SEX HORMONES AND THE GENESIS OF AUTOIMMUNITY

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Introduction: Autoimmune diseases encompass nearly seventy distinct clinical entities. Among the earliest and most intriguing observations within this group of disorders is the discrepancy in disease prevalence between females and males. Systemic lupus erythematosus (SLE) is among the most female-dominant of all autoimmune diseases with a lifetime female:male ratio of 9:1. The sexually dimorphic prevalence of SLE, coupled with the dramatic increase in disease incidence in females after puberty, the reversal of this phenomenon after menopause, and the variation in disease severity throughout the menstrual cycle and pregnancy, has led to investigation of sex hormones for their role in the manifestation of autoimmune disease.

While the utilization of sex hormones for treatment of reproductive system disorders has spanned two millennia and become conventional practice, only recently have sex hormones been appreciated for their role in mammalian immunophysiology. This review explains the role of sex hormones in human immunology, describes the unique expression of sex hormones among patients with SLE, and outlines how an abnormal hormonal milieu contributes to the genesis of autoimmune disease.

Background: In contrast to non-specific protection afforded the host by innate immunity, the acquired immune system purposefully protects the host by distinguishing ‘self’ from ‘non-self’. The acquired immune system, composed almost exclusively of B and T lymphocytes, is that which goes amiss in autoimmune disease. The acquired immune system of females differs from that of males because estrogens encourage immunologic processes driven by CD4+ TH2 cells and B cells, whereas androgens enhance CD4+ TH1 and CD8+ cell activity. Autoimmune diseases mediated by TH2-dominant immunophysiology are proportionately more female-dominant than those conditions driven by TH1-dominant activity (Table 1). Estrogens, androgens, their metabolites, and receptors are all involved in immunoregulation and the development of autoreactivity.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Immunologic mediation</th>
<th>Female patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>TH2</td>
<td>95</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>TH2</td>
<td>94</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Unknown</td>
<td>93</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>TH2</td>
<td>92</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>TH2</td>
<td>89</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Unknown</td>
<td>89</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>TH2</td>
<td>88</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>TH1</td>
<td>75</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Unknown</td>
<td>73</td>
</tr>
<tr>
<td>Polymyositis/Dermatomyositis</td>
<td>Unknown</td>
<td>67</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>TH1</td>
<td>64</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Unknown</td>
<td>52</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>TH1</td>
<td>48</td>
</tr>
</tbody>
</table>

Adapted from Seli E, Arici A. Sex Steroids and the Immune System 2002

Females differ from males in their baseline immunity. In the hormonal milieu of estrogen predominance, which is usual in a healthy female during the reproductive years, the immune
system is pressured toward predominance of CD4+ TH2 mediated immune processes. When compared to healthy males, females have higher immunoglobulin levels at baseline, produce greater quantities of immunoglobulin in response to infection and immunization, have higher CD4:CD8 T cell ratios, and have a greater proportion of TH2 cells, resulting in a specific circulating cytokine profile that promotes antibody production 3-5,7,12,14-16. These trends are reversible with pharmacologic estrogen blockade citation. In contrast, in a state of androgen predominance, CD8 suppressor T cells are upregulated and immunoglobulin synthesis is diminished 6,17,18. In addition to the effects of sex hormones upon ‘preference’ of lymphocyte phenotypes, estrogens also play an important role in the lymphocyte maturation processes which render cells less immunoreactive to self antigens. Estrogens promote rapid shuttling of lymphocytes through developmental processes within the bone marrow and thymus, and encourage maturation of lymphocytes in organs incapable of screening for autoreactivity, such as the liver and spleen. These alterations in lymphocyte maturation lead to a functional bypass of negative selection and tolerance induction, allowing maturation of B and T cells with autoreactive potential 3,15,16,19-21. The net result of estrogen’s influence on the development and activity of lymphocytes is one that causes an increase in cells with autoreactive potential that are primed to form antibody.

Lupus phenotype: Patients with lupus demonstrate unique patterns of estrogen production and estrogen metabolism. Elevated aromatase enzyme activity is a feature common among patients with lupus. Aromatase is a modifier of 17-ketosteroids which converts androgens to estrogens. Aromatase, therefore, raises the ratio of estrogens:androgens 2,3,22,23. Estrogen is also an inducer of aromatase, high estrogen concentrations beget further increase in female hormones and reduction in male hormones 2,3. In addition to elevated estrogen:androgen ratios, patients with SLE metabolize estrogens in patterns distinct from those observed in unaffected controls. Cytochrome p450 isoenzymes CYP1B1 and CYP1A1 convert estradiol to the biologic effectors 16α-hydroxyestrone and 2α-hydroxyestrone, respectively. 16α-hydroxyestrone is among the most biologically active serum estrogens. It activates B and T cells, induces transcription, and promotes cell division. In contrast, the 2α-hydroxy product has little biologic effect 22,24. Patients with SLE have increased activity of CYP1B1 with preferential hydroxylation of estradiol to the more ‘feminizing’ 16α-hydroxy metabolite 10, 11,22,25,26. The altered conversion results in a 20-fold increase in the fraction of high-potency:low-potency estrogens in patients with SLE when compared to healthy controls 22. Interestingly, this happens to be the same ratio as is observed in patients with estrogen-responsive adenocarcinomas of the breast 24.

In addition to having high quantities of a biologically potent estrogen, males and females with SLE have decreased availability of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and DHEA-sulfate 10,11,19,22,25. To underscore the direct relationship between hormones and immune function, it is worthy to mention that not only do patients with lupus have decreased accessible androgens, but the reverse is also true. Androgen deficient males with Klinefelter’s syndrome have a higher incidence of TH2-driven autoimmune diseases (including SLE) than do healthy males 4,27,28.

Lupus Autoreactivity: The hormonal milieu in patients with lupus provides a set-up for autoreactivity. The influence of estrogen encourages lymphocyte maturation without proper negative selection or tolerance induction, and estrogen’s impact stimulates imbalance of the immune system toward TH2 stimulation of B cell antibody synthesis 29. Nonetheless, autoreactivity still requires exposure to self-antigen. In patients with lupus, apoptosis is flawed. Apoptotic cells, by definition those that die while maintaining the integrity of the cell membrane, are not cleared effectively by macrophages. Apoptotic cells are forced into processes of secondary necrosis, breaking down the cellular membrane and exposing phospholipase and DNA 30-34. These previously sequestered substances then become available as antigens, antigens which are an easy stimulus for autoantibody production in light of the lymphocyte phenotype expression among these patients.

Impaired macrophage function in lupus patients does not appear to be inherent. Macrophages extracted from lupus patients and exposed to healthy control serum improve in their phagocytic capacity. In addition, healthy macrophages that are exposed to lupus serum become ineffective scavengers 32,35. This suggests that there is yet an unidentified serologic factor responsible for lupus macrophage impairment. Perhaps, this too, will be a sex hormone 32-36.

References


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