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Review

The X chromosome and the sex ratio of autoimmunity

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ABSTRACT

The number of human conditions that are currently considered to be autoimmune diseases (AID) has been steadily growing over the past decades and it is now estimated that over 10 million people are affected in the United States. One of the major shared features among AID is the predominance in the female sex which in some cases changes with the age at disease diagnosis. Numerous hypotheses have been formulated based on intuitive scientific backgrounds to justify this sex imbalance, i.e. sex hormones and reproductive factors, fetal microchimerism, other sex-related environmental factors, a skewing of the X-chromosome inactivation patterns, and major defects in sex chromosomes. Nevertheless, none of these hypotheses has thus far gathered enough convincing evidence and in most cases data are conflicting, as well illustrated by the reports on fetal microchimerism in systemic sclerosis or primary biliary cirrhosis. The present article will critically discuss the main hypotheses (loss of mosaicism, reactivation, and haploinsufficiency) that have been proposed based on findings in female patients with specific AID along with two additional mechanisms (X-chromosome vulnerability and X-linked polyamine genes) that have been observed in AID models. Further, recent data have significantly shifted the paradigm of X chromosome inactivation by demonstrating that a large number of genes can variably escape silencing on one or both chromosomes. As a result we may hypothesize that more than one mechanism may contribute to the female susceptibility to tolerance breakdown while the possibility that unknown factors may indeed protect men from AID should not be overlooked.

Contents

1. Of women and autoimmunity

Autoimmune diseases (AID) include a wide range of clinical phenotypes collected in over 70 different disorders which are believed to affect over 5% of the world population and account for a significant part of the health care expenditures [1]. In general terms, AID can be distinguished by the wide variability of tissue-specificity or systemic involvement, age of onset, serum autoantibodies, and response to

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immunosuppressive treatments [2,3]. Nevertheless, similarities are considered to outnumber differences in AID and the one feature that is shared by the vast majority of these conditions is the uneven distribution between sexes. This predominance of AID in the female sex accounts for over 80% of patients being women in most autoimmune diseases, as illustrated in Table 1 [4,5]. Even though the female predisposition to AID has been known for over a century, the causes of this sex imbalance remain unknown and several different hypotheses have been proposed in the last few years. A susceptible genetic background is considered to be necessary but appears insufficient to explain both AID onset and the female predominance, while several environmental factors have been suggested as additional players in tolerance breakdown [6]. The proposed factors include sex hormones, fetal microchimerism, sex-specific environmental factors, reproductive history, a skewed X-chromosome inactivation pattern, and major defects of the sex chromosomes. However, none of these hypotheses has thus far gathered enough convincing data, and in most cases reports are conflicting or burdened by technical limitations [7]. It is our opinion, indeed, that one or more mechanisms should account for the female susceptibility to AID but that the same mechanisms are likely to be shared by numerous conditions, thus militating against most proposed factors which failed to be recapitulated in different clinical settings. This is the case for sex hormones, sex-related environmental factors, and fetal microchimerism which will be briefly discussed.

The effect of sex hormones on AID onset and perpetuation was first suggested by their immunomodulatory effects. In particular, the reported role of estrogens in lymphocyte maturation/activation and the synthesis of antibodies and cytokines [8–10] raised great interest. Further, estrogen receptor (ER) ligands modulate both the innate and adaptive immune responses, alter antigen presenting cell (APC) quantitatively and qualitatively both *in vivo* and *in vitro*, and regulate dendritic cell (DC) differentiation [11]. When these observations were used as the background to determine the sex hormone profile of women with AID and controls, results were disappointing with differences failing to reach statistical significance or being inconsistent. As an example of this unresolved dichotomy, we could note that specific AID arise at different ages and reproductive phases (albeit in most cases following menopause) [12,13] while the higher estrogen levels characterizing pregnancy are often associated with an amelioration of several autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) [14–16].

Specific environmental factors manifest different probability of exposure in men and women. This is the case, for example, of the xenobiotics found in cosmetic products such as hair dye or nail polish, both of which have been associated with specific AID.

