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Gender bias in autoimmune diseases
X chromosome inactivation in women with multiple sclerosis

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ABSTRACT

The majority of autoimmune disorders are characterized by female predominance. Several mechanisms have been proposed as explanations for this gender bias, among them X chromosome inactivation. An increased frequency of skewed X inactivation has been found in some autoimmune disorders, like scleroderma and autoimmune thyroid disease, and may thus offer a possible explanation for the female predominance.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, with pathological features of an autoimmune disorder. The incidence of MS in females is approximately twofold compared to the incidence in males. X inactivation does not seem to be part of the explanation for the gender bias in MS. This paper reviews the possible role of X chromosome inactivation in some autoimmune diseases, and describes a recent study of X inactivation in females with MS.

1. Introduction

Multiple sclerosis (MS), like most other autoimmune diseases, is more common in females than in males. This paper reviews the role of X chromosome inactivation in autoimmunity and in MS: A brief summary of possible explanations for the gender bias in autoimmunity is followed by an outline on how the X chromosome may be important for autoimmunity, an introduction to X chromosome inactivation, and a summary of possible consequences of skewed X inactivation both generally and in autoimmunity. Finally, a study of X chromosome inactivation in multiple sclerosis is discussed.

2. Autoimmune diseases and gender

Most autoimmune diseases predominantly affect females. The female to male ratio varies substantially between the different diseases. Highest female to male ratio is seen in Sjögrens syndrome, primary biliary cirrhosis, systemic lupus erythematosus and autoimmune thyroid disease (Table 1).

Several mechanisms have been proposed as explanations for the female predominance in autoimmune diseases [1–3]. Sex hormones, including estrogens, androgens and prolactin are proposed candidates, as they modulate immune response through androgen and estrogen receptors. There seems to be different immune responses between females and males [4], and sex hormone involvement has been described in several autoimmune diseases [2]. In MS and rheumatoid arthritis, patients have varying disease activity during pregnancy, possibly due to fluctuations in the level of estrogens and progesterone [3].

Pregnancy represents an important immunological challenge for females, and could potentially lead to an immune response resulting in subsequent autoimmunity. During a pregnancy, bidirectional cell traffic between mother and child can lead to a subsequent presence of allogenic cells (or DNA), referred to as microchimerism [5]. This has been hypothesized to contribute to the pathogenesis of autoimmunity [6]. In a study of scleroderma, microchimerism was found in blood from patients [7]. These results have been debated. The biological implications of microchimerism are not clear, as fetal microchimerism is common in healthy individuals, and negative findings in autoimmune diseases are also reported [8–12].

3. The X chromosome and autoimmunity

The X chromosome contains several genes related to immune response. Mutations in the transcription factor fork head box P3 (*FOXP3*), leads to IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), which is an inborn error of immune regulation and is characterized by early onset of some autoimmune disorders in boys [13]. X-linked lymphoproliferative syndrome, X-linked severe combined immunodeficiency syndrome and Wiskott–Aldrich syndrome are other examples of X-linked immunodeficiencies, caused by mutations in *SH2D1A*, *IL2RG* and *WAS*, respectively [14–16].

Other X chromosome abnormalities have also been associated with autoimmunity. An increased rate of X monosomy in blood cells has been found in primary biliary cirrhosis, systemic lupus erythematosus and scleroderma [17–19]. Turner syndrome, which is characterized by partial or complete lack of a second X chromosome in females, is

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Table 1
Female to male ratio for autoimmune diseases.

Autoimmune disease	Female to male ratio*
Sjögrens syndrome	9–20:1
Primary biliary cirrhosis	10:1
Systemic lupus erythematosus	9:1
Autoimmune thyroid diseases	8:1
Scleroderma	5:1
Rheumatoid arthritis	4:1
Multiple sclerosis	2–3:1

* Ratios adapted from Lleo et al and Gleicher et al [1,2].

associated with an increased risk for autoimmune diseases above that in the general female population [20]. Furthermore, X-chromosome deletions and translocations are quite common in premature ovarian failure, a condition which is associated with an increased frequency of co-occurring autoimmune diseases [21].

4. X chromosome inactivation

Females have two X chromosomes, and males have one. In order to balance the amount of gene expression between females and males, one of the X chromosomes in females is inactivated.

The X inactivation process happens in early embryonic development [22]. A few days after fertilization, one of the two X chromosomes is randomly silenced—either the X inherited from the father or the X inherited from the mother. The process is permanent, meaning that each daughter cell "remembers" which X chromosome to inactivate. A recent study showed, however, that not all genes on the inactive X chromosome were silenced: 15% of the genes escaped inactivation to some degree, and an additional 10% of the genes showed variable inactivation between females [23].

