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Aicardi–Goutières syndrome: a model disease for systemic autoimmunity

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M. A. Lee-Kirsch,* C. Wolf* and C. Günther†
*Departments of *Pediatrics and †Dermatology, University Hospital, Technical University Dresden, Dresden, Germany*

Summary

Systemic autoimmunity is a complex disease process that results from a loss of immunological tolerance characterized by the inability of the immune system to discriminate self from non-self. In patients with the prototypic autoimmune disease systemic lupus erythematosus (SLE), formation of autoantibodies targeting ubiquitous nuclear antigens and subsequent deposition of immune complexes in the vascular bed induces inflammatory tissue injury that can affect virtually any organ system. Given the extraordinary genetic and phenotypic heterogeneity of SLE, one approach to the genetic dissection of complex SLE is to study monogenic diseases, for which a single gene defect is responsible. Considerable success has been achieved from the analysis of the rare monogenic disorder Aicardi–Goutières syndrome (AGS), an inflammatory encephalopathy that clinically resembles *in-utero*-acquired viral infection and that also shares features with SLE. Progress in understanding the cellular and molecular functions of the AGS causing genes has revealed novel pathways of the metabolism of intracellular nucleic acids, the major targets of the autoimmune attack in patients with SLE. Induction of autoimmunity initiated by immune recognition of endogenous nucleic acids originating from processes such as DNA replication/repair or endogenous retro-elements represents novel paradigms of SLE pathogenesis. These findings illustrate how investigating rare monogenic diseases can also fuel discoveries that advance our understanding of complex disease. This will not only aid the development of improved tools for SLE diagnosis and disease classification, but also the development of novel targeted therapeutic approaches.

Keywords: Aicardi–Goutières syndrome, autoimmunity, nucleic acid sensing, systemic lupus erythematosus, type I interferon

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Correspondence: M. A. Lee-Kirsch, Department of Pediatrics, University Hospital, Technical University Dresden, Fetscherstr. 74, 01307 Dresden, Germany.
E-mail: minae.lee-kirsch@uniklinikum-dresden.de

Systemic lupus erythematosus (SLE) – a prototypic autoimmune disease

SLE is a chronic relapsing autoimmune disease with a wide spectrum of clinical manifestations ranging from subtle symptoms to fatal multi-organ failure. The disease process is initiated by loss of self-tolerance resulting in the production of autoantibodies. The deposition of these autoantibodies as immune complexes in various tissues followed by inflammation and tissue injury is regarded as a

key mechanism in SLE pathogenesis [1]. The systemic nature of the disease is reflected by fevers, fatigue and weakness, as well as multiple organ manifestations. These include arthritis and cutaneous manifestations, which occur in most patients, as well as glomerulonephritis, central nervous system involvement and perturbations of the haematopoietic system [1].

From a clinical perspective, early diagnosis of SLE remains challenging due to its heterogeneous presentation, with no single test being sufficiently specific and sensitive to be diagnostic. Until today, the diagnosis of SLE is based on classification criteria which were defined by the American College of Rheumatology (ACR) 30 years ago [2,3]. Thus, SLE is diagnosed if at least four of the 11 criteria develop at one time or individually over any period of observation [2,3]. However, owing to the often insidious onset and great clinical variability, it may take up to several years until the diagnosis can be established [4]. Although the ACR criteria play only an ancillary role in the clinical setting, they constitute the gold standard for inclusion of patients in clinical trials or genome-wide association studies.

In European countries the prevalence of SLE ranges from 20 to 40 per 100 000 [5]. Prevalence varies considerably across different ethnic groups and is two- to fourfold higher among African Americans, Hispanics and Asians compared to Caucasians [5]. SLE usually affects young women and shows a marked gender disparity, with a female-to-male ratio of 9:1. Paediatric-onset SLE represents 10–20% of all SLE cases and is associated with higher disease severity than adult-onset SLE [6].

Although improvements in medical care have dramatically enhanced the survival of SLE patients, mortality or major reductions of quality-of-life due to severe internal organ damage, co-morbidities such as cardiovascular disease or toxic effects of therapy remain a major concern.

