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Review

Monogenic lupus: Dissecting heterogeneity

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ABSTRACT

Systemic lupus erythematosus (SLE) is a severe lifelong multisystem autoimmune disease characterized by the presence of autoantibodies targeting nuclear autoantigens, increased production of type I interferon and B cell abnormalities. Clinical presentation of SLE is extremely heterogeneous and different groups of disease are likely to exist. Recently, childhood-onset SLE (cSLE) cases have been linked to single gene mutations, defining the concept of monogenic or Mendelian lupus. Genes associated with Mendelian lupus can be grouped in at least three functional categories. First, complement deficiencies represent the main cause of monogenic lupus and its components are involved in the clearance of dying cells, a mechanism also called efferocytosis. Mutations in extracellular DNASE have been also identified in cSLE patients and represent additional causes leading to defective clearance of nucleic acids and apoptotic bodies. Second, the study of Aicardi-Goutières syndromes has introduced the concept of type-I interferonopathies. Bona fide lupus syndromes have been associated to this genetic condition, driven by defective nucleic acids metabolism or innate sensors overactivity. Interferon signalling anomalies can be detected and monitored during therapies, such as Janus-kinase (JAK) inhibitors. Third, tolerance breakdown can occur following genetic mutations in B and/or T cell expressing key immunoregulatory molecules. Biallelic mutations in *PRKCD* are associated to lupus and lymphoproliferative diseases as PKC-δ displays proapoptotic activity and is crucial to eliminate self-reactive transitional B cells. Here we review the literature of the emerging field of Mendelian lupus and discuss the physiopathological learning from these inborn errors of immunity. In addition, clinical and biological features are highlighted as well as specific therapies that have been tested in these genetic contexts.

Systemic lupus erythematosus (SLE) is a rare, multisystem immunological disorder characterized by the presence of autoantibodies targeting nuclear autoantigens, type I interferon production and B cell tolerance breakdown as illustrated by autoantibodies production. SLE represents an heterogeneous disease, with the diagnosis of SLE requiring the presence of 4 out of 11 defined criteria [1–3]. The pathogenesis underlying SLE remains unclear. Interestingly, familial aggregation and higher concordance rates between monozygotic

Abbreviations: AD, Autosomal Dominant; AGS, Aicardi-Goutieres Syndrome; ANA, Anti-Nuclear Antibodies; AR, Autosomal Recessive; BSN, Bilateral strial necrosis; CNS, central nervous system; CVD, Cerebrovascular disease; DSH, Dyschromatosis symmetrica hereditaria; FCL, Familial chilblain lupus; SMS, Singleton Merten Syndrome; SPENCD, Spondyloenchondrodysplasia; SP, Spastic paraparesis; SAVI, STING-associated vasculopathy with onset in infancy

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(20–40%) relative to dizygotic twins and other full siblings (2–5%) suggest a major hereditary component to pathogenesis [4,5]. Genome-wide association studies (GWAS) have identified more than 80 loci as strongly associated with lupus [6–8]. These variants are common and confer small effects on disease susceptibility [9,10]. In contrast, monogenic susceptibility to SLE, for which almost 30 genes have been described in humans, are related to single mutations in DNA-coding regions of the genome [11].

Mendelian inborn errors of immunity have helped unravelling the mechanisms of immune tolerance in humans, and three main pathways have been reported associated to lupus. First, defects in the complement components represent the first genetic cause of SLE identified in humans and highlight the importance of the clearance of apoptotic bodies in lupus pathogenesis [12]. Similarly, extracellular DNAse deficiencies promote SLE secondary to defective clearance of nucleic acids in extracellular microparticles [13,14]. In addition, the importance of type I interferon signalling in SLE is emphasized by the association of lupus phenotype with the type I interferonopathies [15]. Finally, B cells are considered central in lupus pathogenesis [16], with PKCδ deficiency identified as the first B cell related subset of monogenic lupus in humans [17,18].

