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Autoimmune disease and gender: Plausible mechanisms for the female predominance of autoimmunity

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ABSTRACT

A large number of autoimmune diseases (ADs) are more prevalent in women. The more frequent the AD and the later it appears, the more women are affected. Many ideas mainly based on hormonal and genetic factors that influence the autoimmune systems of females and males differently, have been proposed to explain this predominance. These hypotheses have gained credence mostly because many of these diseases appear or fluctuate when there are hormonal changes such as in late adolescence and pregnancy. Differences in X chromosome characteristics between men and women with an AD have led researchers to think that the genetic background of this group of diseases also relates to the genetic determinants of gender. These hormonal changes as well as the genetic factors that could explain why women are more prone to develop ADs are herein reviewed.

1. Introduction

Almost 5% of the world population develops an AD. Of this 5% approximately 78% are women [1] and it is considered the fourth leading cause of disability for them [2]. Women are at 2.7 times greater risk of acquiring an AD than men [3]. The rate between women and men in the most prevalent AD may vary from 9:1 in systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD) and Sjögren's syndrome (SS) to 3:1 in rheumatoid arthritis (RA) and multiple sclerosis (MS) [4–7]. Also, female gender appears to be a risk factor for polyautoimmunity (i.e., more than one AD coexisting in a single patient) [8]. Women tend to have a different age at onset and different disease activity than men. Onset in women is generally observed in the reproductive ages and coincides with the moment when the hormone levels begin to rise. Two good examples are MS and SLE in which women have an early onset. In contrast, men have a late onset which is associated with an increased prevalence of complications. A few disorders like spondyloarthropathies are more common in men [2]. This supports the idea that woman are more prepared evolution-wise to pay the immunological price for the reproductive benefit than men. Fig. 1 depicts the mechanisms that have been proposed to explain the susceptibility of women to ADs, and which will be addressed in this review.

2. Hormones and immune system

Generally, women have a stronger humoral and cellular immune response compared to men. They show a higher CD4:CD8 ratio because of a higher absolute CD4 cell count and a higher level of circulating antibodies [9]. Compared to men, they have more rapid rejection of allograft and reduced incidence and regression of tumors [10].

Estrogens, androgens and prolactin are hormones that have been studied for increasing susceptibility to ADs and can affect both innate and adaptive immune systems [2,11,12]. Estrogens seem to direct the immune system to T-helper 2 (Th2) lymphocyte dominance with the consequence of more B cell activation and antibody production [13]. In contrast, androgen favors the development of a T-helper 1 (Th1) response and CD8+ cell activation [14,15]. Prolactin appears to stimulate both cell and humoral-based immunity [16]. For this modulation of the immune system to be possible, these hormones have to be able to bind to receptors expressed by immune cells. B cells have been shown to express both androgen and estrogen receptors. In murine models, CD8 cells have been shown to express estrogen receptors along with monocytes, neutrophils and natural killer cells [5,17,18]. Other studies suggest that sex hormones like estrogen can regulate

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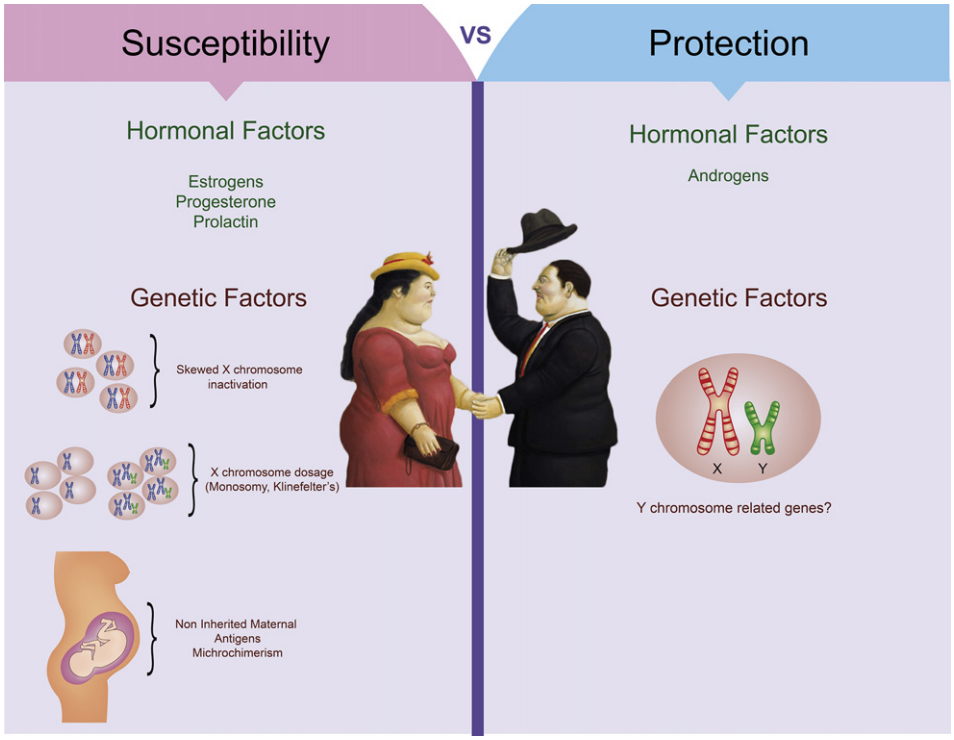