Similarly, urinary tract infections are more common in women and bacteria associated with this type of infection have been proposed as ideal candidates but a causative relation could not be proven possibly due to the long latency between the infection and the AID onset. In the case of primary biliary cirrhosis (PBC) these factors have been suggested, among others, by epidemiological and experimental studies [17–20] but, despite the most recent xenobiotic-induced murine models [7,21], a mechanistic relation can only be hypothesized. Dendritic cells, for examples, are activated by components of hair dyes [22] while phtalate (phthalate) included in nail polish may trigger an SLE-like autoantibody response [23,24]. Finally, a role of sex chromosomes in AID has been proposed based on several mechanisms including fetal microchimerism, X chromosome inactivation patterns, and X-chromosome monosomy and duplication. Fetal microchimerism was first suggested based on the observation that most AID manifest their peak of incidence following the fertile period and maternal and fetal cells are exchanged during pregnancy, leading to fetal cell persistence (i.e. microchimerism) in the mother. Chimeric fetal cells are often hematopoietic and can differentiate into somatic cells in multiple organs, potentially acting as targets for autoimmunity and resembling graft versus-host disease after stem-cell transplantation. Microchimeric cells were first detected in peripheral blood mononuclear cells from patients with systemic sclerosis [25], but other authors have failed to reproduce these findings in the same disease [26] or in PBC [27]. Cumulatively, available data on the role of fetal microchimerism in autoimmunity are weak or inconclusive, as naturally acquired fetal and maternal microchimerism is not uncommon in healthy women [28]. Nevertheless, we note that the concept of chimerism has witnessed a significant evolution over the past years to overcome the simple persistence of fetal cells [29] and now includes more complex and multigenerational chimerisms found in AID [30] such as type 1 diabetes mellitus (T1DM) [31], rheumatoid arthritis [32], and autoimmune thyroid disease [33] or in prototypic female-predominant types of cancer [34]. The proposed role for changes in the X chromosome that may trigger or predispose to autoimmunity will be discussed in further details.

Table 1
Female to male ratio reported for autoimmune diseases. Diseases in which a male predominance is observed are italicized.

Autoimmune disease	Female:male ratio
Addison's disease [1–5]	0.8–2.4
Antiphospholipid antibody syndrome [1–4]	5
Autoimmune chronic hepatitis [4–19]	7
Giant cell arteritis [1–5]	2.5
Graves' disease [33]	7
Hashimoto's disease [33]	5–18
Idiopathic thrombocytopenic purpura [1–5]	3
Multiple sclerosis [73]	2
Myasthenia gravis [1–4]	3
Myositis [1–5]	2
Pernicious anemia [1–5]	2
Primary biliary cirrhosis [90]	10
Primary sclerosing cholangitis [1–19]	*0.6*
Rheumatoid arthritis [30]	2
Sjogren's syndrome [1–5]	9
Systemic lupus erythematosus [73]	9
Systemic sclerosis [3–26]	5
Type 1 diabetes [4–31]	*0.8–1.2*

2. Of X chromosomes and women

The female karyotype includes two X chromosomes, one derived from each parent, while men carry one maternal X and one paternal Y chromosome. To avoid double dosage of X chromosome-derived proteins in females, one of the X chromosomes is randomly silenced during X chromosome inactivation (XCI), which occurs in the early stages of female embryogenesis. Only X-chromosome pseudoautosomal regions (i.e. those with a corresponding allele on the Y chromosome) were thought to escape inactivation and the classical view of this whole chromosome silencing through DNA methylation has been recently challenged and will be discussed in details below. In the classical vision, however, the XCI process results in female cellular mosaicism: in a female, approximately half of the cells express genes derived from the maternal X chromosome and the other half express genes derived from the paternal X chromosome (ratio close to 50:50 when XCI is random) [35]. The X chromosome has numerous genes which, directly or indirectly, are involved in immunity, and naturally occurring variations in one gene copy might result in two distinct alleles with different regulatory and response capacities. For females, this means additional physiological diversity: not only do heterozygous females avoid the effects of deleterious gene-mutations, they also benefit from added diversity when facing new immune challenges, such as microbial infections [36–38]. Thus, deleterious or disadvantageous mutations that occur in an X chromosome-linked gene will result in the functional loss of the protein in all cells in a male, but in only half of cells in a female. However, severe skewing, defined as

