It is common knowledge that autoimmune diseases, for example, systemic lupus erythematosus, are much more prevalent among women. Obviously, this leads to the need to define the gender-related factors that influence susceptibility to autoimmunity. One of the main issues in this respect is pregnancy and pregnancy outcomes and the short- and long-term consequences of children born to mothers with autoimmunity.

The editors of this book provide the readers with up-to-date studies on key issues, reflected in the following titles of chapters: “The impact of autoimmunity on female reproductive success,” “Plausible mechanisms for the female predominance of autoimmunity,” “The role of estrogens and prolactin in the development of autoimmunity,” “Gender differences in autoimmunity associated with exposure to environmental factors” and many others.

**Plausible mechanisms for the female predominance of autoimmunity**

Many ideas are proposed to explain the predominance of autoimmune diseases in females. It is well known that autoimmune diseases are the result of the loss of immunological tolerance to self-antigens; therefore, the process of X chromosome inactivation offers a potential mechanism whereby X-linked self-antigens may escape presentation in the thymus or in other peripheral sites involved in tolerance induction. Although the exact mechanisms that cause X chromosome inactivation are still speculative, we do know that it could result in a situation in which self-antigens on one X chromosome may fail to be expressed at sufficiently high levels in the thymus, yet may be expressed at considerable frequency in peripheral tissues. This could be the stimulus necessary to break the tolerance of the immune system and lead to the development of autoreactive T lymphocytes.

**Gender and regulation of longevity: implications for autoimmunity**

The role of gender in the regulation of longevity may be linked to gender-specific genetic differences, including the expression of sex hormone patterns and the changes in these patterns during an individual’s lifetime. It has been shown that sex hormones have the capacity to regulate the inflammatory process and consequently influence the outcome of infection, thereby affecting longevity. In a human study, females were shown to have a higher survival rate following sepsis when compared with males. Males have also been found to respond to trauma and hemorrhage with depressed splenic and peritoneal macrophage cytokine release compared to females, who in contrast, demonstrated elevated or normal levels. In particular, Th1 cytokines appeared to be differentially increased in female mice in both trauma and sepsis models.

**The role of gender and organ-specific autoimmunity**

Sex hormones are capable of influencing the process of antigen presentation by dendritic cells, macrophages, and homing of lymphocytes to various organs, thereby influencing organ specificity of the autoimmune reaction. Organ-specific autoimmune diseases are caused by genetic, immune mediated damage, and environmental triggers such as viral infections. However, here also, sex hormones could contribute to the development of organ-specific diseases by inducing pro-inflammatory cytokines and, in certain conditions, organ-specific autoantibodies as in Hashimoto’s disease, myasthenia gravis, among others.

**The role of estrogens and prolactin in autoimmunity**

Estrogen and prolactin act as immunostimulators by affecting maturation and selection of autoreactive B cells and autoantibody secretion. Prolactin, on the other hand, leads to the production of interferon-gamma which is an important mediator in lupus nephritis. The involvement of these mediators is repeatedly mentioned and discussed by many authors in the book. Estrogens in human subjects are generally considered to be enhancers of cell proliferation (anti-apoptotic), thus playing a role in the development of autoimmunity. Estrogen induces a genetic program that alters survival and activation of B cells in a B cell-autonomous fashion and thus skew the naïve immune system toward autoreactivity and proliferation. Estrogens may reduce the therapeutic effects of disease-modifying drugs by acting at the level of immune/inflammatory cells in patients with rheumatoid arthritis. Recently, it was stressed that estrogens and their catechol
metabolites seem to play an important role in SLE. The possible mechanisms involve quinine-semiquinone redox cycling of catechol metabolites to generate free radicals that can cause DNA damage. This would probably alter immunogenicity of DNA, leading to induction and elevated levels of SLE autoantibodies cross-reacting with native DNA.

Prolactin is secreted from the pituitary gland as well as from lymphocytes. It interferes with B cell tolerance induction, enhances proliferative response to antigens and mitogens, and increases the production of antibodies and cytokines. Prolactin was also shown to be involved in the maturation of CD4+CD8- thymocytes to CD4+CD8+ T cells via interleukin-2 receptor expression. Prolactin induces a decrease in apoptosis of transitional B cells mediated by anti-immunoglobulin M and may be important in the breakdown of B cell tolerance to self and the development of autoimmunity. In the last two decades multiorgan and organ-specific autoimmune diseases such as SLE, rheumatoid arthritis, multiple sclerosis, Hashimoto’s thyroiditis and others were reported to be associated with hyper-prolactinemia.

THE ROLE OF ENVIRONMENTAL ESTROGENS IN AUTOIMMUNITY

The prevalence of autoimmune diseases has significantly increased over recent years. It has been proposed that this epidemiologic evidence could, in part, be attributable to environmental estrogens, compounds that display estrogen-like activity and are ubiquitously present in the environment. These phytoestrogens can be widely found in foods such as clover and soy. Meat, eggs and dairy products contain relatively high concentrations of estrogens. Estrogens can also be administered through medications (contraceptive pills, hormone replacement therapy, creams). The effects on human health of the synergistic interactions among natural, medical, dietary and environmental estrogens have not yet been fully elucidated. However, there are enough data to support the notion that environmental estrogens do affect the immune system, and to provide evidence for the association between exposure to those compounds and autoimmune diseases. Some of these estrogens were demonstrated to increase the proliferation of splenocytes and the activity of peritoneal macrophages, natural killer cells and cytotoxic T lymphocytes. In other studies, they were shown to increase both IL-2 and IL-5 secretion by EL4 thymoma cells. In contrast, in dentritic cells, environmental estrogens significantly and dose-dependently inhibited the expression levels of maturation-associated cell surface markers CD40 and CD86. Further studies are needed to explicate how environmental estrogens could possibly contribute to the development of autoimmunity.

THE AUTOIMMUNE BASES OF INFERTILITY AND PREGNANCY LOSS

Numerous autoimmune diseases, including but not limited to SLE and antiphospholipid syndrome, may be associated with infertility and pregnancy loss through different putative mechanisms. First, serum autoantibodies such as antiphospholipid, antithyroid, or anti-nuclear antibodies may be directly associated with infertility, regardless of the presence of a clinically overt autoimmune disease. Second, autoimmunity may affect all stages of fertility, via ovarian failure, testicular failure, implantation failure, and pregnancy loss. Third, infertility may also be secondary to vasculitis associated with other conditions such as SLE and diabetes mellitus.

Pro-inflammatory cytokines secreted by Th1 lymphocytes, such as tumor necrosis factor-alpha, interferons, IL-6 and IL-2 are all involved in cellular mediated immunity reactions and placental development, with Th2 anti-inflammatory, normal related cytokines such as IL-4, IL-10, IL-13 and granulocyte-macrophage colony-stimulating factor involved in placental growth and prevention of fetal rejection. The Th1/Th2 shift correlates with the progressive increase of hormones, steroids and estrogens during pregnancy.

This book covers a wide spectrum of additional issues related to gender, pregnancy, sex hormones and autoimmune diseases. It contains a huge amount of information that could be useful for physicians in all subspecialties of medicine – autoimmunologists, rheumatologists, gynecologists, and internists. The book is edited by leading scientists in this field who invited many well-known physicians/scientists to contribute. It is recommended that the book be obtained by all medical libraries in hospitals and medical schools.

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References