PERSPECTIVES: BIOMEDICINE

A Gender Gap in Autoimmunity

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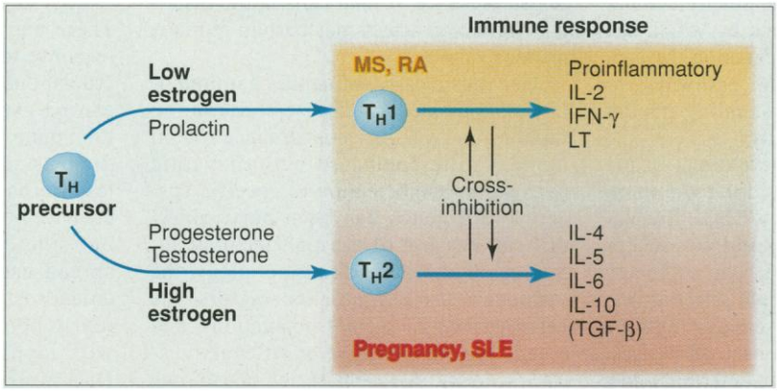
Autoimmune diseases—such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and thyroiditis—affect over 8.5 million people in the United States. Of these, a disproportionate number (about 6.7 million) are women (*1*). In multiple sclerosis and rheumatoid arthritis, the female to male ratio is between 2:1 and 3:1, whereas in lupus the distribution is more skewed, with nine times as many women affected as men (*2*). The precise reasons for this gender bias are unclear.

To promote further understanding of the basis for gender differences in autoimmune disease, a task force of clinical and basic scientists was convened by the U.S. National Multiple Sclerosis Society. The task force summarized what is currently known about sex differences in autoimmunity and developed a research agenda, ranking five areas as priorities for future investigation. In addition, they formulated a policy to encourage collection and examination of data in a gender-stratified manner [see (*3*) for full report].



Hormonal influences. T helper 1 (T_H1) cells secrete proinflammatory cytokines and promote cell-mediated immune responses, whereas T_H2 cells trigger antibody production. In multiple sclerosis (MS) and rheumatoid arthritis (RA), there are features characteristic of a T_H1 immune response directed against autoantigens in the central nervous system and joints, respectively. Pregnancy and systemic lupus erythematosus (SLE) favor a T_H2 environment. Sex hormones (such as progesterone) that promote the development of a T_H2 response antagonize the emergence of T_H1 cells. This may explain why in multiple sclerosis and rheumatoid arthritis disease symptoms improve during pregnancy, whereas in lupus, they do not.

Distinct immune environments in males and females underlie many of the sex differences in autoimmunity. These environments are established by the cytokines released by immune cells, particularly T helper (T_H) lymphocytes. These cells respond to an immune challenge in one of two ways: T_H1 lymphocytes secrete interleukin-2 (IL-2), interferon-γ (IFN-γ), and lymphotoxin, establishing a proinflammatory environment, whereas T_H2 lymphocytes secrete IL-4, IL-5, IL-6, IL-10, and transforming growth factor–β (TGF-β), which promote antibody production (see the figure). Both sets of lymphocytes exert cross-regulatory influences on each other. Females are more likely to develop a T_H1 response after challenge with an infectious agent or antigen, except during pregnancy when a T_H2 environment prevails. This is evident in experimental infections of animals where viruses such as vesicular stomatitis virus or herpesvirus, which require an inflammatory response for resolution, cause milder disease in females. However, lymphocytic choriomeningitis virus, which invades the central nervous system and elicits a T_H1 response, causes more neuropathology in females. Whether humans show similar gender differences in susceptibility to infectious diseases and their outcome remains to be seen.

The degree of immune response also differs between men and women. Immune responses tend to be more vigorous in females, resulting in greater antibody production and increased cell-mediated immunity after immunization. Important questions remain about the differences between males and females in production and secretion of immunomodulatory mediators such as TGF-β, interferons, prostaglandins, and individual T_H1 and T_H2 cytokines.

