Monogenic Autoimmune Diseases

Dae Chul Jeong
Division of Pediatric Rheumatology and Clinical Immunology, Department of Pediatrics, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Monogenic autoimmune diseases (AD) present as lupus-like clinical manifestations with recurrent fever or various vasculopathies. Recurrent fever with an elevation of acute phase reactants and various skin lesions are similar in monogenic AD and autoinflammatory disease. The molecular pathogenesis of adult systemic erythematosus can be understood through monogenic AD based on gene defects: complement, apoptosis, interferonopathy via nucleic acid sensing, tolerance, rasopathies, and others. Skin vasculopathy with chilblains and livedo reticularis, interstitial lung disease, and panniculitis are common occurrences in type I interferonopathy. Some syndromes have been reported to present with autoimmune inflammation and the general clinical findings, including cerebral calcification. Various clinical manifestations in monogenic AD present in accordance with the gene loss- or gain-of-function mutations involved. The monogenic AD for the early onset of more severe lupus-like symptoms or vasculopathy needs to be considered. Furthermore, clinical trials were conducted via targeted therapy for related molecular pathways, because conventional treatments were not effective in managing monogenic AD. (J Rheum Dis 2018;25:213-220)

Key Words. Autoimmune diseases, Genes, Systemic lupus erythematosus, Interferon

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune multi-system disease with various clinical manifestations. SLE is caused by the production of autoantibodies, complement activation, and immune complex deposition [1-3]. Approximately 20% of SLE cases are diagnosed in childhood. Pediatric SLE usually presents around puberty with more severe clinical manifestations than those in adults, however, it has a significantly lower incidence before puberty, and very rare before 5 years of age [1]. The pathogenesis of SLE is associated with multi-factorial pathogenesis including environmental, genetic, or hormonal factors [3-5]. Genome wide association studies have identified genes related with SLE pathogenesis [3].

The incidence of most autoinflammatory diseases (AID) is associated with gene mutations involved in the innate immune system, autoimmune diseases (AD) is related with adaptive immunity [6]. Both AID and AD primarily result in inflammation due to chronic immune activation [7]. Many AD, including SLE, are polygenic, while AID, including familial Mediterranean fever, are identified as monogenic diseases; however, in some cases, AID can also be polygenic, AD is associated with monogenic cause [6,7]. Patients with SLE showed high levels of interferon (IFN) [1,3]. Cytokine production is dependent on activation of cell signaling pathway related with cytokine genes [3,8]. In the pathogenesis of AID or AD, high level of various cytokines was identified, and associated with uncontrolled cytokine production regardless with polygenic or monogenic causes.

Recently, a pediatric monogenic lupus-like phenotype was reported, and is called monogenic lupus in accordance with the genes involved in autoimmune inflammation [9,10]. Understanding of the pathogenesis of
monogenic lupus may provide insights into SLE pathogenesis, although it is classified as an autoinflammatory disease [8,11].

Now, the present article discusses monogenic ADs based on their development and the pathogenesis of autoimmune manifestations.

**MAIN SUBJECTS**

**Clinical manifestations**
Most patients with monogenic or Mendelian lupus developed various early-onset systemic and organ-specific symptoms or signs at a young age [10,12-14]. Fever or elevation in acute phase reactants are frequently identified as systemic inflammation [9,10,14]. Skin rash is one of various manifestations resulting from gene mutations related with autoinflammatory or autoimmune responses [9,10,13-15]. In monogenic autoimmune diseases with gene mutations, organ defects or metabolic manifestations have been reported to be caused by genes involved in organ growth or development [9,10,16]. Auto-antibodies displayed a high or low titer in accordance with the gene mutation at any age [9,10]. Musculoskeletal symptoms were observed in many cases, and cardiopulmonary events including pulmonary hypertension or interstitial lung disease developed [9,10,12-15]. In some patients,