an XCI pattern deviation from the 50:50 ratio, may occur and are not pathologic *per se*. The most common technique used to analyzed XCI patterns is genotyping of a highly polymorphic CAG repeat in the human androgen receptor (AR) gene. *Hpa II* and *Hha I* enzyme restriction sites, located <100 bp from this polymorphic short tandem repeat, are methylated on the inactive X chromosome and non-methylated on the active X chromosome. Polymerase chain reaction (PCR) amplification across this region permits the distinguishing of 2 amplicons with different sizes, corresponding to maternal and paternal X alleles. After enzyme digestion, PCR amplification is possible only for the methylated (uncut) X-chromosome. Densitometric analysis of the 2 alleles indicates the inactivation status of 1 allele compared with the other and reveals the percentage of XCI skewing. A skewed result is defined as one allele being inactivated at >75% while extreme skewing represents an inactivation of >90% [39]. In the general population skewed XCI is sometimes observed, but extreme skewing is rare while being associated with a subgroup of patients with juvenile idiopathic arthritis [40]. Of note, XCI skewing increases significantly in the blood cells of females from the neonatal period to old age and XCI skewing is three-times more frequent at older ages compared to birth [41].

Whether sex hormones during reproductive life (i.e. prepuberty, puberty, and adults before and after menopause) or immunomodulating treatments commonly used in AID may also have an impact on XCI skewing remains to be determined despite the available negative evidence [40,42,43].

As previously mentioned, the new data on additional players such as small, noncoding RNA (snRNA) and on DNA methylation profiling recently undermined the classical dogma of X-chromosome inactivation. DNA methylation remains the most studied phenomenon of gene silencing and X-chromosome inactivation but it has been reported that, in a counterintuitive fashion [44], the inactive chromosome manifests the lower degree of DNA methylation [45], somehow in conflict with the previous data on X inactivation and reversing the established relationship between overall methylation and expression potential as such enhanced methylation is concentrated in the gene body, rather than the promoter [45]. Furthermore, it has been shown that 10–15% of X-linked genes variably escapes silencing and are expressed from both X chromosomes in a proportion of healthy women [46]. Taken altogether, these findings have radically changed our understanding of the biology of X chromosomes and allow specific genes to achieve double or a null expression in physiological conditions [7].

3. Of X chromosomes and female advantages

In general terms, females have a longevity advantage compared to males, and this is true for several mammalian species, including humans [47]. Additionally, the outcome and survival rates from numerous diseases are significantly better for women [48,49]. The X chromosome is partly responsible for the altered responsiveness of the female immune system [35] constituting an immunological advantage. The numerous clinical observations supporting this advantage are now paralleled by theoretical and mathematical models, which confirm that throughout evolution, males have acquired lower immune responsiveness than females [50,51]. This is well illustrated by the superior capacity of women to produce serum antibodies and IgM following stimuli [52,53]. Furthermore, the enhanced susceptibility of males to infections is manifest since birth: male newborns are more prone to septicemia and meningitis, and have higher incidence rates of tuberculosis [54] or more severe infections caused by bacteria or viruses, such as respiratory infections caused by parainfluenza virus and respiratory syncytial virus, as well as those caused by bacteria such as *Staphylococcus* spp., *Escherichia coli*, *Legionella pneumophila* and *Campylobacter* spp. [53,55–58].