Here we report the insights arising from the molecular study of monogenic lupus forms, and illustrate their main clinical and immunological features (Table 1). Tailoring treatment with the underlying genetic molecular defect represent promising strategies.

1. Efferocytosis defects

Every day, hundreds of billion cells die from apoptosis or specialized programs such as neutrophil cell death, defined as NETosis, a neutrophil cell death program associated to extrusion of fibrillary networks called neutrophil extracellular traps (NETs) [19]. Apoptotic bodies and associated extracellular nucleic acids are scavenged by tissue-resident phagocytes (macrophages and dendritic cells) or locally recruited phagocytes [20]. This process is important to prevent the induction of inflammation upon recognition of endogenous pathogen recognition receptors (PRR) ligands. Numerous molecules are involved in the recognition of apoptotic cells and this mechanism is also referred as efferocytosis. In humans, complement deficiencies and the DNASE1L3 deficiency define a subset of monogenic lupus due to efferocytosis defect and excess of apoptotic bodies.

1.1. Complement deficiencies

The complement system plays a role in the innate and adaptive immune response. Complement proteins act as opsonins facilitating the clearance of apoptotic bodies and immune complexes by phagocytes, as well as a lytic agent against pathogens [21]. The early components of the classical pathway (C1q, C1r and C1s) are mainly produced by monocytes, macrophages and dendritic cells while the other subsets are produced by hepatocytes [22]. Genetic defects in complement impair efferocytosis leading to the accumulation of autoantigens in the extracellular environment [23]. Moreover, the complement system is needed to clear immune complexes, the accumulation of which leads to inflammation and organ damage as in the case of nephritis. Complement components have additional immune regulatory functions. For example, C1q is capable to reduce type I interferon production by plasmacytoid dendritic cells [24] and has been recently shown to regulate adaptive immunity by modulating the mitochondrial metabolism of CD8 T cells, thereby preventing self-antigen autoreactivity and promoting viral control [25]. The CR1 and CR2 complement receptors that respectively recognize C1q and C4 are also potent regulators of B cell activation [26,27]. Genetic deficiencies of the early component of the classical pathway C1q/r/s strongly predispose to SLE, with a penetrance of up to 90%. Deficiencies or mutations in other complement proteins of the classical pathway, such as C4 and C2, also promote

Table 1
Monogenic causes of SLE.

Pathways	Gene/Protein	Function	Inheritance	SLE manifestation
Complement Deficiency	*C1QA, B, C*/C1qA, B, C	Efferocytosis	AR	Nephritis, CNS involvement, photosensitivity, arthritis, ANA
	C1R/C1r-*C1S*/C1s		AR	Nephritis, Fever, arthritis, ANA,
	C4A, C4B, C4		AR	Multi-organ involvement; glomerulonephritis, severe photosensitivity
	C2/C2		AR	Photosensitivity and arthritis, mild or absent renal, neurological or pleuropericardial involvement
	C3/C3		AR	Malar rash, photosensitivity, arthralgia and Raynaud's phenomenon
	C5/C5, *C6*/C6, *C7*/*C7*, *C8A*/C8A, *C8B*/C8B, *C9*/C9		AR	Multi-organ involvement
Auto-Antigen Excess	*DNASE1*/DNASE1	Extracellular ds/ss DNA degradation	AD	Systemic lupus, Sjögren syndrome, high levels of anti-nucleosomal antibodies
	DNASE1L3/DNASE1L3	DNA-chromatin degradation in apoptotic bleb	AR	Early-onset SLE, antinuclear antibodies, anti-dsDNA, ANCA
Type I Interferonopathy	*ACP5*/TRAP	Regulate OPN levels though not clearly defined	AR	SPENCD, cytopenias, SLE
	ADAR1/ADAR1	RNA editing silencing detection by RLR	AR	AGS, DSH, BSN, SP
	IFIH1/MDA5	Cytoplasmic dsRNA sensor	AD	AGS, SP, SMS
	RNASEH2A, B, C, RNASEH2A, B, C	DNA:RNA degradation	AR	AGS
	SAMHD1/SAMHD1	Cytoplasmic ssRNA/DNA sensor	AR	AGS, FCL, CVD
	TMEM173/STING	dsDNA sensor	AD	SAVI, FCL
	TREX1/TREX1	Cytoplasmic Ss/dsDNA degradation	AR	AGS, FCL, SLE
Tolerance	*TNFRSF6*/CD95	Apoptosis	AR	SLE with lymphadenopathy
	PRKCD/PKCδ	B cell survival and proliferation	AR	skin and renal involvement cerebral vasculitis lymphoproliferative
	IKZF1/IKAROS	Early lymphocytes development	AD	SLE, Evans syndrome