Direct comparisons of males and females to determine specific differences in the innate and adaptive immune responses is crucial. Such comparisons should encompass all phases of lymphocyte development, including early differentiation, tolerance, and senescence. Although such studies are feasible in animals, direct comparisons in humans pose unique problems—for example, obtaining sufficient enrollment of males with lupus. To carry out such studies, large-scale international cooperation between urban medical centers will be necessary.

The predominance of autoimmune disease among women suggests that sex hormones may modulate susceptibility. Most attention has been directed toward the sex steroids—estrogens, progesterone, and testosterone—that are produced in the ovary and testis. Estrogen's effects on normal immune responses and in autoimmune disease appeared to be contradictory, until it was realized that this hormone has biphasic dose effects, with lower levels enhancing and higher levels (such as those in pregnancy) inhibiting specific immune activities. The recent identification of a second estrogen receptor has prompted new areas of investigation. For example, which estrogen receptor is expressed by different immune cells? What do the two receptors do, and are there gender differences? How is receptor expression regulated? Progesterone promotes the development of human T_H2 cells and so antagonizes the emergence of the T_H1 response (see the figure). Similarly, testosterone has anti-inflammatory properties and exerts immunosuppressive effects in several animal models of autoimmunity.

The sexually dimorphic pituitary hormones, prolactin and growth hormone, as well as liver-derived insulin-like growth factor–1, also affect autoimmune disease. Women have higher levels of these hormones than men. Prolactin and growth hormone enhance autoimmunity, whereas insulin-like growth factor–1 promotes the recovery and repair of injured neural tis-

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sue. These hormones may act directly on immune cells through interactions with specific cell-surface hormone receptors. Alternatively, they may mediate their effects through modulation of the hypothalamic-pituitary-adrenal/gonadal axes. It will be necessary to determine whether there are gender differences in neuroendocrine function that contribute to autoimmune disease.

There are several possible ways in which sex hormones could affect the immune system. They may modulate T cell receptor signaling, expression of activation molecules on T lymphocytes and antigen-presenting cells, transcription or translation of cytokine genes, or lymphocyte homing. Elucidation of the precise cellular and molecular mechanisms by which sex hormones alter immune function, as well as the signal transduction pathways involved, is vital to understanding gender differences in autoimmunity.

There are natural fluctuations in the levels of sex hormones during the menstrual cycle and pregnancy. These fluctuations can be induced by oral contraceptives, and by estrogen replacement therapy after menopause. In multiple sclerosis and rheumatoid arthritis, disease symptoms may worsen before the onset of menses. Future studies will need to determine how normal immune and autoimmune responses change longitudinally during the menstrual cycle; correlating the levels of sex steroids and cytokines with disease severity will also be important.

During pregnancy (as well as before and after birth) there are differences between the diseases. In multiple sclerosis and rheumatoid arthritis, there is a decrease in disease severity during the 9 months of gestation, with a return to prepregnancy levels after birth. This is in contrast to lupus where some studies show that the disease worsens during pregnancy, whereas others show no change. Thus, the particular hormone environment during pregnancy favors a T_H2 response, which halts the progression of the T_H1 immune response associated with multiple sclerosis and rheumatoid arthritis. In lupus, pregnancy further enhances the ongoing T_H2 (antibody-promoting) response. High-priority areas for future investigation include determining the effect of pregnancy on specific immune responses and identifying which particular elements of the immune response change postpartum. Highest priority should be given to identifying the events responsible for postpartum flares in autoimmune disease.

Preliminary observations suggest that oral contraceptives are protective in multiple sclerosis and rheumatoid arthritis, but do not protect against lupus. Large multicenter clinical trials to test oral contraceptives in premenopausal women and estrogen replacement therapy in postmenopausal women with lupus are under way. The data from these trials should help to direct future research.

