Published in final edited form as:
J Allergy Clin Immunol. 2015 January ; 135(1): 272–273. doi:10.1016/j.jaci.2014.07.063.

Impaired receptor editing and heterozygous *RAG2* mutation in a patient with systemic lupus erythematosus and erosive arthritis

Jolan E. Walter, MD, PhD[†,1,2], **Mindy S. Lo, MD**[1], **Katalin Kis-Toth, PhD**[3], **Irit Tirosh, MD**[1], **Francesco Frugoni, MS**[1], **Yu Nee Lee, PhD**[1], **Krisztian Csomos, PhD**[2], **Karin Chen, MD**[4], **Shiv Pillai, MD PhD**[5], **Jonathan Dunham, MD**[6], **George C. Tsokos, MD**[3], **Eline T. Luning Prak, MD PhD**[7,†], and **Luigi D Notarangelo, MD**[1,8,9,†]

[1] Division of Immunology, Boston Children's Hospital, Boston, MA, USA

[2] Division of Pediatric Allergy/Immunology, Massachusetts General Hospital for Children, Boston, MA, USA

[3] Division of Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA

[4] Division of Allergy, Immunology & Rheumatology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT

[5] Cancer Center, Massachusetts General Hospital, Boston, MA

[6] Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

[7] Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[8] The Manton Center For Orphan Disease Research, Boston Children's Hospital, Boston, MA, USA

[9] Harvard Stem Cell Institute, Boston, MA, USA

Keywords

Hypomorphic mutation; Recombination activating gene 2 (*RAG2*); lupus; receptor editing; autoimmunity; central tolerance

[†]Corresponding authors **Addresses for correspondence:** Jolan E. Walter MD PhD Pediatric Allergy/Immunology Program Massachusetts General Hospital for Children Suite 530, 275 Cambridge Street Boston MA 02114 Ph: 617-726-8707 Fax: 617-724-2803 jewalter@partners.org Eline T. Luning Prak MD PhD, Department of Pathology and Laboratory Medicine Perelman School of Medicine, University of Pennsylvania 405B Stellar Chance Labs 422 Curie Blvd. Philadelphia, PA 19104 Ph: 215-746-5768 Fax: 215-573-6317 luning@mail.med.upenn.edu Luigi D. Notarangelo, MD, Division of Immunology, Boston Children's Hospital Division of Immunology, Boston Children's Hospital One Blackfan Circle, 10th floor Boston, MA 02115 Ph: 617-919-2276 Fax: 617-730-0709 Luigi.Notarangelo@childrens.harvard.edu.

Disclosure of potential conflict of interest: Dr. Walter has received federal funding. Drs. Pillai, Luning Prak, Notarangelo have received federal funding and support from private Foundations. Dr. Dunham has received support from private foundations. Drs. Tirosh, Frugoni, Lo, Lee, Kis-Toth, Chen, Luning Prak and Dunham have no conflicts of interest to declare.

To the Editor,

Recently, autoimmunity has been increasingly recognized as a key feature of many monogenic primary immune deficiencies (PID). The development of autoimmunity is likely multifactorial, resulting from the effect of multiple triggers in the setting of a dysregulated immune system.

Mutations of Recombination Activating Gene (*RAG*) 1 and 2 in humans account for a broad spectrum of phenotypes ranging from lack of T and B cells (leading to severe infections and early mortality) to delayed onset autoimmune and/or granulomatous disease (1). The autoimmune phenotype can be variable, from the sole presence of autoantibodies and immune-mediated cytopenias to localized destructive vasculitis. By performing a population-based analysis, we have recently shown that pathogenic *RAG1/2* mutations are present in higher frequency than previously thought and likely contribute to many more undiagnosed cases of combined immunodeficiency or autoimmune disease (2).

