ T cells. Chronic *in vitro* treatment of healthy CD8+ T cells with IFNα was followed by reduced expression of mtDNA-encoded genes, and by an impairment of those cells to become activated, degranulate, and secrete tumor necrosis alpha upon restimulation[79]. The reason behind the apparent resistance of CD4+ T cells to IFNα-induced mitochondrial respiration compromise is not clear and deserves further investigation.

The main mechanisms of mitochondrial disturbance are presented in Figure 1.

IFN as the "informational influence" determinant of SLE

In the field of neurocognition and social behavior, the concept of informational influence has been created to define a change in an individual's decision or behavior based on information received from their peers, with the aim of conforming to social expectancies, particularly in instances of uncertainty or dilemma[80]. It is not unreasonable to propose that, in SLE, IFN-I plays a central role as an informational influence molecule; while it may not provide a sufficient cause for SLE in most patients, its receptor (IFNAR) is expressed in all nucleated cells, and many immune responses are modified by IFNs, so it could serve to prime the specific functions of disparate immune cell types toward disrupted immune responses, as a foundation for multiple variants of autoimmune disease.

While an extensive description of the mechanisms whereby IFN regulates several pathways involved in SLE pathogenesis is beyond the scope of this article, having been comprehensively summarized in other recent reviews[81-84], some new insights on how the IFN-gene signature (IGS) is critical to molding disease development are worthy being mentioned.

One puzzling aspect of IGS in SLE is the lack of its correlation with disease activity, with multiple cohorts showing no variation in expression according to the intensity of clinical manifestations[85]. Transcriptome