Fig. 1. Gender related factors influencing the development of autoimmune diseases (ADs). Main factors explaining the higher prevalence of several ADs in women include hormonal factors, since estrogens and prolactin are immune stimulants while androgens are immune suppressors. Genetic factors include: 1.) Skewed X chromosome inactivation, a potential mechanism whereby X-linked self-antigens may escape presentation in the thymus or peripheral sites that are involved in tolerance induction; 2.) X chromosome dosage: a) X monosomy: through the generation of autoreactive T cells that are not exposed to self-antigens encoded by one of the two X chromosomes, and b) Klinefelter's syndrome: incidence of SLE is higher in XXY males; 3.) Non-inherited maternal antigens (NIMAs) acting as modulators of the immune repertoire; 4.) Microchimerism: microchimeric cells might be targeted as foreign cells they could be implicated in the pathogenesis of ADs and 5.) Although genetic protective associations of genes in the Y chromosome have not been found in humans, rodent models suggest that unexplored regions or genes in the Y chromosome may play a role in the protection of men to the most relevant ADs.

antigen presentation by macrophages and dendritic cells through production of transforming growth factor beta [19,20].

3. Hormones and autoimmune diseases

3.1. Systemic lupus erythematosus

SLE has a significant predominance in women. It tends to worsen during pregnancy and to remit after menopause. This suggests that sex hormones are crucial for SLE regulation [21,22]. Estrogen and prolactin act as immune-stimulators by affecting maturation and selection of autoreactive B cells and autoantibody secretion [23,24]. About 22–33% of SLE patients have mild to severe hyperprolactinemia [25]. Gutierrez et al. showed that unstimulated peripheral blood monocytes in SLE patients produce more prolactin than they do in healthy patients [26]. Prolactin leads to the production of interferon-gamma which is an important mediator in lupus nephritis [27]. Bromocriptine, an inhibitor of prolactin secretion, has shown beneficial effects in both murines and humans [28]. An imbalance between hormone relationships can result in lower immune-suppressive androgens and higher immuno-enhancing estrogens. Women with SLE tend to have lower androgen levels than healthy women [29]. Likewise, men with the disease have elevated serum levels of 16-hydroxyestrone and estrone causing an imbalance between these hormones. Some of them have hypoandrogenism, low levels of testosterone and elevated levels of luteinizing hormone [22,30]. Testosterone is thought to suppress anti-double stranded DNA antibody production [22].

3.2. Sjögren's syndrome

This disease is also one of the most prevalent ADs among women. Verheul et al. studied the effect of gender hormone predominance by doing a gonadectomy on the non-obese diabetic (NOD) mouse, an accepted SS model [31]. This caused a worsening of the disease but the use of additional estrogen doses did not change the outcome of the disease. This may suggest a stronger protective effect on the part of androgens than a vulnerability because of estrogens [22,31]. SS primarily affects women during the fourth and fifth decades of life, with a woman:man ratio of 9:1 [32]. In men SS is uncommon. Since there are few reports on the clinical and immunological differences of SS, each one of them with small sample sizes, we wanted to combine the results of those reports in order to find differences between males and females with statistical significance.

Publications were identified through a systematic search done by two independent experts in Pubmed using the [Mesh] terms "Sjögren's syndrome" and "men". The only limit applied was "title". Descriptive statistics were used to define the subject's characteristics. Categorical variables were compared using the chi^2 test. Results under $p = 0.05$ were considered as statistically significant. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable, with a confidence interval (CI) of 95%.

According to all the cases published so far (Tables 1 and 2) women with SS have more anti-Ro antibodies and Raynaud's phenomenon than men. Conversely, men with SS are at higher risk for lymphoma and neurological involvement than women. Accordingly, male gender should be considered as a new risk factor for lymphoma development in patients with SS [33,34].

Table 1
Systematic review of the clinical and immunological manifestations observed in patients with SS.