The phenomenon of autoimmunity in RAG deficiency is potentially due to disruption of both T and B cell tolerance checkpoints (3, 4). In particular, breakage of central B cell tolerance is likely secondary to impaired receptor editing, wherein re-expression of RAG proteins in the bone marrow initiates secondary rearrangement of the light chain locus to decrease antibody self-reactivity (4). In humans, efficiency of receptor editing may be estimated by measuring rearrangements that involve the cryptic heptamer in the J-C intron (termed “iRS-RS rearrangement”) of the *IGK* locus (5). Using this assay, low levels of iRS-RS rearrangement, and hence impaired receptor editing, have been demonstrated in a subgroup of subjects with systemic lupus erythematosus (SLE) and type 1 diabetes (5). Here, we report that a subset of these previously described SLE patients were tested for the presence of *RAG* gene mutations. In particular, we selected SLE patients with normal (n=5) or low (n=5) iRS-RS rearrangement. All ten patients had a wild-type sequence of the *RAG1* gene. All five patients with normal receptor editing levels also had normal variants of *RAG2*. However, of the five patients with low iRS-RS rearrangement levels, one patient was found to carry a heterozygous missense *RAG2* mutation (c.C123G; p.C41W). Homozygosity for this mutation has been previously reported in a patient with Omenn syndrome (2). Moreover, the RAG2 p.C41W mutant has been shown to cause impaired V(D)J recombination (4-10% of wild-type) secondary to diminished DNA binding and cleavage activity *in vitro* (6).

The SLE patient carrying a heterozygous *RAG2* p.C41W mutation is a 44-year-old Hispanic female. She was diagnosed at 23 years of age when she presented with polyarthritis, Raynaud phenomenon and sicca symptoms. Other clinical manifestations that developed in the course of her disease include serositis (pleuritis and pericarditis), hive-like rashes, and class V lupus nephritis. Laboratory studies were notable for leukopenia and hypocomplementemia. Serologic studies showed high-titer anti-nuclear antibody and presence of antibodies to dsDNA, Smith, RNP, histone, SSA and cardiolipin. Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies were undetectable. She was also noted to have history of recurrent infections, which were attributed to her medication regimen; she was treated with prednisone, hydroxychloroquine, and leflunomide. Arthritis

with erosive changes remained her most prominent symptom, while her other manifestations responded well to increased doses of prednisone. She never received B cell-directed therapies such as rituximab or belimumab, or other immunosuppressive medications such as cyclophosphamide or TNF-α inhibitors.

The patient was hospitalized at 39 years of age for arthritis flare, pleurisy, bursitis and streptococcal sepsis. Laboratory evaluation at the time of her hospitalization was significant for T and B cell lymphopenia (ALC: 600 cells/$mm^{3;}$ CD3+ lymphocytes: 504 cells/mm^3; $CD19^+$ B lymphocytes: 32 cells/mm^3). The T cell lymphopenia was mostly related to decreased CD4+ cell count ($CD4^+$: 275 cells/mm^3; $CD8^+$: 201 cells/mm^3). While both T and B cell lymphopenia are well documented in SLE, and may be due in part to anti-lymphocyte antibodies, this degree of B cell lymphopenia is unusual (7). Lupus patients with erosive arthritis may represent a distinct clinical subset of SLE. In one study, this subset was characterized by largely non-white women with a propensity for mild nephritis, Sjogren's syndrome and Raynaud's phenomenon (8). Other studies of arthritis-predominant lupus patients have implicated anti-cardiolipin, anti-dsDNA, and anti-Ro/La antibodies (9). Our patient's presentation appears to fit this clinical subset of SLE well, raising the question of whether receptor editing defects might be more prevalent in this specific group.

The effect of heterozygous *RAG* mutations on B and T cell tolerance has not been thoroughly examined. Most heterozygous parents of children with biallelic *RAG1* or *RAG2* mutations appear healthy, but no studies have formally assessed clinical or laboratory signs of autoimmunity in these subjects. In mice, significant impairment in B and T cell development has been reported in aged *Rag1-S723C* heterozygous mice with low recombinase activity (10). These changes include decreased numbers of $CD4^+$ $CD8^+$ thymocytes, increased pro-, and decreased numbers of preand early B cells. Our group has reported impaired receptor editing in *Rag1-S723C* homozygous mice but heterozygous mice have not yet been formally evaluated (10).

While impaired receptor editing due to a *RAG* mutation may have contributed to the pathogenesis of SLE in the patient described here, additional factors likely played an important role in the development of autoimmunity. For example, elevated BAFF levels in the setting of B cell lymphopenia could relax the stringency of B cell selection (11). Furthermore, HLA genotype and environmental triggers may also contribute to the final autoimmune phenotype.

In summary, we have identified a patient with SLE and erosive arthritis and low receptor editing associated with a heterozygous *RAG2* mutation. This finding broadens the phenotypic spectrum of gene defects typically associated with severe immunodeficiency, and also highlights the role of identifying specific genotype-phenotype correlations within heterogeneous presentations of lupus.

