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Understanding Systemic Lupus Erythematosus Physiopathology in the Light of Primary Immunodeficiencies

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Abstract
Introduction Associations between systemic lupus erythematosus (SLE) and primary immunodeficiencies (PIDs) were analyzed to gain insight into the physiopathology of SLE. Some PIDs have been consistently associated with SLE or lupus-like manifestations: (a) homozygous deficiencies of the early components of the classical complement pathway in the following decreasing order: in C1q, 93% of affected patients developed SLE; in C4, 75%; in C1r/s, 57%; and in C2, up to 25%; (b) female carriers of X-linked chronic granulomatous disease allele; and (c) IgA deficiency, present in around 5% of juvenile SLE.
Discussion In the first two groups, disturbances of cellular waste-disposal have been proposed as the main mechanisms of pathogenesis. On the other hand and very interestingly, there are PIDs systematically associated with several autoimmune manifestations in which SLE has not been described, such as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), immunedysregulation polyendocrinopathy enteropathy X-linked (IPEX), and autoimmune lymphoproliferative syndrome (ALPS), suggesting that mechanisms considered as critical players for induction and maintenance of tolerance to autoantigens, such as (1) AIRE-mediated thymic negative selection of lymphocytes, (2) Foxp3+ regulatory T cell-mediated peripheral tolerance, and (3) deletion of auto-reactive lymphocytes by Fas-mediated apoptosis, could not be relevant in SLE physiopathology. The non-description of SLE and neither the most characteristic SLE clinical features among patients with agammaglobulinemia are also interesting observations, which reinforce the essential role of B lymphocytes and antibodies for SLE pathogenesis.
Conclusion Therefore, monogenic PIDs represent unique and not fully explored human models for unraveling components of the conundrum represented by the physiopathology of SLE, a prototypical polygenic disease.

Keywords Systemic lupus erythematosus · primary immunodeficiencies · complement deficiencies · chronic granulomatous disease · agammaglobulinemia · APECED · IPEX · ALPS

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Introduction

Primary immunodeficiency diseases (PIDs) represent a large collection of monogenic entities whose genetic defects and whose defective underlying immune mechanisms have already been identified in most of them [1]. Interestingly, there are certain PIDs systematically associated with autoimmunity, while in others, autoimmune manifestations have rarely or never been described, even

with patients presenting recurrent and/or chronic infections [2]. Moreover, there are PIDs in which systemic lupus erythematosus (SLE) is practically the only autoimmune manifestation, such as in the complement deficiencies and in chronic granulomatous disease (CGD), while in others, even in those strongly associated with autoimmune manifestations, SLE has never been observed. Thus, monogenic PIDs may represent unique and privileged human models for unraveling the components of the conundrum represented by SLE physiopathology, a prototypical polygenic disease. Also, notably, some PIDs represent natural "knockout" human models for various lupus susceptibility genes, such as Fas, FasL, ICOS, TACI, Fc receptors, CD40L, IFN-γ, C1q, C1r/s, C4, C2, MBL, among others.

The aim of this review is to analyze the associations between PIDs and lupus to gain understanding of SLE pathophysiology. In Table 1, PIDs are classified according to the degree of association with SLE or lupus-like manifestations. The main PIDs consistently associated with SLE as well as some PIDs strongly associated with autoimmunity but not with SLE are discussed in the text.