	Molina et al. [35]		Anaya et al. [36]		Drosos et al. [37]		Cervera et al. [38]		Horvath et al. [39]		Gondran et al. [40]	
Country	USA		USA		Greece		Spain		Hungary		France	
Sex	$M = 36$	$F = 69$	$M = 13$	$F = 26$	$M = 12$	$F = 30$	$M = 19$	$F = 204$	$M = 60$	$F = 432$	$M = 42$	$F = 377$
Age at onset	50	NA	39	39.5	45.3	46.4	55	53	55.6	56.1	56.9	53.3
FM: Sicca *N* (%)	NA	NA	5 (38.5)	19 (73)	9 (75)	23 (77)	NA	NA	NA	NA	NA	NA
FM: Parotiditis *N* (%)	NA	NA	3 (23)	3 (11.5)	2 (17)	4 (13)	NA	NA	NA	NA	NA	NA
FM: EGM *N* (%)	NA	NA	5 (38.5)	4 (15.4)	1 (8)	3 (10)	NA	NA	NA	NA	NA	NA
RF N (%)	8 (22)	35 (51)	8/11 (72.7)	12/20 (60)	8 (67)	16 (53)	5 (31)	89 (46)	16 (27)	102 (24)	22 (52)	161 (43)
ANAS *N* (%)	19 (53)	38 (55)	11 (84.6)	19/24 (79)	4 (33)	23 (77)	13 (68)	139 (69)	22 (37)	272 (63)	32 (76)	28.3 (76)
Anti Ro *N* (%)	7 (19)	31 (45)	8 (61.5)	16 (61.5)	2 (17)	19 (63)	3 (16)	73 (37)	45 (75)	345 (80)	21 (50)	172 (46)
Anti La *N* (%)	2 (6)	14 (20)	6 (46.1)	8/23 (34.8)	1 (8)	11 (37)	3 (16)	44 (23)	31 (52)	214 (49)	14 (33)	114 (31)
Articular Involvement *N* (%)	17 (47)	25 (36)	7 (53.8)	13 (50)	1 (8)	14 (47)	4 (21)	93 (46)	41 (68)	181 (42)	16 (38)	186 (49)
Muscular involvement *N* (%)	NA	NA	NA	NA	NA	NA	NA	NA	5 (8)	29 (7)	4 (10)	59 (16)
Lymphopenia *N* (%)	NA	NA	5 (38.5)	4 (15.4)	NA	NA	NA	NA	NA	NA	3 (8)	68 (26)
Lymphoma *N* (%)	NA	NA	2 (15.4)	2 (7.7)	NA	NA	NA	NA	2 (3)	10 (2)	4 (9.5)	13 (3.45)
Raynaud's Phenomenon *N* (%)	NA	NA	3 (23)	5 (19.2)	1 (8)	3 (10)	0	28 (14)	4 (7)	134 (30)	12 (29)	160 (42)
Neurological *N* (%)	19 (53)	27 (39)	3 (23)	4 (15.4)	NA	NA	2 (11)	18 (9)	NA	NA	11 (26)	82 (21)
Pulmonary *N* (%)	NA	NA	1 (7.7)	6 (23)	0	1 (3)	3 (16)	16 (8)	0	10 (2)	8 (19)	62 (16)
Vasculitis *N* (%)	9 (25)	23 (33)	NA	NA	NA	NA	0	25 (12)	9 (15)	104 (24)	NA	NA
Renal *N* (%)	NA	NA	1 (7.7)	1 (3.8)	NA	NA	NA	NA	3 (5)	19 (4)	NA	NA

M: male; F: female; FM: first manifestation; RF: rheumatoid factor; EGM: extraglandular manifestation; ANAS: anti-nuclear antibodies; NA: not available.

3.3. Rheumatoid arthritis

Similar hormone imbalances in RA have been shown in many studies. Synovial fluid levels of estrogens relative to androgens are significantly elevated in both male and female RA patients and have activation effects on macrophage and fibroblast proliferation [41,42]. The treatment with tumor necrosis factor-α (TNF-α) blockers affects hormone levels in the synovial fluid before affecting the serum levels and seems to block the conversion from androgens to estrogens induced by aromatase [43,44].

Active RA is characterized by an activity peak early in the morning and correlated with prolactin plasma levels observed at that time [45]. A decreased amount of serum androgens has also been associated with disease susceptibility [46]. Men with the disease show low serum levels of testosterone as well as dehydroepiandrosterone [47]. This data is consistent with the hypothesis that androgens are anti-inflammatory hormones [48].

3.4. Systemic sclerosis (SSc)

This disorder is a polymorphic and heterogenic systemic disorder with inflammation, fibrosis and vascular damage. It has a 3:1 woman to man ratio [49,50]. Shi-Wne et al. showed that estrogens could induce fibroblast dysfunction in SSc and the female predisposition to the disease [51]. Straub et al. demonstrated that the association between high prolactin and low DHEA serum levels was an important factor for increased SSc severity [52].

3.5. Multiple sclerosis

Evidence indicates that gender affects the susceptibility and course of MS with a higher prevalence and better prognosis in woman than men. The improvement in the disease during late pregnancy has also been linked to hormonal changes. The disease itself can affect the levels of sex steroids by damaging hypothalamic regions and causing dysfunction of the hypothalamo–pituitary–gonadal axis [53]. In MS patients, prolactin secretion could rise [54]. Meanwhile, male MS patients may have low testosterone levels and higher estradiol levels and these findings are associated with a greater degree of brain tissue damage [55]. Table 3 summarizes hormonal influences and clinical findings in ADs.

3.6. Pregnancy

Pregnancy results in changes in disease activity for some of the autoimmune disorders. Signs and symptoms of MS and RA lessen during pregnancy and postpartum may be associated with disease exacerbation. Meanwhile, SLE is often exacerbated during pregnancy [62] and disease activity is associated with a worse fetal outcome [63,64].

Pregnancy may induce changes in the maternal immune system in order to protect the fetus. A shift from the prevailing Th1 response to a type Th2 could be seen and attributed to an increased progesterone level [65,66]. Also, pregnant women have enhanced immunoglobulin production and an increased production of autoantibodies [10,67].

A worse pregnancy outcome has been found in SLE patients, with glomerulonephritis being the main disease manifestation threatening both maternal and fetal health [63,68]. Imbasciati et al. showed that normocomplementemia and low dose aspirin therapy during pregnancy were independent predictors of a favorable fetal outcome. Experts support the idea that pregnancy can start only if the disease is inactive and close monitoring must be done [69].

Table 2
Meta-analysis of clinical and immunological manifestations in male patients with SS as compared with female patients.