We propose that breach of RAG-dependent tolerance checkpoints due to receptor editing may play a role in the pathogenesis of SLE for some patients. With this case report we urge for increased awareness of monogenic immune defects in autoimmune diseases that are otherwise considered to be of multifactorial origin.

Acknowledgments

This work was partly supported by the National Institute of Allergy and Infectious Diseases, NIH grant 5P01AI076210-04 (L.D.N.), National Institute of Allergy and Infectious Diseases, NIH U54AI082973 (L.D.N.), Manton Foundation (L.D.N.), National Institute of Allergy and Infectious Diseases, NIH grant 5K08AI103035 (J.E.W.) the March of Dimes grant 1-FY13-500, the Lupus Research Institute (E.L.P. and J.D.), the Jeffrey Modell Foundation (L.D.N.), National Institute of Allergy and Infectious Diseases, NIH grant R01 AI 42269-18 (G.A.T).

References

1. Schuetz C, Huck K, Gudowius S, Megahed M, Feyen O, Hubner B, et al. An immunodeficiency disease with RAG mutations and granulomas. N Engl J Med. 2008; 358(19):2030–8. [PubMed: 18463379]
2. Chen K, Wu W, Mathew D, Zhang Y, Browne SK, Rosen LB, et al. Autoimmunity due to RAG deficiency and estimated disease incidence in RAG1/2 mutations. J Allergy Clin Immunol. 2014; 133(3):880–2. e10. [PubMed: 24472623]
3. Poliani PL, Facchetti F, Ravanini M, Gennery AR, Villa A, Roifman CM, et al. Early defects in human T-cell development severely affect distribution and maturation of thymic stromal cells: possible implications for the pathophysiology of Omenn syndrome. Blood. 2009; 114(1):105–8. [PubMed: 19414857]
4. Walter JE, Rucci F, Patrizi L, Recher M, Regenass S, Paganini T, et al. Expansion of immunoglobulin-secreting cells and defects in B cell tolerance in Rag-dependent immunodeficiency. J Exp Med. 2010; 207(7):1541–54. [PubMed: 20547827]
5. Panigrahi AK, Goodman NG, Eisenberg RA, Rickels MR, Naji A, Luning Prak ET. RS rearrangement frequency as a marker of receptor editing in lupus and type 1 diabetes. J Exp Med. 2008; 205(13):2985–94. [PubMed: 19075293]
6. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, et al. Partial V(D)J recombination activity leads to Omenn syndrome. Cell. 1998; 93(5):885–96. [PubMed: 9630231]
7. Odendahl M, Jacobi A, Hansen A, Feist E, Hiepe F, Burmester GR, et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. J Immunol. 2000; 165(10):5970–9. [PubMed: 11067960]
8. Richter Cohen M, Steiner G, Smolen JS, Isenberg DA. Erosive arthritis in systemic lupus erythematosus: analysis of a distinct clinical and serological subset. British journal of rheumatology. 1998; 37(4):421–4. [PubMed: 9619894]
9. Simon JA, Granados J, Cabiedes J, Morales JR, Varela JA. Clinical and immunogenetic characterization of Mexican patients with ‘rhupus’. Lupus. 2002; 11(5):287–92. [PubMed: 12090562]
10. Giblin W, Chatterji M, Westfield G, Masud T, Theisen B, Cheng HL, et al. Leaky severe combined immunodeficiency and aberrant DNA rearrangements due to a hypomorphic RAG1 mutation. Blood. 2009; 113(13):2965–75. [PubMed: 19126872]
11. Stohl W, Scholz JL, Cancro MP. Targeting BLyS in rheumatic disease: the sometimes-bumpy road from bench to bedside. Current opinion in rheumatology. 2011; 23(3):305–10. [PubMed: 21330926]

Key Messages

1. We describe here a patient with systemic lupus erythematosus carrying a *RAG2* missense heterozygous mutation and with evidence of impaired central B cell tolerance
2. Our case provides novel insights into mechanism that may contribute to loss of tolerance in lupus

Capsule Summary

The clinical spectrum of RAG deficiency has expanded to cases with dominant features of autoimmunity. We describe a patient with lupus and evidence of impaired central B cell tolerance carrying a *RAG2* missense heterozygous mutation.