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FORUM REVIEW ARTICLE

Biological Sex As a Critical Variable in CD4$^+$ Effector T Cell Function in Preclinical Models of Multiple Sclerosis

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Abstract

Significance: T cells play a pivotal role in maintaining adaptive immune responses against pathogens. However, misdirected T cell responses against self-tissues may lead to autoimmune disease. Biological sex has profound effects on T cell function and is an important determinant of disease incidence and severity in autoimmune diseases such as multiple sclerosis (MS).
Recent Advances: Many autoimmune diseases skew toward higher female incidence, including MS; however, it is has become increasingly more accepted that men living with MS are more prone to developing a progressive disease course and to having worsened disease outcomes.
Critical Issues: In this review, we discuss what is known about the role of biological sex on T cell development and differentiation, examining evidence that male sex can augment T helper 17 (Th17) responses. Next, we outline what is known about sex differences in animal models of MS, and about the distinct roles played by sex hormones *versus* sex chromosomes in pathogenesis in these models. Finally, we discuss recent advances that examine the molecular basis for worsened disease outcomes in males, with a particular focus on the role played by Th17 cells in these models.
Future Directions: Better understanding the role of biological sex in T cell function may pave the way to effective personalized treatment strategies in MS and other autoimmune diseases. *Antioxid. Redox Signal.* 37, 135–149.

Keywords: sex differences, multiple sclerosis, experimental autoimmune encephalomyelitis, CD4$^+$ T cell, sex hormones, sex chromosomes, Jarid1c

Introduction

CD4$^+$ T CELLS are a critical component of the adaptive immune system, which governs antigen (Ag)-specific detection of, and response to, pathogens. CD4$^+$ T cells rapidly proliferate and differentiate into effector subsets upon recognition of cognate Ag presented by major histocompatibility complex (MHC) class II complexes on the surface of antigen-presenting cells (APCs). They subsequently traffic to sites of inflammation, where they recruit immune effector cells such as CD8$^+$ T cells, B cells, macrophages, neutrophils, or eosinophils, among others. Due to their great inflammatory potential, T cell responses are subject to tight regulatory control, most notably to avert reactions to self-tissues. Nevertheless, these mechanisms are imperfect, with $\sim$6 in 100 individuals in the Western world having an autoimmune disease (108). Autoimmunity thus represents a major public health burden worldwide.

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Multiple sclerosis (MS) is a chronic neurodegenerative disease of the central nervous system (CNS) for which there is currently no cure. MS has a high rate of prevalence in Western countries: for example, in Canada, as many as 1 in 350 individuals are affected (84). MS is considered an autoimmune disease in which T and B cells cross the blood/brain barrier (BBB) and launch an inflammatory attack against CNS myelin. This inflammatory immune response affects both myelin sheath and axons leading to neuronal dysfunction (91). MS has a heterogeneous presentation of disease, manifesting in affected individuals as fatigue, pain, motor deficit, visual disturbances, and cognitive impairment (33). Around 80% of patients will initially present relapsing/remitting (RR) disease, and 30%–60% of these will transition to a secondary progressive form that is currently refractory to treatment (63).

As is the case for many autoimmune diseases, the failure of central, thymically enforced tolerance of T cells results in the presence of myelin-specific T cells in the mature immune repertoire; furthermore, peripheral immune activation of these myelin specific T cells is important in MS pathogenesis. In RR-MS, activated T cells specific for myelin Ags, such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), have been identified in the blood and cerebrospinal fluid of MS patients. These activated T cells migrate to the CNS and are subsequently reactivated upon recognition of myelin Ag *in situ*. This leads to an inflammatory cascade of events resulting in MS symptoms in affected individuals (27).

While the central role of adaptive immune responses in RR-MS is well-established, its role in progressive MS is a matter of active debate. Those arguing against a role for lymphocytes in progressive MS have relied on evidence that many existing immunomodulatory MS disease-modifying therapies (DMT) are ineffective in this form of disease, and that progressive MS lesions tend to be immunologically silent as visualized by magnetic resonance imaging. On the contrary, it is now known that B cell- and T cell-rich ectopic lymphoid organs can form in the CNS meninges (70) and that they increase in frequency during secondary progressive MS (66, 92), where they can potentially secrete inflammatory mediators and trophic growth factors to support immune cells trapped in the parenchyma behind a closed BBB. Indeed, axonopathy in progressive MS correlates with T and B cell accumulation (42). Furthermore, the B cell depleting DMT ocrelizumab is the first therapy to show efficacy *versus* primary progressive MS (73), and the lymphocyte trafficking antagonist siponimod shows activity during the active phase of MS (57).

Sex is a critical variable in most physiological processes, with adaptive immune function being no exception. ''Sex'' refers to the biological attributes governed by the expression and function of sex hormones and/or sex chromosome components. While the terms are often used interchangeably in the literature, sex is distinct from ''gender,'' which refers to socially and/or culturally defined features. Sex differences have long been of interest to immunologists, in part, because many autoimmune diseases, including MS, show a striking bias toward female incidence. Indeed, MS affects three times as many women as men. However, it is now understood that the proportion of MS-affected men who develop a progressive disease course exceeds that of MS-affected women (37). Furthermore, there is a growing body of evidence suggesting that male sex enhances the function of inflammatory T helper 17 (Th17) $CD4^+$ effector T cells that are pivotal in autoimmunity.

In this review, we outline what is known about the role of biological sex in effector $CD4^+$ T cell function. We then describe evidence for the role of sex in distinct mouse models of MS, with a particular focus on models of progressive disease and on studies of the relative contribution of sex hormones/chromosomes to disease processes.

Effector T Cell Subsets

Upon recognition of cognate Ag in peripheral lymphoid tissue, T cells can differentiate into distinct effector subtypes that are dictated by the cytokine milieu present at the time of activation. T cell effector subsets are traditionally defined by master transcription factors (TFs) that drive each fate, as well as by their production of signature cytokines (51). The developmental cues, master TFs, and signature cytokines characteristic of the best-described $CD4^+$ T cell effector subtypes (Th1, Th2, Th17, Tfh, Treg) are depicted in Figure 1.

Th subsets play distinctive roles in physiologic and maladaptive immune responses. The classic Th1/Th2 paradigm, proposed over 40 years ago by Mosmann *et al.* (74), held that inflammatory $CD4^+$ Th1 cells induce cell-mediated immunity to intracellular pathogens, while Th2 cells promote humoral, antibody-mediated responses that are directed against extracellular invaders and that feature prominently in allergy/asthma. In the mid-2000s, the IL-17A-producing Th17 subset was discovered to be distinct from Th1 cells (49, 62). Both Th1 and Th17 cells drive cell-mediated immune responses: Th1 cells primarily attract macrophages to sites of infection/inflammation, while Th17 cells recruit neutrophils (106).

T follicular helper (Tfh) cells provide essential help to B cell responses by spurring the development of germinal centers while also providing essential cell/cell signals (28). T regulatory cells (Treg), which can arise both from central thymic selection and extrathymically, are characterized by their expression of the X-linked TF FoxP3 and they actively suppress inflammatory responses (77).

Th1, Th17, Tfh, and Treg have all been described as playing pivotal roles in CNS autoimmunity. In this review, we discuss the role of sex as a variable in the function of these subtypes. It is important to keep in mind, however, that the list of effector T cell subpopulations is continually expanding and that the search for novel populations is an active field of study. In addition, while we focus on $CD4^+$ T cells in this review, we note that a similar paradigm exists for $CD8^+$ (Tc) effector cells as well. In addition, it is now accepted that B cells also play an important role in MS pathogenesis, with B cell-depleting anti-CD20 therapeutic regimens being highly effective. Furthermore, as CD20 is not expressed on plasma B cells, it is probable that B cells in MS act *via* Ag-presentation or other functions not related to their ability to secrete antibody (109).