PIDs Consistently Associated with SLE or Lupus-Like Manifestations

Complement Deficiencies

Although homozygous complement deficiencies represent rare conditions, and are estimated to be found in less than 1% of SLE patients, their study has substantially contributed to the development of new concepts concerning the pathogenetic mechanisms of SLE [3–5]. Complete deficiency of any of the early components of the classical complement pathway (C1q, C1r, C1s, C4, and C2) represents the strongest single genetic risk factor for the development of SLE identified up to now. A striking feature is that SLE or lupus-like syndromes have been the predominant autoimmune disorders observed in all complement deficiencies, while other autoimmune diseases were rarely described in association with them. SLE or lupus-like manifestations have been identified in respectively 93% of homozygous C1q-deficient, in 75% of C4-deficient, in two thirds of C1r/C1s-deficient, and in up to 25% of C2-deficient individuals (Table 2) [4–6]. Interestingly, lupus-like disease susceptibility drops to around or below 10% in patients with deficiency of C3, and only isolated cases have been reported as associated with deficiencies of the late components of the membrane attack complex (C5–9; see Table 2). Cases of SLE have also been reported among patients with hereditary C1 inhibitor deficiency, who present chronically low levels of C4 and C2 [5, 7]. In both human beings and murine models, the degree of association as well as the severity of the disease is hierarchical depending on the position of the deficient component in the classical pathway. SLE association is less clear for partial deficiencies, as well as for MBL (mannose-binding lectin) complete defects.

Taken collectively, these clinical data point out that the early components of the classical complement pathway, independently of C3 activation, have a critical protective activity against the development of SLE. The first hypothesis

Table 1 Association between PIDs and SLE or Lupus-like Manifestations

Consistently associated	Some isolated SLE or lupus-like case reports	Not associated
C1q deficiency [3–5]	C3 deficiency [4, 5]	APECED[a] [17–20]
C4 deficiency [4, 5]	Hereditary C1 inhibitor deficiency [4, 7]	IPEX[a] [2, 21, 22]
C1r/s deficiency [4, 5]	Deficiencies of MAC components [4, 5]	Wiskott-Aldrich syndrome[a] [43, 44]
C2 deficiency [4–6]	CVID[a] [31–35]	Omenn syndrome[a] [2]
Female carriers of X-linked CGD allele [9, 10]	IgG subclass deficiency [2]	X-linked agammaglobulinemia [28–30]
X-linked and AR CGD [9, 10]	Hyper-IgM syndrome probably due to AID or UNG deficiency [41]	X-linked Hyper-IgM syndrome (CD40L defects) [36, 37]
IgA deficiency[a] [13–15]	ALPS[a] [24–26]	Hyper-IgM due to CD40 deficiency [38]
	Hyper-IgE syndrome [2]	Defects of IL-12/IL-23-IFN-γ axis [45]
	Prolidase deficiency[b] [42]	DiGeorge anomaly [46]
		Ataxia-telangiectasia syndrome [2]
		Chédiak–Higashi syndrome [2]
		FcγRIIIb deficiency [47]
		Autoinflammatory disorders [1, 2]

CGD chronic granulomatous disease, *MAC* membrane attack complex, *ALPS* autoimmune lymphoproliferative syndrome, *APECED* autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, *IPEX* immune dysregulation, polyendocrinopathy, enteropathy X-linked, *CVID* common variable immunodeficiency, *AID* activation induced cytidine deaminase, *UNG* uracil-N-glycosilase

[a] PIDs frequently associated with other autoimmune manifestations

[b] Entity not classified as a PID, although affected patients are prone to infections

Table 2 Homozygous Complement Deficiencies and Susceptibility to SLE or Lupus-like Manifestations [3–7]