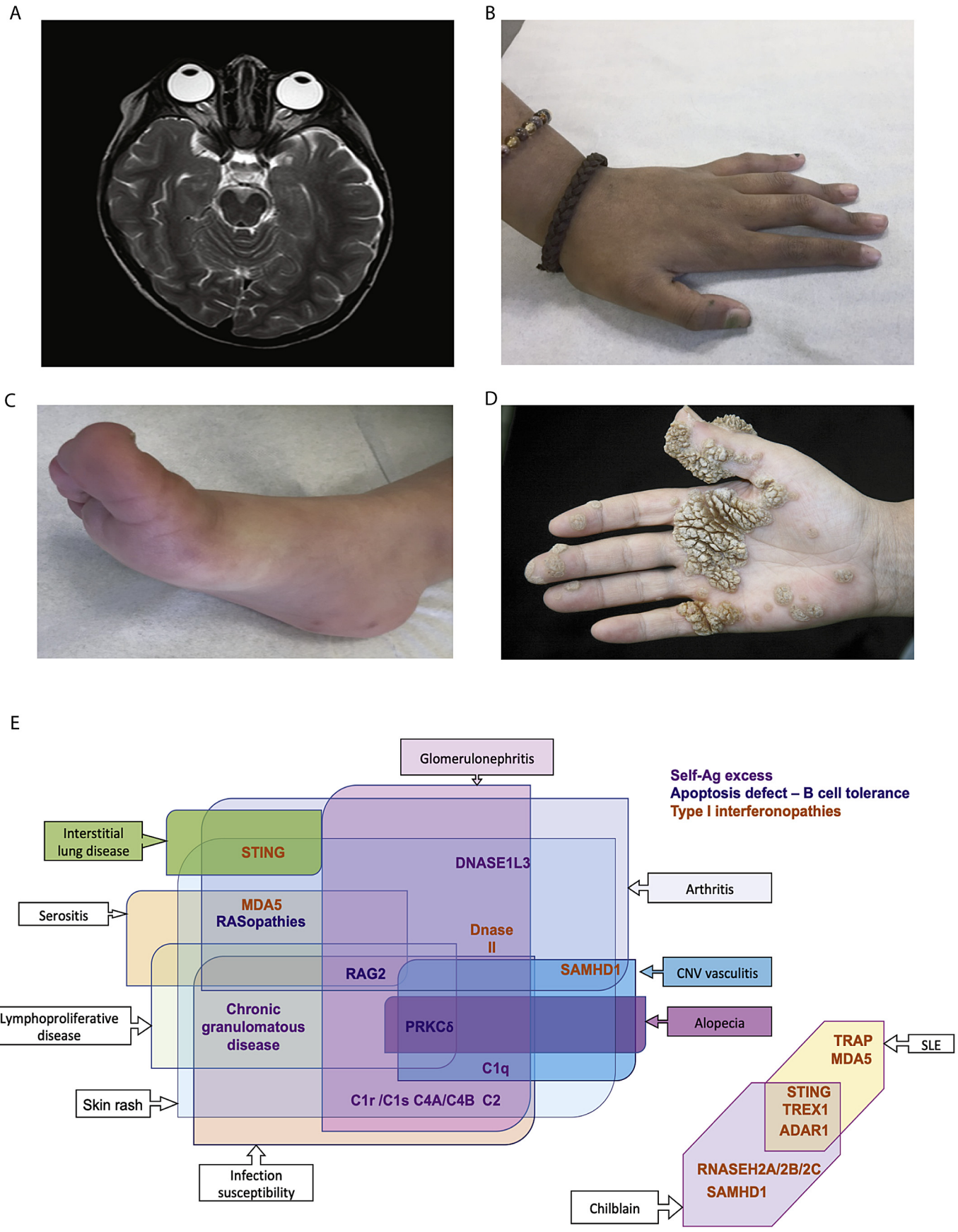

Fig. 1. Clinical features of monogenic lupus. A: Cerebral MRI (T2 sequence showing temporoparietal hypersignal in a C1R deficient patient with meningitis, B: Jaccoud's arthropathy in a patient with type I interferonopathy, C: chilblain lupus in type I interferonopathy, D: papillomatosis of the hand of patient with PKCδ deficiency, E: synthesis of clinical features of monogenic lupus).

systemic autoimmunity such as lupus with the following risk: 10–20% in C2 deficiency and 75% in C4 deficiency [28].

Complement deficiencies are associated with early-onset lupus manifestations, with a sex ratio (ie predominance in females) less biased than that of adult-onset SLE. The phenotype is severe, in particular because of recurrent life-threatening infections such as meningitis (Fig. 1A). Photosensitive skin rash is very common in all complement deficiencies whereas severe arthritis is mostly seen in patients with C2 deficiency, and lupus nephritis in C4A/C4B-defective monogenic lupus. The prevalence of antinuclear antibodies (ANA) is usually high whereas only 20% of patients display anti-dsDNA. Conversely, anti-Ro/SSA antibodies are positive in 80% of patients with C1q and C4 deficiencies. Low CH50 with normal serum levels of C4 and C3 is evocative for a complement deficiency.

1.2. Extracellular DNASE deficiencies

Additional enzymes involved in digestion of extracellular nucleic acids are also critical for the maintenance of immune tolerance. DNASE1 is an extracellular DNA-degrading enzyme, which is present in both serum and urine. Dnase1-deficient mice develop ANA and glomerulonephritis [29]. Four SLE cases were reported with a mutation in *DNASE1* exhibiting very high levels of anti-nucleosomal antibodies [30,31]. DNASE1L3 is a homologue of DNASE1 containing a positively charged C-terminal peptide, which confers the ability to remove DNA chromatin associated to extracellular microparticles; Dnase1L3 deficient mice develop SLE-like phenotype [14].