Genetic basis of SLE

There is substantial evidence for a strong genetic component of SLE. SLE shows familial aggregation, with an estimated sibling recurrence risk of 15. In addition, the concordance rate among monozygotic twins (approximately 35%) is 10-fold higher compared to dizygotic twins (approximately 3%) [7]. The incomplete concordance of disease expression in monozygous twins also supports the role of non-genetic factors in the disease aetiology. Environmental factors implicated in SLE include ultraviolet (UV) light, viral infection and certain drugs [1,8,9].

The genetic basis for susceptibility to SLE has been subject to intense investigation, both in humans and in animal models. Candidate gene or genome-wide association studies have led to the identification of more than 20 risk loci [10,11]. The implicated genes encode proteins important for adaptive immunity and autoantibody production [human leucocyte antigen (HLA) class II alleles, *CTLA4*, *PTPN22*, *BLK*, *BANK1*, *TNFS4*], cell disposal and immune-complex processing (*C1q*, *C2*, *C4*, *FCGR2A*, *FCGR3A*), proteins with roles in innate immunity relating to leucocyte adhesion (*ITGAM*) and cytokine signalling pathways (*TNFAIP3*, *TNIP1*, *STAT4*, *IRF5*, *IRAK1*, *IFIH1*, *TREX1*, *CSK*) [10–12].

Collectively, these findings highlight the complexity and heterogeneity of SLE pathophysiology and provide a framework which will allow further dissection of genetically determined primary disease pathways. However, they also raise important questions with respect to the transfer of genetic findings into an understanding of disease pathology. Indeed, finding causative relationships between genotypic and phenotypic variation and translating this knowledge into clinically relevant concepts continues to be an important task.

Lessons learned from monogenic disease

In contrast to multi-factorial polygenic diseases, the clinical phenotype and the associated molecular pathology of a monogenic disorder can be attributed to the pleiotropic effects of a single gene defect. In fact, the elucidation of rare monogenic autoimmune syndromes such as autoimmune polyglandular syndrome type 1 (APS1) caused by mutations in autoimmune regulator (AIRE) and the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome due to mutations in forkhead box protein 3 (FoxP3) have contributed substantially to our understanding of mechanisms underlying central and peripheral tolerance [13].

Recent studies on rare Mendelian disorders associated with lupus phenotypes have provided novel insights into disease mechanisms that are also highly relevant to complex SLE. Aicardi–Goutières syndrome (AGS) is an autosomal recessive inflammatory encephalopathy that clinically mimics *in-utero*-acquired viral infection despite the absence of detectable viral infection [14]. AGS patients commonly feature signs that are also observed in patients with SLE, including activation of type I interferon (IFN), cutaneous chilblain lesions, arthritis, anti-nuclear antibodies, reduced complement and haematological abnormalities [15–17]. AGS is caused by bi-allelic mutations in at least six genes encoding enzymes involved in the metabolism of intracellular nucleic acids. These include 3′ repair exonuclease 1 (TREX1; DNASE III) [18], the three subunits of the ribonuclease H2 (RNASEH2A, RNASEH2B, RNASEH2C) [19], SAM domain and HD domain-containing 1 (SAMHD1) [20] and the RNA-specific adenosine deaminase (ADAR1) [21]. Heterozygous mutations in TREX1 cause additional inflammatory phenotypes characterized by autoimmunity, including autosomal-dominant familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, and autosomal-dominant retinal vasculopathy with cerebral leucodystrophy [22–25]. In

addition, dominant AGS can be caused by heterozygous *de-novo* TREX1 mutations [26,27], while familial chilblain lupus has also been described in a family with SAMHD1 mutation [28]. Moreover, it was shown that rare *TREX1* variants confer a high risk for complex SLE [29], a finding that has been confirmed in patients with neuropsychiatric SLE as well as in a large multi-ethnic SLE cohort [30,31]. These findings not only underscore the contribution of rare gene variants to the genetic susceptibility to complex SLE, but also illustrate how studies on monogenic diseases can advance our understanding of complex disease. Thus, AGS can be viewed as a model disease for systemic autoimmunity. This also implies a possible role of the other AGS genes as risk factors of complex SLE.