Complement deficiency	Frequency of SLE/lupus-like manifestations (%)	Main functional defects	Main lupus clinical features	Susceptibility to infections
C1q	93	Impaired clearance of apoptotic debris and dissolution of immune complexes (IC)	High frequency of glomerulonephritis and central nervous system disease; marked photosensitivity	Encapsulated bacteria
C4	75	Impaired clearance of IC; defective humoral immune response	Multi-organ involvement; glomerulonephritis in 30%	Encapsulated bacteria
C1r/C1s	57	Impaired clearance of IC	Multi-organ involvement; glomerulonephritis in 30%	Encapsulated bacteria
C2	10–25	Impaired dissolution of IC	Prominent cutaneous (photosensitivity) and articular involvement; mild or absent renal, neurological or pleuropericardial involvement; low frequency of ANA; high frequency of anti-Ro antibodies	Pyogenic infections; invasive infections due to encapsulated bacteria; *Streptococcus pneumoniae* sepsis and meningitis
Hereditary C1 inhibitor deficiency	23 case reports	Spontaneous activation of the complement pathway with consumption of C4 and C2	Systemic or discoid lupus erythematosus; high frequency of photosensitivity and ANA	Normal resistance to infections
C3 deficiency	3 case reports	Defective MAC, defective bactericidal activity, defective humoral immune response	SLE; malar rash, photosensitivity, arthralgia and Raynaud's phenomenon	Recurrent pyogenic infections
C7 deficiency	3 case reports	Defective MAC, defective bactericidal activity	Systemic lupus erythematosus	Neisserial infections
C6 deficiency	3 case reports	Defective MAC, defective bactericidal activity	One DLE and 2 SLE patients	Neisserial infections
C9 deficiency	2 case reports	Defective MAC, defective bactericidal activity	SLE with renal involvement	Neisserial infections
C5 deficiency	2 case reports	Defective MAC, defective bactericidal activity	One patient with membranous glomerulonephritis and arthritis and one patient with DLE	Neisserial infections
C8 deficiency	1 case report	Defective MAC, defective bactericidal activity	Photosensitivity, malar rash, alopecia, arthritis and nephritic syndrome	Neisserial infections

DLE discoid lupus erythematosus, *MAC* membrane attack complex, *IC* immune complexes, *ANA* antinuclear antibodies

to explain these observations invokes the role of complement in physiological waste disposal, in particular, the processing and clearance of dying cells and immunecomplexes [3, 5]. It has been demonstrated that C1q is essential for proper clearance of apoptotic cells, considered as the primary source of self antigens which break tolerance during SLE development. SLE associated with complete C1q deficiency is a severe condition, which tends to appear early in life, with no female predominance. There is no description of C1q deficiency among healthy individuals, reinforcing the crucial role of C1q for immune homeostasis [5]. The second hypothesis, which does not exclude the first one, proposes that complement also plays a role in activation of B and T lymphocytes and that complement deficiency causes autoantibody production by impairing the normal mechanisms of tolerance induction and maintenance [5, 8].

Chronic Granulomatous Disease

CGD is a genetically heterogeneous disease characterized by recurrent life-threatening infections with bacteria and fungi due to severely impaired phagocyte intracellular killing. CGD is caused by defects of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase system, which is responsible for the generation of superoxide and other reactive oxygen species in phagocytic cells. The X-linked form, caused by mutations of the *CYBB* gene, accounts for more than 75% of the cases [9]. In the large US series of

368 CGD patients, ten (2.7%) presented discoid lupus (DLE) and 2 (0.5%) SLE. [9]. In the same study, a number of first-degree female relatives were reported as having SLE or DLE (20 with DLE and two with SLE from 290 kindreds), lupus manifestations being significantly more common among the mothers, grandmothers, maternal counterparts, and/or maternal aunts of the X-linked CGD patients. Interestingly, female carriers do not present abnormal susceptibility to infections. More recently, Cale et al. [10] investigated 19 carrier mothers of the X-linked CGD allele for the presence of lupus manifestations. It is remarkable that 12 mothers presented photosensitivity, seven presented arthralgia, and eight had mouth ulcers. Anti-nuclear antibodies were positive in five patients, four of whom reported photosensitivity. One patient had anti-double-stranded DNA (dsDNA), and another presented lupus anticoagulant. An explanation for such a strong association between CGD and lupus was given by Brown et al. [11] and Sanford et al. [12] who observed impaired exposure of phosphatidyl serine on neutrophils from X-linked GCD patients and concluded that these patients may have an increased risk of developing lupus due to abnormal apoptosis coupled to abnormal clearance of apoptotic cells, a mechanism equivalent to that proposed in complement deficiencies. Therefore, it is possible that one of the pathogenetic factors underlying lupus-like features in CGD could be a defective neutrophil apoptosis. These data might suggest that *CYBB* and other CGD-related genes could be lupus-susceptibility genes.