From an evolutionary standpoint it is quite intuitive that the presence of one X chromosome represents a significant disadvantage for mammalian males, as every newly arisen recessive mutation on the X chromosome will be phenotypically expressed [35], as well illustrated by X-linked diseases [59]. In these conditions, the immune system can be impaired at different levels encompassing innate and adaptive immunity key functions such as infectious agents phagocytosis or lymphocyte differentiation based on the absence or dysfunction of immune cells or impaired cytokine-mediated signaling [60–62].

4. Of X chromosomes and the onset of autoimmunity

Some hypotheses have been suggested to explain why X chromosome inactivation skewing or other X chromosome-associated abnormalities that will be discussed later may contribute to disturbances in self recognition and ultimately to tolerance breakdown and AID. These hypotheses include the loss of mosaicism, the reactivation and the haploinsufficiency based on findings in female patients with specific autoimmune disorders (an illustration of these mechanisms is provided in Fig. 1). Nevertheless, the same AID may recognize signs of all or possibly none of the proposed mechanisms in subgroups of patients. This suggests that these mechanisms are not universal and that the same disease may manifest different pathogenetic mechanisms.

4.1. Loss of mosaicism

The loss of mosaicism hypothesis states that disturbances in random XCI may result in autoimmunity [63–65], as first proposed by Kast [64] and later developed by Stewart [65] and Ozcelik [63]. Women with random mosaicism possess two populations of dendritic cells (DCs) that express either maternal or paternal X-linked self antigens for thymic negative selection, and potentially autoreactive thymocytes are negatively selected by both DC populations. Conversely, a woman with severe XCI skewing will have, for example, the preferential inactivation of the paternal X chromosome. In this case, T cells will be only tolerized by DCs expressing maternal X-linked self antigens and autoreactive T cells specific for paternal X chromosome self antigens will escape negative selection and enter the periphery [65]. This hypothesis was supported first by the report of nonspecific, polyclonal T cell activation in several female patients with SLE [66]. In this scenario, self antigens encoded by the X chromosome may prime the non-tolerized X-reactive T cells, and these T cells may thus activate B cells presenting the same endogenous X-chromosome self antigen [65,67]. It is well established that SLE disease activity is associated with polyclonal B cell activation and, according to this model, the 'polyreactive' T cells are each specifically reactive to a particular B cell-derived X-chromosome-associated self antigen [65]. Autoimmune thyroid diseases (AITD) and systemic sclerosis (SSc) are also associated with a high degree of XCI skewing despite the fact that the AR gene was used to determine the XCI pattern thus limiting the value of this observation [68–71]. Conversely, patients with Sjögren's syndrome and PBC do not have X chromosome inactivation skewing in blood cells, indicating that this is not a common characteristic of all autoimmune diseases [63,72]. Moreover, even if skewed inactivation pattern is a common feature of women affected by autoimmune diseases, it does not necessarily lead to autoimmunity in all women, as XCI patterns in peripheral lymphocytes from women with SLE, multiple sclerosis, or RA are similar to age-matched healthy women [73]. A second line of evidence to support this hypothesis is provided by the observation that men with a XXY karyotype (i.e. Klinefelter's syndrome) have a 14-fold higher risk of developing SLE than XY men [74]. In this case, it has been suggested that one of the X chromosomes of XXY men is subject to inactivation, and evidence shows that XCI skewing is a common characteristic of Klinefelter's syndrome, thus ultimately leading to disease onset [65].

