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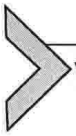

VOLUME ONE HUNDRED AND TWENTY SIX

ADVANCES IN IMMUNOLOGY

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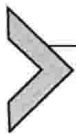

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CONTENTS

CHAPTER ONE

NOD.H-2h4 Mice: An Important and Underutilized Animal Model of Autoimmune Thyroiditis and Sjogren's Syndrome

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Contents

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Abstract

NOD.H-2h4 mice express the K haplotype on the NOD genetic background. They spontaneously develop thyroiditis and Sjogren's syndrome, but they do not develop diabetes. Although autoimmune thyroid diseases and Sjogren's syndrome are highly prevalent autoimmune diseases in humans, there has been relatively little emphasis on the use of animal models of these diseases for understanding basic mechanisms involved in development and therapy of chronic organ-specific autoimmune diseases. The goal of this review is to highlight some of the advantages of NOD.H-2h4 mice for studying basic mechanisms involved in development of autoimmunity. NOD.H-2h4 mice are one of relatively few animal models that develop organ-specific autoimmune diseases spontaneously, i.e., without a requirement for immunization with antigen and adjuvant, and in both sexes in a relatively short period of time. Thyroiditis and Sjogren's syndrome in NOD.H-2h4 mice are chronic autoimmune diseases that develop relatively early in life and persist for the life of the animal. Because the animals do not become clinically ill, the NOD.H-2h4 mouse provides an excellent model to test therapeutic protocols over a long period of time. The availability of several mutant mice on this background provides a means to address the impact of particular cells and molecules on the autoimmune diseases. Moreover, to our knowledge, this is the only animal model in which the presence or absence of a single cytokine, IFN-γ, is sufficient to completely inhibit one autoimmune thyroid disease, with a completely distinct autoimmune thyroid disease developing when it is absent.

1. INTRODUCTION

NOD.H-2h4 mice are an important and underutilized model for studying the spontaneous development of autoimmune thyroiditis and Sjogren's syndrome (SS). NOD.H-2h4 mice were derived by crossing NOD mice with B10.A(4R), followed by multiple backcrosses to NOD using offspring that expressed the major histocompatibility complex (MHC) haplotype of the B10.A(4R) mouse. NOD.H-2h4 mice express the K haplotype at the K and I-A loci, they do not express I-E, and they express the b haplotype at H-2D (Podolin et al., 1993). NOD.H-2h4 mice have a relatively high incidence of mild insulitis, but they do not develop diabetes (Podolin et al., 1993; Wicker, Todd, & Peterson, 1995). Because they express an MHC haplotype (H-2K) that is a susceptibility haplotype for autoimmune thyroiditis (Vladutiu & Rose, 1971), they spontaneously develop a high incidence of autoimmune thyroiditis. The incidence and kinetics of development of thyroiditis are greatly accelerated by addition of sodium iodide (NaI) to the drinking water, but iodine is not essential for spontaneous autoimmune thyroiditis (SAT) development in wild-type

(WT) NOD.H-2h4 mice (Braley-Mullen, Sharp, Medling, & Tang, 1999; Hutchings et al., 1999; Rasooly, Burek, & Rose, 1996). Thyroid lesions start to develop in most mice 3–4 weeks after they are given NaI in their drinking water. In our colony, thyroid lesions reach maximal severity with an average severity score of 2–3 + 8–9 weeks after they are given 0.05–0.08% NaI in their water. Thyroid lesions are then maintained with little change in severity for many months (Braley-Mullen et al., 1999). Mice rarely, if ever, become clinically hypothyroid; their serum T4 levels are almost always within the normal range of 4–8 μg/dL using T4 ELISA kits (Leinco, St. Louis, MO). Thyroid lesions develop in both males and females. There are no significant sex differences in severity scores, although we and others find that males tend to have somewhat more consistent scores in the moderately severe 2–3 + range (Braley-Mullen et al., 1999; Rasooly et al., 1996). In our colony, SAT develops comparably whether mice are maintained in barrier or conventional housing conditions, whereas others have reported that thyroiditis is more severe in conventionally housed mice (Burek, Talor, Santana, & Rose, 1998). Thyroid lesions in SAT have a characteristic histology, with clusters of B cells and CD4 + T cells being the predominant feature (Yu, Medling, Yagita, & Braley-Mullen, 2001). CD8 + T cells are less numerous and are scattered throughout the thyroid. Germinal center-like structures, characteristic of tertiary lymphoid organs, are also common in thyroids of mice with SAT (Hong & Braley-Mullen, 2014; Yu et al., 2001).