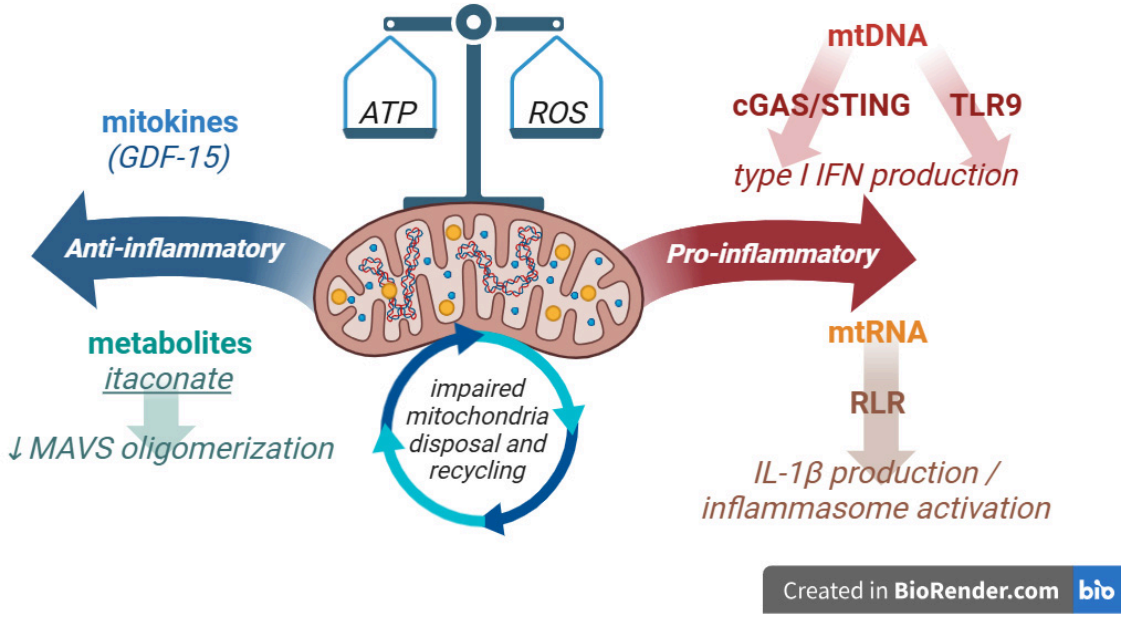

Figure 1. Mitochondrial dysfunction in systemic lupus erythematosus (SLE). In SLE, mitochondrial respiration is impaired, with a shift of the ratio between adenosine triphosphate (ATP) and reactive oxidative species (ROS) production, with accumulation of the latter. Given the proximity between the respiratory chain complex and mitochondrial nucleic acids, mtDNA has been proved to be particularly susceptible to oxidative damage. Oxidized mtDNA, in turn, can be recognized as a damage-associated molecular pattern, and trigger type I interferon (IFN) production through activation of cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-STING and of toll-like receptor 9 (TLR9). Additionally, in SLE monocytes, mtRNA was shown to activate RIG-like receptors (RLRs), induce the production of interleukin-1beta (IL-1β) and activate inflammasome, thus contributing to another pro-inflammatory pathway. Healthy cells are usually able to promptly deal with dysfunctional mitochondria, either by ejecting oxidized mtDNA into nucleoids redirected to lysosomes for degradation, or by recycling mitochondria through mitophagy. However, those mechanisms seem to be defective in SLE. Further, in SLE, the anti-inflammatory mitokine growth differentiation factor 15 (GDF 15), despite increased production, is not enough to put a brake into the inflammatory milieu. Similarly, the anti-inflammatory metabolite itaconate, which acts by reducing mitochondrial antiviral signaling protein (MAVS) oligomerization, seems to be reduced in SLE. As a consequence, increased MAVS oligomers become available as adaptors for the sensors melanoma differentiation-associated protein 5 (MDA-5) and retinoic acid-inducible gene 1 (RIG-1), themselves key to IFN production. Figure created in BioRender.com.

analysis revealed the persistence of IGS in monocytes, but not in T or B lymphocytes, of clinically inactive SLE individuals. Given that monocytes contribute with a greater number of transcripts than any other cell in circulation, this would suggest an explanation for the stability of IGS over time, as the changes in other cells' transcripts would not be possible to detect in serial measures[86]. This difference in interferon-stimulated gene (ISG) expression between cell types can be measured using a flow cytometric assay for tetherin, a cell surface protein encoded by the ISG BST-2. The expression of tetherin on memory B cells was shown to be associated with clinical features better than its expression on monocytes[87]. ISG expression may also be epigenetically regulated[88]. Confirming this, another study showed that only about 1 in 8 SLE individuals fluctuated their IGS, and that those who changed from a high to a low IGS were receiving treatment with high (above 25 mg/day) prednisone doses[89]. This may also be why some sets of ISGs show greater variability and correlation with clinical features than others[90,91].

In this sense, determinants of an individual's baseline IFN expression are much sought, as they might be decisive in modulating the risk of disease initiation and progression[92]. Along this line, variability in genetics and epigenetics across populations has gained traction, with an ever-increasing acknowledgment of idiosyncrasies in disease phenotype being attributed to gene expression variation within ethnic groups. A differential genetic burden of the IGS has been recently described in individuals of East Asian ancestry, in

whom it was consistently shown an enrichment of the IGS in multiple cell types (monocytes, natural killer cells, T and B lymphocytes), compared to individuals of European background, aligning with the classical statement that Europeans tend to present with milder SLE symptoms[93].

Likewise, it is a well-recognized fact that SLE tends to be more severe and treatment-refractory in individuals of African ancestry[94], although there has been much contention whether the observed worse outcomes are driven mainly by disparities in access to healthcare, or by intrinsic peculiarities in the genetic background of people from African descent[95]. A study of the methylome of SLE individuals, separated by their ethnic background (European or African Americans - AA), shed new light on this topic by evidencing that, despite most of the hypomethylated sites being within interferon-regulated genes for either ethnicity, the hypomethylation pattern was more robust in AA - as an example, the IFN-induced protein 44 gene was exclusively found to be hypomethylated in AA SLE individuals[96].

Notwithstanding the relevance of evaluating IGS in established disease, it is perhaps even more informative to analyze the IFN expression of individuals at risk of SLE in the so-called pre-clinical phase. As expected, individuals positive for ANA who eventually progressed to classifiable SLE presented a higher IFN score both in blood and skin compared to healthy controls[92], and subsequent RNA-sequencing in PBMCs of progressors confirmed a strong IGS prior to disease diagnosis[97]. Strikingly, the latter study also showed a downregulation of genes encoding the mitochondrial OXPHOS complex components in those who evolved to classifiable SLE, independent of the IGS, implying that defective mitochondria respiration and anomalous expression of IFN may jointly decide the fate of ANA-positive individuals[97]. Meanwhile, ANA-positive individuals who did not progress to SLE, highly common in the general population, were revealed to have complex transcriptomic abnormality and IFN production, suggesting that antibody- and IFN priming can lead to a dynamic immune equilibrium that maintains health.

More than skin deep: epidermis as the hub connecting environmental and genetic determinants of SLE flares?