	Men[a]	Women[a]	*N*	Chi	*P* value	OR	95% CI
Age at onset (Years, Mean ± SD)	50.3 ± 7	49.6 ± 6.7					
FM:Sicca	14 (56)	42 (75)	56/81	2.92	0.08	0.42	(0.14–1.28)
FM:Parotiditis	5 (20)	7 (12.5)	12/81	0.77	0.38	1.75	(0.42–7.19)
FM:EGM	6 (24)	7 (12.5)	13/81	1.71	0.19	2.21	(0.56–8.66)
RF	67 (36)	415 (36.4)	482/1320	0.01	0.92	1.02	(0.72–1.42)
ANAS	101 (55.5)	519 (45.6)	620/1320	6.16	0.013	1.49	(1.07–2.06)
Anti Ro	86 (47.3)	656 (57.6)	742/1320	6.88	0.0086	0.66	(0.48–0.91)
Anti La	57 (31.3)	405 (35.5)	462/1320	1.26	0.26	0.83	(0.58–1.17)
Articular involvement	86 (47.2)	512 (44.9)	598/1320	0.32	0.56	1.10	(0.79–1.52)
Muscular involvement	9 (8.8)	88 (10.8)	97/911	0.40	0.52	0.79	(0.36–1.69)
Lymphopenia	8 (14.5)	72 (17.8)	80/458	0.37	0.54	0.78	(0.33–1.81)
Lymphoma	8 (6.9)	25 (2.9)	33/950	4.73	0.029	2.42	(0.98–5.81)
Raynaud's Phenomenon	20 (13.6)	330 (30.8)	350/1215	18.47	0.00001	0.36	(0.21–0.59)
Neurological	35 (31.8)	131 (19.3)	166/786	8.79	0.003	1.94	(1.21–3.10)
Pulmonary	12 (8.2)	95 (8.8)	107/1215	0.07	0.78	0.92	(0.47–1.77)
Vasculitis	18 (15.6)	152 (21.5)	170/820	2.10	0.14	0.68	(0.38–1.18)
Renal	4 (5.4)	20 (4.3)	24/531	0.18	0.67	1.27	(0.36–4.09)

FM: first manifestation; EGM: extraglandular manifestation; ANAS: anti-nuclear antibodies; RF: rheumatoid factor; OR: odds ratio; CI: confidence interval.
[a] Data correspond to numbers (percentage) except if indicated otherwise.

The improvement of MS and RA during pregnancy may be linked to the transition from Th1 response to a Th2 state. Postpartum worsening may be associated with the return to the Th1 environment [10]. After pregnancy, a flare may be induced in RA by breastfeeding through the actions of prolactin [70]. Several studies have confirmed the spontaneous improvement of RA during pregnancy and an increased risk of flare after delivery. The decreased RA activity during pregnancy may well be the net result of complex pregnancy-related hormonal and immunological alterations. In fact, the increased levels of cortisol, estrogen and vitamin D have been implicated in lowering the pro-inflammatory cytokines, interleukin-12 and TNF-α, during pregnancy. This improvement in symptoms occurs predominantly in the third trimester when estrogen and progesterone are at their peak [64,71]. Pregnancy does not appear to cause disease deterioration in patients with SSc [2,64]. Table 4 addresses the effects of pregnancy in patients with different ADs.

3.7. Other hormonal influences

Changes in the disease severity during menses, menopause and hormonal contraceptive use are also described. In young patients, an early age at menarche has been associated with doubling the risk of SLE and RA [73,74]. Also the worsening of symptoms in RA, SLE and MS has been reported prior to the onset of menses [74,75]. In older women, RA has a high incidence at menopause [77] while onset of SLE is less common in postmenopausal women [10,78]. The use of oral contraceptives in MS is associated with a decrease in disease incidence [6,79]. In SLE, their use is associated with disease exacerbation [80] and the safety of estrogens in lupus

Table 3
Hormonal influences and clinical findings in autoimmune diseases.

Autoimmune disease	Estrogen	Androgens	Prolactin
SLE	Affects maturation and selection of autoreactive B cells [56]. Increases autoantibody secretion [23,24]. Men have elevated serum levels of 16-hydroxyestrone and estrone [22,30].	Testosterone suppresses anti-ds-DNA antibody production [22]. Women tend to have lower androgen levels than healthy women [29]. Men tend to have hypoandrogenism, low levels of testosterone and elevated levels of luteinizing hormone [22,30].	Affects maturation and selection of autoreactive B cells [23,24,56]. Prolactin leads to the production of interferon-gamma [27]. 22–33% of patients have mild to severe hyperprolactinemia [25]. Unstimulated peripheral blood monocytes produce more prolactin than the ones in healthy patients [26].
SS	Ovariectomy in mice leads to a condition mimicking the disease [57], and aromatase deficient mice, which do not synthesize estrogen, develop a destructive infiltration of B-lymphocytes in the salivary gland, resembling the human syndrome [58]. Women who had surgery for breast cancer, and were treated with aromatase inhibitors for total estrogen depletion, tend to develop sicca syndrome with elevated titers of antinuclear antibodies [56,59].	More protective effect of androgens than vulnerability because of estrogens in murine models [22,31].	Levels are significantly higher than controls. Levels did not correlate with disease duration, autoantibody levels, or focal score in biopsies, but did correlate with the score of internal organ disease [26,56,60,61]
RA	Activating effects on macrophage and fibroblast proliferation. Synovial fluid levels of estrogens relative to androgens are significantly elevated in both male and female patients [41,42].	Men show low serum levels of testosterone as well as dehydroepiandrosterone [47].	Activity early in the morning correlated with levels of the hormone at that time [45].
SSc	May Induce fibroblast dysfunction [51].		High prolactin related to increased severity [52].
MS		Affected men show low testosterone levels and higher estradiol levels [55].	Secretion may be increased [54].

SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, RA: rheumatoid arthritis, SSc: systemic sclerosis, MS: multiple sclerosis.

Table 4
Autoimmune diseases and pregnancy.

Systemic lupus erythematosus	Rheumatoid arthritis	Multiple sclerosis	Systemic sclerosis	Sjögren's syndrome
Often exacerbates during pregnancy [62]. Disease activity has been associated with a worse pregnancy outcome[63]. Glomerulonephritis is the main concern.	Often improves during pregnancy, especially in the third trimester when estrogen and progesterone are at their peak [10,70]. Flares may be induced by breastfeeding through the action of prolactin [70].	Often Improves during pregnancy, especially in the third trimester when estrogen and progesterone are at their peak [10,70].	Pregnancy does not appear to cause disease deterioration [2].	Although pregnancy seems to have a low impact on disease, there is risk for the offspring to present neonatal SLE [72].

SLE: systemic lupus erythematosus.

erythematosus national assessment (SELENA) study shows that hormone replacement therapy with estrogens can induce mild exacerbations [81].

4. Genetic factors

It is well known that females and males are different in their basic immune response with most of the evidence gathered from work done on rodents [4]. Female rodents have a more vigorous response after immunization than males and produce higher levels of antibodies and activated T lymphocytes. In the case of humans, it has not been possible to duplicate these results with most investigations yielding conflicting conclusions [4,82]. However, women are known to have higher levels of circulating antibodies, absolute counts of CD4+ T lymphocytes and higher production of cytokines and antibodies in response to infection [18,76,82,83]. Not only do women and men differ in their normal immune response but there are also differences between them in the prevalence, presentation and severity of ADs. This leads to the notion that increased immune function imparts increased susceptibility to autoimmunity in women [2,18,84,85]. There are multiple hypotheses about the genetic mechanisms that could explain the sex bias in ADs. Nevertheless, the exact pathways are largely unexplored and are still far from being clearly understood.

4.1. X chromosome inactivation

Unlike the gene-poor Y chromosome, the X chromosome contains over 1000 genes that are essential for proper development and cell viability. However, females carry two copies of the X chromosome, resulting in a double dose of X-linked genes. To correct this imbalance, mammalian females have evolved a unique epigenetic mechanism of dosage compensation: the X chromosome inactivation. Female mammals transcriptionally silence one of their two X chromosomes in a random, complex and highly coordinated manner early in embryogenesis [86]. The inactivated X chromosome then condenses into a compact structure called the Barr body, and it is stably maintained in a silent state. In theory, this process should be sufficient to establish equal expression of genes on the X chromosome in female and male cells. Notwithstanding, it is now known that under physiological conditions, the X chromosome is only partially inactivated and about 10–15% of the genes may be expressed by both X chromosomes in female cells [12,18,84]. Thus, females are functional mosaics for the X-linked genes.

The X chromosome inactivation is generally random in somatic tissue and once chosen, the inactivation is kept stable and the same chromosome is inactivated in all progeny cells. However, in many cases the inactivation may be skewed for stochastic reasons or because of severe mutations [87]. Despite the inactivation of the X chromosomes being random or non-random, the pattern within an individual is dynamic during life and older females may manifest a skewed pattern as an acquired trait that is not pathogenic by itself [88].

Skewed X chromosome inactivation happens when one of the two alleles (either from the mother or the father) is in the active X chromosome in more than 75% of cells [87]. Skewing of X chromosome inactivation is expressed as a percentage deviation from equal inactivation (50:50) of the alleles. Extreme skewing is defined as a greater than 40% deviation from a 50:50 distribution (one of the two alleles in the active X chromosome in $\geq$90% of cells) [89,90]. It has been noted that skewed inactivation is more prevalent in patients with ADs than in healthy controls [2,84,90–92].

It is well known that ADs are the result of the loss of immunological tolerance to self-antigens, therefore, the process of X chromosome inactivation offers a potential mechanism whereby X-linked self-antigens may escape presentation in the thymus or in other peripheral sites that are involved in tolerance induction [89]. Although the exact mechanisms that cause X chromosome inactivation are still speculative, in theory, this could result in a situation in which self-antigens on one X chromosome may fail to be expressed at sufficiently high levels in compartments such as the thymus, and yet may be expressed at considerable frequency in peripheral tissues. This could be the stimuli necessary to break the tolerance of the immune system and lead to the development of autoreactive T lymphocytes [89]. Another important aspect of extremely skewed X chromosome inactivation is that it does not lead to the breakdown of self tolerance in all females. This means that there must be a second event to break down self tolerance: a mutation leading to loss of mosaicism, and second, heterozygosity for the non-synonymous variants of the putative critical genes [91].

Another hypothetical mechanism could be that skewed X chromosome inactivation could lead to the inactivation of a gene that protects against autoimmunity, or over-expression of a susceptibility gene thus leading to increased AD [84]. Table 5 summarizes case-control reports that evaluated the patterns of X chromosome inactivation in patients with ADs.

The inconsistencies found in some reports that fail to demonstrate a significant difference between the patterns of inactivation of patients compared to controls may be due to differences in etiology, pathophysiology and unknown mechanisms by means of which skewed X chromosome inactivation may influence female biased autoimmunity [89,99]. Also, age differences, sample sizes, different definitions of cut-off points for skewed X inactivation might explain the discrepancies. Likewise, the possibility that tissues other than blood would be more appropriate for finding a significant difference in skewed X chromosome inactivation patterns has to be considered [89,99].