<p>| Table 1. The monogenic autoimmune diseases with corresponding pathogenesis and phenotype |
|-----------------------------------------|-----------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Gene</th>
<th>Proteins</th>
<th>Inheritance</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement/ immune clearance</td>
<td>C1QA/C1QB/ C1QC</td>
<td>C1q</td>
<td>AR</td>
<td>SLE with rashes, GN, CNS, anti-dsDNA often negative, recurrent infection</td>
</tr>
<tr>
<td></td>
<td>C1R</td>
<td>C1r</td>
<td>AR</td>
<td>SLE with rashes, GN, recurrent infection</td>
</tr>
<tr>
<td></td>
<td>C1S</td>
<td>C1s</td>
<td>AR</td>
<td>SLE with rashes, GN, recurrent infection</td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>C2</td>
<td>AR</td>
<td>SLE with arthritis, rashes, auto-antibodies often negative, recurrent infection</td>
</tr>
<tr>
<td></td>
<td>C4A, C4B</td>
<td>C4</td>
<td>AR</td>
<td>SLE with variable phenotype, rashes, proliferative GN, recurrent infection</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>TNFRSF6</td>
<td>Fas</td>
<td>AD</td>
<td>Autoimmune lymphoproliferative syndrome (ALPS), autoimmune cytopenias</td>
</tr>
<tr>
<td>Immune clearance</td>
<td>TNFRSF6</td>
<td>FasL</td>
<td>AD</td>
<td>ALPS, SLE with lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>DNASE1</td>
<td>DNase1</td>
<td>AD</td>
<td>SLE: high titer anti-nucleosomal antigens</td>
</tr>
<tr>
<td></td>
<td>DNASE1L3</td>
<td>DNase1L3</td>
<td>AD</td>
<td>Anti-dsDNA antibodies, low C3/C4, GN and positive ANCA: very young age of onset</td>
</tr>
<tr>
<td>Nucleic acid sensitio/Type I IFN</td>
<td>TRED1</td>
<td>TRED1</td>
<td>AR/AD</td>
<td>AGS: FCL; SLE with severe CNS disease</td>
</tr>
<tr>
<td></td>
<td>SAMHD1</td>
<td>SAMHD1</td>
<td>AR</td>
<td>AGS: FCL</td>
</tr>
<tr>
<td></td>
<td>ADAR1</td>
<td>ADAR1</td>
<td>AR/AD</td>
<td>AGS</td>
</tr>
<tr>
<td>Nucleic acid senstion/Type I IFN</td>
<td>IFI1</td>
<td>IFI1, MDA5</td>
<td>AD</td>
<td>AGS</td>
</tr>
<tr>
<td></td>
<td>RNASEH (2A, 2B, 2C)</td>
<td>RNaseH2 complex</td>
<td>AR</td>
<td>AGS</td>
</tr>
<tr>
<td></td>
<td>NEIL3</td>
<td>NEIL3</td>
<td>AR</td>
<td>Recurrent infection; autoimmune cytopenias</td>
</tr>
<tr>
<td></td>
<td>ACP5</td>
<td>TRAP</td>
<td>AR</td>
<td>Spndyloenchondrodysplasia, autoimmune cytopenia; recurrent infection</td>
</tr>
<tr>
<td>Apoptosis/ Tolerance</td>
<td>PRKCD</td>
<td>PKCδ</td>
<td>AR</td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td>RAG2</td>
<td>RAG2</td>
<td>AR/AD</td>
<td>Leaky SCID; Omenn syndrome: autoimmune cytopenia; granuloma</td>
</tr>
<tr>
<td>Ras/MAPK</td>
<td>SHOC2</td>
<td>Shoc2</td>
<td>AD</td>
<td>Noonan syndrome; SLE with polyarthritis</td>
</tr>
<tr>
<td></td>
<td>KRA5</td>
<td>K-Ras</td>
<td>AD</td>
<td>Noonan syndrome; SLE</td>
</tr>
<tr>
<td>Collagen degradation</td>
<td>PEPRD</td>
<td>PEPRD</td>
<td>AR</td>
<td>Polidase deficiency; sever leg ulcers; SLE</td>
</tr>
</tbody>
</table>