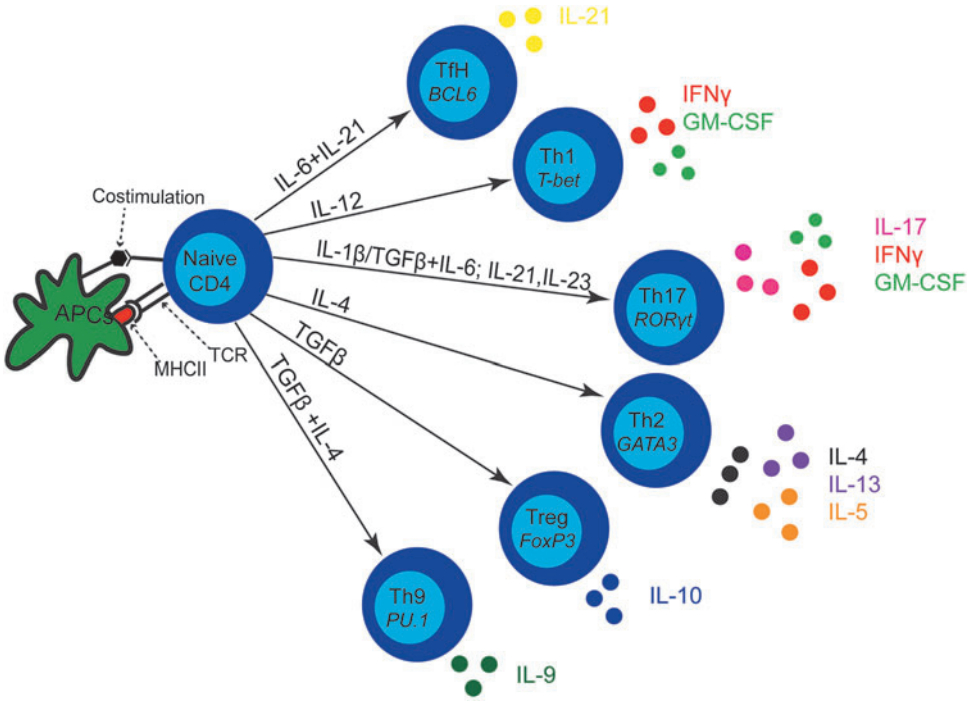

FIG. 1. Effector CD4$^+$ T cell (Th) subset development. The presence of soluble cytokine cues (shown above the *arrows*) is essential to the development of Th subsets upon activation of naive T cells. These differentiation factors drive the expression of master transcription factors (*italics*) that reinforce the specific Th phenotype. Each Th subset is further characterized by its production of signature cytokines. Th, T helper cell. Color images are available online.

Role of Sex in Regulating T Cell Effector Function

Sex-mediated effects on Th1

Sex-specific differences in T cell function have been an area of intense research interest. CD4$^+$ T cells express estrogen receptor (ER)α and ERβ (83) as well as the androgen receptor (65). Female murine T cells exhibit enhanced proliferative responses upon *ex vivo* rechallenge with an immunizing peptide (112); ER signaling appears crucial, as female CD4-*Cre*$\times$*ER*$\alpha^{fl/fl}$ CD4$^+$ T cells display defective proliferation in response to agonistic antibodies to CD3 and CD28 (72). Furthermore, in a human study, a greater proportion of lamina propria lymphocytes (LPL) from healthy women were positive for the proliferation marker Ki67 compared with LPL from healthy men (90).

Intriguingly, these studies also demonstrated that Th1 responses may be exacerbated in females (Fig. 2). Female mouse T cells showed upregulation of the Th1 signature cytokine interferon (IFN)γ upon Ag recall (112), while both peripheral CD4$^+$ and LPL from healthy women had increased expression of IFNγ and the Th1-associated chemokine RANTES relative to men (90). Estrogen contributes to Th1 skewing in females, as exogenous *in vivo* administration of 17-β-estradiol increases production of IFNγ from CD4$^+$ T cells in an ERα-dependent manner from two different mouse strains (67). Exogenous administration of estrogen in ovariectomized female mice also augments expression in T cells of the chemokine receptors CCR1–5 that are ligands for the Th1-associated chemokines RANTES and MIP1α; furthermore, estrogen sensitizes T cells to MIP1α-mediated downstream signaling (71). Curiously, while testosterone does not appear to directly inhibit IFNγ production from CD4$^+$ T cells, it does induce IL-10 production (65), which can inhibit Th1 responses, when exogenously applied to both male and female T cells.

Overall, the literature thus indicates that Th1 responses are increased in females and that female sex hormones contribute directly to this phenomenon. Nevertheless, at least one report has suggested that the Th1:Th2 ratio is increased in men rather than women (45). Furthermore, the role of estrogens in regulating Th1 cell function may be nuanced, as it was shown that estriols can induce a shift toward a Th2 cytokine profile

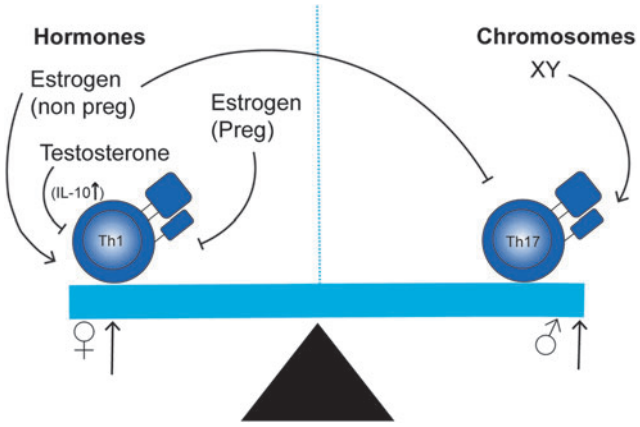

FIG. 2. Sex-linked factors that regulate Th1 and Th17 function. Estrogens can augment Th1 responses (67, 71), although they can also inhibit Th1 at concentrations similar to those observed at pregnancy (110). Testosterone can induce immunomodulatory IL-10 (65). Several reports indicate that Th17 responses are enhanced in males (50, 53, 56, 64, 99, 112). Estrogen can inhibit the capacity of Th17 cells to infiltrate the site of inflammation (5), while male XY exacerbates Th17 cell pathogenicity in an adoptive transfer model of EAE (35). EAE, experimental autoimmune encephalomyelitis; Th1, T helper 1; Th17, T helper 17. Color images are available online.

when exogenously administered to human T cells at concentrations similar to those seen during pregnancy (110).

Sex-mediated effects on Tfh and Treg

Tfh cells provide essential help to B cell responses. Choi and colleagues identified a molecular regulatory circuit that specifically controls their responses in females (59, 82). In the absence of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ, female, but not male, mice show a Tfh-dependent increase in autoimmune pathology. Female sex hormones synergize with PPARγ to effect this regulation, as concomitant treatment of male mice with exogenous estradiol, plus a PPARγ agonist, reduced Tfh frequency (82). Furthermore, aged female, but not male, ERα-knockout mice displayed an increased autoimmune phenotype characterized by elevated frequencies of Tfh and germinal center B cells (59).