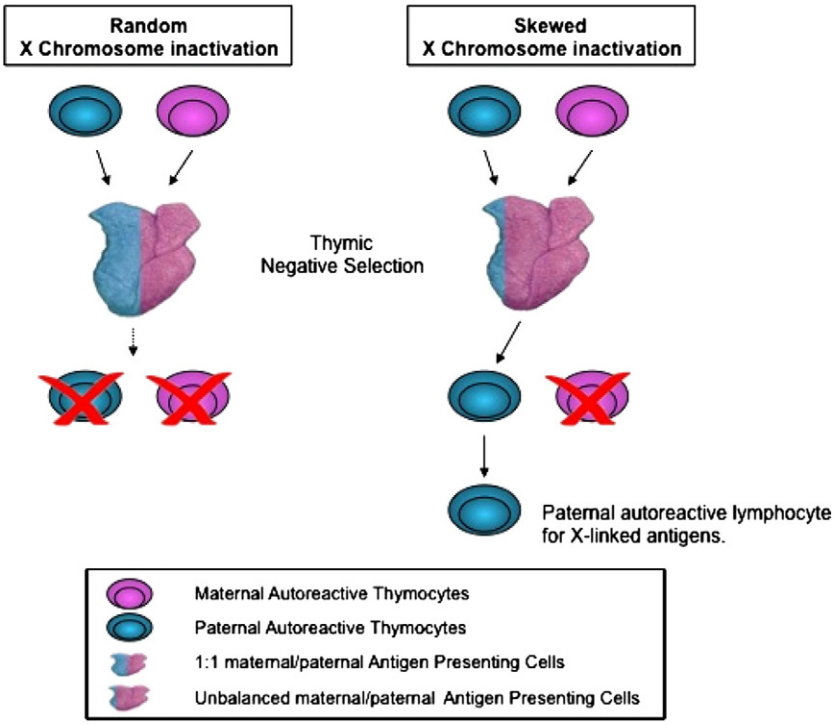

Fig. 1. A schematic view of the loss of mosaicism hypothesis. The extreme skewing of X chromosome inactivation (represented on the right) causes the breakdown of self tolerance in the thymus and the persistence of autoreactive lymphocytes for X-linked antigens.

4.2. Reactivation

According to this second hypothesis, the reactivation of genes from the inactive X chromosome may contribute to autoimmunity [75]. The mechanisms leading to inactive X chromosome reactivation remain enigmatic but this could lead to overexpression of X-linked genes involved in immune functions, which in turn would be responsible for overproduction of autoantibodies [76] or tolerance breakdown, as in the case of FoxP3 [77]. Alternatively, overexpression of X-linked genes could disrupt the equilibrium in the mechanism of fine-tuning protein expression and generate protein aggregates that would trigger responses against self antigens [78]. Reactivation of CD40L on the inactive X chromosome has been found in T cells of female patients with SLE [76,79] and its methylation appears to play a major role in determining the serum polyclonal hyper-IgM characterizing PBC [80]. It was proposed that regulatory sequences on the inactive X chromosome would be demethylated in T cells from these patients, resulting in CD40L overexpression [76]. Indeed, CD4+ T cells from female patients with SLE express two-fold higher CD40L than males, and these CD40L overexpressing CD4+ T cells stimulate an increased IgG production by autologous B cells correlating with SLE disease activity [79]. Similar gene dosage effects may be the consequence of other changes not resulting in the reactivation of methylated X-linked genes. The duplication of the Tlr7 gene is associated with an SLE-like disease in mice [81] while XX female mice are more susceptible to pristane-induced SLE and experimental autoimmune encephalomyelitis as a model of multiple sclerosis than XYSry-female mice (with an inserted Sry transgene) [82]. Female mice had identical gonadal and hormonal background, which suggests that double dosage of the X chromosome may itself confer susceptibility to autoimmunity.