Fetal cells persist in the maternal circulation for years after birth, a state known as microchimerism. It has recently been proposed that these cells are involved in the initiation and postpartum flares of autoimmune disease, but exactly how microchimerism is involved in susceptibility to autoimmune disease, its initiation, and severity is not known. Moreover, it will be important to determine whether the continued presence of fetal cells in the maternal circulation affects postpartum immune responsiveness.

Genetics clearly influences autoimmunity, as indicated by disease clustering in families and a higher concordance rate in monozygotic compared with dizygotic twin pairs. Identification of specific susceptibility genes has been particularly difficult because of the multifactorial nature of autoimmune disease etiology, the influence of environmental factors, the heterogeneity of patient populations, and a wide spectrum in time of onset and disease severity. A recent series of genome exclusion mapping studies in defined multiple sclerosis patient populations reported differing results (*4*). However, they did identify a possible genetic linkage at chromosome 6p21—close to the major histocompatibility complex (MHC)—and hinted at possible linkages on chromosomes 5 and 19. The MHC has been implicated in experimental autoimmune encephalomyelitis (the animal model of multiple sclerosis), in human and animal studies of type I diabetes, in rheumatoid arthritis, and in most other autoimmune diseases. These findings have prompted the suggestion that there may be MHC- and non-MHC–linked candidate genes that are the same for different autoimmune diseases, as well as genes unique to a given disease, that determine the susceptibility of the target organ.

It is not known whether there is a genetic basis for gender differences in autoimmunity. If there is, then this will be the focus of much future research. However, the notion that genes conferring susceptibility to autoimmune disease may themselves be regulated by sex hormones also needs to be seriously considered.

Many autoimmune diseases differ in their clinical presentation between women and men. In multiple sclerosis, onset of symptoms in women appears to be earlier than in men, but men tend to exhibit a more progressive and severe disease course. In lupus, women first show disease symptoms during childbearing years, whereas men tend to show disease later in life. Differences in the rate of disease progression and presentation have been ascribed to sex-linked genetic factors and to the effects of sex hormones on injury and repair mechanisms. Carefully controlled studies in animals and humans are needed to ascertain the precise molecular basis for gender differences in the course and severity of autoimmune diseases, and in their characteristics at onset.

Gender differences in the course of autoimmune disease have implications for treatment. For example, when should therapy be initiated in men and women? There may be gender-specific effects in response to therapy as well as disease. A crucial question is whether sex hormones can be used therapeutically to treat autoimmune disease. Thus far, trials of androgens such as Danazol, Cyproterone, testosterone, 19-nortestosterone, and others have been conducted in lupus patients, but side effects have precluded widespread use. The exception is dehydroepiandrosterone (DHEA), which is currently being tested in men and women with lupus in a large multicenter trial. Data available thus far indicate that side effects are few and acceptable.

Although gender differences in autoimmune disease are well recognized, sexual dimorphism in the immune response and the importance of sex hormones in promoting differences between men and women need further study. Data gathered in ongoing and future analyses should be stratified on the basis of sex. In the past decade, there has been an explosion of information on immune mechanisms important in the pathogenesis of autoimmunity. In vitro examination of the effects of sex steroids on these pathways, and investigation in experimental animal models and in human clinical trials should help to clarify important gender- and sex hormone–related issues in autoimmune pathogenesis. Such clarifications may ultimately lead to improved therapies for autoimmune disease.

References

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2. P. B. Beeson, *Am. J. Med.* **96**, 457 (1994).
3. www.sciencemag.org/feature/data/983519.shl. The full report compiled by the Task Force on Gender, Multiple Sclerosis and Autoimmunity discusses the effects of gender on susceptibility to and severity of autoimmune disease. The report reviews the existing data on sexual dimorphism in the immune response, sexual dimorphism in infectious diseases, sex hormone regulation of the immune/autoimmune response and possible mechanisms of hormone action.
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