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Genetic and hormonal factors in female-biased autoimmunity

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Abstract

Autoimmunity is controlled both by the environment and by genetic factors. One of the most well defined genetic factors is polymorphisms, with some alleles of particular genes promoting autoimmune diseases, whereas other alleles either not affecting susceptibility to disease or, in some cases actually inhibiting the appearance of such illnesses. Another genetically controlled factor, gender, also plays a profound role in the incidence of autoimmune diseases. For example, Systemic Lupus Erythematosus (SLE) occurs much more frequently in females than in males in both mice and man. The genetic differences that make some individuals susceptible to autoimmunity and protect others could act in many ways and affect many tissues. In this review we will discuss how gender may act on the cells of the immune system and thereby influence the predisposition of the host to autoimmune diseases.

Keywords

autoimmunity; sex hormones; X chromosome; TLR7

INTRODUCTION

The normal function of the immune system is to protect organisms against infections. However, in some individuals, the immune response attacks the tissues of its own host, destroying them and thereby causing disease. There are more than 80 different so-called autoimmune diseases in human beings, and in 2001 the NIH estimated that about 5% of the population in the USA suffered from some type of autoimmune disease with a cost to the taxpayer of about $100 billion/year [1]. Each autoimmune disease is primarily defined by the tissue being attacked and can be divided into two main categories: single organ or multi-organ. Examples of single target organ autoimmune diseases include type I diabetes, in which the immune response destroys the beta cells that produce insulin in the pancreas. In

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patients with multiple sclerosis, the immune response attacks cells in the brain, while in rheumatoid arthritis, the immune response causes inflammation and destruction of the joints. The situation is more complicated in multi-target organ or systemic diseases such as Systemic Lupus Erythematosus (SLE). In patients with lupus the immune system makes antibodies against DNA and other material present in the nuclei of all cells. These antibodies bind their targets and give rise to problems in organs such as the kidneys, causing inflammation and leading to tissue damage and malfunction.

To a large extent, predisposition to autoimmune disease is genetically inherited in human beings. If one member of a pair of identical twins has SLE, there is a 14-60% likelihood that the other member of the pair will get the disease [2]. Shared inheritance of the same alleles of polymorphic genes probably underlies this high risk. For example, in lupus certain alleles of Fc receptors have been shown to be involved in the induction of the disease and these will of course be identical in identical twins [3-5]. Also diminished or altered expression of pro-apoptotic proteins, such as Bim or Fas, in immune system cells leads to lupus–like disease in mice and, where studied, in man [6, 7].

Although disease in close family relatives is an indicator that an individual may develop autoimmunity, it is by no means inevitable. For example, although close family relatives of a patient with SLE are 25 times more likely to get the disease than the general population, still only about 2% of close family relatives of a patient will actually develop the disease. In spite of the fact that lupus and other autoimmune diseases are in part genetically inherited, it is still difficult to predict which individuals are likely to develop the disease and which are not. Moreover, while B cells clearly play a key role in the progression of lupus, it is still unclear whether they are the major players at the time of disease onset.

Another genetically controlled factor that has come to the attention of immunologists and rheumatologists, is gender. It is well established that gender plays a profound role in the incidence of autoimmunity with diseases such as lupus occurring much more frequently in females than in males, both in mice and man. In general, females have stronger humoral and cellular immunity than men [8]. This is manifested by higher levels of circulating antibodies, higher numbers of circulating CD4 T cells, enhanced cytokine production in response to infection, and rapid rejection of allografts. These are probably the major reasons why most immunologists prefer to use female animals in their studies. Unfortunately, one of the drawbacks for such strong immunity is apparently the increased susceptibility to autoimmune diseases among females.

In this review recent advances in our understanding of the nature of female-biased autoimmunity will be discussed. We will discuss what gender-based factors affect development and function of the immune system and whether understanding the mechanisms leading to female predisposition to certain autoimmune disease might give an insight into the etiology of the disease.

The effect of sex hormones on immune cells

The predominance of females among the patients with different autoimmune diseases, such as SLE, gave rise to a great interest in the role of sex hormones in the immune system. The evidences for the influence of sex hormones on autoimmune diseases include the changes in disease severity during pregnancy and during specific periods of the menstrual cycle. It has been suggested that estrogens can enhance the immune response while androgens and progesterone suppress it [9].