Functional properties of TREX1, RNase H2, SAMHD1 and ADAR1

Progress in understanding the cellular and molecular functions of the AGS-associated genes has led to the identification of a number of novel pathways of the intracellular nucleic acid metabolism (Fig. 1). The cytosolic 3′–5′ exonuclease TREX1 degrades ssDNA originating from apoptotic DNA damage or DNA replication stress [32–34]. Chronic DNA damage checkpoint activation in TREX1-deficient mouse embryonic fibroblasts was shown to be accompanied by the appearance of a short ssDNA species within the cytosol [34]. Sequence analysis of cytosolic ssDNA from TREX1-deficient mouse cells has demonstrated a significant increase in reverse-transcribed DNA derived from endogenous retro-elements [35], highly repetitive sequence elements which account for almost half of the mammalian genome. Endogenous retro-elements such as L1 elements, long terminal repeat (LTR) retrotransposons and endogenous retroviruses represent the remnants of ancient infections with exogenous retroviruses. They are transcriptionally active and potentially capable of retrotransposition via a reverse-transcribed RNA-intermediate [36,37]. In contrast to the human genome, where retrotransposition events are rare, the mouse genome harbours highly active endogenous retro-elements such as intracisternal A-particle (IAP) elements that can retrotranspose autonomously [38]. Interestingly, the loss of Toll-like receptor (TLR)-dependent sensing of retro-element-derived nucleic acids in mice results in autoimmunity and leukaemia, further highlighting the potential threat caused by uncontrolled retro-element activity [39,40].

TREX1-deficient mice develop an autoimmune-mediated myocarditis [41]. This phenotype is dependent upon type I IFN activation initiated in non-haematopoietic cells, and concomitant genetic inactivation of the type I IFN system results in complete rescue of the phenotype [35,42]. Notably, the autoimmune myocarditis of TREX1-deficient mice, although not responsive to the nucleoside analogue azidothymidine, was shown to be ameliorated by anti-retroviral therapy targeting the retroelement-encoded reverse transcriptase [35,43]. However, whether unabated retro-element activity is also the primary cause of autoimmunity in patients with AGS or SLE remains to be investigated.

The heterotrimeric RNase H2 degrades RNA within an RNA : DNA hybrid or cleaves the phosphodiester bond 5′ of a single ribonucleotide embedded within a DNA duplex, and represents the major RNase H activity at sites of genome replication and repair [44,45]. Studies in RNase H2-deficent yeast and mice have established a pivotal role of RNase H2 for genome integrity. RNase H2 mediates the removal of ribonucleotides misincorporated during genome replication by replicative DNA polymerases [46–