4.2. X chromosome dosage

4.2.1. X chromosome monosomy

Another mechanism that has been proposed to explain female biased autoimmunity is the X chromosome monosomy based on

Table 5
Case-Control reports investigating associations of X chromosome inactivation patterns and autoimmune diseases.

Ref.	Year	AD (*n*)	*n* (patients/controls)	% (*n*) skewed inactivation in informative patients	Significant Skewed X-Chromosome inactivation	Comments
Chitnis et al.[a] [89]	2000	JD (45)	167/30	JD: 13.7	No	Effect of skewing depends on the pattern of inactivation in selected tissues (differences in X inactivation patterns between oral mucosa (ectoderm) and peripheral blood (mesoderm) in the same individual)[b]
		MS (58) SLE (46) JIA (18)		MS: 19.52 SLE: 13.7 JIA: 13.73 Controls: 17.9		Sample size for each AD might have been too small to find significant differences.
Özbalkan et al. [92]	2004	SSc	70/160 (Informative: 55/124)	SSc: 64 (35)	Yes ($p < 0.0001$)	Skewed X chromosome inactivation does not lead to development of SSc in all women; therefore a subsequent event must be necessary to break down self tolerance.
				Controls: 8 (10)		Random pattern of X chromosome inactivation in skin, oral mucosa and hair follicle samples was observed.
Ozcelik et al. [93]	2005	AITD (HT: 89, GD: 29)	110/160 (Informative: 83/124 [HT: 67; GD: 16])	AITD: 34 (28) [HT: 34.3 (23); GD: 31 (5)] Controls: 8 (10)	Yes ($p > 0.0001$)	Five randomly selected patients showed skewing in the same direction for thyroid and oral mucosa biopsy.
Brix et al. [94]	2005	AITD	32/96	External controls: AITD: 34 (11) [HT: 31 (4); GD: 37 (7)]	Yes	Twin case-control study:
		(HT: 13, GD: 19)		Controls: 11.4 (11)	(External controls: $p = 0.003$; Within-pair comparison: $p = 0.03$)	1. External controls: Twin individuals with AITD (cases) with matched, unrelated control twin individuals
				Co-Twin comparison: AITD twins: 42 (11) Healthy twins: 12 (3)		2. Within-pair comparison: 26 twin pairs discordant for AITD: the healthy twin was the control.
Uz et al. [90]	2007	SSc	125/160 (Informative: 94/124)	SSc: 34 (32) Controls: 8 (10)	Yes ($p < 0.0001$)	Skewed X chromosome inactivation does not lead to development of SSc in all women; therefore a subsequent event must be necessary to break down self tolerance.
Knudsen et al. [95]	2007	MS (260 RR-MS, 108 SP-MS, 94 PP MS)	568/132 (Informative: 462 patients)	MS: 17 (77) [RR-MS: 15 (38); SP-MS: 20 (22); PP-MS: 18 (17)]	No (Patients vs. controls: $p = 0.137$;	Post hoc tests with Bonferroni correction showed no significant differences between the groups.
				Controls: 11 (15)	Comparisons between groups of MS: $p = 0.37$)	X chromosome inactivation pattern does not seem to explain the female predominance observed in MS in general: PBMC does not reflect real skewing patterns of other tissues that might be more relevant in the development of autoimmunity.
Miozzo et al.[a,c] [96]	2007	PBC	166/226 (Informative: 146/195 [Healthy controls: 155, CHC: 40])	PBC: 42 (70) CHC: 47 (23) Healthy Controls: 41 (72)	No	The study evaluated X chromosome inactivation patterns and X chromosome mononosomy patterns. A preferential X chromosome loss independent of the X chromosome inactivation pattern was found.
Yin et al. [97]	2007	AITD (GD: 87, HT: 47)	134/69 (Informative: 113/58 [GD: 70, HT: 43)	AITD: 27 (31) [GD: 29 (20) HT: 26 (11)]	Yes ($p = 0.004$)	There was no correlation of skewed X chromosome inactivation and age. There was no correlation between the degree of skewed X chromosome inactivation and the age of AITD onset.

Uz et al. [91]	2008	JIA	81/211 (Informative: 62/155)	JIA: 22.6 (14) Controls: 7.1 (11)	Yes ($p = 0.0036$)	Deleterious X-linked mutations could influence the survival of cells that inactivate a normal X chromosome and leave the mutant X transcriptionally active
Chabchoub et al. [98]	2008	RA (106) AITD (GD: 58, HT: 87)	251/257 (Informative: 176/170 [RA: 76, AITD: 100])	RA: 34.2% (26) AITD: 26 (26)	Yes (RA vs. Controls: $p < 0.0001$; AITD vs. controls: $p < 0.0015$)	Results suggest influence of age in the differences in X chromosome skewed inactivation.

AD: autoimmune disease, JD: juvenile diabetes, MS: multiple sclerosis, SLE: systemic lupus erythematosus, JIA: juvenile idiopathic arthritis, SSc: systemic sclerosis, AITD: autoimmune thyroid disease, GD: Grave's disease, HT: Hasimoto's thyroiditis, RA: rheumatoid arthritis, RR-MS: relapsing-remitting multiple sclerosis, SP-MS: secondary progressive multiple sclerosis, PP-MS: primary progressive multiple sclerosis, PBMC: peripheral blood mononuclear cells, PBC: primary biliary cirrhosis, CHC: chronic hepatitis C.