When referring to a type I IFN signature in SLE, most studies, in fact, restrict their assessment to IFN-α and its transcriptional repertoire, as the principal module (i.e., set of genes) upregulated in SLE individuals, M1.2, is mainly driven by IFN-α[98]. Although this is appropriate for blood biospecimens, it might not be applicable to other tissues, in which other IFN subtypes can be of as much or even higher relevance than IFN-α. Such seems to be the case in the skin, where, under certain inflammatory conditions, keratinocytes turn into factories of IFN-κ, which primes these cells for an ensuing IFN response[99]. Non-lesional skin from SLE patients has been demonstrated to overexpress IFN-κ, which seems implicated in sensitizing the epidermis to photodamage, by facilitating keratinocyte apoptosis following ultraviolet (UV) exposure, and activating dendritic cells (DCs) infiltration[100]. While plasmacytoid dendritic cells do not sustain IFN-I production in chronic autoimmunity such as the At-Risk state or SLE, this is not the case for keratinocytes, in keeping with their function as a barrier organ[101]. Sustained IFN-κ production by keratinocytes in histologically normal skin is present in the At-Risk phase of the disease, indicating that danger signals within "target" organs precede inflammation.

In line with this, an older study showed that an SNP in the IFN-κ gene, rs12553951C, was associated with an increased risk of SLE in European American males[102]. It should be emphasized that this SNP did not augment the risk in AA individuals, evidencing that a darker skin phototype may counterbalance the susceptibility to IFN-κ-mediated effects on keratinocytes by naturally reducing UV penetration. Thus, the development of cutaneous involvement in SLE appears to require both a permissive genetic background and an environmental trigger (UV light), which constitutes the principle behind the universal recommendation of photoprotection as a measure against skin flares in SLE individuals[103].

While a clear pattern of seasonality for skin flares has been described, peaking in spring and summer, corresponding to periods of increased UV exposure[104,105], a recent observational study in Egyptian SLE individuals also stated an increased incidence of LN during the summer[106]. This is intriguing, particularly in light of a study suggesting that the inverse transmigration of neutrophils - from UV-damaged skin to the kidney - can promote kidney injury in a murine model of SLE[107]. According to this study, after skin irradiation with UVB, an increase in IL-17 in both skin and blood mediates neutrophil skin infiltration and neutrophilia, respectively, which was accompanied, on the following day, by increased expression of inflammatory genes, such as IL-1β, s100a9, and lipocalin-2, in the mice's kidney. A very elegant experiment, in which neutrophils were marked with a photoactivatable green fluorescent protein, demonstrated that about 20% of neutrophils infiltrating the kidney were UV-exposed, and had thus passed through - and were primed by - the skin[107]. This reinforces the concept of SLE as a true systemic condition, with a flare in one organ engendering a flare in another. It must be taken into account, however, that while those findings hold true for mice, they have not been confirmed in humans thus far.

Not only neutrophils are conditioned by the IFN-rich environment of SLE-affected skin. Another study demonstrated that skin fibroblasts, together with keratinocytes, are prominent sources of type I IFN, and that they interact with T cells and DCs in the dermo-epidermal junction, training those cells to maladjusted behaviors - in the case of Treg cells, impairing their tolerogenic function, and in the case of myeloid cells, aiding the transition of monocytes into CD16+ DCs, and the expression of several pro-inflammatory cytokines by the latter[108,109].

Type III IFN is also relevant to SLE-related skin inflammation. Antiviral defense by IFN-λ has been suggested as particularly beneficial at barrier sites, with epithelial cells expressing high levels of the receptor IFNLR1[110]. Moreover, mesangial cells were also shown to respond to IFN-λ by the synthesis of chemokines, thus permitting migration to and invasion of the kidney by monocytes[111].

Further, an *in vitro* study with healthy human dermal fibroblasts showed that those cells respond to IFN-λ by increasing collagen I, IV, and VII expression via activation of tumor growth factor beta 1, suggesting yet another role of IFN-λ in promoting skin healing and scarring[112]. Endorsing the applicability of those mechanisms to SLE pathogenesis, a study of Taiwanese individuals with SLE found that an SNP haplotype in the genes of IFN-λ3 and -λ4 (rs8099917T-ss469415590TT-rs12979860C-rs4803217C) in human peripheral blood was associated with an enhanced risk of LN[113].

In a mouse model, the increase in IFN-λ was prompted by upstream activation of TLR7. Interestingly, in the same year this study was published, another murine study reported that the type II IFN subtype, IFN-γ, is produced by follicular helper T cells upon TLR7 stimulation, subsequently leading to the formation of GCs and autoreactive B cells[114]. Those studies collectively reaffirm the importance of TLR7 to SLE pathogenesis, being one of the chief intracellular receptors whose aberrant activation can trigger disease initiation. In consonance with those experimental models, gain-of-function mutations in TLR7 have been recently described as monogenic causes of SLE[114,115]. In a murine model that replicates the TLR7 mutation detected in humans, the overexpression of TLR7 determined increased B cell survival. Genetically manipulating the mice to impede GC formation did not rescue the lupus phenotype, suggesting that autoreactive B cells may have an extrafollicular origin[114]. Thus, even B cell-centered lupus pathology may have innate origins.