4.3. Haploinsufficiency

A third hypothesis states that haploinsufficiency for X-linked genes results in AID development [83,84], as first suggested by the observation that patients with X chromosome monosomy (loss of one X chromosome; X0 karyotype), such as those with Turner's syndrome, commonly manifest immune changes [85]. Turner's syndrome is characterized by the absence of all or part of one of the X chromosomes, and women with this syndrome have, for example, an increased risk of developing AITD and inflammatory bowel diseases [86,87]. The haploinsufficiency of genes located in the pseudoautosomal region (PAR) 1 of sex chromosomes has been proposed to contribute to the defects observed in Turner's syndrome [88] and these genes, present in two copies in both XX females and XY males, are only present in one copy in X0 females, and this may be functionally insufficient. PAR 1 contains 26 genes and, although some have been associated with the mental retardation observed in Turner's syndrome, only few are involved in immune functions. Women with isochromosome-Xq are also more prone to developing AITD and inflammatory bowel diseases, also suggesting that an imbalanced expression of genes from the short arm of the X chromosome may be a predisposing factor for developing these disorders [86]. More recently, AID with a female predominance and a late-age onset such as PBC, SSc, and AITD were reported to be characterized by a higher X chromosome monosomy rate in peripheral B and T cells, suggesting again that haploinsufficiency for X-linked genes may be a crucial factor [83,89,90]. The mechanism behind loss of one X chromosome from these cells is not known but appears to increase with age, a phenomenon commonly observed in healthy women. It has been proposed that a gradually acquired haploinsufficiency for specific X chromosome-linked genes (from PAR or genes that permanently escape inactivation in normal females) in peripheral B and T cells could be responsible for the generation of autoantibodies [89]. Despite these theories, few genes contained in the X chromosome have been specifically associated with one or more AID. However, it is unlikely that mutations or different methylation in a single gene would be responsible for the higher susceptibility of females to autoimmunity, as recently illustrated in female twins with PBC [91]. In this study the X chromosome genes variably escaping inactivation were compared in terms of expression and methylation between

Table 2
X chromosome abnormalities reported in autoimmune diseases including systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD), primary biliary cirrhosis (PBC), and systemic sclerosis (SSc).

Site		Clinical phenotype	References
Xp22.33	Xp22.33;Yp11.2 translocation causing triplication of genes	Severe SLE	[115]
Xq26	Demethylation of CD40LG on the Xi in T cells in women, leading to over-expression of CD40LG in CD4+ T cells.	SLE	[76]
X, AR gene	Skewed X chromosome inactivation	AITD, SSc	[68,69]
X, 4 sites	Random X chromosome inactivation	PBC	[116]
Xp11.23	Mutated JM2 fork head-related protein	X-linked autoimmunity-allergic dysregulation syndrome	[117]
X, specific site not identified	Chromosomal abnormalities in peripheral blood cells. Half of MS abnormalities were X-related.	Multiple sclerosis	[118]
Xp21.2	Various defects in cytochrome B β subunit and carriers of X-linked chronic granulomatous disease	SLE-like symptoms in some female carriers and some male patients with X-CGD.	[108,119]
X, duplication	Higher incidence of lupus in males with Klinefelter's syndrome (XXY)	SLE	[120]
X, monosomy	Higher frequency in peripheral T and B cells from female patients	PBC, SSc, AITD	[84,90,109]

monozygotic twin sisters discordant for the disease and data suggested that CLIC2 and PIN4 may be associated with the disease through epigenetic mechanisms.

4.4. Epigenetics and polyamines

Numerous AID, including SLE and RA, are characterized by an abnormal methylation pattern of their lymphocyte DNA [44]. As a final topic for our discussion, we will touch on a hypothesis that relates loss of X-linked dosage compensation to the alterations in methylation observed in AID [92] and, more specifically, the elevated levels of polyamines. Polyamines are ubiquitous small flexible cations that are essential for cell growth and proliferation [93,94]. The charge distribution and length of polyamines give them the potential for unique interactions, such as connecting anionic points in intramolecular and intermolecular complexes. Their putative functions and interactions include the histone acetylation [95], the maintenance of the blood–brain and blood–nerve barrier permeability [96], the modulation of ion channels [97], the modulation of nuclear receptor interactions, such as increasing the affinity of estrogen receptor for DNA [98] [99], DNA repair [100], and stabilizing Z-DNA [101]. Because of the importance of polyamines, the synthesis and recycling of polyamines are tightly controlled processes, particularly for spermidine and spermine, and their precursor, putrescine. A hypothesis has been proposed that explains some autoimmune diseases as occurring due to loss of dosage compensation of X-linked polyamine genes at Xp22.1, which impact intracellular methylation [102] with unpredictable effects. The two genes of interest are spermine synthase (SMS), an enzyme involved in synthesizing spermine from spermidine; and spermidine/spermine-N1-acetyltransferase (SAT1), an enzyme involved in recycling spermine and spermidine. Overexpression of SMS would lead to increased levels of spermine, particularly when unbound spermidine is available, as under cellular stress conditions (ex. UV light or viral activity). Over-expression of SAT1 increases recycling of polyamines. Increased polyamine synthesis uses decarboxylated S-adenosylmethionine (dcSAM), created from S-adenosylmethionine (SAM) by SAMDC. The resulting decrease in SAM, the cell methyl donor, would ultimately affect the methylation of DNA in the nucleus thus fitting in the proposed model for AID [103–105].