pulmonary hemorrhage with primary immune dysregulation, called COPA syndrome, has been reported to result from genetic defects deterring the transport of cargo between the Golgi complex and the endoplasmic reticulum [17]. Furthermore, recurrent infections are frequent because of gene mutations associated with the immune responses [9-11]. The clinical features of monogenic lupus include a significantly younger age at onset, and relatively lower frequency of joint manifestations in familial lupus [18].

**Pathogenesis of autoimmune manifestations based on monogenic defects (Table 1)**

1) Complement

Familial SLE due to complement deficiency have been reported as early as the 1950s [19]. The complement system contributes to the elimination of apoptotic cells and immune complexes on opsonization or clearance of apoptotic cells or immune complexes [9,10,16]. C1q has a role for toll-like receptor induced cytokine production and immune complex-induced IFN-1 production by dendritic cells [10,20]. C1q deficiency was reported to result in photosensitive skin rash, nephritis, oral ulceration, and arthritis at young-age. In C1q deficiency, C3 and C4 present as normal levels; however, total hemolytic complement levels are low. Furthermore, anti-Ro antibodies were more commonly detected than anti-DNA antibodies [16,20]. C1s/1r and C2 are important for the classical pathway; C4, for complement activation [20,21]. The patients with C1s/C1r deficiency presented with severe skin disease, glomerulonephritis (GN), recurrent bacterial infections, and had anti-Ro or anti-extractable nuclear antigen (ENA) antibodies with lower titers of anti-DNA antibodies. Anti-nuclear antibodies (ANA) may not be present or may be present in low titer [21].

Patients with C4 deficiency had severe skin diseases and GN with anti-Ro antibodies [20]. The prevalence of homozygous C2 deficiency in the European population is higher than that in other races; however, only 10% to 30% of them developed SLE [22]. SLE patients with C2 deficiency have severe skin disease with cutaneous vasculitis, malar rash, discoid rash, and arthritis with anti-Ro antibodies. Some of them had anti-cardiolipin antibodies [16,23].

2) Apoptosis

Inherited mutations of Fas and Fas ligand, which play an important role in apoptosis, lead to autoimmune lymphoproliferative syndrome, characterized by immune cytopenia, GN, and autoimmune hepatitis at an early age [24,25]. Defective nucleic acid or DNA from dead cells serves as an immunogen to drive T and B cells response. DNase1, encoded by DNASE1, is the major endonuclease capable of cleaving ssDNA and dsDNA. Patients with DNASE1 mutations presented with SLE phenotype with higher titers of anti-nucleosome antibodies [16,26]. In particular, DNase IL3 is capable of translocating from the cytoplasm to the nucleus for cleaving DNA during apoptosis or necrosis [27]. Two phenotype of DNASE1L3 mutation presented as hypocomplementemic urticarial vasculitis, characterized by malar rash, photosensitivity, GN, raynaud phenomenon, arthritis with multiple auto-antibodies, and young-onset SLE [9,10,16].