Both the MHC and the NOD background genes are important for development of SAT, as mice expressing the K haplotype and other background genes (e.g., CBA/J and AKR/J) do not develop SAT even if NaI is added to the drinking water, and mice expressing another thyroiditis susceptibility haplotype (H-2q) on the NOD background do not develop SAT (H. Braley-Mullen, unpublished results). Because NOD.H-2h4 mice differ from NOD only at the MHC locus, and all background genes are the same (Wicker et al., 1995), we have generated many mutant NOD.H-2h4 mice by crossing NOD mutants generated by others onto the NOD.H-2h4 background (Yu et al., 2002; Yu, Maiti, Dyson, Jain, & Braley-Mullen, 2006; Yu, Sharp, & Braley-Mullen, 2006b).

This review describes what is known regarding the development of two distinct autoimmune thyroid diseases that develop in NOD.H-2h4 mice when IFN-γ is present versus when IFN-γ is absent, and the effects of particular gene knockout mutations on these diseases. We will also discuss the use of NOD.H-2h4 mice as a model for studying SS, the development of

which can be greatly accelerated in some of the NOD.H-2h4 mutant strains described here. WT NOD.H-2h4 mice that were rederived from mice in our breeding colony are available as cryopreserved stock (Jax Stock 004447), and many of the mutants described here have been donated to MMRRC and will soon be available. The MMRRC stock numbers of those strains are provided in Tables 1 and 2.

2. SPONTANEOUS AUTOIMMUNE THYROIDITIS

2.1. SAT in WT NOD.H-2h4 mice/importance of iodine

After the initial description of NOD.H-2h4 mice (Podolin et al., 1993), three laboratories, including ours, obtained mice from Dr. Linda Wicker and established breeding colonies. The first reports from these three laboratories established that nearly all NOD.H-2h4 mice of both sexes develop thyroid lesions and produce autoantibodies to mouse thyroglobulin (MTg) following administration of NaI in the drinking water (Braley-Mullen et al., 1999; Hutchings et al., 1999; Rasooly et al., 1996). While many NOD.H-2h4 mice eventually develop thyroiditis without NaI supplementation of the drinking water, thyroiditis develops more slowly and in a much lower percentage of the mice. Addition of NaI to the drinking water of groups of age- and sex-matched mice provides a model in which essentially all mice develop SAT that reaches maximal severity 8–9 weeks after NaI water is begun. After this time, thyroid lesions become chronic and persist for the life of the animal. Continued administration of NaI in the water is not essential for maintenance of established thyroiditis in the chronic phase (H. Braley-Mullen, unpublished). The histology of the thyroid lesions, production of autoantibodies, etc., are indistinguishable whether or not the water is supplemented or not supplemented with iodine. The extent to which mice not given NaI in their water develop thyroid lesions likely varies in different facilities, but in our colony, about 50% of WT NOD.H-2h4 mice have thyroid lesions and circulating anti-thyroglobulin antibodies at 8 months of age (Braley-Mullen et al., 1999; Ellis, Hong, et al., 2013; our unpublished results). A wide range of iodine concentrations, from 0.005% to 0.5%, have been used by various investigators and are reported to promote SAT development to a similar extent (Burek et al., 1998). The most commonly used concentrations are 0.05–0.15% in different laboratories (Braley-Mullen et al., 1999; Burek et al., 1998; Ellis, Hong, et al., 2013; Horie et al., 2011; Nagayama, Horie, Saitoh, Nakahara, & Abiru, 2007). Addition of NaI to the drinking

Table 1 IFN-γ+ NOD.H-2h4 mice and mutants for understanding mechanisms in SAT and Sjogren's syndrome

