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Gender as risk factor for autoimmune diseases

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Abstract

Most autoimmune diseases occur significantly more frequently in women than men. This female preponderance for abnormal autoimmune function has largely gone unexplained. Many investigations have concentrated on the effects of female and male sex hormones on immune function, by suggesting that estrogens favor the antibody production-enhancing Th2 response and, by doing so, possibly, increase the risk towards abnormal autoimmune function. Others have suggested that women are genetically predisposed towards abnormal autoimmune function, possibly because the X chromosome may confer susceptibility towards tolerance breakdown. Recent developments have, however, opened new research avenues. The possible association between persistent *fetal–maternal* microchimerism and the development of autoimmune diseases has attracted special interest. Since, in analogy to allogeneic organ transplantation, *fetal–maternal* (and *maternal–fetal*) microchimerism may play an important role in the immunologic tolerance of the fetal semi-allograft, female preponderance for autoimmune diseases may be understood as a consequence of increased allogeneic cell traffic in females (in comparison to males), increased risk for long-term microchimerism and, therefore, as a consequence of the former two, the development of abnormal autoimmunity. Under an evolutionary view point the occurrence of autoimmune diseases, in general, can be seen as the price to be paid for successful reproduction. In view of increased exposure to cell traffic, women, of course, would be expected to pay a higher price, reflected in more autoimmunity.

Keywords: Autoimmunity; Autoimmune diseases; Gender; Gender differences; Microchimerism; Cell traffic; Pregnancy; Vaginal delivery; Cesarean section; Sex hormones; Evolution

To be a woman is something so strange, so confusing and so complicated that only a woman could put up with it.

–Kierkegaard

Why is it that approximately 78% of roughly 80 medical conditions, currently believed to be autoimmune in nature, affecting 5–8% of the general population, are bound to occur in women? [1]. Much has been written in attempts to explain this overwhelming female preponderance, and theories abound. A definite answer is, however, still lacking. This review is an attempt at summarizing long held beliefs, but also at integrating more recent concepts, which so far may not have received adequate attention.

Our ultimate purpose is, however, to call attention to the fact that there must be considerable evolutionary purpose and value to the pathophysiology, responsible for women's dramatically increased predisposition towards abnormal autoimmunity. If such purpose and value did not exist, it is difficult to believe that evolutionary pressures would have maintained such an obvious risk to health and well-being. We have previously noted that, when challenged, evolution favors the creation of new life over its maintenance [2]. It, therefore, is tempting to speculate that, in some ways, exposing women

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to the risks of autoimmune diseases somehow serves a larger evolutionary goal. And there, of course, is no more valued evolutionary goal than creating new life.

An exploration of female preponderance in almost all autoimmune diseases (interestingly, there are a few exceptions), from such an evolutionary view point, thus opens new, and interesting, intellectual challenges by providing opportunity for the exploration of new experimental models which may add in the understanding of abnormal autoimmune function, but also with allograft transplant tolerance and the still unresolved puzzle of the fetal semi-allograft, tolerated by a principally hostile maternal immune system.

1. Traditional concepts

There is ample evidence that sex hormones can affect the immune system and that female and male hormones do so in, at times, opposing ways [3,4]. For example, Th1 and Th2 responses appear affected by androgenic or estrogenic preponderance, respectively: androgens favor the development of a Th1 response and activation of CD8 cells [5], while estrogens seem to direct the immune system towards Th2 dominance, where B lymphocytes are activated and antibody production flourishes [4]. Pregnancy, a high estrogen state, is of course, characterized by Th2 preponderance, and failure to establish Th2 dominance has been associated with increased risk for (immunological-induced) pregnancy loss [6,7]. This observation suggests that adjustments of the immune response are a necessity for normal pregnancy. As will be discussed in more detail below, one, therefore, can conclude that women are paying an *immunological price* to reproduce successfully.

A unique pattern of high potency estrogen production has been implicated in some women with systemic lupus erythematosus (SLE) [8], and is believed to represent a possible trigger for the development of disease in genetically predisposed individuals [9]. Androgenization with the mild male hormone dehydroepiandrosterone (believed to restore a more balanced Th1/Th2 ratio), on the other hand, has recently been demonstrated to decrease SLE flares and corticosteroid requirements [10].

Some investigators question the premise that sex hormones can quantitatively modulate immune responses. Amongst them, Lockshin argues that differences observed are the consequence of varying exposure levels to environmental factors, variances in vulnerability periods and, possibly, in threshold levels to hormone exposure [11]. If sex hormones could qualitatively affect autoimmune function, one would also expect to see correlations between frequency and severity of disease. Paradoxically, however, men, who comparatively suffer far less frequently from autoimmune diseases, experience significantly more severe disease when affected [12,13]. This observation indirectly also supports the contention that women are evolutionary prepared to pay an immunological price for the success of pregnancy because, assuming the necessity of such a routine immunologic adjustment, one, indeed, would expect less severe disease in prepared individuals and more severe disease in those who are unprepared.

Gender differences in autoimmunity have also been explained based on genetic factors. It now is widely accepted that most autoimmune diseases require a multitude of susceptibility genes to, working in concert, initiate phenotypic expression of disease [14]. Such genetic predisposition appears to foster a universal predisposition towards abnormal autoimmunity, and not only for one, specific disease [14]. We recently demonstrated this in a multigenerational follow-up of offspring from women with autoimmune diseases, who developed diseases at significantly increased rate in comparison to offspring from normal controls, but only rarely exhibited the same autoimmune diseases as their mothers [15]. Individual autoimmune diseases may thus only represent the phenotypical expression of a general genetic predisposition towards abnormal autoimmune function, most likely activated by specific environmental factors that may determine which specific disease is phenotypically expressed [16,17]. In our previously noted study, we were surprised to note that the most prevalent autoimmune disease in offspring was type 1 diabetes mellitus, while their mothers mostly exhibited classical autoimmune diseases, such as SLE and rheumatoid arthritis [15]. Such environmental factors could, in turn, be represented by sex hormone levels or, as Lockshin suggests [11], different vulnerability periods or threshold levels to such factors, with such differences not only differentiating between men and women, but, possibly, also between individuals of the same gender.

Based on the observation that some women with autoimmune diseases demonstrate an increased prevalence of X monosomic cells in peripheral blood, it has also been suggested that the X chromosome confers susceptibility to the break down of tolerance and, by doing so, predisposes women to more autoimmune risk [18,19]. Finally, excessive bidirectional HLA class II compatibility between mothers and their male offspring has been associated with an increased risk for SLE [20]. This observation has been interpreted as supportive for the importance of *fetal–maternal* microchimerism in the etiology of autoimmune diseases (see below). Unusually low levels of HLA antigens have previously been associated with the occurrence of autoimmunity [21].

2. Microchimerism

From very early on, pregnancy is characterized by bidirectional cell traffic between mother and child [22]. The amount of cell traffic increases with gestational age and, except for some complications of pregnancy (such as preeclampsia/eclampsia), reaches a peak with delivery [23], when mode of delivery of the child determines its volume: as was recognized in HIV-infected mothers, neonatal HIV infections of newborns can be minimized if offspring are delivered by cesarean section. An operative delivery, prior to the onset of labor, minimizes *maternal-to-fetal* cell transfusions [24]. In contrast, as has been known for decades from the experience with Rh-sensitized mothers, cesarean section deliveries maximize *fetal-to-maternal* cell traffic, requiring higher dosages of anti-D immunoglobulin than with vaginal delivery [25].