3) Type I interferonopathy

IFNs are well described as a soluble defense factor produced by cells treated with inactivated, non-replicating viruses [12,14]. Pattern recognition receptors including Toll-like receptors detect pathogen in the cytoplasm or endosomes of infected cells. Cytosolic sensors, GMP-AMP synthetase (cGAS), interact with pathogens, and induce IFN-1 production. After apoptosis or necrosis, DNA, such as that of pathogens, bind to cGAS, and activates the adaptor protein receptor protein stimulator of IFN gene (STING), which translocates to the endoplasmic reticulum, leading to an interaction with TANK-binding kinase 1 and the subsequent phosphorylation of IFN-regulating factor-3 (IRF-3). Phosphorylated IRF-3 then translocates into the nucleus and activates the production of IFN-1 and proinflammatory cytokines [12,16,28]. Viral RNA is detected by retinoic acid inducible gene (RIG)-like receptors family including RIG-1, melanoma differentiation-associated gene 5 (MDA5) in the cytosol. Activated RIG-1 or MDA5 translocates to the mitochondria to activate mitochondrial antiviral signaling (MAV5), at the external mitochondrial membrane. Activated MAV5 interacts with TBK1 to activate IRF3 [12,16,28]. The production of IFN-1 was related with the expression of numerous genes. Type I interferonopathies result from the loss-of-function or gain-of-function mutations in genes associated with IFN production, and proteasome dysfunction (Figure 1) [12,28].

1) Loss-of-function mutations with increased cytosolic DNA or RNA/DNA hybrid sensing. Genes related with increased cytosolic DNA are DNA 3’-repair exonuclease (TREX1) and control of the

dNTP pool (SAMHD1). Genes with RNA/DNA hybrid sensing are ribonuclease H2 (RNASEH2A, RNASEH2B, RNASEH2C), and polymerase (POLA1).

(2) Loss-of-function mutations with a defect in RNA editing and abnormal sensing of self-nucleic acid RNA species in the cytosol, including that for RNA editing (ADAR1).

(3) Gain-of-function mutations with constitutive activation of cytosolic interferon signaling pathways or increased sensitivity to cytosolic nucleic acid ligands; STING and RIG including MDA5, and RIG-1.

(4) Loss-of-function mutations in molecules limiting IFN receptor signaling leading to uncontrolled IFN-stimulating genes (ISG) expression. Such genes are inhibitor of ISG transcription (USP18, and ISG15).

(5) Proteasome dysfunction with increased IFN signaling; PSMA3, PSMA4, and PSMBB.

(6) Loss-of-function mutations in TRAP/ACP5, and C1q.

4) Tolerance

PKC δ plays an important role in T or B cell activation [29], and is crucial for B cell negative selection [30]. In SLE, the autoreactive B cells are not eliminated in B cell development. A Homozygous PRKCD mutation is induced to reduce PKC δ expression and activity, and autoreactive B cells are not controlled through hyperproliferative responses to B cell stimulation via B cell receptor [31]. RAG1/RAG2 genes are necessary for V(D)J recombination with T and B cell receptor, and B cell re-
Receptor editing in the bone marrow during development of lymphocytes [32]. Patient with a heterozygous mutation in RAG2 presented with SLE manifestations including lupus nephritis, erosive arthritis, etc. [33].

5) Rasopathies
Ras is a small GTPase activated downstream of the TCR signaling pathway, and necessary for T cell maturation [34]. Some patients with Noonan syndrome are reported to have lupus-like phenotypes, and have gain-of-function mutations with constitutive stimulation of T cell proliferation and inhibition of T cell apoptosis [35].

Clinical features of monogenic molecular defects
1) Aicardi-Goutiéres Syndrome
Aicardi-Goutiéres Syndrome (AGS) resembles with congenital viral infection, in that neonatal encephalopathy with basal ganglia calcification and white matter changes are observed [36]. Patients with AGS are associated with high level of type I IFN in the serum and cerebrospinal fluid [37]. AGS patients showed neurological phenotype, and developed glaucoma, chilblains, and autoimmune symptoms [38]. Mutations are observed in the following genes in AGS: RNASEH2B, TREX1, RNASEH2C, SAMHD1, ADAR, RNASEH2A, and IFN-induced with helicase C domain 1 (IFIH1) [38,39].

(1) TREX1
Approximately 60% of patients with TREX1 gene mutations had at least 1 autoimmune manifestation: thrombocytopenia, leucopenia, ANA, skin lesions, oral ulceration, arthritis, or anti-dsDNA or ENA antibodies [37]. Some patients presented with SLE phenotypes and central nervous system (CNS) disease with severe Raynaud phenomenon [40].