[a] All studies defined skewed X chromosome inactivation as >80% of skewing except for the ones marked, which defined X chromosome inactivation as >50% (Chitnis et al. [77]) and >75% (Miozzo et al. [84]) respectively.

[b] Unpublished observations.

[c] The percentages of skewed X chromosome inactivation were calculated considering all patients (informative and non-informative patients).

the observed increased incidence of autoimmune disorders in diseases such as Turner's syndrome [100–102]. Furthermore, several reports have found the rate of X monosomy to be significantly increased in peripheral white blood cells of patients with primary biliary cirrhosis (PBC), AITD and SSc as well as with age [96,100,103]. It is also notable that increased X monosomy rates have been found more frequently in peripheral T and B lymphocytes than in other blood cell populations without evidence of microchimerism that would explain the existence of the monosomic cells [100–105]. However, these findings could not be duplicated in a study of female patients with SLE, in which the authors proposed that the methylation pattern rather than the monosomy of the X chromosome, along with other hypotheses, might have a more preponderant role in female biased autoimmunity, but this needs further research [104]. Invernizzi et al. offers an explanation of how X monosomy might be associated with autoimmunity by hypothesizing that X chromosome monosomy may cause a haploinsufficiency in X-linked genes that escape X chromosome inactivation and, as a consequence, autoreactive T cells are not exposed to self-antigens encoded by one of the two X chromosomes. Therefore, these autoreactive T cells may be exposed to these self-antigens and react against them with the consequent development and perpetuation of an autoimmune response [102,105]. However, it is more likely that X chromosome alterations would generate a negative impact on the immune system homeostasis and this deregulation would affect B and/or T lymphocytes directly [102]. Case-control reports evaluating X chromosome monosomy are summarized in Table 6.

4.2.2. Klinefelter's syndrome

Observations that the incidence of SLE is higher in XXY males (Klinefelter's syndrome) and low in XO females (Turner's syndrome) have pointed towards an X chromosome gene-dosage effect in female biased autoimmunity. This takes into account not only the monosomy of the X chromosome but also the "over-dose" of it [2]. The first case report of SLE and Klinefelter's syndrome occurring in the same patient was in 1969 by Oritz-Neu et al. [106]. They reported 3 cases with this association. Subsequently, other case reports have surfaced in the literature [107].

In experimental models of mice, Smith-Bouvier et al. found that sex chromosomes contributed to female biased susceptibility to AD. Transgenic SJL mice were created to permit a comparison between XX and XY within a common gonadal type (gonadectomized mice) to remove any intercurrent effects of sex hormones that might mask effects of sex chromosomes. Results show that mice that were XX, as compared with the ones that were XY, demonstrated greater susceptibility to both experimental autoimmune encephalomyelitis and pristane-induced lupus [108]. Scofield et al. studied 378 multiplex SLE families with 76 male SLE patients and 138 patients with non-familial SLE and found a >13-fold higher prevalence of Klinefelter's syndrome than is found in the general male population ($p < 0.001$) [109]. So far, the stronger association has been found between Klinefelter's syndrome and SLE. The relationship of 47XXY to other ADs needs further investigation.

4.3. Non-inherited maternal antigens (NIMAs)

These molecules are defined as antigens in the offspring which are not encoded by the inherited alleles of the offspring but by the mother's alleles and are passed to the offspring through microchimerism. Non-inherited maternal antigens occur when there is maternal–fetal genotype incompatibility [2]. It has been established that some ADs are significantly more frequent in subjects who carry certain HLA antigens. However, not all of the carriers are affected by these entities and likewise, a significant proportion of

Table 6
Case-Control reports investigating associations of X chromosome monosomy and autoimmune diseases.

Ref.	Year	AD	*N* (patients/ controls)	% ±SD X chromosome monosomy	Significant X chromosome monosomy	Technique	Comments
Invernizzi et al. [103]	2004	PBC	100/100 (Controls: CHC: 50, Healthy: 50)	PBC: 10.3 [7.5–14][a] Controls: 2.2 [1.2–3.9][a]	Yes ($p < 0.0001$)	FISH	The PBC group had significant higher rates of monosomy of the X chromosome than the chronic hepatitis C or healthy groups.
Invernizzi et al. [100]	2005	SSc AITD	88/100 (Patients: SSc: 44 [LSSc: 34, DSSc: 10] AITD: 44 [HT: 32, GD: 12])	SSc: 6.2 ± 0.3 AITD: 4.3 ± 0.3 Controls: 2.9 ± 0.2	Yes (SSc vs. Controls: $p < 0.0001$; AITD vs. Controls: $p < 0.0001$)	FISH	Cells with monosomy X did not have evidence of the presence of Y chromosome and thus were not microchimeric. The rate of monosomy X was found to increase with age. No significant differences in monosomy rates were observed in patients with different types of SSc and between patients with GD and HT.
Invernizzi et al. [104]	2007	SLE	44/73	SLE: 2.67 ± 0.22 Controls: 2.9 ± 0.17	No ($p = 0.396$)	FISH	The rate of X monosomy was found to increase with age both in patients and healthy subjects.
Miozzo et al. [96]	2007	PBC	166/266	PBC: 39 CHC: 17.5 Healthy Controls: 24	Yes ($p = 0.006$)	QF-PCR analysis of 4 X-linked STRs. (HUMARA, DXS8105, DXS996, P39)	X chromosome loss and X chromosome inactivation patterns were studied. Only a small subset of patients and controls had both a preferential X loss and a skewed X chromosome inactivation pattern, suggesting that both processes are independent.

