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Age-associated B cells: are they the key to understanding why autoimmune diseases are more prevalent in women?

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Abstract

“A significant body of research suggests roles for sex hormones as well as genetic factors in the development and/or progression of autoimmunity.”

Keywords

age-associated B cells; autoimmunity; TLR7; women; X chromosome

The normal function of the immune system is to protect the host against infection. The failure of the immune system to recognize its own cells and tissues as ‘self’ results in the damage of organs leading to their malfunction and causing autoimmune disease. Although each autoimmune disease is unique and leads to the dysfunction of a specific organ or population of cells, there is one common feature between many of them – sex-biased predisposition. It is well known that females are more predisposed to many autoimmune diseases than males although the reason for this sex bias is not completely understood. A significant body of research suggests roles for sex hormones as well as genetic factors in the development and/or progression of autoimmunity [1–3]. Although hormones and genetics are known to contribute to the incidence of autoimmunity, little is known about how these phenomena actually affect the immune system to subvert it from its normal function. In this article, we will briefly describe the main factors that are important for sex bias in

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autoimmune diseases and will review recent findings on a new population of B cells that predominantly appears in females and plays a role in autoimmunity [4, 5].

Factors involved in the female bias of autoimmunity

The two most obvious and most intensively studied factors that can be involved in the female bias among autoimmune diseases are differences in sex hormones and chromosomal composition. As far as sex hormones are concerned, it is well documented that the severity of rheumatoid arthritis and multiple sclerosis decreases during the pregnancy [6, 7]. Additionally, animal studies revealed that gonadectomy affects the severity and/or onset of autoimmune diseases in (NZB $\times$ NZW) F1 mice (a murine model of systemic lupus erythematosus) and NOD mice [8, 9]. Sex hormone receptors are expressed by different populations of innate and adaptive immune cells and affect the function of the immune system [1]. For example, sex steroids influence antigen presentation by dendritic cells and macrophages through the production of TGF- β and affect T-cell-mediated immunity by skewing Th1/Th2 responses [10, 11]. Immunoglobulin secretion and the numbers of immunoglobulin-secreting B cells are also affected by the levels of sex hormones [12]. However, no significant differences in sex hormone levels between autoimmune patients and healthy controls have been reported, indicating that there must be additional factors explaining overall female bias in many autoimmune diseases.

Recent studies have shown that gender-biased autoimmunity is also significantly influenced by genes present on sex chromosomes [3]. Since females have two X chromosomes and males have only one, genes located on this chromosome might differ in their expression level between males and females. To avoid these differences in the expression levels, one X chromosome in females is inactivated (lyonized) [13]. However, it has been reported that lyonization of the X chromosome is not complete, both in mice and humans [14, 15], resulting in overexpression of some of these genes from partially nonlyonized parts of the X chromosome, which can contribute to autoimmune disease in females [3]. In particular, it has been proposed that the X chromosome-encoded *Tlr7* gene might be one of the genes with differential expression levels in female versus male cells that might trigger autoimmunity [16].

Age-associated B cells & their role in female bias of autoimmunity

Although the contributions of hormones and X chromosome-encoded genes to autoimmunity are quite well accepted, the exact mechanisms by which they influence these diseases are not well understood. With this in mind, Cancro's group and our own recently studied the effects of gender on the composition of leukocytes in normal healthy mice and compared these differences with those in healthy and autoimmune humans [4, 5]. A particular population of B cells, named age-associated B cells (ABCs), bearing CD11b and CD11c, but not CD21, was found at a much higher frequency in aged female mice than in young females, or males of any age [4, 5]. Moreover, this population was found at a higher frequency in young healthy autoimmune-prone mice [4] and also in elderly women with rheumatoid arthritis, scleroderma or common variable immunodeficiency with autoimmune symptoms [17, 18]. ABCs secreted autoantibodies upon stimulation *in vitro* and depletion of these cells *in vivo* resulted in a reduction of autoreactive antibodies. Human ABC-like cells also produce autoantibodies [18]. Development of ABCs in mice required intact TLR7 signaling as both MyD88^{-/-} and TLR7^{-/-} aged female mice failed to accumulate ABCs. Additionally, autoimmune-prone mice that lacked TLR7 also failed to accumulate ABCs and failed to develop autoantibodies.

The classic ligand for TLR7 is viral single-stranded RNA; however, it has been reported that host RNA can also trigger TLR7 signaling when delivered to the endolysosomes [19]. It is possible that host RNA, released from dying cells, can be bound and internalized by B cells with receptors specific to such RNA or attendant proteins. In this case, RNA will enter the endolysosomes where it can trigger TLR7 signaling simultaneously with B-cell receptor signaling, leading to the autoantibody production. The failure to inactivate the second X chromosome happens more frequently with age, potentially leading to elevated levels of TLR7 expression and therefore higher sensitivity in older females. This may explain the female-specific accumulation of ABCs and female-biased autoimmunity with age.

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The appearance of ABCs at early ages in autoimmune prone mice and in human patients suffering from autoimmunity suggests their role in these disorders [4, 17, 18]. ABCs contribute to autoimmunity by the production of autoantibodies, but this is probably not their only function. It is still unclear how ABCs affect other immune cells in particular – T cells which is a subject of future research. Also, although ABCs are generated from follicular B cells [5] the exact process leading to their generation is, as yet, unknown.

Overall, the discovery that TLR7 expression affects autoimmune symptoms and the generation of ABCs has shed some light on the phenomenon of the female-bias of some autoimmune diseases. However, many questions remain about the appearance and functions of ABCs; questions that we hope will be answered in the future.

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Biographies