Treg are considered critical in maintaining maternal tolerance to the allogeneic fetus (88). Thus, it is perhaps unsurprising that female sex hormones are important regulators of Treg frequency and function. ER and progesterone receptor are expressed on $CD4^+CD25^+$ Treg (7), and estradiol enhances the suppressive capacity of both mouse (75) and human (86) Treg. Interestingly, the presence of $FoxP3^+$ cells correlates with serum estradiol during the menstrual cycle of fertile women, peaking at the late follicular phase (9). On the contrary, male sex has been implicated in maintaining/promoting Treg function in specific contexts. Transient chemical castration of male subjects caused a reduction in circulating $CD4^+CD25^+$ frequency (79), while in a spontaneous colitis model characterized by severe pathology in females, Treg were impaired in female but not male animals (47). Strikingly, an elegant recent study from the group of Kallies (100) showed that $IL\text{-}10^+$ visceral adipose tissue (VAT) Treg are increased in male mice, and that the phenotype relies on an androgen receptor-driven regulatory circuit that promotes secretion of the VAT Treg growth factor IL-33 from stromal cells. Altogether, these findings suggest that while female sex hormones are important in promoting Treg function under physiologic conditions, male sex may also positively influence the function of these cells in pathology- or tissue-specific contexts.

Male sex may augment Th17 cell function

Intriguingly, a number of studies have reported that male sex increases the frequency and activation of Th17 cells (Fig. 2). The first reports came from models of autoimmune heart disease, in which T cells from male mice immunized with class II-restricted myosin heavy chain-alpha peptide showed enhanced IL-17 production upon Ag recall. Passive transfer of these reactivated male T cells resulted in an IL-17-dependent heart phenotype, as *in vivo* IL-17 blockade ameliorated disease in recipient animals (56). In coxsackievirus B3-induced myocarditis, male mice developed more severe pathology, and presented a higher frequency of Th17 cells in the spleen and heart compared with females (64). Furthermore, in collagen Ag-induced arthritis, exogenous estradiol reduced disease severity while inducing an accumulation of Th17 cells in peripheral lymph nodes as opposed to the inflamed joints (5).

In a human study, microarray analysis of T cells from healthy men and women showed that while numerous inflammatory Th1-related genes such as *IFNG* and *IL12RB* were upregulated in female cells, *IL17A* was strongly upregulated in male cells (50). In another study, restimulated $CD4^+$ T cells from healthy men showed enhanced expression of both IL-17A mRNA and protein relative to female cells; mechanistically, this effect was dependent on the nuclear receptor PPARγ1, as siRNA of PPARγ1 reduced IL-17A expression from male cells (112). These findings are further supported by those in the context of allergic rhinitis, in which Th17 cells are increased in the peripheral blood of men (99). Expression of the IL-17 receptor β-subunit on $CD4^+$ T cells from male children correlates with their serum expression of immunoglobulin E (IgE), a marker of severe allergic pathology; such a relationship was not observed in females (53). It must be noted that not every analysis of human samples has identified an association between male sex and Th17 frequency/activation: one study found that female peripheral and gut $CD4^+$ T cells had higher intrinsic IL-17 expression relative to male cells (90). However, on the balance, these findings indicate that male sex may be an important positive regulator of Th17 cells. Indeed, our group has also recently published (35) that male sex exacerbates Th17 cell-mediated pathology in a model of chronic progressive CNS autoimmunity (discussed in the 1C6-Th17 adoptive transfer section).

Sex As a Variable in Regulating MS Incidence and Severity

MS is subject to striking sex dichotomies [extensively reviewed in Refs. (37, 38, 102)]. It is well established that the incidence of MS is higher in women compared with men (37). Curiously, however, this sex bias in MS incidence is only manifested after puberty (38), suggesting a central role for sex hormones in regulating disease processes. Indeed, testosterone is potentially protective in MS: lower circulating testosterone has been found to be correlate with worsened disease outcome in MS-affected men (21), and in a phase II trial, exogenous testosterone was shown to halt, and possibly reverse, neurodegeneration in men with MS (61, 93). This argues for a model in which male sex hormones reduce MS disease burden, while female sex hormones increase it. However, it is additionally known that pregnancy, an event characterized by high circulating levels of estrogen, can have a suppressive effect on MS disease burden (102).

While relapsing MS incidence favors women, the sex balance in progressive MS is closer to 1:1. Male sex is a risk factor for poor MS outcomes such as reaching an Expanded Disability Status Scale score of 6—requiring a walking aid to walk for 100 m (30, 60). Brain atrophy is also higher in men with MS, and male sex is also predictive of cognitive difficulties in the context of MS (103). The contribution of biological sex to MS incidence and outcomes is thus complex. In the next section, we detail what is known about the role played by biological sex in experimental autoimmune encephalomyelitis (EAE) models of MS.

Sex As a Variable in Regulating MS-Like Disease in EAE

EAE is an umbrella term referring to multiple animal (typically rodent) models of CNS autoimmunity. EAE is considered

to recapitulate the immune aspects of MS pathogenesis, with paralytic/vision disturbances being most readily modeled [reviewed in greater detail in Rangachari and Kuchroo (87)]. EAE is classically induced by active immunization of susceptible mouse strains with encephalitogenic proteins/peptides that are frequently derived from myelin components or from other CNS cells such as neurons or astrocytes. Active immunization protocols initiate a T cell-driven response, although they may also be used to interrogate APC or B cell function. Adoptive transfer of activated, autologous, encephalitogenic T cell clones, or of activated transgenic T cells with Ag specificity to encephalitogenic epitopes, is another commonly used approach. The latter is particularly useful in isolating the contributions of effector T cells to immune pathogenesis, as the initial steps in T cell activation are bypassed.

EAE can be subject to striking sex-specific differences in a strain- and protocol-dependent manner. In this section, we review what is known about the role of sex in disease outcomes in these models (Fig. 3).

SJL/J models of EAE

Active immunization of SJL/J mice with proteolipid protein $(PLP)_{139–151}$ induces an RR form of EAE that is reminiscent of the disease seen in ~80% of MS patients from onset (69). RRMS is more common in women, and thus, it is intriguing that EAE on the SJL/J strain tends to be more severe in female mice. Active immunization of male SJL/J mice resulted in an acute monophasic disease course that was not followed by relapses as was the case in female mice (15). Adoptive transfer of female $PLP_{[139–151]}$-reactivated splenocytes induced EAE of increased severity relative to that caused by male cells, irrespective of the sex of the recipient animal (13). Furthermore, peptide-restimulated female splenocytes favored the production of IFNγ over immunomodulatory IL-10, while male cells showed the opposite tendency (14). Thus, sex differences in the T cell compartment were likely the source of worsened disease in female mice. In addition, several lines of evidence implicate testosterone as an ameliorative factor in SJL/J EAE. Gonadectomy of male SJL/J rendered them susceptible to severe active immunization EAE (16). Furthermore, exogenous testosterone reduced the ratio of IFNγ:IL-10 from female splenocytes (14) and *in vivo* administration of testosterone similarly reduced EAE severity and increased T cell-derived IL-10 in an MBP immunization model (29). Collectively, these findings indicated that female SJL/J are prone to worsened EAE, with their lower levels of testosterone being a potential factor.

