SEX STEROID HORMONES AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Disordered Immunoregulation

My laboratory has been studying the influence of sex steroid hormones on the expression of systemic lupus erythematosus (SLE) in the classic model for lupus, the NZB/NZW F_1 (B/W) strain (1–3). In this model, female mice die several months earlier than males. They have an earlier onset of LE cells, antinuclear antibodies, immune complex nephritis, and death from renal failure. Numerous organs become markedly infiltrated with lymphocytes and plasma cells, including the lungs and the salivary glands. The etiology of their disease is multifactorial and includes genetic, immunologic, hormonal and possibly viral components.

Workers in our laboratory have long considered that the key to unraveling the pathogenesis of autoimmune disease in mice lay in studying the disordered state of immune regulation which they manifest (4,5). The viral component, we argued, would probably be an ordinary virus recoverable equally well from normal mice. The unusual expression of virus in lupus mice arose because the immune system failed to adequately cope with the virus (5).

Thus, the primary cause of murine lupus is genetic. The role of the virus is primarily as a precipitating factor. By analogy, the role of drugs in drug-induced lupus might also be as precipitating factors in patients predisposed to illness because of genetic mechanisms. Of course, these genetic mechanisms need not necessarily be immunologic, but could involve aspects of drug metabolism. It is noteworthy that drugs which induce lupus in human beings do not influence the illness in NZB mice.

The immunoregulatory abnormalities in the NZB and B/W strains involve T cells, B cells, macrophages and probably other cells as well. There has been a great deal of interest and some degree of controversy about which cell is involved primarily. The initial culprit was thought to be the T cell. This idea was supported by the discovery of natural thymocytotoxic autoantibody in lupus serum which has the ability to kill suppressor T cells. This autoantibody contributes to the deficiency of suppressor T cells which exists in human and murine lupus. How important this mechanism might be in vivo is still uncertain. Additional evidence for T cell abnormalities relates to the deficiency of thymic hormones which develops in NZB and B/W mice.

In recent years, much evidence has also accumulated to suggest that B cell abnormalities arise primarily and not simply as a consequence of suppressor T cell deficiency. Lupus mice behave as if under the influence of intrinsic polyclonal B cell activators. This seems analogous to the influence of lipopolysaccharide in normal mice.

This controversy between the T cell and B cell schools is probably resolvable when one considers that the immune system is a network of interacting components. In all likelihood, the primary defect is in a stem cell; this defect is then transmitted into both T and B cell lineages. Furthermore, the defect in the macro-

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phages could be even more important than the T and B cell abnormalities. Regulation of the immune response by macrophages expressing Ia on the cell surface is an early and critical event in the network of immunologic control.

Immunoendocrinology

Spontaneous lupus, in contradistinction to drug-induced lupus, is predominantly a female disease. The female-to-male ratio can be as high as 15 to 1, although it varies with age and racial characteristics. This ratio is only 2 to 1 when one considers women prior to the onset of menses or postmenses. These clinical observations suggest that sex hormones influence the development of systemic lupus erythematosus. Furthermore, patients with Klinefelter's syndrome also have an increased incidence of lupus. These patients are males with an extra X chromosome (XXY). They are under a hyperestrogenic influence, develop gynecomastia, and fail to develop normal male secondary sex characteristics.

My laboratory has found that sex hormones play a major role in modulating immunopathologic events, probably explaining the female predominance of lupus. These studies can be seen in the broad context of a field that might be called immunoendocrinology, representing the overlap between the twin disciplines of immunology and endocrinology. This overlap is bidirectional. Our studies demonstrate the influence of endocrine factors on immune reactivity.

However, there are also examples of immunity regulating the endocrine system, often leading to disease. For example, Graves' disease is a hyperthyroid condition in which autoantibodies react with TSH receptors. Some patients with extreme insulin-resistant diabetes mellitus make antibodies to the insulin receptor. Neuroendocrine influences might be superimposed on the immune and endocrine systems, creating pathways by which the brain could control vital immune and endocrine mechanisms. Considerable evidence is accumulating to support a role for neuroendocrine factors in immunity.

Our experiments were summarized in an earlier Kroc Foundation meeting (6). They demonstrate the ability of androgen to suppress murine lupus. Castration of male B/W mice results in an accelerated pattern of disease expression identical to females. Castrated male mice develop autoantibodies, immune complex nephritis, and uremia at essentially the same rate as females. Although castration of female B/W mice does not ameliorate disease, a therapeutic effect can be achieved by administering male hormone to females. Androgen-treated female B/W mice can live a normal lifespan with little or no evidence of autoimmunity.

We have recently studied the effects of androgen and estrogen in another mouse model for lupus, the MRL-*lpr/lpr*. This mouse develops a form of lupus even more accelerated than that of the B/W strain. We have recently found that the administration of androgen to the MRL-*lpr/lpr* mouse also suppresses autoimmunity.

We have devoted considerable attention over the last 2 years to defining the mechanisms by which sex steroid hormones exert these effects. Many experiments dealing with T and B lymphocyte number and function yielded inconclusive results. However, we have two positive findings that appear to be important.

With Dr. Hannah Shear from New York University (7), we have studied the clearance in mice of IgG-coated autologous erythrocytes. Lupus patients show delayed clearance of such particulate immune complexes. Likewise, B/W mice have a delayed clearance which becomes abnormal first in females. Clearance in female B/W mice can be improved by the administration of androgen; in males, it is made worse by the administration of estrogen. Presumably these effects on clearance are mediated by actions of sex steroid hormones on macrophages and other cells of the reticuloendothelial system. Thus, the macrophage may be an important target site for sex hormones.

In collaboration with Dr. Penti Siiteri, we have obtained evidence for sex steroid hormone receptors in mouse thymus (8). We do not know whether these receptors are on thymocytes or on thymic epithelium. We suspect that they are on thymic epithelium, the endocrine component of the thymus. Such a model would create an endocrine circuit in which gonadal products might influence thymic hormone production. Furthermore, if sex steroids act on macrophages and thymic epithelium, then their ability to influence lymphocyte activity could be indirect rather than direct.

We have recently investigated another aspect of immunoendocrinology, the role of interleukin-2 (IL-2, T cell growth factor) in autoimmunity. This material can be considered an immunologic hormone which is secreted by one T lymphocyte population and influences the behavior of a second T lymphocyte subset. IL-2 is produced by $Lyt1^{+}23^{-}$ cells and leads to the differentiation of a whole range of effector cells. We find a deficiency of IL-2 in all autoimmune-susceptible strains of mice (9). This deficiency is most notable in MRL-*lpr/lpr* mice which develop the most severe expression of murine lupus. A deficiency of IL-2 is also present in

C57BL6/*lpr* mice which are a garden variety C57BL/6 mice into whom the *lpr* gene has been introduced by 8 cycles of cross-intercross mating (10). These C57BL/6 mice develop lupus and lymphoproliferation very similar to that which occurs in MRL-*lpr/lpr* mice. Thus, in two strains of mice (MRL and C57BL6), the *lpr* gene results in both IL-2 deficiency and the lupus syndrome.

Our current work is directed toward unraveling the mechanisms by which IL-2 deficiency leads to autoimmune disease. We have preliminary evidence that androgens maintain IL-2 activity in murine lupus, suggesting a relationship between sex steroid hormones and immune modulators (11). The multifactorial nature of autoimmune disease may at times seem complicated and confusing. However, it also offers opportunities for new therapeutic approaches based on mechanisms which, although outside the classic immune system, can nevertheless restore immune regulation.

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