(2) IFIH1 and MDA5
Patients with mutations in these genes presented with clinical features of AGS and lupus-like phenotype with GN and skin rash [41]. Some patients had anti-aquaporin4 antibodies, positive ANA, and anti-dsDNA antibodies [42].

(3) SAMHD1 (approximately 13% of AGS)
The patients with SAMHD1 mutation presented with chilblain lupus with or without CNS disease, arthritis, mental retardation and microcephaly [43].

(4) RNaseH2
Approximately one-third of AGS patients with RNASEH2 variants presented with a positive ANA. Clinical features in these patients are variable from mild SLE with or without organ involvement to sever chilblains of fingers or toes with arthralgia and elevated anti-dsDNA antibodies [44].

(5) ADAR1 (adenosine deaminase acting on RNA)

2) Familial SLE
Familial SLE is rare; however, it has been reported in several patients with mutations in TREX1, SAMHD1, ACP5, DNase1, DNase1L3, PRKCD, and complements genes with C1q/r/s and C4 subunits [14].
In TREX1 mutation, skin lesions at the extremities were presented along with chilblains after cold exposure, and other symptoms were similar to those of SLE [45]. Some patients have been reported to present with retinal vasculopathy with cerebral leukodystrophy, characterized by loss of vision, stroke, dementia, Raynaud phenomenon, and GN [46]. In SAMHD1 mutation, lupus-like symptoms presented with chilblains, and photosensitivity [43]. In DNASE1 mutation, affected patients presented with positive ANAs, high frequency of ANCA, and lupus nephritis [47]. In DNASE1L3 mutations, patients presented with severe hypocomplementic urticarial vasculitis syndrome, fatigue, fever, continuous elevation of acute phase reactants, and GN [48].

3) STING associated vasculopathy with onset in infancy (SAVI)
SAVI results from gain-of-function mutations in STING, and may not be extremely uncommon [13-15]. Systemic manifestations were rash with fever and elevation of acute phase reactants, malaise, growth failure, and chronic anemia such as systemic inflammation. Skin lesions were characterized by prominent cold-sensitive acral area, presented as violaceous plaques and/or nodules, and distal ulcerations [14,15,49]. Skin lesion presented at early-onset, and characterized by livedo reticularis, or painful ulceration, and Raynaud phenomenon in some cases. The skin pathologic findings revealed diffuse endothelial inflammation with neutrophil infiltrates and microthrombosis, but no immune complex deposition [13,14]. Pulmonary involvement is not symptomatic; however, interstitial lung disease develops without vasculitis. Hilar and paratracheal lymphadenopathy are usually identified [13-15].
The auto-antibodies including ANA, anti-cardiolipin and anti-β 2 glycoprotein antibodies displayed a low-titer, and anti-neutrophil cytoplasmic antibodies were detected in some cases [14,15].
4) **Proteasome-associated autoinflammatory syndrome (PRAAS)**

PRAAS results from loss-of-function mutations in the genes regulating proteasome function [13,14,28]. Various phenotypic diseases with disease severity were reported as joint contracture, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy [50], Nakajo-Nishimura syndrome with nodular erythema, elongated and thickened fingers and emacination [51], Japanese autoinflammatory syndrome with lipodystrophy, and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) [52,53].

PRAAS is characterized by early onset nodular, panniculitis-like, violaceous skin lesions with atypical neutrophil infiltrates, muscle atrophy, lipodystrophy, failure to thrive and deformities of hands and feet due to joint contractures resulting from chronic inflammation. Recurrent episodes of periodic fever with elevation of acute phase reactants are usually presented as autoinflammatory disease [12-14,53]. Auto-antibodies were not detected, although there were low-titer in some cases [50-53].