AD: autoimmune disease. PBC: primary biliary cirrhosis, CHC: chronic hepatitis C, SSc: systemic sclerosis, LSSc: Limited systemic sclerosis, DSSc: Diffuse systemic sclerosis, AITD: Autoimmune thyroid disease. GD: Grave's disease, HT: Hashimoto's thyroiditis, SLE: systemic lupus erythematosus, FISH: fluorescent in situ hybridization, QF-PCR: quantitative fluorescent polymerase chain reaction, STRs: short tandem repeats.
[a] Geometric mean [95% Confidence Interval].

patients with an HLA-associated disease do not carry the predisposing allele. Although many factors influence this situation, one of the possible explanations that have been raised is the NIMA hypothesis, which states that NIMAs modulate the immune repertoire in the offspring and thus, they might have an influence on protecting or predisposing to ADs [2,110,111]. The first attempts to demonstrate this association were done by ten Wolde et al. [110].

Although many of the studies that have addressed the association between NIMA and ADs have failed to find it [110–115], when results were combined, significant differences were found between the frequency of NIMAs, especially HLA-DR4$^+$ and Shared Epitope (SE)$^+$ NIMAs, in RA patients who were negative for DRB1*04 and SE [114]. However, this could not be duplicated in SLE [112]. Interestingly, another case-control study found that NIMAs of HLA DRB1 alleles that encode the aminoacid sequence DERAA had a protective effect [116]. In this study, the offspring of mothers positive for these alleles had a lower risk of RA (OR 0.25; $p = 0.003$) [116]. Akesson et al. found a significant association of HLA-DR4$^+$ and HLA-DR3$^+$ NIMAs with type 1 diabetes [117]. Guthrie et al. found the association between HLA-DRA$^+$ NIMAs to be statistically significant only in females with a younger onset of RA which gives us a possible explanation for conflicting results in studies evaluating NIMAs role in female biased autoimmunity [118].

5. Microchimerism

Microchimerism is defined as the movement of hematopoietic stem cells from fetal to maternal circulation or from maternal to fetal circulation (fetal microchimerism and maternal microchimerism respectively) as long as these cells persist [2,119,120]. Although considered to be a normal phenomenon, it has been observed that microchimerism might play a role in the development of ADs [120]. It has been postulated that if these cells are targeted as foreign cells they could be implicated in the pathogenesis of ADs [2].

A number of studies have provided clear evidence that microchimerism is associated with SSc although a causal mechanism has not yet been clearly established [121]. SSc is an AD with a strong predilection for women and affects them 3–10 times more than men [4,82,122,123]. It has a peak incidence in women after child bearing years and clinical similarities to chronic graft versus host disease [120]. All of this has led researchers to think that microchimerism plays an important role in the pathogenesis of the disease. Nelson et al. and Artlett et al. found that women with SSc have male DNA in their blood and skin lesions more often, and in greater quantities, than unaffected women ($p = 0{,}0007$ and $p < 0.001$ respectively) [124,125].

There is some evidence for an association of long term maternal microchimerism in other ADs such as MS and AITD. In a study of twins who are discordant for MS, microchimerism was associated with MS in affected females from monozygotic concordant pairs when compared to both affected ($p = 0.020$) and unaffected ($p = 0.025$) females in monozygotic discordant pairs [126]. In another study of female patients with Hashimoto thyroiditis by Klintschar et al. microchimerism was shown to be significantly more common in Hashimoto patients than in patients suffering from nodular goiter, which suggests a role for microchimerism in the development of Hashimoto's disease. However, the hypothesis that microchimerism was just a bystander in a process triggered by other mechanisms is also possible [127]. Although such findings could not be duplicated in a study of female patients with SLE [128], it does not rule out the possibility that microchimerism may play an important role in the complex pathogenesis of ADs.

Even though microchimerism is expected to be found only in women who have given birth to a son, male DNA has been found in the peripheral blood of nulliparous women. Possible sources proposed for this male DNA include an unrecognized pregnancy with a male fetus or unrecognized male twin, transfer from an older male sibling through the maternal circulation to a female fetus, or sexual intercourse [129].

Interestingly, microchimeric cells themselves are not the only ones implicated in the mechanism by which microchimerism influences the development of ADs. Rack et al. found that women with RA had microchimerism of HLA alleles associated with RA – but not with other alleles unrelated to the disease– more frequently and at higher levels compared with healthy female controls [130].

6. Conclusions

The more frequent the AD and the later it appears, the more women are affected. The most convincing explanation of female biased autoimmunity remains the hormonal theory. Estrogens are potent stimulators of autoimmunity and androgens seem to play a protective role in the process. We strongly believe that ADs are complex and multifactorial entities and, although hormone differences may have a strong influence on the predisposition of women to ADs, there is enough evidence to state that genetic factors are important as well. Major understanding of not only the hormonal and genetic factors but also the epigenetic processes related to sex differences in ADs may bring further insight and answers regarding this issue, since ADs constitute a leading cause of death among young and middle-aged women [131]. The majority of studies focus on why women are predisposed to ADs. We propose that additional efforts be made to explore the other side of the story: why are ADs less prevalent in males and could there be a group of protective factors that explains this phenomenon?

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