Strain (MMRRC Stock #)	Phenotype	References
WT NOD.H-2h4 (Jax 004447)	SAT/Sjogren's	Rasooly et al. (1996), Braley-Mullen et al. (1999)
B −/−	SAT resistant without Treg depletion/Sjogren's resistant	Yu, Maiti, et al. (2006)
TCR-α −/− (037148)	SAT resistant/source of B cells and APC	Yu, Ellis, Dunn, Kehry, and Braley-Mullen (2012)
IL-4 −/−	SAT comparable to WT	Yu et al. (2002)
IL-10 −/−	SAT comparable to WT	H. Braley-Mullen (unpublished)
IL-17 −/−	Reduced SAT without Treg depletion	Horie, Abiru, Sakamoto, Iwakura, and Nagayama (2011)
IFN-γR −/−	SAT resistant	Yu, Sharp, and Braley-Mullen (2006); Horie et al. (2011)
CD40 −/− (037352)	SAT resistant	Kayes, Fang, et al. (2013)
CD154 −/−	SAT resistant	H. Braley-Mullen (unpublished)
CD28 −/− (037138)	SAT is more severe/Sjogren's is more prevalent	Ellis, Hong, Zaghouani, and Braley-Mullen (2013)
CD28 −/− B −/− (037353)	Develop SAT/source of T cells/few functional Treg	Ellis, Hong, et al. (2013), Ellis and Braley-Mullen (2014)
Foxp3 GFP	SAT-like WT/used to purify/track Treg	Ellis, Wan, and Braley-Mullen (2013), Yu et al. (2012)
Foxp3GFPB −/−	SAT resistant/used to track Treg	Ellis and Braley-Mullen (2014)
Foxp3DTR B −/− (037354)	SAT resistant/develop SAT after DT treatment	Ellis and Braley-Mullen (2014)

Jax or MMRRC stock numbers in parentheses.

Table 2 IFN-γ −/− NOD.H-2h4 and mutants for studying mechanisms in TEC H/P and Sjogren's syndrome

Strain (MMRRC Stock #)	Phenotype	References
IFN-γ −/− (037140)	SAT resistant; develop TEC H/P (60% at 9 months of age)	Yu et al. (2002), Yu et al. (2006b), Yu, Sharp, and Braley-Mullen (2008)
B −/− (037144)	TEC H/P resistant; source of CD40+ T cells for transfers	H. Braley-Mullen (unpublished)
B −/− CD40 −/−	TEC H/P resistant; source of CD40 −/− T cells for transfers	Kayes, Fang, et al. (2013); unpublished
SCID (037139)	TEC H/P resistant; used for adoptive transfer of TEC H/P	Yu, Sharp, and Braley-Mullen (2006a), Yu, Fang, Sharav, Sharp, and Braley-Mullen (2011), Kayes, Fang, et al. (2013)
CD28 −/− (037141)	High incidence of severe TEC H/P; Sjogren's	Kayes and Braley-Mullen (in preparation)
CD4 −/− CD28+	Low incidence of severe TEC H/P	Yu, Downey, and Braley-Mullen (2013)
CD8 −/− CD28+	TEC H/P resistant	Yu et al. (2013)
CD4 −/− CD28 −/−	High incidence of severe TEC H/P; Sjogren's	Kayes and Braley-Mullen (in preparation)
CD8 −/− CD28 −/−	High incidence of severe TEC H/P; Sjogren's	Kayes and Braley-Mullen (in preparation)
CD40 −/− CD28 −/− (037143)	High incidence of severe TEC H/P; some Sjogren's	Kayes and Braley-Mullen (in preparation)
TCR-α −/− (037147)	Resistant to TEC H/P; B cell source for transfer experiments	H. Braley-Mullen (unpublished)
TCR-α −/− CD40 −/− (037149)	Resistant to TEC H/P; source of CD40 −/− B cells	H. Braley-Mullen (unpublished)
PD-1 −/− (037145)	Moderate incidence of severe TEC H/P; Sjogren's	Braley-Mullen (in preparation)

The MMRRC stock numbers are indicated in parentheses.

water has no effect on development of spontaneous or experimentally induced thyroiditis in other strains of mice, including strains such as CBA/J and DBA/1 that express thyroiditis susceptibility haplotypes such as H-2K and H-2Q (Braley-Mullen et al., 1999; our unpublished results). Because iodine supplementation of the drinking water is essential for the NOD.H-2h4 mouse to be a useful model for studying autoimmune thyroiditis, some investigators use the term I-SAT (iodine-induced SAT) to emphasize the importance of iodine in thyroiditis development (e.g., Horie et al., 2009; Kolypetri, Carayanniotis, Rahman, et al., 2014). Conversely, our laboratory uses the term SAT to distinguish an autoimmune disease that is not dependent on immunization for its development from experimentally induced models of thyroiditis (EAT) that require immunization with thyroglobulin and adjuvant for their development.