Many studies suggest that sex hormones have effects on both the innate and adaptive immune systems. In order to affect the immune system directly, sex hormones have to be

able to bind to their receptors, which therefore need to be expressed by the cells of the immune system. Classical steroid hormone receptors are intracellular so that the hormone/receptor interactions occur inside the cell after the hormone diffuses across the cell membrane [10]. The hormone/receptor complex then translocates to the nucleus where it functions as a transcriptional complex [11]. Thus the question of the presence of the steroid receptors in immune cells is critical for further investigation of the role of sex hormones in the immune system. Many reports indicate that sex hormone receptors are expressed by different populations of innate and adaptive immune cells. B cells have been shown to express both estrogen and androgen receptors while there is no evidence for progesterone receptor expression [12, 13]. In T cells, only $CD8^+$ T cells express estrogen receptors while $CD4^+$ T cells do not express any of the steroid receptors [14]. Estrogen receptors were also found in monocytes [12], neutrophils [15] and murine NK cells [16] and androgen receptors were detected in murine macrophages [17] (Table 1). Overall these data indicate that sex hormones can affect the function of the immune cells directly via binding to the steroid receptors.

Is there, however, any evidence that sex hormanes can act directly on cells of the immune system? In fact many reports indicate various effects of sex hormones on cells of both the innate and adaptive immune system. Some of the effects produced by sex hormones on the innate immune system include the regulation of antimicrobial peptide expression in urogenital tissues [18, 19], recruitment of neutrophils, macrophages and antigen presenting cells to the vaginal epithelium and ovaries [20, 21] and regulation of NK cell activity [22]. There is also a lot of evidence to suggest an important role for sex hormones in the adaptive immune system. For example, sex steroids affect antigen presentation by dendritic cells and macrophages probably through the production of TGFβ which is regulated by estrogen [23]. Hormones also affect T cell mediated immunity. For example in humans, women produce higher Th2 cytokine responses than men, a finding that is consistent with the higher antibody titers in females [24]. However, mouse studies have shown opposite results, since administration of estrogen to ovariectomised mice caused enhanced Th1 (non IgG1 promoting) responses when compared to untreated ovariectomised animals [25]. Interestingly, estrogen treatment also resulted in reduced numbers of total $CD4^+$ and $CD8^+$ T cells, a result that may be due to decreased IL-2 and IL-2 receptor levels in or on blood lymphocytes of the estrogen treated animals [26].

Immunoglobulin secretion by B cells and the numbers of Ig-secreting cells are also affected by the levels of sex hormones. For example, the numbers of IgG and IgA secreting B cells in spleen, lymph nodes and peripheral blood mononuclear cells (PBMCs) in female rhesus macaques change during the menstrual cycle [27]. These data were confirmed by in vitro studies using PBMCs from male macaques. Progesterone treatment in vitro led to a decreased number of IgG and IgA secreting cells in cultured macaque PBMCs while treatment with estrogen had the opposite effect. Interestingly, both progesterone and estrogen treatments were ineffective in the absence of $CD8^+$ T cells, suggesting the existence of an unxpected interplay between $CD8^+$ T cells and B cells. Similar observations, indicating an increase in both IgG and IgA secreting cells in response to estrogen, were made with human PBMCs [28]. Thus, it is clear that changes in the levels of sex hormones led to a number of changes in both innate and adaptive immune cells, affecting antigen presentation, numbers of T and B cells and antibody secretion.

Role of sex hormones in the development of autoimmunity

Female prevalence in autoimmune diseases and the effects of sex hormones on the immune system in general lead to the hypothesis that different levels of the various sex steroid hormones in males and females can explain the predominance of women among the patients suffering from certain autoimmune diseases. In fact, hormonal influences had been reported

for some autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA). It is well documented that the severity of these diseases decreases during pregnancy especially during the third trimester when the levels of progesterone and estrogen are the highest [29, 30]. However pregnancy does not have the same effect on SLE patients, in whom the disease is often worst or unaffected during this time. Both phenomena can be explained by the skewing of the Th1/Th2 responses upon hormonal influences. Since high level of hormones during pregnancy enhances the Th2 response, this may suppress RA and MS which are predominantly driven by Th1 response. In contrast, SLE is mostly mediated by autoantibodies which may be increased under Th2 conditions [31]. Another observation supporting this theory is that male RA patients have lower testosterone levels compared to healthy control subjects [32].

These data have been confirmed in studies of animal models of different autoimmune diseases. Animal models of RA and MS (collagen-induced arthritis and experimental autoimmune encephalomyelitis (EAE)) have decreased disease activity during pregnancy similar to the human patients [33]. The same effect has been found in EAE mice treated with hormones which mimic the environment of pregnancy [34].