**Diagnostic and therapeutic approaches**

Most patients with monogenic autoimmune diseases experience atypical or incomplete lupus-like symptoms in infancy or at a pre-pubertal age; signs of vasculopathy such as ulceration, chilblain or stroke, panniculitis with or without lipodystrophy, and interstitial lung disease are commonly observed [9,10,14]. Furthermore, many children experienced recurrent episodes of fever with elevation of acute phase reactants, and skin rash. Therefore, we compare our clinical findings between interleukin-1-induced AID and IFN-induced AD (Table 2) [13].

There are no definite treatment strategies for monogenic autoimmune diseases because of different genetic pathways underlying their pathogenesis, although conventional treatments with steroid or disease modifying antirheumatic drugs have been used [13]. Recently, several clinical trials using targeted therapy with JAK1/2 inhibitors reported promising results for monogenic autoimmune diseases [54]. Moreover, monoclonal antibodies for IFN-α (Sifalimumab) and IFNRI (Anifrolumab) have revealed preliminary positive outcomes in type I interferonopathy [55,56].

**CONCLUSION**

The etiology and pathogenesis of many diseases have been identified through the genetic studies using new generation sequencing. In genetic diseases on inflammation, patients experienced recurrent episodes of fever with various skin manifestations and elevation of acute phase reactants. Clinical manifestations are similar

### Table 2. Differences in clinical manifestations of IL-1 and IFN-mediated autoinflammatory diseases

<table>
<thead>
<tr>
<th>Organ</th>
<th>IL-1 mediated diseases</th>
<th>IFN-mediated diseases (CANDLE, SAVI, AGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>CRP closely correlates with disease activity Granulocytosis with flares</td>
<td>CRP only elevated in severe disease Lymphopenia, leucopenia with flares</td>
</tr>
<tr>
<td>CNS</td>
<td>Aseptic neutrophilic meningitis Arachnoid adhesion (Severe disease)</td>
<td>Mild lymphocyte meningitis Basal ganglion calcifications, CNS vasculopathy, white matter disease</td>
</tr>
<tr>
<td>Skin/Vessel</td>
<td>Neutrophilic dermatitis (urticaria-like with a mature neutrophil infiltrate)</td>
<td>Panniculitis (&quot;immature&quot; neutrophils), lipoatrophy, Vasculitis (chilblain-like lesion) microthrombotic disease</td>
</tr>
<tr>
<td>Lung/Heart</td>
<td>Serositis, pericarditis</td>
<td>Pulmonary fibrosis/Interstitial lung disease Hypertension, pulmonary hypertension</td>
</tr>
<tr>
<td>MSK</td>
<td>Osteomyelitis, bony overgrowth, fasciitis, arthralgia</td>
<td>Myositis, non-erosive arthritis, arthralgia</td>
</tr>
<tr>
<td>ENT</td>
<td>Hearing loss (inflammatory)</td>
<td>None</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctivitis, anterior uveitis</td>
<td>Glaucoma, episcleritis</td>
</tr>
<tr>
<td>Serology</td>
<td>40% lupus anticoagulant positive</td>
<td>40% ~ 50% lupus anticoagulant positive in CANDLE/SAVI, Some with other variable/transient autoantibodies</td>
</tr>
</tbody>
</table>

between AID including cryopyrin associated periodic fever syndrome and monogenic lupus and type I interferonopathies. However, many monogenic autoimmune diseases may present with vasculopathies with different skin lesion compared with AID, and lupus like symptoms or findings with or without auto-antibodies. In infant or very young children with lupus like manifestations, monogenic autoimmune diseases must be considered, and further genetic studies are required for patients and their families. Furthermore, we conducted clinical trials with targeted therapy or monoclonal antibodies for monogenic autoimmune diseases.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**

29. Salzer E, Santos-Valente E, Keller B, Warnatz K, Boztug K. Protein kinase C delta promotes transitional B cell-negative selection and limits proximal B cell receptor signaling to enforce tolerance. Mol Cell Biol 2014;34:


