A Role for *Satb1* in Thyroid Autoimmunity?

Sandra M. McLachlan and Basil Rapoport

Dear Editor:

A recent publication by Tanaka *et al.* described the spontaneous development of Sjögren's syndrome in C57BL/6 mice with a conditional knockout of the *Satb1* gene in hematopoietic cells (1). *Satb1* (special AT-rich sequence binding protein) is a genome organizer involved in establishing immune tolerance by impairing negative selection of T cells in the thymus and reducing the efficacy of regulatory T cells. Not mentioned by Tanaka *et al.* (1) is that Sjögren's syndrome also develops in NOD.H2^{h4} mice that spontaneously develop autoimmune thyroiditis [reviewed by Braley-Mullen and Yu (2)]. We wish to point out that our recent genetic analysis of NOD.H2^{h4} mice revealed that a locus associated with thyroid autoimmunity contains the *Satb1* gene (3).

NOD.H2^{h4} mice were derived by substituting the major histocompatibility class (MHC) molecule I-A^k on chromosome 17 from B10.A4R mice for I-A^{g7} in diabetes-prone nonobese diabetic (NOD) mice [reviewed in Braley-Mullen and Yu (2)]. Instead of developing type 1 diabetes, NOD.H2^{h4} mice develop thyroiditis in association with autoantibodies to thyroglobulin and thyroid peroxidase. In searching for the genetic basis for these traits, we observed highly significant linkage for thyroglobulin antibodies (LOD

scores >4) to a locus on chromosome 17 (3). This locus includes portions from the B10.A4R (27.3–44.8 Mb) and NOD.H2^{h4} (44.8–75.96 Mb) strains, the former containing *MHC* region genes (Fig. 1).

Because there was also strong linkage to adjacent non-*MHC* region genes from the NOD.H2^{h4} mice, we reviewed the genes within this region (3) and noted the presence of *Satb1* at 51.9 Mb (Fig. 1), a gene with a role (as mentioned above) in immune tolerance. We therefore speculated that polymorphisms in genes like *Satb1* could contribute to the loss of immune tolerance to thyroid autoantigens and the development of thyroid autoimmunity in NOD.H2^{h4} mice (3). In addition to Sjögren's syndrome in conditional *Satb1* knockout mice (1), lymphocytic infiltrates were previously observed in lung, liver, and stomach. However, thyroid tissue does not appear to have been examined, and it would be of interest to know if autoantibodies to thyroid autoantigens arise in these animals.

With the new information that *knockout* of *Satb1* in C57BL/6 mice leads to multi-organ autoimmunity, if *Satb1* contributes to thyroid autoimmunity in NOD.H2^{h4} mice, then *Satb1* is either nonfunctional or has a variable phenotype that may also lead to Sjögren's syndrome. In mice with the conditional *Satb1* knockout, Sjögren's syndrome develops

FIG. 1. Left panel: Schematic illustration of the chromosome 17 locus linked to TgAb in NOD.H2^{h4} mice and its origin from the autoimmune NOD mouse strain (gray shading) and the nonautoimmune B10A.4R strain (speckled shading). Right panel: Linkage analysis (high resolution map) for this Chromosome 17 locus including the gray and speckled shading to emphasize the origin of genes from the NOD and B10.A4R strains [adapted with permission from McLachlan SM *et al.* 2017 (3)].

rapidly being apparent in 4 week old mice, whereas in the NOD.H2^{h4} strain, Sjögren's syndrome is rare in 8 week old mice and the symptoms are most evident in 1 year old females (2). This difference in time course is consistent with the total absence of *Satb1* in the knockout strain versus the possibility of a dysfunctional *Satb1* protein in NOD.H2^{h4} mice.