The four-core genotype model as a tool to dissect the contribution of sex hormones *versus* sex chromosomes. The roles of androgens and estrogens/progesterone in autoimmunity have been extensively studied. However, sex-based

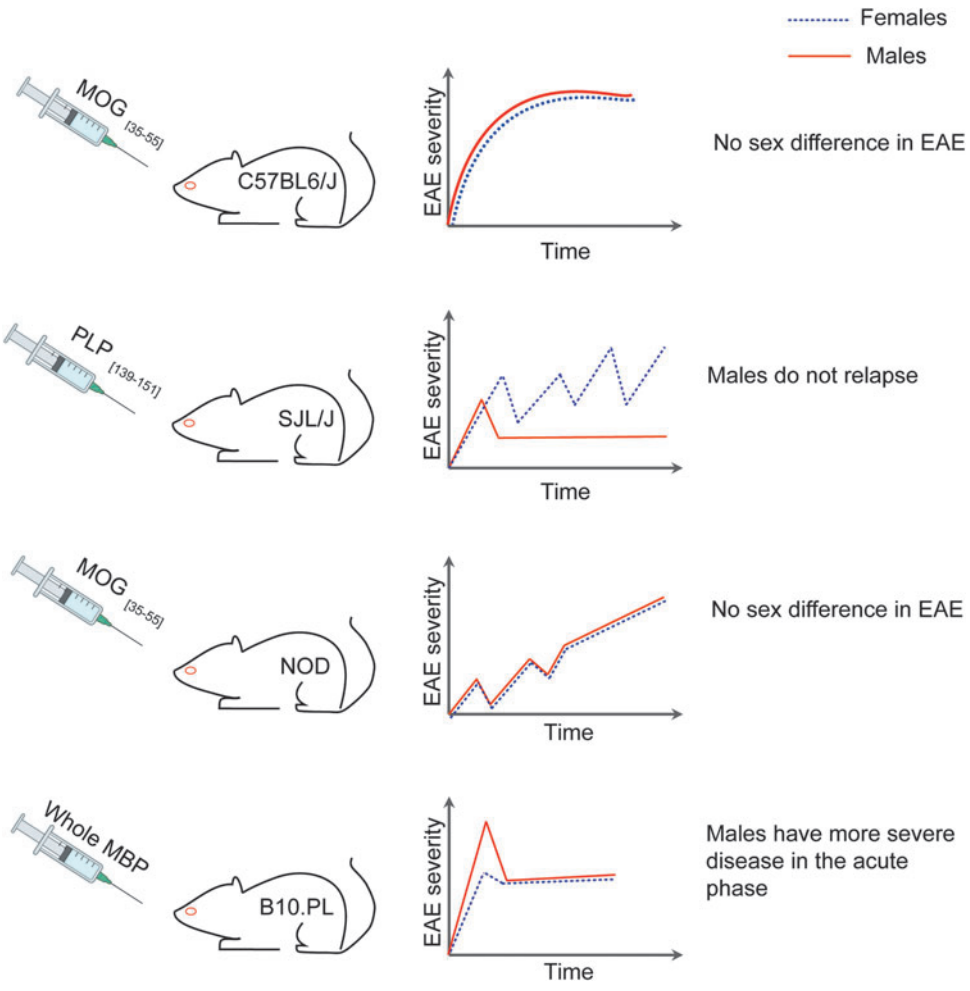

FIG. 3. Sex as a variable in commonly used models of active immunization EAE. In C57BL6/J mice, no sex differences are observed upon active immunization with $MOG_{[35–55]}$ (80). In SJL/J mice, females develop a relapsing/remitting pattern upon active immunization with $PLP_{[139–151]}$, while males show an acute nonremitting course with a lower overall disease burden (13, 15). $MOG_{[35–55]}$-immunized NOD mice display a relapse/chronic disease pattern with no sex differences observed (80). Male B10.PL mice develop EAE of greater severity in the acute phase when immunized with whole MBP (80). MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; NOD, nonobese diabetic; PLP, proteolipid protein. Color images are available online.

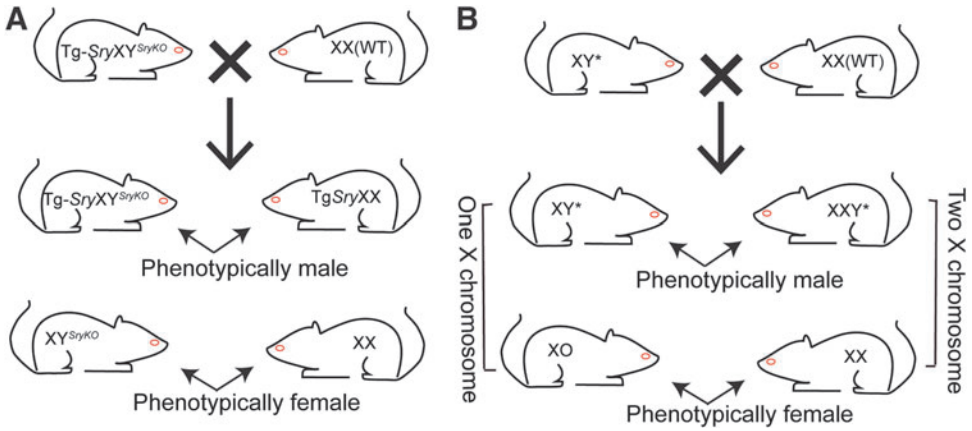

FIG. 4. Mouse models for dissecting the role of sex hormones and sex chromosomes and for studying X chromosome dosage. (A) FCG mouse model. The testes-determining gene *Sry* is knocked out of the Y chromosome (Y^{SryKO}) and is crossed to a transgenic strain that expresses Sry on autosomal chromosome 3 (Tg-*Sry*). Upon crossing phenotypically male Tg-*Sry*XY^{SryKO} with wild-type XX females, one can generate phenotypic males with XX and XY chromosomes and phenotypic females with XX and XY chromosomes. FCG mice allow one to separately interrogate the biological functions of sex chromosomes *versus* hormones. **(B)** XY* model. An aberrant Y chromosome rearrangement permits meiotic rearrangement of X and Y. Crossing XY* males to XX results in male mice with two X chromosomes (XXY*) and female mice with one X (XO), as well as males and females with one X apiece. This model permits one to study the effects of X chromosome dosage. FCG, four-core genotype. Color images are available online.

phenotypes may also arise from the contributions of sex chromosome complement (XX *vs.* XY). The elegant four-core genotype (FCG) mouse strain permits one to dissect the relative contributions of sex hormones and chromosomes to biological processes [reviewed in Arnold and Chen (8) and presented in Fig. 4]. FCG mice are double transgenics in which the testes-determining gene *Sry* is knocked out of the Y chromosome (Y^{SryKO}), but is ectopically expressed on chromosome 3 (Tg-*Sry*). In the presence of *Sry*, mammals are hormonally male; in its absence, they default to a female hormonal pathway. Thus, when hormonally and chromosomally male Tg-*Sry* XY^{SryKO} mice are crossed to XX females, the resultant progeny have one of four phenotypes: (i) hormonally and chromosomally male (Tg-*Sry* XY^{SryKO}), (ii) hormonally and chromosomally female (XX), (iii) hormonally male and chromosomally female (Tg-*Sry* XX), (iv) hormonally female and chromosomally male (XY^{SryKO}).

Use of the FCG model on the SJL/J background revealed unexpected roles for chromosomal factors in EAE outcomes. Upon active immunization, XX SJL/J mice developed disease of greater severity than XY^{SryKO} mice. Similarly, Tg-*Sry* XX developed more severe EAE than Tg-*Sry* XY^{SryKO}. Thus, worsened outcomes were associated with female sex chromosomes irrespective of the hormonal context. Adoptive transfer of XX T cells induced disease of greater severity than XY^{SryKO} T cells, indicating that these effects were localized in the T cell compartment (94).