DNASE1/DNASE1L3 deficiencies lead to the accumulation of extracellular nucleic acids which can be recognized by DNA/RNA sensors such as Toll-like receptors (TLR7 and TLR9) then promoting type I interferon production [32]. Moreover, circulating DNA can bind autoantibodies leading to immune complex formation with associated organ damage. DNASE1L3 deficiency was identified in familial SLE cases with the association of ANA, anti-dsDNA and ANCA and also as a form of hypocomplementemic urticarial vasculitis [13,33]. Lupus nephritis is frequent and beside low complement fractions C3 and C4 and positivity of ANA and anti-dsDNA antibodies, ANCA positivity is evocative [34].

1.3. Other defects in phagocytosis

The X-linked form of chronic granulomatous disease (CGD) is due to *CYBB* mutations. *CYBB* encodes the 91-kD glycoprotein component of the ROS-generating enzyme NADPH oxidase or NOX2 (nicotinamide adenine dinucleotide phosphate) and has been connected to lupus phenotype. The link between CYBB and SLE is thought to be secondary to the increase of NETosis, releasing high amounts of intracellular DNA and self-antigens outside the cells. In mice prone to autoimmunity, Nox2 deficiency exacerbates the disease [35]. Furthermore, NETs inhibition exacerbated lupus phenotype [36]. NOX2-derived reactive oxygen species may regulate T cell activation by oxidizing self-antigen-derived peptides limiting autoimmune arthritis, as recently proposed [37]. CGD is characterized by recurrent-life threatening infections by bacteria and fungi [38,39] and some patients also display inflammatory manifestations ranging from Crohn's disease to discoid lupus or SLE [40]. X-linked carriers are at a higher risk for skin manifestations such as discoid lupus erythematosus and photosensitivity, and generally present with a strong susceptibility to recurrent infections, especially by catalase positive organisms [41,42]. Arthritis, glomerulonephritis and Raynaud's phenomenon were rarely described. Autoantibody screening is generally negative, even in patients with a lupus-like phenotype [41,43].