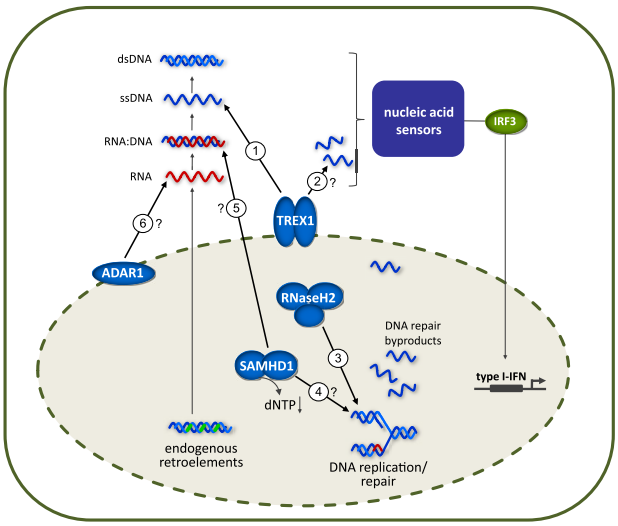

Fig. 1. Functional properties of three prime repair exonuclease 1 (TREX1), ribonuclease H2 (RNase H2), SAM domain and HD domain-containing protein 1 (SAMHD1) and adenosine deaminase acting on RNA 1 (ADAR1) within the intracellular nucleic acid metabolism. TREX1 degrades cytosolic ssDNA arising during reverse transcription of endogenous retro-elements (1) and during replication stress (2). Loss of TREX1 function results in accumulation of cytosolic DNA. RNase H2 removes single ribonucleotides from DNA (3). RNase H2 deficiency induces genome instability associated with DNA damage signalling. The triphosphohydrolase SAMHD1 down-regulates the intracellular dNTP pool required for DNA synthesis. Absence of SAMHD1 may contribute to inappropriately increased DNA synthesis (4) or promote reverse transcription of endogenous retro-elements (5). The RNA-editing enzyme ADAR1 deaminates adenosine to inosine of RNA species that may derive from endogenous retro-elements (6) or microRNAs. This modification is thought to alter the immune-activating properties of the edited RNA species or to interfere with transcriptional control of type I interferon (IFN). Functional impairment of TREX1, RNase H2, SAMHD1 or ADAR1 results in quantitative or qualitative imbalances within the intracellular nucleic acid homeostasis. Inadequately accumulated nucleic acids are recognized as danger signals by innate immune sensors that activate type I IFN leading to inflammation and autoimmunity.

49]. Moreover, ribonucleotides were shown to represent the most common endogenous nucleotide base lesion in replicating cells occurring at a rate of one ribonucleotide per 7000 bases of DNA [47]. Single- or double-strand DNA breaks at sites of ribonucleotides resulting from spontaneous hydrolysis or by topoisomerase-I-mediated cleavage induces a DNA damage response to activate DNA repair [50]. Indeed, complete RNase H2 deficiency in mice is embryonally lethal due to a massive p53-dependent DNA damage response [47,48]. Interestingly, unlike AGS patients, RNase H2-deficient mice do not develop type I IFN activation [47,48]. This suggests that RNase H2 mutations in patients with AGS are hypomorphic, and that type I IFN activation may result from a low-level DNA damage response.

SAMHD1 functions as a deoxyguanosine-triphosphate (dGTP)-dependent phosphohydrolase which converts deoxynucleoside triphosphates (dNTPs), the building blocks of DNA replication, to the constituent deoxynucleoside and inorganic triphosphate, thereby regulating the intracellular dNTP pool [51]. SAMHD1 deficiency could therefore promote inappropriately increased DNA synthesis. SAMHD1 restricts infection of myeloid cells with human immunodeficiency virus type 1 (HIV-1) [52,53] by depleting the dNTP pool required for reverse transcription of the viral RNA genome in a cyclin A-dependent manner [54–56]. This is in contrast to TREX1, which facilitates HIV-1 infection by degrading non-productive reverse transcripts of the viral RNA genome, thereby preventing an anti-viral response [57]. Interestingly, interaction with as yet unknown endogenous nucleic acids was shown to be an integral function of SAMHD1, as AGS-associated SAMHD1 mutations have lost this property [58–60]. In addition, SAMHD1 was also shown to possess exonuclease activity [60]. The physiological functions of SAMHD1 in the absence of retroviral infection are unknown. However, given that SAMHD1 is regulated by cyclin A/CDK1-dependent phosphorylation [55,56], and that imbalances in the intracellular dNTP pools can cause genome instability [61], SAMHD1 may also be involved in the maintenance of genome integrity.

Adenosine deaminase acting on RNA 1 (ADAR1) is an RNA-editing enzyme, which catalyzes the deamination of adenosine to inosine in dsRNA [62]. Studies in ADAR1-deficient mice have shown that editing of dsRNAs by ADAR1 is required for the self-renewal capacity of haematopoietic stem cells by suppressing apoptotic type I IFN signalling [63]. It is hypothesized that ADAR1 alters the immunoreactive properties of dsRNA molecules derived from retro-elements or inhibits microRNAs involved in the regulation of the IFN signalling pathway [64]. In addition, ADAR1 has been implicated both in the promotion and restriction of viral infection [65].