Interestingly, by using bone marrow (BM) chimeric approaches on the FCG strain, Voskuhl and colleagues were able to show that the male SJL/J CNS was uniquely susceptible to injury during EAE, as XY^{SryKO} host mice developed EAE of greater severity relative to XX, regardless of whether XX or XY^{SryKO} BM was implanted (36). Importantly, both XY^{SryKO} and XX are hormonally female, leading them to conclude that the cause of increased disease susceptibility lay with male sex chromosomes. The phenotype was then linked to differential expression of TLR7 within the male and female CNS. It is probable that the increase in T cell inflammation in the XX immune system is dominant over the greater vulnerability of the XY^{SryKO} CNS to injury, thus explaining why intact female SJL/J develop more severe EAE relative to males upon adoptive transfer (94). The segregation of sex hormone and chromosome effects thus has deepened our understanding of pathology in this mouse strain.

Use of consomic strains to identify a role for Y chromosomal elements in EAE. When B10.S strain mice are intercrossed with SJL/J, the F2 progeny present a mixture of clinical courses upon active immunization with SJL/J spinal cord homogenate. These include acute progressive, relapse/remitting, and chronic nonremitting disease (22). By analyzing large cohorts of these F2 mice, Teuscher and colleagues were able to identify a number of autosomal genetic loci that can regulate disease outcomes in a sex-specific manner (22, 23). Next, they pinpointed a curious parent-of-origin (POO) effect through which EAE pathology was selectively reduced in F2 females whose sires and grandsires had an SJL/J-origin Y chromosome. This suggested that male genetic regulatory elements could have important effects on female descendants. Crossing XX C57BL6/J (B6) female mice with B6 males that carried consomic Y chromosome variants with known associations with autoimmune disease, they showed again that female progeny of these crosses had differential severity of EAE depending on the Y chromosome possessed by their sires (98). Young SJL/J males bearing a B10.S-derived Y chromosome showed increased EAE severity relative to age-matched SJL/J (95), and male B6 mice with an SJL/J-derived consomic Y chromosome showed reduced EAE burden relative to WT B6 (26), indicating that genes on the SJL/J Y can directly repress pathogenicity. This effect is potentially due to SJL/J expressing fewer copies of the *Sly* and *Rbmy* Y-linked multicopy genes (26). Thus, sex chromosomal factors may indeed collaborate with sex hormones to reduce EAE severity in SJL/J males.

B6 EAE

The $MOG_{[35–55]}$-dependent active immunization model on the B6 strain results in a relatively rapid (<30 days) disease course that can take an acute monophasic or stable chronic form, depending on the specific experimental parameters used (17). The B6 model is widely used, in part, because of its rapid disease course and also because of the wide array of genetically modified strains available on this background. However, there are no grossly observable differences in disease incidence or severity between male or female mice (80). Furthermore, disease development was similar between all four genotypes in FCG × B6 mice (94).

Nevertheless, careful analysis of specific immune marker genes has revealed sex-associated phenotypes in this model. In one study, deletion of the sodium channel Nav1.5 in astrocytes selectively worsened EAE in female but not male B6 mice, indicating that this molecule suppresses neuroinflammation in a sex-specific manner (81). Furthermore, the B6 model has been used to uncover important insights on the contribution of sex chromosomes to T cell function in EAE. For example, Voskuhl and colleagues found that the X chromosome ''silencing escape'' gene *Kdm6a* is expressed more highly in *in vitro*-activated XX B6 T cells compared with the XY^{SryKO} counterparts; conditional knockout of Kdm6a in T cells reduced the severity of EAE upon $MOG_{[35–55]}$ immunization (55).

The same group also found that five X-linked genes—*Msl3*, *Prps2*, *Hccs*, *Tmsb4x*, and *Tlr7*—were actually expressed more highly in XY^{SryKO} *versus* XX $CD4^+$ T cells (46). Next, they used the XY* genetic model (Fig. 4) to identify a POO imprinting effect that could explain upregulation of X genes in male T cells. In this model, the Y chromosome (Y*) has an aberrant chromosomal rearrangement that permits the meiotic recombination of X and Y, which is normally not possible. Mating of XY* to WT XX generates four genotypes at F1 that differ in X chromosome dosage: (i) XX females, (ii) XY* males, (iii) XY^{*X} (effectively XO) females, and (iv) XX^{Y*} males (1). The dam-derived X chromosome of XY^{*X} mice thus carries a maternal epigenetic imprint (X_mO). By subsequently crossing XY^{*X} to a wild-type XY male, one can obtain X^{Y*X} mice in which X comes from the sire and thus they bear a paternal imprint (XpO). Analysis of the loci of the five differentially expressed X-genes revealed that they were methylated to a greater degree in XpO, suggesting that paternal POO effects may account for differences in X-linked gene expression in T cells (46).

Together, these findings indicate the pertinence of studying the role of sex even when differences between males and females may not be immediately apparent: here, biological sex may regulate specific inflammatory/regulatory pathways that can influence disease severity in the B6 model.

Nonobese diabetic/ShiLtJ EAE

As their name suggests, nonobese diabetic (NOD) mice spontaneously develop T cell-dependent insulitis and pancreatic beta-cell destruction. They are additionally susceptible to developing other autoimmune diseases such as thyroiditis and EAE (40). When immunized with $MOG_{[35–55]}$, NOD-EAE mice may develop relapses and remissions followed by a chronic worsening phase in a disease course that is reminiscent of relapsing/progressive MS (11, 68). In addition to the spinal cord, inflammatory lesions in NOD-EAE are also observed in midbrain/hemispheric structures such as the dentate gyrus, fimbrium, and caudate putamen (31). This is important because other, less chronic, models of EAE have been criticized for implicating only the spinal cord and brain stem.

It should be noted that Baker *et al.* presented data in which they considered the disease pattern of individual $MOG_{[35–55]}$-immunized NOD mice monitored over 60 days. Only a subset of these mice showed a progressive pattern of phenotype (10). They argued that when viewing the mean disease curve of multiple NOD-EAE mice considered together, the appearance is created of a late-stage progressive course when in actuality it may be the result of an increased frequency of relapse in individual mice at these later time points. Indeed, using an adoptive T cell transfer model on the NOD genetic background, we ourselves have found that a little over half of the mice show a progressive course when their disease courses are considered individually, and about one-fifth show a progressive course preceded by at least one relapse. The remainder of mice present relapses only, or a stable disease course marked by neither distinct relapses nor progression (35). We regard this heterogeneity as advantageous, as it permits us to interrogate the factors and mechanisms that may either augment or diminish the incidence of a progressive course.

Sex is an important regulator of diabetes in NOD mice, as a higher incidence is seen in females (58). Sex steroids appear crucial, as orchiectomy of males increases the incidence of diabetes, while ovariectomy of females decreases it (41). By contrast, male and female $MOG_{[35–55]}$-immunized NOD mice develop EAE of similar incidence and severity (80). However, we have recently shown that effector $CD4^+$ T cells from $MOG_{[35–55]}$-specific T cell receptor (TcR) transgenic ''1C6'' mice on the NOD genetic background display a striking sex difference in EAE severity upon adoptive transfer. Male 1C6 Th17 induce severe chronic disease upon adoptive transfer to NOD.*Scid* recipients (35). These data, discussed in greater detail in the 1C6-Th17 adoptive transfer section, suggest that active immunization of NOD mice may mask cell-specific sex differences.