Turning to autoimmune thyroid disease in humans, despite evidence for a contribution by regulatory T cells, the major susceptibility genes identified do not include *SATB1*, which is located on chromosome 3. Only two thyroid autoimmunity susceptibility genes in humans are located on chromosome 3. First, *LPP* (LIM domain containing preferred translocation partner in lipoma) was included in seven newly identified loci for thyroid autoimmunity in a United Kingdom population (4). Its location on chromosome 3 (188,153,050..188,890,671 Mb) is upstream of *SATB1* (18,345,388..18,445,588 Mb). The second thyroid autoimmunity susceptibility gene on chromosome 3, *KALRN* (kalirin RhoGEF kinase), linked to development of thyroid peroxidase autoantibodies (5), is also located in a different chromosome 3 region (124,033,341..124,726,325 Mb). Nevertheless, because of the similarity of the NOD.H2^{h4} thyroiditis model to human Hashimoto's disease, re-examining *SATB1* as a candidate gene for thyroid autoimmunity may be of value.

Acknowledgments

This work was supported by the National Institutes of Health Grants DK54684 (S.M.M.).

Author Disclosure Statement

No competing financial interests exist.

References

1. Tanaka Y, Sotome T, Inoue A, Mukozu T, Kuwabara T, Mikami T, Kowhi-Shigematsu T, Kondo M 2017 *SATB1* Conditional knockout results in Sjögren's syndrome in mice. *J Immunol* **199**:4016–4022.
2. Braley-Mullen H, Yu S 2015 NOD.H-2h4 mice: an important and underutilized animal model of autoimmune thyroiditis and Sjögren's syndrome. *Adv Immunol* **126**:1–43.
3. McLachlan SM, Lesage S, Collin R, Banuelos B, Aliesky HA, Rapoport B 2017 Genes outside the Major Histocompatibility Complex Locus are linked to the development of thyroid autoantibodies and thyroiditis in NOD.H2h4 mice. *Endocrinology* **158**:702–713.
4. Cooper JD, Simmonds MJ, Walker NM, Burren O, Brand OJ, Guo H, Wallace C, Stevens H, Coleman G, Franklyn JA, Todd JA, Gough SC 2012 Seven newly identified loci for autoimmune thyroid disease. *Hum Mol Genet* **21**:5202–5208.
5. Medici M, Porcu E, Pistis G, Teumer A, Brown SJ, Jensen RA, Rawal R, Roef GL, Plantinga TS, Vermeulen SH, Lahti J, Simmonds MJ, Husemoen LL, Freathy RM, Shields BM, Pietzner D, Nagy R, Broer L, Chaker L, Korevaar TI, Plia MG, Sala C, Volker U, Richards JB, Sweep FC, Gieger C, Corre T, Kajantie E, Thuesen B, Taes YE, Visser WE, Hattersley AT, Kratzsch J, Hamilton A, Li W, Homuth G, Lobina M, Mariotti S, Soranzo N, Cocca M, Nauck M, Spielhagen C, Ross A, Arnold A, van de BM, Liyanarachchi S, Heier M, Grabe HJ, Masciullo C, Galesloot TE, Lim EM, Reischl E, Leedman PJ, Lai S, Delitala A, Bremner AP, Philips DI, Beilby JP, Mulas A, Vocale M, Abecasis G, Forsen T, James A, Widen E, Hui J, Prokisch H, Rietzschel EE, Palotie A, Feddema P, Fletcher SJ, Schramm K, Rotter JJ, Kluttig A, Radke D, Traglia M, Surdulescu GL, He H, Franklyn JA, Tiller D, Vaidya B, de Meyer T, Jorgensen T, Eriksson JG, O'Leary PC, Wichmann E, Hermus AR, Psaty BM, Ittermann T, Hofman A, Bosi E, Schlessinger D, Wallaschofski H, Pirastu N, Aulchenko YS, de la CA, Netea-Maier RT, Gough SC, Meyer Zu SH, Frayling TM, Kaufman JM, Linneberg A, Raikonen K, Smit JW, Kiemeny LA, Rivadeneira F, Uitterlinden AG, Walsh JP, Meisinger C, den Heijer M, Visser TJ, Spector TD, Wilson SG, Volzke H, Cappola A, Toniolo D, Sanna S, Naitza S, Peeters RP 2014 Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. *PLoS Genet* **10**:e1004123.

Address correspondence to:
Sandra M. McLachlan, PhD
Thyroid Autoimmune Disease Unit
Cedars-Sinai Research Institute
and UCLA School of Medicine,
8700 Beverly Blvd, Suite B-131
Los Angeles, CA 90048

E-mail: mclachlans@cshs.org