Autoimmune disorders: a need for better understanding

Why are translational research efforts to identify the pathogenetic underpinnings of human autoimmunity so critical? Autoimmune disease affects at least 1 in 31 Americans and has been reported to be the second-highest cause of chronic illness, the top cause of morbidity in women, and among the top ten causes of death in women under the age of 65 (1–4). It could be argued that systemic lupus erythematosus (SLE), an autosomal-recessive encephalopathy in children that is characterized by mutations in numerous nucleic acid repair enzymes and elevated IFN levels. Phenotypically, patients with AGS and SLE share many similarities. Ribonuclease H2 (RNase H2) is a nucleic acid repair enzyme that removes unwanted ribonucleotides from DNA. In this issue of the JCI, Günther and colleagues provide an in-depth investigation of the mechanisms underlying the link between defective removal of ribonucleotides in AGS and SLE, and these findings will likely serve as a strong springboard to provide novel therapeutic inroads.

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AGS, SLE, and RNASEH2 mutations: translating insights into therapeutic advances

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Systemic lupus erythematosus (SLE) is a severe autoimmune disease characterized by the presence of nucleic acid– and protein-targeting autoantibodies and an aberrant type I IFN expression signature. Aicardi-Goutières syndrome (AGS) is an autosomal-recessive encephalopathy in children that is characterized by mutations in numerous nucleic acid repair enzymes and elevated IFN levels. Phenotypically, patients with AGS and SLE share many similarities. Ribonuclease H2 (RNase H2) is a nucleic acid repair enzyme that removes unwanted ribonucleotides from DNA. In this issue of the JCI, Günther and colleagues provide an in-depth investigation of the mechanisms underlying the link between defective removal of ribonucleotides in AGS and SLE, and these findings will likely serve as a strong springboard to provide novel therapeutic inroads.
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Given that parents of patients with AGS exhibited mild autoimmune features, additional efforts to consider clinical evaluation and counseling of couples with RNASEH2 allelic variants should be further explored. It also likely that nucleic acid repair may be altered by as-yet undiscovered variants of other genes, and large-scale sequencing efforts could result in genome-wide identification of such AGS- and SLE-associated mutations. Furthermore, the search for allelic variants that protect against development of autoimmune disease, especially SLE, is important, and more work in this area is greatly needed.

The findings of Günther and colleagues (12) add additional clean fuel to the fire, strengthening the emerging notion that SLE is not one disease, but a compilation of a constellation of diseases with differing genotypes but related phenotypes. It is clear that the various SLE-associated phenotypes cannot be explained simply by the presence of specific risk alleles. "Lupusomics," loosely defined as systems-level analyses integrating genetics, epigenetics, transcriptomics, proteomics, and metabo-

Figure 1. Normal function of nucleic repair enzymes. Patients with AGS harbor mutations in genes that encode proteins involved in nucleic acid repair and sensing. TREX1 prevents retroelement DNA reverse transcription (i). SAMHD1 converts deoxyribonucleotide triphosphate (dNTP) into nucleoside and triphosphate (ii). RNase H2 (composed of the subunits RNASEH2A, RNASEH2B, and RNASEH2C) removes ribonucleotides (R) from DNA, a process that can occur during transcription (iii). ADAR1 destabilizes double-stranded RNA (dsRNA) by deaminating adenosine (A) to inosine (I) (iv). MDAS (encoded by IFIH1) is a RIG-I-like receptor dsRNA helicase enzyme that serves as a dsRNA sensor to stimulate a type I IFN response (v). The IFIH1 mutation is the only known gain-of-function mutation; the other genes harbor loss-of-function mutations. Genetic variants of genes encoding TREX1, SAMHD1, RNase H2, and MDAS are associated with SLE as well. Allelic mutations of genes encoding these proteins ultimately result in dysfunction and disease through accumulation of excess intracellular nucleic acid and inappropriate activation of innate immunity.

colleagues in this issue that provides many answers about the role of RNase H2 in human autoimmunity (12). The authors conducted an in-depth, international, multicenter investigation focused on understanding the mechanisms that underlie the link between the defective removal of ribonucleotides from DNA and the development of systemic autoimmune disease. Specifically, they found that parents of patients with AGS who are heterozygous for genes encoding RNase H2 subunits (RNASEH2A–RNASEH2C) exhibit lupus-like autoimmune features, although to a lesser extent than most diagnosed SLE patients. This observation prompted Günther et al. to examine patients with SLE. In a subset of SLE patients, allelic variants of all three RNASEH2 subunit genes were identified, and all of these mutations decreased RNase H2 function. The presence of these risk alleles was further validated in a second cohort of patients with SLE. Moreover, the presence of RNASEH2 variants that resulted in reduced enzyme activity or complex stability correlated with increased risk of SLE. This functional dose response of RNASEH2 allelic variants with SLE risk provides compelling evidence that RNASEH2 mutations are linked with lupus susceptibility. Additionally, cells from patients with AGS or SLE with RNASEH2 allelic variants exhibited elevated levels of ribonucleotide-bound genomic DNA, an increased DNA damage response, and increased type I IFN production. Interestingly, in vitro experiments demonstrated cyclobutane pyrimidine dimer formation in ribonucleotide-bound DNA in response to UV irradiation, a result that may explain the photosensitivity and exacerbation of skin disease common in SLE patients with RNASEH2 mutations.

Conclusions and future directions

Even though much can be learned from studies that directly involve human participants, more rigorous investigation is also needed, and validation of the results of Günther and colleagues (12) in animal models is imperative for exploring potential therapeutic strategies. For example, development of a model that allows induction of RNase H2 deficiency after parturition may allow examination of this deficiency in mature animals, the timing of which might better reflect human disease. Given that parents of patients with AGS exhibited mild autoimmune features, additional efforts to consider clinical evaluation and counseling of couples with RNASEH2 allelic variants should be further explored. It also likely that nucleic acid repair may be altered by as-yet undiscovered variants of other genes, and large-scale sequencing efforts could result in genome-wide identification of such AGS- and SLE-associated mutations. Furthermore, the search for allelic variants that protect against development of autoimmune disease, especially SLE, is important, and more work in this area is greatly needed.

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lomics (to name a few) will provide greater clarification and phenotypic refinement that could result in highly targeted therapeutic approaches. It should also be noted that retroviral RNase H2 is a critical enzyme for HIV replication, making the present results pertinent not only to autoimmune disease, but also to the identification of novel therapeutic targets that could slow and/or prevent HIV replication (13). Conversely, existing HIV drugs could have therapeutic benefit for patients with AGS and have shown early promise in TREX1-deficient mice (14).

Overall, the findings by Günther and colleagues (12) directly apply to the health of patients with AGS, the parents of patients with AGS, and patients with SLE who harbor RNASEH2 mutations. There are many challenging goals in medicine, and it could be argued that two of the most important are preventing and curing disease. It is possible that the mechanistic insights provided by Günther et al. (12) could be targeted to improve genomic integrity and blunt both the DNA damage response and the aberrant type I IFN response. In addition, this study — and future genetic studies like it — represent the first steps to break SLE down into specific genetic disease classifications that are responsible for specific clinical manifestations. Ideally, these findings will serve as a strong springboard to provide novel targeted therapeutic inroads for patients with AGS and SLE.

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