2. Type I Interferonopathies

Interferons (IFN) are cytokines with an essential role in antiviral defence and display key regulatory functions in innate and adaptive immune responses. Type I IFN represent the largest family of IFNs, including IFNα, which comprises 13 distinct subset and IFN-β. Exacerbated IFNα signalling represents a hallmark of systemic lupus erythematosus [44].

Monogenic type I interferonopathies refer. to a group of diseases associated with an upregulation of type I interferon expression. Jean Aicardi and Françoise Goutières described a familial progressive neonatal encephalopathy mimicking a congenital viral infection, Interestingly, some patients with Aicardi-Goutières syndrome (AGS), also present features of systemic autoimmunity [45]. Patients display a wide range of neurological manifestations, from isolated cerebral calcifications to an early-onset encephalopathy, with cerebral atrophy and leukoencephalopathy. High levels of type I interferon were found in the serum and cerebrospinal fluid of these patients [46]. Loss of function mutations of the DNA 3′ repair exonuclease 1 TREX1 were the first identified genetic cause of AGS [47]. This enzyme plays a crucial role in the metabolism of intracellular DNA and prevents its detection by innate immune sensors and the type I interferon activation [48]. Indeed, the detection of intracellular nucleic acids through various innate immune sensors leads to type I interferon production in response to the activation of regulation factors, IRF (IFN regulatory factors) [43]. Of note, interferon production is triggered by the detection of exogenous nucleic acids from viruses but also by intracellular nucleic acids derived from endogenous retroviral sequences present in our genome (HERV). Considering that type I interferon plays a primary pathogenic role in these disorders, Crow and colleagues proposed to group them as «Type I interferonopathies» [44]. Thereafter, numerous additional genes have been reported as causal for AGS and are linked to IFN signalling upregulation [49,50].

The excessive production of interferon can appear through three different pathways:

- Defect in nucleases (*TREX1*, *SAMHD1*, *ADAR1*, *RNASEH2*, *RNASEH2B*, *RNASEH2C*) leading to the accumulation of endogenous nucleic acids
- Constitutive activation or enhanced sensitivity of an innate immune sensor, for example MDA5 and RIG-I (*IFIH* and *DDX58* mutations respectively) or adaptor molecules downstream the innate sensors (such as STING, encoded by *TMEM173*, downstream the receptor cGAS)
- Defective negative feedback of the interferon pathway (*ISG15* mutations).

Type I interferons then bind to the heterodimeric receptor (IFNAR 1 and IFNAR 2) and activate the JAK-STAT signalling pathway and induce the transcription of hundreds of interferon-stimulated genes (ISG) [44,51].

Type I interferonopathies manifestations are very heterogeneous and comprise overlapping phenotypes [52]. Herein, we review common traits associated with the different forms, as well as gene-specific features (Table 1).

Chilblain lesions as well as severe neurodevelopmental features are the most evocative manifestations of a type I interferonopathy (Fig. 1B). Penetrance and expressivity differ and neurological symptoms without autoimmunity or isolated type I IFN signature can be also observed in affected individuals. The frequency of lupus-like manifestations and chilblain depends on the gene involved (Fig. 1E). The systemic phenotype of the newly described type I interferonopathy linked to biallelic mutations in DNASE2 is relatively broad with clinical features evocative of an autoinflammatory syndrome and various autoimmune manifestations. Transient life-threatening anemia in the neonatal period was particularly noticeable in those patients [53].