129.S1/SvImJ (SV.129) EAE: evidence for sex-specific regulation of T cells by PPARα

SV.129 mice are, like B6 mice, H-2^b-restricted, and similar to B6, show no overt differences in disease severity between males and females upon immunization with $MOG_{[35–55]}$. However, Dunn and Steinman observed that deficiency in the nuclear receptor PPARα increased disease severity in males and not females (39). This sex differential was T cell dependent, as immunization of male KO $CD4^+ \rightarrow Rag^{-/-}$ resulted in more severe disease than that seen in male WT $CD4^+ \rightarrow Rag^{-/-}$, while no differences between female KO $CD4^+ \rightarrow Rag^{-/-}$ and male WT $CD4^+ \rightarrow Rag^{-/-}$ were observed. Mechanistically, PPARα expression was greater in male $CD4^+$ and was dependent on the presence of androgen (39). In a follow-up study, it was then found that PPARα preferentially inhibited Th1 cell differentiation by male $CD4^+$ by limiting chromatin accessibility of the *Ifng* locus (111). These data add to the mounting evidence that the PPAR family of nuclear receptors may regulate effector T cell function in a sex-specific manner.

B10.PL EAE

B10.PL mice develop EAE upon immunization with MBP determinants. While immunization with the encephalitogenic MBP_{1-11} (Ac1-11) resulted in no gross differences in EAE incidence and severity between the sexes (12), males immunized with whole MBP developed disease in the acute phase that was much more severe than that seen in females (80). In the case of the former, while no sex difference was initially seen, immunized males, but not females, showed improved recovery when receiving a tolerizing oral dose of Ac-11 (12). In the case of the latter, gonadectomy of female mice increased their susceptibility to severe outcomes, suggesting that estrogen may be protective in this model (80). Another work on the B10.PL strain has shown that estrogen may have an important role in synergizing with vitamin D3 (itself an important protective factor in human MS) to reduce EAE severity specifically in female mice (96).

Virally mediated models of demyelination

Intracerebral inoculation of Theiler's murine encephalomyelitis virus (TMEV) leads to CNS demyelination. In SJL/J mice, TMEV inoculation causes greater disease severity in males (3). Another group showed that B6 males also presented greater susceptibility and disease severity upon TMEV inoculation. Intriguingly, gonadectomized males developed disease of even greater severity, although treatment of these mice with estrogen reduced disease severity by reducing Th1 responses (43). Thus, both testosterone and estrogen reduce symptomology in this model; the underlying propensity for severe disease in males may be linked to sex chromosomes, a possibility that remains to be explored.

Sex Differences in T Cell Transgenic Models of Progressive EAE

One critique of many EAE models is that they rarely feature the relapse/progressive disease course that is so common

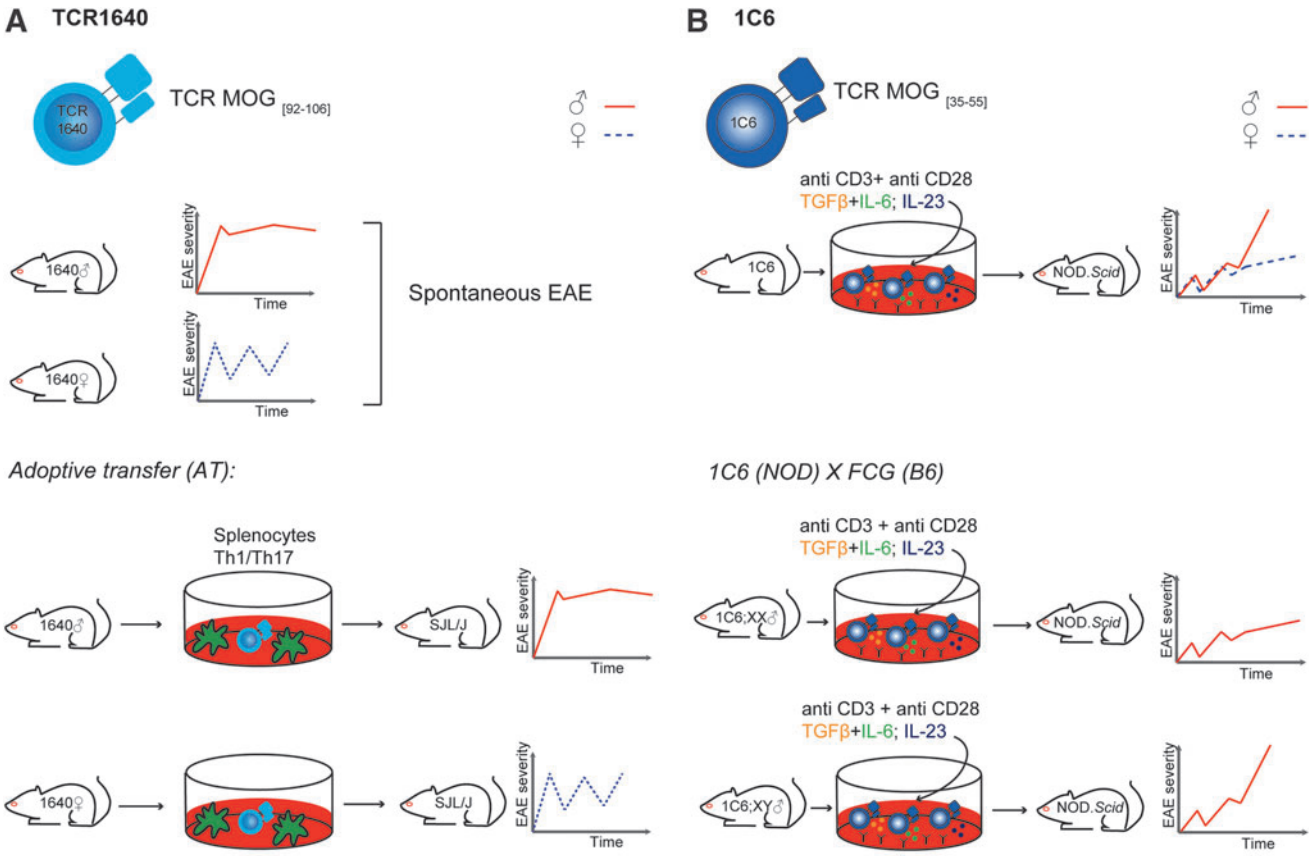

FIG. 5. TCR transgenic models of progressive EAE. (A) The TCR1640 transgenic TCR is on the SJL/J background and is directed against $MOG_{[92-106]}$. These mice develop spontaneous EAE that is characterized by a progressive course in males and an RR pattern in females (85). When splenocytes are isolated from presymptomatic TCR1640 mice, stimulated with anti-CD3 under mixed Th1/Th17 differentiation conditions, and transferred to SJL/J mice, the hosts show differences in disease pattern that are dictated by the sex of the transferred cells: recipients of stimulated male splenocytes develop progressive disease, while recipients of female cells show RR disease (34). **(B)** The 1C6 transgenic TCR is on the NOD background and is directed against $MOG_{[35-55]}$. When naive 1C6 $CD4^+$ T cells are differentiated under Th17 conditions and are transferred to NOD.*Scid* recipients, a sex-dependent difference in disease severity is observed by which mice receiving male Th17 develop worsened progressive EAE relative to those receiving female Th17. When FCG × 1C6 (B6 × NOD) F1 T cells were studied, it was found that Tg-*Sry* XY^{SryKO} (XY ♂) Th17 cells induced disease of greater severity than Tg-*Sry* XX (XX ♂) Th17 cells, indicating that male XY chromosomes contribute to Th17-driven progressive EAE (35). RR, relapsing/remitting; TCR, T cell receptor. Color images are available online.

in MS. Here, we describe two models that can help reveal the immune features of RR *versus* progressive CNS autoimmunity. Both exploit transgenic T cell specificities to myelin Ag, and notably, both present striking sex differences that are reminiscent of human pathology (Fig. 5).