Despite the diversity of the nucleic acid metabolizing pathways, in which TREX1, RNase H2, SAMHD1 and ADAR1 participate, the lack of function of all AGS-associated enzymes appears to result in the intracellular accumulation of nucleic acid species that are recognized as danger signals by sensors of the innate immune system, which then trigger the pathogenic type I IFN response.

Nucleic acid degradation as negative regulator of the innate immune response

SLE is characterized by a chronic overproduction of type I IFN, indicating that an inappropriate activation of anti-viral immunity is key to SLE pathogenesis [66,67]. Type I IFNs (IFN-α, IFN-β) have pronounced immune-stimulatory effects that promote the loss of B cell and T cell tolerance, dendritic cell activation and autoantibody production [68]. The targets of these autoantibodies are ubiquitous self-antigens, including nucleic acids. These anti-nuclear antibodies form complexes with nuclear antigens released from dying cells [69,70]. Immune complex deposition in the capillary bed followed by local complement and leucocyte activation results in destructive tissue inflammation. In addition, these immune complexes represent an important stimulus for more type I IFN production by dendritic cells, further fuelling the autoimmune response [71].

Studies in patients and mouse models suggest that this pathogenetic chain can be initiated by a broad spectrum of different mechanisms. These include defects of B and T cell tolerance due to impaired apoptosis, or uncontrolled T cell co-stimulation resulting from inappropriate expression of co-stimulatory receptors [68]. Furthermore, defects in mechanisms responsible for the removal of apoptotic cells and cellular debris were shown to cause lupus or lupus-like disease in humans and mice including, for example, deficiency in complement components C1q, C3 and C4 [72].

Compelling evidence suggests that it is the nucleic acid component of the accumulating apoptotic cells which causes disease by triggering pathogen sensors of the innate immune system [71]. Virus infection is detected primarily by the recognition of viral nucleic acids. This is accomplished by germline-encoded receptors belonging to the class of pattern recognition receptors, which initiate innate inflammatory responses upon the sensing of danger-associated molecular patterns. Double-stranded and ssRNA as well as ssDNA derived from endocytosed material are sensed in the endosome by TLRs (TLR-3, -7, -8 and -9) [71]. In the cytosol or nucleus, known sensors for dsRNA include the retinoic acid-inducible gene (RIG)-like helicase receptors RIG-I, melanoma differentiation-associated 5 (MDA5) and the aspartate–glutamate–any amino acid–aspartate/histidine box-containing helicases, DHX36 and DHX9 [73]. The pyrin and HIN domain-containing protein family (PYHIN) proteins AIM2 and IFI16 as well as DDX41 and cyclic guanosine monophosphate–adenosine monophosphate (GMP–AMP) synthase are cytosolic receptors for dsDNA [73,74]. Many of these nucleic acid sensors

trigger an anti-viral type I IFN response. In this context, it is of critical importance that mammalian nucleic acid sensors are characterized by limited capacity to discriminate between self and non-self (i.e. microbial) DNA or RNA. Consequently, an IFN response can, in principle, also be initiated by endogenous nucleic acids. This implies that the organism must be equipped with efficient means to avoid inappropriate recognition of endogenous nucleic acids in order to prevent activation of immune responses leading to autoimmunity.