Interstitial pneumonia with skin vasculitis is evocative for the STING-associated vasculitis with onset in infancy (SAVI) and interstitial lung disease represents the first symptom of the disease [54,55]. Tendon rupture, subluxation for the hands, reminiscent of *Jaccoud's*

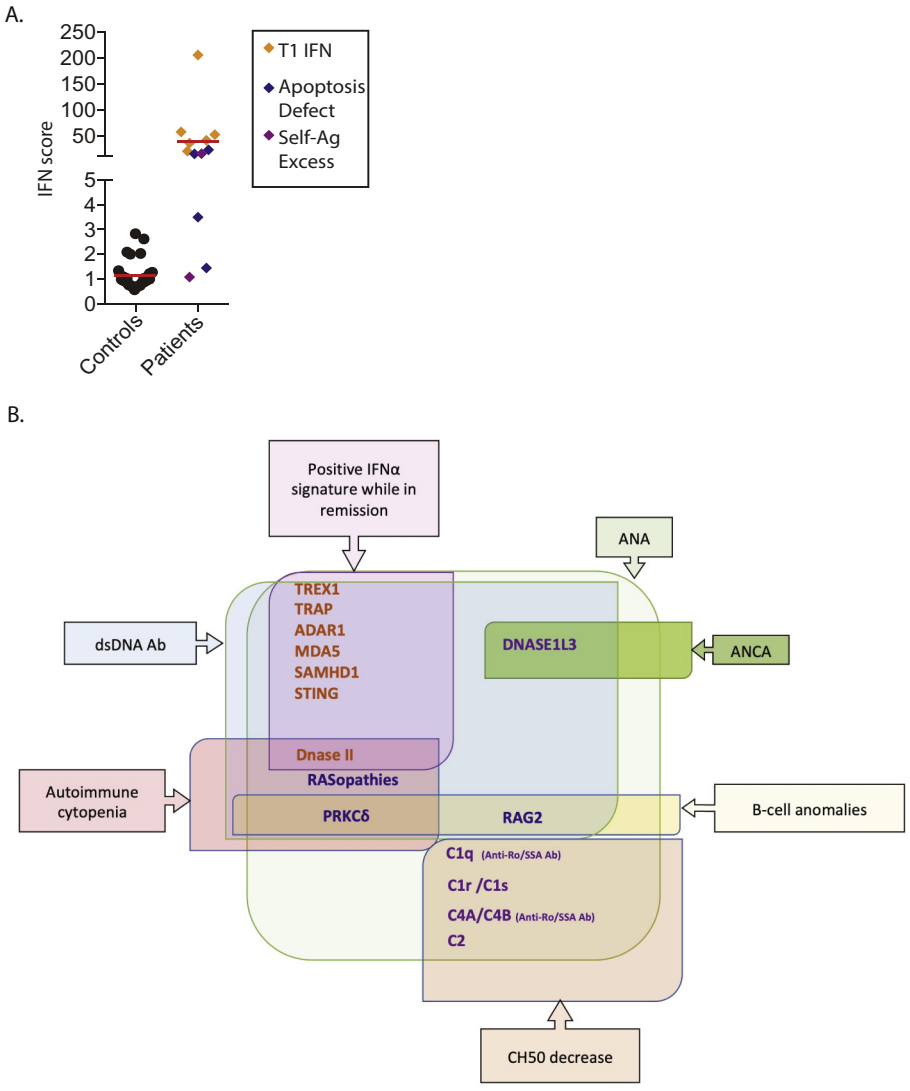

Fig. 2. Biological features of monogenic lupus. A: Type I Interferon signature in patients with monongenic lupus, B: Synthesis of biological features of monogenic lupus.

arthopathy (Fig. 1C) have been observed in MDA5-related type I interferonopathy [56]. ANA and dsDNA antibodies have been recorded in type I interferonopathies but are inconsistent.