Selective IgA Deficiency

Selective IgA deficiency (IgAD) is the most common PID (1:400–1:3,000 among healthy blood donors). The prevalence of this PID in various SLE series has been estimated as 1–4.6% and is, therefore, ten to 50 times higher than the described for the general population [13, 14]. More recently, Cassidy et al. [15] detected a frequency of 5.2% in 77 juvenile SLE (JSLE) patients, while the frequency of this PID in 152 adult onset SLE patients was of 2.6%. We detected three patients with selective IgA deficiency (<7 mg %) and two patients with partial IgA deficiency (14 and 21 mg%, respectively) in a series of 49 consecutive JSLE at our hospital (unpublished data). Additionally, anti-IgA antibodies have been detected in 58–100% of the patients with IgAD and SLE [14, 15]. No significant differences in clinical presentation and in disease severity have been found comparing IgA-deficient SLE patients with those with normal IgA levels [14, 15].

The strong association between IgAD and SLE, as well as with other systemic and organ-specific autoimmune disorders, has not been fully elucidated yet, and many hypotheses to explain this association have been proposed [15]. As secretory IgA plays a key role as an initial barrier to prevent infections and food antigen absorption, its lack in the mucosal tracts of IgAD patients may expose these individuals to several environmental antigens, favoring an enhanced immune response to such antigens and a chronic T and B cell activation. In its turn, serum monomeric IgA has been regarded as a discreet "housekeeper" of the immune system, with multiple anti-inflammatory functions. A novel hypothesis about the anti-inflammatory role of monomeric serum IgA is proposed in another review of this issue. According to that hypothesis, the interaction of serum IgA with the FcαRI on cell membrane would result in partial phosphorylation of FcRγ-associated FcαRI, notably in the ITAM motif, thus inducing recruitment of the SHP-1 tyrosine phosphatase [16]. This in turn leads to deactivation of several immune response pathways, and consequently, inflammatory reactions and autoimmunity would be prevented. In contrast, the lack of engagement of FcαRI by IgA in IgA-deficient individuals would result in the abolishment of FcαRI-inhibitory signaling.

PIDs Not Associated with SLE

In contrast to the previous group, there are some PIDs in which SLE or lupus-like manifestations have not been observed, and those may also be relevant for the comprehension of SLE physiopathology.

Diseases of Immune Dysregulation

It seems paradoxical that SLE or lupus-like manifestations have not been described in PIDs highly associated with autoimmunity, such as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX), and autoimmune lymphoproliferative syndrome (ALPS) [1, 2]. Indeed, these disorders represent unique human models to analyze the involvement of pivotal mechanisms for tolerance induction and maintenance, such as (1) thymic negative selection of lymphocytes, that is, central tolerance; (2) regulatory T cell-mediated peripheral tolerance; and (3) Fas-mediated apoptosis of autoreactive lymphocytes in SLE pathogenesis, and their study strongly suggests that these mechanisms are not crucial players in SLE pathophysiology.

Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy

APECED, also called APS-1 (autoimmune polyglandular syndrome type 1), is associated with loss-of-function mutations of the autoimmune regulator (*AIRE*) gene [2]. AIRE was shown to exert its critical function in medullary epithelial

cells of the thymus by promoting ectopic expression of peripheral tissue antigens. It has been considered as a central molecule in the thymic selection of lymphocytes. Therefore, in defective AIRE expression, autoreactive T cells escape negative selection, migrate to the periphery, and thus cause disease. APECED has been considered a prototypical disease of central tolerance breakdown. Besides mucocutaneous candidiasis, APECED patients present a series of organ-specific autoimmune manifestations: hypoparathyroidism, hypoadrenalism, ovarian or testicular failure, hypothyroidism, insulin-dependent diabetes mellitus, chronic hepatitis, alopecia, and vitiligo have been the most frequently described [17–19]. Candidiasis usually manifests first, in the first years of life, while endocrinopathies appear later in childhood or adolescence or even in adulthood, as patients usually have a long survival if adequately treated. Strikingly, these patients rarely present systemic autoimmune manifestations and cytopenias. Although almost all APECED patients have multiple autoimmune manifestations, so far none have been described as fulfilling criteria for SLE diagnosis. In addition to this fact, although APECED patients present high levels of various organ-specific autoantibodies, ANA (antinuclear antibody) titers have been constantly observed as being negative or low (<1:80) [20]. In the series studied by Perniola et al., only one patient was described with positive anti-Sm antibodies, while none presented anti-dsDNA. The absence of SLE among the APECED series strongly suggests that AIRE-mediated thymic selection of lymphocytes is not a critical pathway in SLE pathogenesis, allowing us to speculate that this would be a pivotal mechanism for the induction of tolerance to tissue-restricted antigens but perhaps not to ubiquitously expressed autoantigens.

Immunodysregulation Polyendocrinopathy Enteropathy X-Linked

IPEX is associated with mutations of *FOXP3*, which is essential for development and functions of regulatory T cells (Treg). It is usually a fatal condition, with multiple organ-specific and systemic autoimmune manifestations, mediated by both T cells and antibodies, typically observed from the first weeks of life. Inflammatory enteropathy, insulin-dependent diabetes mellitus, thyroiditis, Coombs' positive hemolytic anemia, and thrombocytopenia are frequent. Neutropenia, autoimmune hepatitis, nephritis, and vasculitis have also been described, accompanied by a variety of autoantibodies to multiple targets [2, 21, 22]. Diagnosis of SLE has not been established neither in the "classical" IPEX babies nor in the few older children with less severe phenotypes. One can argue that most IPEX patients do not survive enough to develop SLE.

Studies concerning Treg cells in SLE patients have shown lower percentages with variable results in regards to their functional activity as well as to levels of FOXP3 mRNA and protein, and, thus, further observations are necessary to reach conclusions about the role of Treg cells in SLE pathogenesis [23].

Autoimmune Lymphoproliferative Syndrome

ALPS is characterized by defective lymphocyte apoptosis and homeostasis, due, in most cases, to mutations of the Fas gene, but ALPS phenotype has also been associated with mutations of the Fas ligand, caspases 10 and 8, and NRAS (neuroblastoma rat sarcoma oncogene) [24, 25]. Although cytopenias are the most characteristic autoimmune manifestations of ALPS patients, who also usually present high titers of autoantibodies, only one description of an ALPS patient (with Fas ligand mutation) fulfilling SLE diagnostic criteria has been found in more than 200 patients already described [24, 26]. Antinuclear antibodies have been observed in ALPS patients, but, except for the above-mentioned patient, there is no description of anti-dsDNA or other SLE-related autoantibodies.

On the other hand, homozygous Fas- (*lpr*) and FasL- (*gld*) deficient mice, a natural knockout model of ALPS, present features that resemble SLE. Regarding the study of apoptosis pathways in SLE patients, increased apoptosis rates as well as increased expression of Fas receptor on their lymphocytes have been observed, and the last finding correlated with disease activity [27]. There is a hypothesis that accelerated apoptosis of circulating lymphocytes or impaired clearance of apoptotic cells in patients with SLE may lead to the presence of increased amounts of intact nuclear antigens at the extracellular tissue and drive an autoimmune response with production of autoantibodies. However, the study of ALPS patients suggests that the Fas-mediated lymphocyte apoptosis pathway does not seem to be critical for the physiopathology of SLE.

Agammaglobulinemia and Common Variable Immunodeficiency

X-linked agammaglobulinemia (XLA) is a disorder of B-cell maturation characterized by the absence of mature B cells, very low serum levels of all immunoglobulin isotypes, and lack of specific antibody production, and which has been associated with *BTK* mutations. Remarkably, among the large series of XLA patients, there is no description of SLE, although these patients may develop chronic arthritis (around 15% of cases), dermatomyositis, and scleroderma [28–30]. It has not been established so far if the neutropenia frequently seen in agammaglobulinemic patients is of autoimmune nature. SLE diagnosis is obviously difficult to be established in the absence of autoantibodies, but it is noteworthy that XLA patients do not present the most characteristic SLE features,

such as cutaneous and oral manifestations, renal involvement and serositis. This "human model" highlights that B lymphocytes and antibodies are essential for SLE pathogenesis and has implications in the rationale for the indication of anti-CD20 therapy for severe manifestations of SLE.

The rarity of SLE descriptions among common variable immunodeficiency (CVID) patients (estimated as present in 1:25,000–1:50,000 in general population) reinforces the pivotal role of antibodies in SLE pathophysiology [31, 32]. To note, cytopenias are the most frequent autoimmune manifestations associated with CVID, described in up to 22% in large CVID series [32]. Interesting observations are those related to the CVID patients whose underlying molecular defects were already identified, i.e., defects of ICOS, TACI, BAFF-R, CD19, and MSH5, and no SLE was observed among the still restricted number of families so far described [33–35].

Hyper-IgM Syndrome due to Defects of CD40–CD40 Ligand Pathway

Immunodeficiency with hyper-IgM (HIGM) is characterized by normal to increased serum IgM levels and very low or undetectable IgG, IgA, and IgE, and part of the cases are due to defects in the CD40–CD40 ligand pathway. SLE or lupus-like manifestations have not been reported among X-linked HIGM series, associated with CD40L (CD154) defects [36, 37], nor in the few cases so far identified of HIGM due to CD40 deficiency [38]. These observations suggest that severely impaired CD40–CD40L pathway do not favor SLE development, perhaps as a consequence of defective B cell activation coupled to deficient immunoglobulin class switching. In their turn, SLE patients with active disease present increased percentages of CD4+, CD8+ T lymphocytes, and surprisingly, B lymphocytes expressing CD40L, favoring the idea that SLE patients present a chronic lymphocyte activation [39]. Thus, the study of HIGM may provide useful insights into the role of the CD40–CD40L pathway in SLE development.

Concluding Remarks

The "experiments of nature" represented by PIDs effectively teach us useful lessons for the comprehension of underlying mechanisms leading to the development of SLE. On one hand, the PIDs highly associated with SLE or lupus-like manifestations, i.e., deficiencies of the early components of classical complement pathway and CGD, point out to the relevance of defective mechanisms of cellular waste-disposal in SLE physiopathology. The most impressive lesson is given by complete C1q deficiency, which may be considered as practically a monogenic form of SLE. On the other hand, the group of "syndromes with autoimmunity" is also very informative, as APECED, IPEX, and ALPS, albeit highly associated with other autoimmune manifestations, and the human "knockout" models for *AIRE*, Foxp3+ Treg cells, and Fas-mediated apoptosis, respectively, are not associated to SLE.

Further unique lessons in the understanding of SLE pathogenesis are given by antibody deficiencies. XLA demonstrates in an unequivocal fashion the essential role of B lymphocytes and antibodies in SLE development. Moreover, the study of CVID patients reinforces the lessons learned from XLA. Observations from patients with various antibody deficiencies show that those with severely impaired IgG production (such as XLA, CVID, and HIGM syndrome) are not prone to SLE, even if they are able to synthesize IgM, as in HIGM due to AID (activation-induced cytidine deaminase) and UNG (uracil-*N*-glycosilase) deficiencies [40, 41]. Taken collectively, data from the different predominantly antibody deficiencies suggest that IgG is crucial for the development of SLE.

As human models of autoimmune disorders, PIDs represent unique and not fully explored opportunities for a better comprehension of SLE. While the PIDs strongly associated with SLE point out to mechanisms to be more extensively explored, the not-associated ones indicate mechanisms not relevant or pathways whose severe impairment may prevent SLE development, such as CD40-CD40L and IL-12/IFN-γ pathways (Table 1).

Addendum in proof After the acceptance of this manuscript, a study by Martire et al described one more X-linked CGD patient with SLE and another with discoid lupus erythematosus in a multicenter Italian series of 60 CGD patients (Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol, 2008;126:144–156).

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