5. The unifying hypothesis of X chromosome vulnerability

The vulnerability of the X chromosome may constitute the missing link to unite all previously discussed hypotheses for AID sex predominance which are summarized in Table 2. As mentioned, dosage compensation is the fundamental purpose of XCI and its loss may be restricted to a few genes at the abnormality site or be more extensive [92]. First, one SLE case was observed in an XX man who had an Xp22.33;Yp11.2 translocation that resulted in duplication of PAR1 genes and a partial trisomy of some genes, most interestingly, the translocation included the genes for the alpha subunit of the interleukin-3 receptor (IL-3 being a growth factor for proliferation and differentiation of hematopoietic stem cells) and CD99 (a transmembrane protein involved in adhesion and apoptosis of T cells) [106]. Second, a gene dose effect could also be mediated by XCI-escaping genes that will have a variable degree of expression in women [107], as discussed for PBC [91]. Third, a different hint at the vulnerability of the X chromosome is gathered from X-linked chronic granulomatous disease (X-CGD), an X-linked recessive disease affecting phagocytes that impairs the capacity to generate superoxide anions that are converted to hydroxyl radicals, hydrogen peroxide, and other radicals. These oxidants are crucial to counteract and destroy infectious agents (particularly bacteria) ingested by phagocytes and patients are thus immunocompromised and prone to bacterial infections. The disease is associated with the cytochrome B β subunit gene (CYBB) mapping at Xp21.2; which explains why only men are affected. Of relevance to the present discussion, there are numerous reports of SLE-like symptoms in X-CGD patients and mothers who carry the X-CGD mutation [108]. This observation may suggest that Xp21.2 mutations may trigger the overexpression of genes from that region [92]. Fourth, we submit that the enhanced X chromosome monosomy observed in women with late-onset AID also supports our hypothesis. The later observation that such a phenomenon was not common to a prototypic disease for early-onset such as SLE [109] appears to confirm that the high replication rate of lymphocytes may accumulate transcription errors over the years thus favoring tolerance breakdown if the X chromosome is affected [110].

6. Final remarks and future developments

Why women? Following efforts in sex hormones and other female-limited factors, the past decade has provided numerous lines of evidence to potentially explain the female predominance of autoimmune diseases. While we must acknowledge that the current clinical epidemiology providing the known sex ratios illustrated in Table 1 may be burdened by various flaws that include disease awareness and other types of physician-related bias (possibly including socioeconomic factors in mainly private health care systems). As an example, while we recognize that the female to male ratio is significantly higher for identified PBC

cases compared to the prevalence of the highly specific autoantibody [6] we should also note that physicians are biased toward diagnoses that are more pertinent to a specific sex, as in the case of coronary heart disease in men [111]. Accordingly, we are in need of true population-based epidemiology to determine the sex ratio in incident cases and not only in tertiary care centers in which one sex could be under-represented, as well represented by the variable ratios observed for type 1 diabetes in different age groups and geographical areas [112]. Similarly, we are convinced that only a multidisciplinary approach ranging from epigenetics [113] to the growing area of microRNA [114], from next-generation genomics to exone sequencing, from serum autoantibodies to clinical phenotyping with appropriate classification criteria will provide solid answers to what is perhaps a more appropriate question such as: why not men?

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