Type I interferon protein dosage is not available in routine medical practice to date because of very low circulating levels [57]. However, Rice et al. showed that the type I interferon upregulation was correlated with the increased expression of a subset of six interferon stimulated genes (ISG) (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2* and *SIGLEC1*) in AGS patients, the so-called interferon signature [58]. Interferon signature can be used both for the diagnosis of type I interferonopathies and to follow disease activity, and is also very sensitive to differentiate monogenic and complex type I Interferonopathies from inflammasomopathies. Interferon signature might be also useful to dissect the distinct monogenic lupus (Fig. 2A) [59,60].

3. Other subsets of type I interferonopathies

Proteasome-associated autoinflammatory syndrome (PRAAS) is another autoinflammatory disease consisting in recurrent fever, panniculitis and lipodystrophy and is associated with positive interferon signature. *PSMB8* encodes a proteasome subunit, and its mutation leads to proteasome dysfunction, accumulation of ubiquitinylated proteins and autoinflammation [61]. The X-linked reticulate pigmentary disorder (XLRPD) is a genodermatosis with autoinflammatory features linked to the intronic mutation of *POLA1*, which encodes a catalytic subunit of the DNA-polymerase-α.

Mutations in *ACP5* encoding Tartrate-resistant acid phosphatase type 5 (TRAP) are transmitted through an autosomal recessive mode and are responsible for spondylo-enchondrodysplasia (SPENCD) with skeletal dysplasia, growth retardation, neurological involvement and systemic autoimmunity. The latter condition represents an increased susceptibility for Sjögren's syndrome, systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, hypothyroidism, inflammatory myositis, Raynaud's syndrome and vitiligo [62]. TRAP is expressed in osteoclasts, macrophages and dendritic cells, thus explaining both skeletal and autoimmune involvements in SPENCD patients.

4. B and T cell tolerance breakdown

The hallmark of SLE is the presence of a wide range of autoantibodies indicating the presence of autoreactive lymphocytes. Ineffective deletion of autoreactive T or B cells could trigger autoimmunity and disrupt self-tolerance [63]. The importance of apoptosis defects in human autoimmunity was underlined by the discovery of mutations in the pro-apoptotic molecule CD95/Fas defining the Autoimmune Lymphoproliferative Syndrome (ALPS). ALPS is an inherited

disease characterized by a chronic non-malignant lymphadenopathy, hepatosplenomegaly, expansion of $CD3^+TCR\alpha/\beta^+CD4^-CD8^-$ double negative T (DNT) cells and other autoimmune features such as presence of autoantibodies and autoimmune cytopenia [64,65]. Of note, no full-blown lupus has been described so far with this specific genetic background. A few other patients have been described with homozygous *CD95L/FASL* mutations that abolish the protein function [66,67] or heterozygous *CD95L/FASL* mutations with a dominant negative effect [68]. In addition, the MRL/lpr mice represent a model of systemic autoimmunity with a mutation in the Fas receptor gene (lpr) [69] as well as the CD95L (gld) deficiency [70].

Another example of monogenic SLE is the protein kinase C-δ (PKC-δ) deficiency. PKC-δ is a pro-apopotic molecule essential in B cell survival and apoptosis, and PKC-δ knock-out mice develop systemic autoimmunity [71,72]. We identified an homozygous missense mutation in *PRKCD* in three siblings with childhood-onset SLE [17]. PKC-δ expression was reduced, which led to a B cell apoptosis defect and an accumulation of immature transitional B cells. Additional cases of PKC-δ deficiency have been reported, the main clinical features comprising skin lesions and alopecia, lymphoproliferative disease with lymphadenopathy, hepatosplenomegaly and mild to severe infection susceptibility, both to bacteria and viruses [73-76]. Chronic Epstein Barr virus or cytomegalovirus replication have been reported [73]. One of our patients presented at the age of 30 with severe papillomatosis illustrating the defective immune control of a wide range of viruses (Fig. 1D). Lupus nephritis is frequent and cerebral vasculitis has also been reported. Immunophenotyping in these patients reveals a B-cell deficiency with an expansion of transitional B cells and a decrease of memory B cells [17]. ANA, ENA and dsDNA antibodies are generally positive, with normal complement levels.