Many studies have addressed the potential mechanisms by which iodine supplementation promotes development of autoimmune thyroid diseases. Iodine is known to be an important environmental trigger for thyroiditis in both humans and animals (Allen, Appel, & Braverman, 1986; Bagchi, Brown, Urdanivia, & Sundick, 1985; Burek & Talor, 2009; Rose et al., 2002). NOD and NOD.H-2h4 thyrocytes constituitively express the adhesion molecule ICAM-1 (Bonita, Rose, Rasooly, Caturegli, & Burek, 2002), and iodine can enhance ICAM-1 expression on NOD.H-2h4 thyrocytes, due, at least in part, to its ability to cause generation of reactive oxygen species (Burek & Rose, 2008; Sharma et al., 2005; Sharma, Traore, Trush, Rose, & Burek, 2008). Iodine could also induce damage to thyrocytes, resulting in apoptosis and/or necrosis, and this may impact development of thyroiditis (Bagchi, Brown, & Sundick, 1995; Carayanniotis, 2011; Kolypetri & Carayanniotis, 2014) Iodine supplementation can also lead to increased iodination of thyroglobulin (Barin, Talor, Sharma, Rose, & Burek, 2005; Carayanniotis, 2007; Li & Carayanniotis, 2006) or thyroglobulin-derived peptides (Li, Jiang, & Carayanniotis, 2007; Carayanniotis, 2007), resulting in increased immunogenicity, although one study indicated that development of SAT in NOD.H-2h4 mice is not associated with enhanced iodination of thyroglobulin (Kolypetri, Noel, Carayanniotis, & Carayanniotis, 2010). Importantly, a very recent study by the same group (Kolypetri, Carayanniotis, Rahman, et al., 2014) showed that NOD.H-2h4 mice developing SAT have thyroid infiltrating T cells that respond to a well-characterized iodinated peptide of thyroglobulin. Therefore, there are multiple ways in which iodine supplementation of the drinking water can influence development of SAT, and at this time, it is unknown if one or more of these factors is most important for promoting SAT development in NOD.H-2h4 mice.

2.2. B cells and autoantibodies in SAT

As reported by our laboratory as well as others, essentially all NOD.H-2h4 mice that develop SAT produce autoantibodies to MTg, whereas mice with minimal or no thyroiditis generally do not have detectable levels of anti-MTg autoantibody (Braley-Mullen et al., 1999; Rasooly et al., 1996). Because NOD.H-2h4 mice, like NOD mice, have a defect in processing of IgG2A (Prins et al., 1993), they do not produce IgG2A autoantibody and the MTg IgG autoantibody is comprised of IgG1 and IgG2b subclasses (Braley-Mullen, Chen, Wei, & Yu, 2001). The levels of MTg autoantibodies generally correlate reasonably well with SAT severity scores (Braley-Mullen et al., 1999; Rasooly et al., 1996). NOD.H-2h4 mice also produce antibodies to thyroid peroxidase (TPO) (Chen et al., 2010; Verma et al., 2000). Anti-TPO antibodies develop later than anti-MTg autoantibodies (Chen et al., 2010), but the extent to which anti-TPO levels correlate with SAT severity scores is unknown. The fact that most mice with SAT produce MTg autoantibodies suggests that an unknown epitope of thyroglobulin is the initiating autoantigen for SAT. Although WT NOD.H-2h4 mice that develop SAT produce MTg autoantibodies and those that do not have SAT do not generally have detectable anti-MTg autoantibody, there are several examples of mice that do not produce autoantibody, yet they develop SAT. As will be discussed in more detail below, B cell-deficient (B−/−) NOD.H-2h4 mice and transgenic (Tg) NOD.H-2h4 mice with nitrophenyl (NP)-specific B cells that do not secrete immunoglobulin develop SAT if their Treg are transiently depleted (Yu, Maiti, et al., 2006). Interestingly, thyroids of NP Tg mice that develop SAT after transient Treg depletion have many thyroid infiltrating B cells, even though their B cells are NP-specific and are not specific for thyroid antigens (Yu, Maiti, et al., 2006). In addition, thyroids of CD28−/− NOD.H-2h4 mice produce very low levels of autoantibodies but develop more severe SAT than WT NOD.H-2h4 mice (Ellis, Hong, et al., 2013), and transfer of high titer anti-MTg autoantibodies to B−/− mice does not result in SAT (Braley-Mullen & Yu, 2000). These results indicate that although autoantibodies in WT NOD.H-2h4 mice with SAT can be a useful predictor of whether or not they have SAT, autoantibodies probably contribute minimally, if at all, to the pathology of SAT.

B cell-deficient (B−/−) NOD.H-2h4 mice do not develop SAT (Braley-Mullen & Yu, 2000), and WT NOD.H-2h4 mice depleted of B cells by administration of anti-IgM at birth or given anti-CD20 as adults