TCR1640 mice

TCR1640 transgenic mice on the SJL/J background express an ectopic TcR directed against $MOG_{[92–106]}$ (85). These mice develop spontaneous EAE in the absence of an immunogen or adjuvant, with >85% of TCR1640 females developing RR disease, while >50% of males develop progressive disease (85). These differential outcomes are reminiscent of what is seen in humans, in which the RRMS incidence favors women, while men with MS are more likely to develop a progressive course. In a recent study, adoptive transfer approaches were used to show that sex differences in the TCR1640 strain were indeed driven by the sex of the T cells (34). When splenocytes from presymptomatic female TCR1640 mice were differentiated *in vitro* under mixed Th1/17 conditions and then transferred to SJL/J recipients, the resulting disease tended to take an RR course. By contrast, male TCR1640 splenocytes largely transferred progressive disease. These dichotomies were observed irrespective of the sex of the recipients. Annotated RNA-seq analysis indicated that transcripts associated with negative regulation of T cell immunity were upregulated in female TCR1640 cells. This suggested that in females such genes might repress the progressive phenotype induced by male cells, and implied that T cell activation pathways are essential to progressive disease.

1C6-Th17 adoptive transfer

1C6 transgenic mice bear a TcR specificity for $MOG_{[35–55]}$ on the NOD background. The transgenic TcR is derived from a class II-restricted $CD4^+$ T cell clone; however, it is expressed on both $CD4^+$ and $CD8^+$ T cells in these mice (4, 107). Thus, 1C6 mice represent a useful model to study myelin Ag-specific effector T cell responses in RR→progressive disease (54).

In a recent report (35), we found that adoptive transfer of *in vitro*-differentiated male 1C6 Th17 to lymphocyte-deficient NOD.*Scid* mice resulted in a severe, progressive EAE phenotype, with over half of recipients attaining ethical endpoints before the end of the 10-week (70 days) monitoring period. By contrast, recipients of female 1C6 Th17 developed milder disease. In agreement with Baker *et al.* (10), we found that not all mice developed a progressive course, thus highlighting the importance of considering individual disease patterns, and not just mean disease curves, in NOD-EAE. Overall, we noted that the number of relapses was higher in female cell recipients, while the rate of progressive incidence was greater in males. Importantly, sex mismatch experiments confirmed that male T cells induced aggressive disease, irrespective of the sex of the recipient.

Strikingly, splenic and CNS-infiltrating male Th17 from mice with rapid symptomology showed increased production of IFNγ, but not IL-17, relative to female T cells from mice sacrificed in parallel. While male 1C6 Th1 cells induced disease of greater severity compared with female Th1 cells, Th1-mediated disease rarely resulted in ethical endpoints being attained; furthermore, no differences in the frequency of progressive disease were observed between the sexes. Thus, while it is possible that IFNγ itself might play a contributing role in the extremely severe disease induced by male Th17 cells, it is additionally possible that it might mark a phenotype of Th17 functional plasticity that has been associated with worsened outcomes in autoimmune disease (2, 24, 97). Indeed, CNS-infiltrating male 1C6 Th17 cells from recipients that experienced poor outcomes tended to express higher amounts of TCF-1, a marker of Th17 plasticity (35). Interestingly, pathogenic Th17 cells have been characterized as positive for the Th1 transcription T-bet (105) as well as for the inflammatory cytokine granulocyte and macrophage colony stimulating factor (104). By contrast, nonpathogenic Th17 tend to secrete IL-10 (76). It has also been found that CNS-infiltrating pathogenic Th17 cells can injure neurons *via* their release of glutamate, suggesting that they may be directly cytotoxic (19). Going forward, it will be interesting to investigate whether sex can regulate this cytotoxic function of Th17 cells.

Strikingly, gonadectomy of male or female 1C6 mice did not appear to affect disease outcomes upon Th17 generation and adoptive transfer. This indicated that sex hormones might be secondary to sex chromosomes in mediating differences in EAE severity. Direct comparison of Tg-*Sry* XY^{SryKO} and Tg-*Sry* XX 1C6 Th17 on an NOD:B6 F1 background revealed that the former transferred disease of greater severity. In addition to confirming these findings in pure NOD-background mice, it will be interesting to also interrogate the phenotype of XY^{SryKO} *versus* XX 1C6 Th17, to observe whether the pathogenic effect of XY is also seen in the context of female sex hormones.

Jarid1c: a putative X-linked inhibitor of Th17 pathogenicity. A key finding of the above work is that the X-linked lysine demethylase Jarid1c/KDM5c (Fig. 6) can repress pathogenic Th17 responses (35). We identified Jarid1c by first analyzing a published data set of pathogenic (CNS-infiltrating) *versus* nonpathogenic (peripheral immune tissue) Th17 cells from B6-EAE (44). We searched for X-linked genes that were downregulated in pathogenic Th17, reasoning that these genes might repress disease caused by female cells. We next compared these differentially regulated X genes with a list of splenic mouse genes that escape second-copy silencing of the X chromosome (18). Of the three remaining transcripts of interest (*Jarid1c*, *Utp14a*, and *Pbdc1*), only Jarid1c was downregulated in male CNS-infiltrating 1C6 Th17 cells. Overexpression and pharmacological inhibition approaches revealed that Jarid1c reduces the severity of 1C6 Th17-mediated EAE. Importantly, we also found that Jarid1c was sharply reduced in $CD4^+$ T cells from sex-aggregated MS-affected individuals as opposed to healthy controls (35). Further comparing Jarid1c expression in $CD4^+$ T cells from men with MS and women with MS, we found it was downregulated in men with MS compared with women with MS (35).

Jarid1c is a member of the Kdm5 family of histone H3K4 demethylases that are recruited to both enhancer and promoter elements (89). Recent findings have linked the methylation state of lysines to the transcriptional state of genes (48, 89, 101). Jarid1c represses transcriptional activity at promoter sequences by removing methyl groups from permissive euchromatic H3K4me3 marks; in its absence, transcriptional activity is deregulated (78). We find that, in