Another subset of disease with apoptosis dysregulation is illustrated by the RASopathies. Noonan syndrome and Noonan-related syndromes represent neurodevelopmental syndromes due to germline mutations in genes that participate in the rat sarcoma/mitogen-activated protein kinases (RAS/MAPK) pathway (PTPN11, SOS1, RAF, KRAS or NRAS, and SHOC2). Lupus phenotype has been reported in such patients and autoimmune features were not different from those presented by the general SLE population [77], with polyarthritis, autoimmune cytopenia, serositis, ANA and anti dsDNA antibodies.

IKAROS mutations were also identified in 4 patients with autoimmunity including one fulfilling early-onset SLE criteria [78]. IKAROS mutations were reported as causal for common variable immunodeficiencies [79], with decreased lymphocyte populations (B, T and NK cells). *IKZF1* encodes the IKAROS zinc finger transcription factor which is crucial in early steps of haematopoietic development, as demonstrated by a knock-out model [80,81]. Finally, recombination-activating 1 or 2 genes (*RAG1/2*) represents a crucial enzyme involved in the V(D)J recombination and BCR to TCR variability generation. While loss-of-function *RAG* mutations are associated with severe combined immunodeficiencies, hypomorphic mutations have been linked to autoimmunity [82-84. Interestingly a *RAG2* mutation has been reported in a lupus patient [82]. The patient carrying the heterozygous *RAG2* mutation presented with classical lupus-like systemic phenotype with arthritis and skin involvement, Raynaud's phenomenon, sicca syndrome, serositis and class V lupus nephritis. She had a history of recurrent infections attributed to her medication regimen. She presented with classical lupus-associated biomarkers with high titres of ANA and dsDNA antibodies and hypocomplementemia.

Biological abnomalities from different monogenic lupus syndromes are reported in Fig. 2B.

5. Towards precision medicine in SLE

SLE heterogeneity explains the so far limited success of clinical trials in lupus. With advent of NGS, our understanding of genetic causes of early-onset SLE is improving at a fast rate. This knowledge will not only allow a better stratification of patients, but also a rationale, personalized design of treatments. Moreover, the identification of causal genes may increase the number of targets for drug treatment of these diseases.

Considering the central role of type I interferon in the pathogenesis, Mendelian interferonopathies might benefit from type I interferon inhibition. JAK inhibitors are promising because they block the signalling downstream the IFN receptor. Baricitinib and ruxolitinib are both JAK1/2 inhibitors and have shown interesting preliminary results for their safety and efficacy in SAVI and CANDLE [85,86], although the IFN score was not totally abrogated in SAVI patients. Anifrolumab is a fully human monoclonal antibody that neutralises the IFNα receptor and has been reported as effective in non-monogenic lupus, especially in the context of high IFN signatures. It is a good candidate for treatment of type I interferonopathies. The main side effect is represented by herpes zoster infections [87]. Finally, as the HERV are supposed to be partially responsible for the increase of intracytoplasmic nucleic acids in AGS with enzymatic defects, it has been recently suggested that reverse transcriptase inhibitors used for patients with human immunodeficiency virus (HIV) may represent an option by targeting the endogenous retroviruses and thereby decreasing the IFN signature [88].

B cell targeting therapies or bone marrow transplantation may represent interesting options in B cell related monogenic lupus. Rituximab and ofatumumab have been reported as effective in siblings with PKC-δ deficiency [89].

Efferocytosis defect is actually the most challenging situation. No drug can promote efferocytosis and bone marrow transplantation has been proposed in severe C1q deficiencies [90].

In conclusion, monogenic lupus is a recently recognized field of diseases. Understanding better the underlying genetic causes will bring insight in the mechanisms of human immune tolerance and lupus pathogenesis, and likely lead to the discovery of novel therapeutic options to cure the disease.

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