Several studies indicate that changes in sex hormone levels caused by castration of animals influences the severity and/or the onset of different autoimmune diseases such as diabetes, RA, EAE and SLE [33]. For example, in (NZBxNZW) F1 mice (a murine model of SLE) the onset of disease is significantly delayed in males compared to females, while castration of males makes the onset of the disease similar to that in untreated female mice of the same strain. Similarly, ovariectomy of female (NZBxNZW) F1 mice significantly delays the onset of disease making it similar to that in untreated males of this strain [35]. Similar results were shown for NOD mice where the ovariectomy of female mice decreased the severity of diabetes [33]. These data suggest both protective roles for male hormones and disease accelerating properties of female hormones.

Gonadectomy data suggested the possibility for the hormonal treatment of autoimmune diseases. In fact, the effect of hormonal therapy was reported for EAE mice since treatment of EAE females with testosterone led to decreased disease activity. This was explained by higher levels of IL-10 production by autoantigen-specific T cells and this is consistent with the finding that autoantigen specific T cells from male EAE mice in general produce more IL-10 compared to female cells [36].

In vitro studies of human PBMCs from SLE patients indicated that treatment of these cells with estrogen enhances total IgG production as well as anti-dsDNA autoantibody levels. The effect was partially IL-10 dependent and autoantibodies were not secreted by healthy control PBMCs treated in the same way [37]. However, in a separate study, it was shown that estrogen induced total IgG and IgM production by PBMCs from healthy males and females while testosterone had the opposite effect [37, 38]. These data suggest that sex hormones can directly affect the pathogenesis of autoimmune diseases by elevating the total level of immunoglobulins and enhancing autoantibody production. This indicates that female hormones can influence the onset of autoimmune disease. However, the studies of sex hormone levels in female patients with different autoimmune diseases did not reveal any significant differences to healthy controls. This indicates that, despite the important role of sex hormones in autoimmunity, there must be other factors that explain the overall female bias of such diseases [39].

Role of X chromosome complement in development of autoimmunity

In addition to a their different levels of various sex hormones, females and males differ in their content of sex chromosomes with females having, of course, two X chromosomes and

males an X and a Y. This chromosomal difference may also play a role in the female bias for some autoimmune diseases. Studies on the role of sex chromosomes in autoimmunity have been delayed due to insufficient understanding of the complex regulation involved in X and Y chromosome biology. Although there is a small set of Y-linked genes, there are about 1000 genes that are unique to the X chromosome and are not encoded on the Y chromosome. Moreover, about 70% of X-linked genes with a known function have direct association with human diseases. The X chromosome has several unique features which not only separate sex-related studies from the conventional genetic research but also makes them extremely complicated. Such X-chromosome specific features include the process of X-inactivation and partial escape from it, mosaic expression of X-linked genes in females, male hemizyozity, and the spontaneous loss of one X chromosome (X monosomy) in females.

Hemizygosity of the X chromosome in males leads to high numbers of diseases (not necessarily autoimmune diseases) associated with genes encoded on it. Malfunctions of X-encoded specific genes can be directly involved in abnormalities in the immune system of males, due to fact that these genes are monozygous in this sex. For example Mutations and/or altered expression of CD40 ligand, common γ chain, FOXP3 (forkhead box P3) and other genes encoded on the X chromosome are more often manifest in males that females, and are known to be the cause of immune disorders such as XSCID (X-linked severe combined immunodeficiency) or IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) [40, 41]. These diseases are most dramaticly manifestated in males while females can often compensate or reduce severity due to the second X chromosome with an intact gene.

The observation that in females only one X chromosome is actively transcribed while the other one is condensed and heterochromatic, allowed Mary Lyon to propose that one X chromosome is randomly inactivated in female cells, a process also known as Lyonization [42]. While, theoretically, this process should be sufficient to establish equal expression of X chromosome encoded genes in female and male cells, it is now known that the X chromosome is only partially inactivated. It has been found that about 10-15% of genes can be expressed by both X chromosomes in female cells [43]. Such escape of inactivation results in the increased expression of certain genes in female compare to male cells. Random X-chromosome inactivation in somatic cells makes females functionally mosaic for X-linked genes, and results in allelic differences of transcribed genes among the same cell type in the host organism. Considering that humans, unlike inbred mice populations, posses high allelic gene diversity, such heterogeneity might be an additional genetic risk factor for autoimmunity. To complicate the picture further, while for the whole female organism this process is relatively random, this may not be the case for individual cell, group of cells, or an organ. Such skewing of X inactivation can be both beneficial and dangerous for the organism. For example, it has been shown that a high percentage of women with sclerosis manifest skewed or non-random X which may have a profound effect on the pathogenesis of the disease [44]. On the other hand, in the case of Wiskott-Aldrich syndrome, inactivation of the X chromosome that carries the defective gene can prevent the disease in females [45].