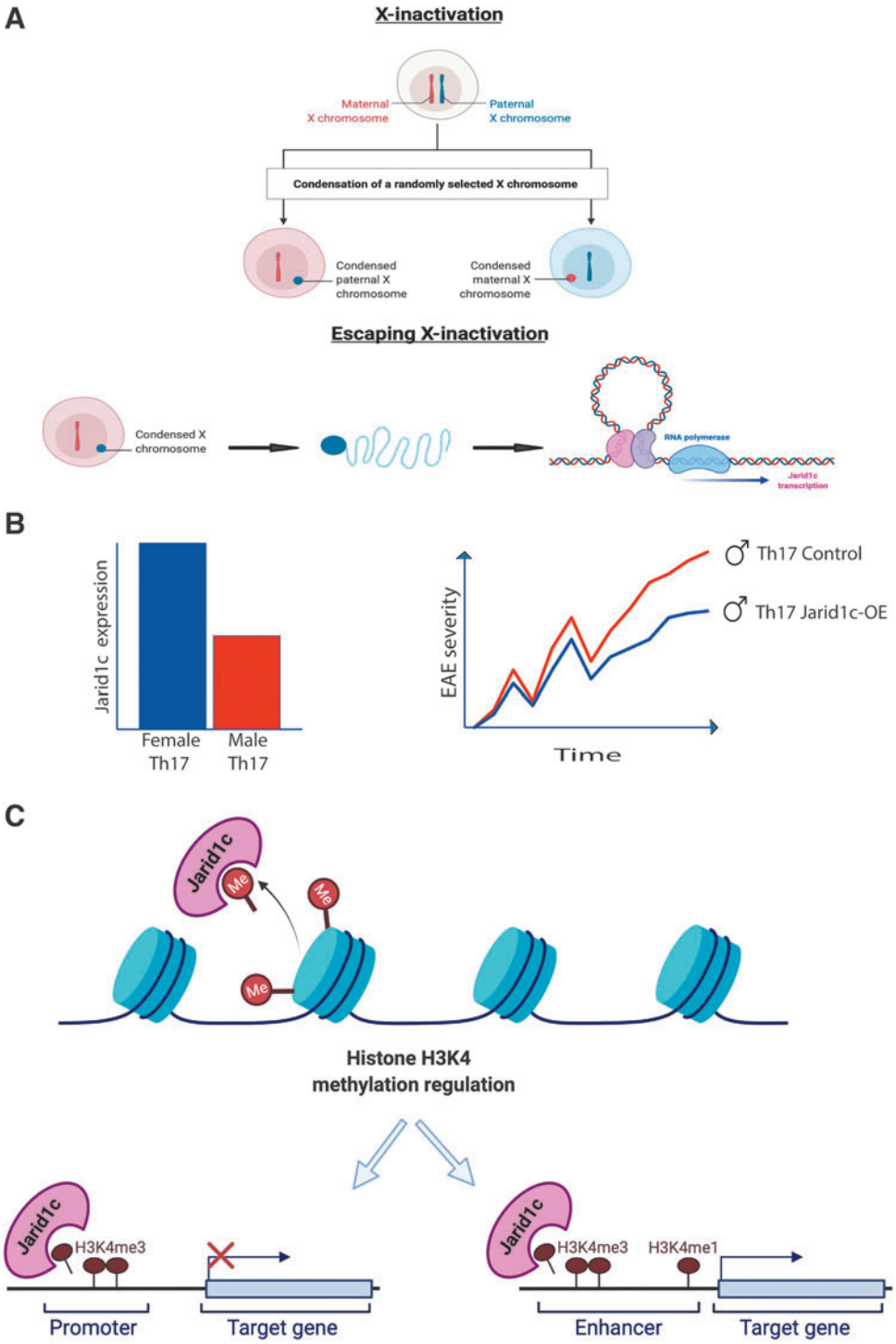

FIG. 6. Jarid1c an X-linked gene that can regulate Th17 cell pathogenicity. (A) Stochastic inactivation of either paternal or maternal X alleles in female cells ensures equivalent dosage of X genes between males and females. However, 15%–25% of all X genes escape second-copy inactivation in humans (25). Jarid1c is one of several X-linked genes to escape X chromosome inactivation in mouse spleen (18). **(B)** Jarid1c is downregulated in CNS-infiltrating male 1C6 Th17 cells and overexpression of Jarid1c cDNA in male Th17 reduces their pathogenicity in the 1C6 adoptive transfer model (35). **(C)** Jarid1c is an H3K4 demethylase that removes methyl (Me) groups from euchromatic H3K4me3. At promoter sites, Jarid1c can inhibit transcription by reducing the number of permissive H3K4me3 marks. At enhancer sites, however, it may promote gene expression by increasing the relative frequency of permissive H3K4me1 marks (78). CNS, central nervous system. Color images are available online.

addition to reducing the pathogenicity of male Th17 cells, overexpression of Jarid1c reduces their expression of IFNγ (35). It is thus tempting to speculate that Jarid1c could be recruited to the promoter region of the IFNγ gene to inhibit its transcription. Alternately, it may target upstream regulators of IFNγ such as T-bet or Stat1. However, recent findings indicate that the roles played by Jarid1c in transcriptional regulation may be more nuanced than previously suggested. For example, it can further repress gene transcription by complexing with the adaptor molecules SUV39H1 and DDB1 to actually augment repressive heterochromatic H3K9me3 marks (89). Interestingly, Jarid1c may augment gene expression by reducing the frequency of H3K4me3 relative to that of the permissive H3K4me1 marks that predominate at gene enhancer sites (78). Therefore, the precise mechanisms by which Jarid1c regulates transcription in phenotypically plastic Th17 cells remain to be elucidated.

More generally, the role of Jarid1c in immune function is recently starting to come into focus. In dendritic cells (DCs), Jarid1c associates with the transcriptional repressor PCGF6 to enforce a quiescent state. Knockdown of Jarid1c enhanced the expression of activation markers such as MHC class II,

CD80, and IL-12p40 in both baseline and activated DCs (20). These data, together with ours, could suggest that Jarid1c may act as a broad-scale repressor of inflammatory immune responses. However, more work is required to better understand the molecular basis for Jarid1c-mediated inhibition of pathogenic Th17 responses.

Future Perspectives

In an era of precision/personalized medicine, biological sex is a critical factor to consider, and it is one of the best recognized variables to affect MS incidence and outcomes. Remarkably, however, it has received limited consideration as a factor that can influence responses to MS therapy. Indeed, the majority of phase III clinical trials in MS either do not conduct baseline analyses of the role of sex, or lack sufficient power to sensitively detect sex differences (52). $CD4^+$ T cells play critical roles in MS pathogenesis, and as discussed here, many of their functions are regulated in a sex-specific manner and could pave the way for new treatment approaches. For example, one could envisage strategies that target Th1-specific cell surface receptors, such as CD226 (32), in women, or Th17-specific receptors, such as CCR4 or CCR6 (6), in men. Thus, going forward, increased appreciation of the role of sex in pathogenic T cell responses may help us to design more effective individualized treatment modalities for MS-affected individuals.

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Authors' Contributions

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Abbreviations Used

Ag = antigen
APC = antigen-presenting cell
B6 = C57BL6/J
BBB = blood/brain barrier
BM = bone marrow
CCR = C-C chemokine receptor
CD = cluster of differentiation
CNS = central nervous system
DC = dendritic cell
DDB1 = DNA damage-binding protein 1
DMT = disease-modifying therapy/therapies
EAE = experimental autoimmune encephalomyelitis
ER = estrogen receptor
FCG = four-core genotype
FoxP3 = forkhead box P3
IFN = interferon
IL = interleukin
Jarid = Jumonji AT-rich activating domain
LPL = lamina propria lymphocytes
MBP = myelin basic protein
MHC = major histocompatibility complex
MIP = macrophage inflammatory protein
MOG = myelin oligodendrocyte glycoprotein
MS = multiple sclerosis
NOD = nonobese diabetic
PLP = proteolipid protein
POO = parent-of-origin
PPAR = peroxisome proliferator-activated receptor
Rag = recombination-activating gene
RANTES = regulated on activation, normal T cell expressed and secreted
RR = relapsing/remitting
Scid = severe combined immunodeficiency
siRNA = short interfering ribonucleic acid
SJL = Swiss James Lambert
Sry = sex-determining region Y
SUV39H1 = suppressor of variegation 3–9 homologue 1
SV.129 = 129.S1/SvImJ
Tc = cytotoxic T cell
TcR = T cell receptor
TFs = transcription factors
Tfh = T follicular helper
Tg = transgenic
Th = T helper cell
Th1 = T helper 1
Th2 = T helper 2
Th17 = T helper 17
TLR = Toll-like receptor
TMEV = Theiler's murine encephalomyelitis virus
Treg = T regulatory cells
VAT = visceral adipose tissue
X_m = maternal X
Xp = paternal X