The X inactivation process leads to females being mosaics for two different cell types, one with the maternal X active and one with the paternal X active (Fig. 1). The process is stochastic, so most females will have approximately equal amounts of the two cell types (random X inactivation pattern). A few females will by chance (or in rare cases due to a mutation) have a skewed X inactivation pattern, where one of

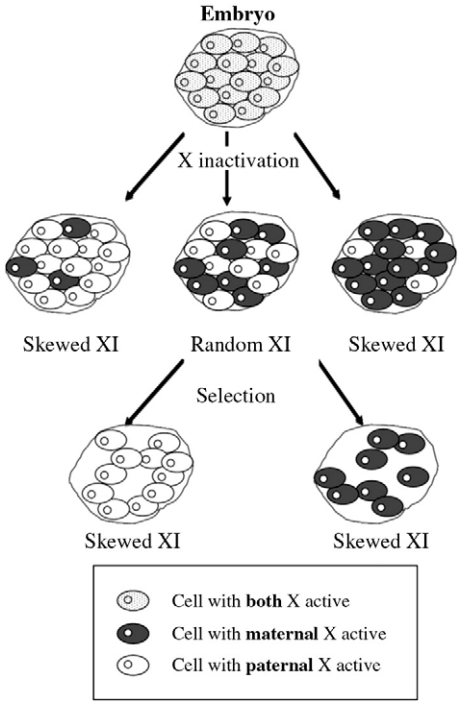

Fig. 1. X chromosome inactivation in female mammalian cells.

Table 2
Skewed X chromosome inactivation in healthy females.

Age (years)	Subjects	Skewed X inactivation (≥75%)	Skewed X inactivation (≥80%)	Skewed X inactivation (≥90%)	References
Newborn	590		5%	0.5%	[28]
Newborn	450	14.2%		2.7%	[29]
≤25	121	28%	21%	7%	[30]
≤32	229	11%		3%	[24]
≤43	444	27.9%		4.5%	[29]
Child bearing age	415		14%	4%	[28]
≥60	66	38%		23%	[24]
≥60	139	48%	32%	16%	[30]
≥64	146		35%		[27]
≥101	33		67%	18%	[25]

the cell types predominates. Females with random X inactivation pattern can also, due to selection against or in favour of cells with a specific genotype, acquire a skewed X inactivation pattern. X inactivation pattern is sometimes recorded as percentage of the shorter allele to the sum of both alleles, and expressed within a range of 0 and 100%. Degree of skewing is calculated as the percentage of the predominantly inactive allele to the sum of both alleles, ranging from 50 to 100%. Skewed X inactivation is defined differently by different investigators, but in terms of percentage of cells with the predominantly inactive X, 75%, 80% and 90% are commonly accepted cut-offs.

The frequency of skewed X inactivation in healthy females varies between studies, Table 2. Elderly females more often exhibits a skewed X inactivation pattern than younger females [24–26]. This age-related increase seems to start around the age of 55–60 years, and continues throughout life [27].

5. Consequences of skewed X inactivation

A skewed X inactivation pattern does not necessarily have a clinical influence. But if one of the X chromosomes carries a mutated gene, the proportion of cells with the mutated X active can have a major effect on development of disease in the female. This is illustrated in haemophilia A, an X-linked disease caused by mutations in the factor VIII gene. As most of the females have a random X inactivation pattern, in female carriers of the disease, the proportion of cells with the normal X active produces sufficient gene product (factor VIII), and the females will be unaffected. There have, however, been reported females affected with haemophilia, and this has been explained by an unfavourably skewed X inactivation pattern, [31,32].

The phenomenon of monozygotic twins discordant for X-linked disease have for some diseases been attributed to different X inactivation patterns in the twins [33]. This has been reported in monozygotic twins discordant for Duchenne muscular dystrophy, where the twins both had a mutation, but only one was affected [34,35]. X inactivation analysis showed that the carrier twin had random X inactivation pattern, while the affected twin had an unfavourably skewed X inactivation pattern.

6. X inactivation and autoimmunity

A hypothesis that X chromosome inactivation mosaicism could be involved in autoimmune response was stated 11 years ago by Jeffrey Stewart [36]. The hypothesis can basically be described by three events: 1) Presume a skewed X inactivation in thymus. 2) The T cells entering the thymus to be educated for tolerance are educated to be tolerant only to self-antigens encoded by one of the two X chromosomes—the one predominantly active in the thymus. 3) As these T cells travel to peripheral tissues, they will react to self antigens encoded by the other X chromosome when cells with this X chromosome active are encountered, leading to an autoimmune