Another manifestation of the change in the expression levels of X-linked genes may be caused by spontaneous loss of one X chromosome, resulting in X monosomy. A series of studies by P. Invernizzi et al. demonstrated that in female patients with systemic sclerosis and autoimmune thyroid disease there is an increased frequency of blood cells containing only one X chromosome [46, 47]. This was not the case among SLE patients [46, 47]. Although it is still not clear what factors induce the process of X chromosome loss, it may be a compensatory mechanism to downregulate expression of those genes which escaped X-inactivation.

Another example of how altered expression of X-linked genes can lead to the development of autoimmunity was recently revealed in the BXSB mouse strain. Due to translocation of part of the X chromosome to the Y chromosome, these mice develop a lupus-like autoimmune syndrome with a higher frequency among males [48]. S. Bolland's group showed that the translocation results in the duplication of the gene encoding Toll-like receptor 7 (TLR7) and that this duplication and consequent overexpression of TLR7 is responsible for the accelerated autoimmunity. Such a definitive conclusion was questioned, however, by an other study that suggests a role for additional genes in Y-linked acceleration of lupus-like disease [49-51]. Nevertheless, the role of TLR7 in female-biased autoimmunity requires additional attention for several reasons. For example, overexpression of TLR7 beyond 2-fold is sufficient to drive development of lupus-like disease [50]. Interestingly, female mice have higher type I interferon production than male mice in response to TLR7 stimulation [52]. Therefore, it is important to assess the level of TLR7 expression in immune cells from female and male organisms and whether, and to what extent, and in what tissues, the TLR7 genomic region escapes X-inactivation.

Despite emerging data about the role of X-encoded genes in autoimmunity, until recently there have been no studies that have directly examined the role of X chromosome in autoimmune diseases. Recent elegant studies by R. Voskhul's group made an attempt to demonstrate a role for sex chromosomes in the generation of immune responses and in the development of autoimmunity [53, 54]. The authors created mice which had different compliments of sex chromosomes (XX or XY) but possessed the same gonads (ovaries or testes). Gonadectomy of such mice allowed for direct assessment of the role of sex chromosomes in the immune response and susceptibility to autoimmune diseases. The authors tested two independent models of induced autoimmune diseases, EAE and pristane-induced lupus. Possession of a XX, as opposed to an XY sex chromosome complement conferred greater disease severity in both models. Moreover, *in vitro* cytokine analysis revealed that T cells from XY mice produced increased amounts of Th2 cytokines such as IL-4, IL-5, IL-13, cytokines that have been shown to have a protective effect in autoimmunity [54].

These results clearly demonstrated that differences in sex chromosome complement have a significant impact on the immune system, and along with the hormonal differences, is a key contributing factor to female-biased autoimmunity.

FUTURE FOCUS

With the knowledge that gender affects autoimmunity, attention has been paid to the consequences of gender-driven differences on immune cell function. These cells express sex hormone receptors and of course contain the sex chromosomal make up characteristic of their host, so differences caused by gender could act directly on these cells. There is an increasing number of observations of different immune cell populations that display changes in their number and/or activation status during progression of autoimmunity. Recent findings demonstrated that gender also can have a significant impact on immune cell homeostasis and function, leading to significant differences in immunity between animals of different genders, with female predominance in autoimmunity. Therefore, immunologic changes that happen in different genders with age might not only increase our understanding of sex- and age-related immune system alterations, but also can shed some light on phenomenon of female-biased autoimmunity.

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Take-home massages

- Sex hormones can modulate Th1 and Th2 responses
- Fluctuations in sex hormones can affect severity of autoimmune diseases
- Unique features of the X chromosome and its complex regulation delayed our understanding of its role in autoimmunity
- The X chromosome complement directly contributes to female-biased autoimmunity

Table 1
Expression of steroid receptors by murine immune cells

Several studies has suggested the expression of progesterone receptors by lymphocytes during pregnancy but it has yet to be proven.

	Estrogen receptors	Androgen receptors	Progesterone receptors
B cells	+	+	-
CD4 T cells	-	-	-
CD8 T cells	+	-	-
Monocytes	+	-	-
Neutrophils	+	-	-
NK cells	+	-	-
Macrophages	-	+	-