Nucleolytic degradation of endogenous nucleic acids plays an important role in protection from inappropriate and pathogenic activation of innate sensors [75]. Lack of DNase I, the major dsDNA-degrading enzyme in serum, in humans and gene-targeted mice, promotes lupus-like disease [76,77]. Mice deficient for DNase II, an enzyme essential for endolysosomal degradation of DNA in macrophages, develop massive IFN-dependent autoimmunity [78]. Mutations in the intracellular DNase I-like 3 were also shown to cause a dominant form of lupus erythematosus [79]. The association of the AGS-associated genes TREX1, RNase H2, SAMHD1 and ADAR1 with systemic autoimmunity illustrates the importance of co-ordinated pathways orchestrating the degradation of endogenous nucleic acids that are produced continuously during normal cell metabolism, in order to avoid detrimental activation of the innate immune system. While the pathways implicated in AGS pathogenesis, such as apoptotic DNA damage, DNA replication/repair and endogenous retro-elements, have revealed novel cell-intrinsic mechanisms for the initiation of autoimmunity, one important unresolved issue is the exact origin and molecular properties of the accumulating nucleic acid species in patients with AGS. Another important question relates to the nature of innate pattern recognition receptors that mediate the induction of type I IFN. Do cells deficient in RNase H2 or SAMHD1 also activate the STING/TBK1/IRF3 pathway as do TREX1-deficent cells? [80]. Interestingly, TREX1-deficient mouse and human fibroblasts were also shown to activate anti-viral genes in an IFN regulatory factor-3 (IRF3)-mediated, type I IFN-independent manner, which is accompanied by expansion of the lysosomal compartment [80], raising the question as to whether an increased lysosomal activity could contribute to autoimmunity. Finally, it will be important to understand which cells initiate and sustain the pathogenic type I IFN response. Elucidation of the responsible sensors and their signalling pathways may lead to the identification of new target molecules for therapeutic intervention.

Implications for targeted therapeutic intervention

At present, no effective cure for SLE is known and current approaches rely primarily upon unspecific immunosuppression with corticosteroids and cytostatic drugs or the anti-malarial hydroxychloroquine, with considerable side effects [1]. The search for novel more effective, more specific and less toxic drugs is complicated by the clinical heterogeneity of the patient population, which poses a major challenge regarding not only the assessment of disease activity but also for the establishment of reliable clinical outcome measures that can be applied to the evaluation of drug responses [81]. The lack of suitable biomarkers has further impeded efforts to evaluate new SLE therapeutics in clinical trials, underpinning the need for more specific tools for diagnosis, disease classification and assessment of disease activity.

During recent years, a number of promising biologicals have been developed that target specific lymphocyte populations [cytotoxic T lymphocyte antigen 4 (CTLA4), CD20, CD22, B lymphocyte stimulator/B cell activating factor (BLyS/BAFF), inflammatory cytokines interleukin (IL)-6, IL-10, IFN-α, IFN-γ] or other molecules and their testing in SLE has raised hopes considerably, with several being currently under investigation in Phase II or Phase III clinical trials [82,83]. The B cell inhibiting monoclonal antibody against BlyS/BAFF, belimumab, the first biological approved for SLE, has shown modest success in a subgroup of serologically active SLE patients [84]. This observation exemplifies that due to the multi-factorial pathogenesis of SLE a new drug may have beneficial effects in perhaps only a subset of patients. The extraordinary genetic and phenotypic heterogeneity of SLE requires knowledge of the full spectrum of disease mechanisms in order to provide individually tailored therapeutic intervention. The elucidation of TREX1-associated forms of lupus has set the stage towards a classification of disease subentities based on pathogenic criteria and is expected to have an impact upon clinical decision-making. Thus, it is conceivable that SLE patients with the TREX1 mutation may benefit particularly from type I IFN blockade. Conversely, given the link of TREX1 and RNase H2 to increased DNA damage [34,47,48], a more cautious use of genotoxic drugs such as azathioprine or methotrexate might be advisable. It will also be of interest to determine whether or not patients with TREX1-associated AGS or lupus, like TREX1-deficient mice, suffer from uncontrolled activation of endogenous retro-elements [35] and, if so, if they respond to anti-retroviral therapy [43].

Conclusion

The discovery of the genetic causes of AGS and familial chilblain lupus has established a novel role of the intracellular nucleic acid metabolism in the control of the innate immune response and has provided novel insight into mechanisms of immune tolerance. As there are more AGS genes to be discovered, future work is expected to broaden our understanding further of how the organism can protect itself against inappropriate immune activation caused by

self nucleic acids, while sustaining a prompt and efficient immune defence against foreign nucleic acids derived from invading pathogens. This may not only be of relevance to other autoimmune conditions characterized by a deregulated type I-IFN response, such as Sjögren's syndrome, dermatomyositis and systemic sclerosis [85,86], but may also reveal novel pathways that could potentially be targeted for therapeutic intervention.

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Disclosures

The authors declare no conflicts of interest.

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