A key protein responsible for guaranteeing the proper location of TLR7 in endosomes is UNC93B1. Variants encoding the UNC93B1 gene have been identified in patients with early-onset SLE, presumably because of enhanced sensitivity to TLR7 ligands, resulting in the exaggerated production of type I IFN as a

Table 1. Compilation of representative genes with well-known variants associated with susceptibility to SLE and/or LN

Gene variant	Risk of SLE	Mechanism	Reference
Complement factor 1q (C1q)	Nonsense or missense mutation: ↑ (monogenic) rs653286 SNP: ↓	Decreased clearance of cell debris and immune complexes	[22,26]
Dnase1L3	Loss of function variant: ↑ (monogenic)		[27]
GDF 15	rs1054564 SNP: ↓	Mitochondrial stress leading to increased IFN expression?	[67]
IFN-κ	rs12553951C SNP: ↑	Retention of pro-inflammatory cytokines in skin?	[102]
IFN-λ	rs8099917T-ss469415590TT-rs12979860C-rs4803217C SNP haplotype: ↑ (LN)	Cytotoxicity to kidney cells?	[113]
TLR7	Missense gain of function mutation: ↑ (monogenic)	Increased survival of autoreactive B cells	[114,115]

downstream effect[116]. Additional proof supporting the pivotal role of TLR7 in SLE development comes from preliminary results of a phase II randomized clinical trial testing a TLR7/8 inhibitor, enpatoran, showing efficacy compared to placebo in both systemic and cutaneous lupus[117].

A compilation of exemplar genes with well-known variants associated with SLE and/or LN susceptibility is summarized in Table 1.

Many a mickle makes a muckle, and many a loop makes a lupus

The present review intends to summarize some prominent molecular and cellular disturbances involved in the initiation and progression of SLE. While we describe a wide range of potential causal mechanisms, it must be emphasized, nonetheless, that SLE is an eminently complex and heterogeneous disorder; therefore, an all-encompassing description of the other incredibly diverse pathways, regulatory and counter-regulatory loops that have been noted as contributory to SLE pathogenesis is beyond the scope of this manuscript. A few molecules and mechanisms are still worth mentioning, though, and below, we refer the reader to other reviews that deal with them in detail.

Among the many genes that confer susceptibility to SLE, human leukocyte antigen (HLA) polymorphisms have been the first to be described as increasing the risk of developing SLE[118], and recently, an ingenious study evidenced how an epitope of the DRB1*03:01 allele, in the presence of IFN-γ, was able to trigger autoimmune features mirroring SLE in a murine model[119]. On the other hand, non-classical HLA molecules may intervene as breaks to the inflammatory cascade by inducing tolerance and engaging suppressor molecules, as is the case of HLA-G, thoroughly reviewed in refs.[120,121]. Finally, still on the topic of polymorphisms in genes encoding transmembrane receptors crucial to immune functions, it is indisputable the relevance of Fc-gamma receptor (FcγR) polymorphisms to the risk of developing SLE and LN, particularly the FcγRIIb[122]. Comprehensive reviews are available in refs.[123,124].

Regarding environmental factors that have been hypothesized to impact SLE pathogenesis, the immunomodulatory role of vitamin D has been a consistently recurring topic, as reviewed in refs.[125,126]. Another frequently cited example of how environmental factors may shape the immune system is the growing body of research linking gut microbiome composition to SLE manifestations, as reviewed in refs.[127,128].

CONCLUSION

Collectively, the data summarized here provide an often-overlooked yet highly significant perspective on SLE pathogenesis with important implications for therapeutics. Although adaptive immune changes are

undoubtedly involved in SLE, a range of potent mechanisms related to cellular respiration, mitochondrial dysfunction, and subsequent IFN-mediated signaling also contribute to disease progression. These mechanisms may affect not only circulating immune cells but also stromal and parenchymal cells within so-called "target organs", which actively participate in pathogenesis in response to local environmental stressors. Such metabolic and innate immune mechanisms may evade current therapeutic approaches, potentially explaining the persistence of disease memory and treatment resistance.

DECLARATIONS

Authors' contributions

Conceptualization, data curation, writing - original draft, visualization: Macêdo MB
Conceptualization, writing - review and editing, supervision, project administration: Vital E

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Macêdo MB declared that there are no conflicts of interest. Vital E has received grants paid to his employer from Roche and AstraZeneca. Honoraria from AstraZeneca, Novartis, Pfizer, UCB, Abbvie, Aurinia, BMS, Roche, Otsuka, Lilly, Dianthus, Viatris, Ventus, CESAS, MedScape.

Ethical approval and consent to participate:

Not applicable.

Consent for publication

Not applicable.

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