

Molecular and clinical evidence of the role of estrogen in lupus

Regina Vidaver

The Society for Women's Health Research Scientific Advisory Meeting on Sex Differences in Immunology and Autoimmunity was held at Longwood Medical in Boston, MA, USA on 8 November 2001.

For decades, scientists and physicians have suspected that estrogen and other steroid hormones play a role in systemic lupus erythematosus (SLE) and other autoimmune diseases [1,2]. SLE, for example, affects between six and ten times as many women as men. In women, lupus strikes generally after puberty and before the menopause. Some female SLE patients have abnormal estrogen metabolism, and in others, antihormonal therapy seems to alleviate symptoms. However, explanations for the sex-associated differences in susceptibility have often been anecdotal and sometimes contradictory.

'SLE...affects between six and ten times as many women as men.'

At this meeting, several leading researchers described their latest efforts to determine the molecular mechanisms underlying the role of sex hormones in SLE. Also, they presented preliminary results from experimental therapies designed to subvert or exploit these mechanisms in patients. SLE remits and relapses spontaneously, so doctors must remain vigilant to protect their patients' organs from irreversible destruction.

Altering estrogen metabolism as a potential therapy

Robert Lahita (New York, NY, USA) has looked for an explanation for the higher prevalence of SLE in women based on estrogen metabolism. Lahita and colleagues have found elevated activity of one of two estrogen metabolic pathways in lupus patients. They have devised a therapy based on reducing the flux through this pathway, which produces feminizing 16-hydroxy (16-OH) estrogen

derivatives. Preliminary results from ongoing clinical trials show that the 16-hydroxylase inhibitor, indole-3-carbinol, can shift the system towards the production of less-feminizing 2-OH derivatives.

Lahita is working also on another experimental therapy using the weak androgen dehydroepiandrosterone (DHEA). Androgens are thought to be beneficial to SLE patients; women with the disease have elevated levels of the enzyme aromatase, which decreases the level of available androgens by converting them to estrogens. Preliminary results from a current, double-blind, multicenter trial of DHEA suggest that the drug has beneficial effects on some symptoms but is not likely to be of use for severe cases of SLE.

Molecular mechanisms of the effect of estrogen on apoptosis

To address the question of how changes in estrogen metabolism affect the immune system, Gil Mor (New Haven, CT, USA) described his studies on the role of estrogen at the molecular level. Mor has found that estrogen is involved not only in the regulation of inflammatory stimuli, but might also be a key factor in regulating apoptosis. He has found that one of the major immune targets of estrogen is the macrophage population, and that estrogen stimulates these cells to produce anti-inflammatory cytokines, such as interleukin-4 (IL-4), IL-6 and IL-10.

Other work from Mor's laboratory has revealed the direct impact of estrogen on Fas and Fas ligand (FasL), the receptor and ligand, respectively, that are associated most commonly with the induction of apoptosis [3]. It turns out that, in addition to other elements, the FasL promoter contains an estrogen-responsive element, which binds the estrogen-estrogen-receptor complex and drives expression of the gene encoding FasL. The relationship between estrogen and FasL expression has profound

consequences for cells expressing both FasL and the estrogen receptor but also, for any cell expressing the Fas receptor, because FasL can act in a paracrine fashion, inducing the apoptosis of neighboring cells. Excessive apoptosis might flood the immune system with intracellular self-antigens, increasing the probability of an autoimmune response. By contrast, inhibition of the cell-death pathway might prevent the clonal deletion of T cells, leading to autoimmune lymphoproliferation. Thus, balanced apoptosis is crucial to ensuring good health. In mice, for example, the inactivation of Fas or FasL by mutation results in a disease that resembles human SLE. These findings might lead ultimately to a mechanistic model for one effect of estrogen on the immune response.

'The relationship between estrogen and FasL expression has profound consequences...'

Effects of estrogen on B cells

In further research linking estrogen to apoptosis, Ansar Ahmed (Blacksburg, VA, USA) has found that estrogen might help B cells, including autoreactive B cells, to survive the body's normal apoptotic culling processes. In mouse models, Ahmed and colleagues have found that estrogen increases the expression of interferon γ [4], which in turn, increases the production of nitric oxide. They are investigating the role of nitric oxide in blocking the cell-death process. In the same mice, estrogen shrunk the thymus, leading possibly to impaired T-cell selection or the dysregulation of T cells. Ahmed noted that to maintain health, there is a complex regulatory balance between T cells and B cells, called immunological tolerance. When this homeostasis is disturbed, the immune system can become deranged, leading to an autoimmune attack. Estrogen then can break B-cell tolerance.

Ahmed drew a distinction between autoimmunity, which might serve a

Key outcomes of the meeting

- Estrogen affects apoptosis through a variety of factors, including Fas, FasL, IFN- γ and nitric oxide.
- Proper destruction of autoreactive B cells is crucial to maintaining health. Estrogen can interfere with B-cell tolerance.
- Aberrant T-cell–B-cell interactions have been observed in SLE patients; estrogen is involved in such interactions.
- Potential therapies for lupus on the horizon include altering estrogen metabolic pathways and the use of estrogen receptor antagonists.
- Estrogen is not the only factor contributing to women's disproportionate affliction with lupus.

physiological function, and autoimmune disease. After observing that estrogen-treated lupus-prone mice have a higher incidence of autoimmune disease, whereas androgens seem to suppress the disease, Ahmed began to wonder about the effects of estrogen on the normal immune system. His research group is studying these issues at the cellular and molecular level in mouse models and the results might ultimately be important for healthy women exposed to estrogenic compounds.

'...balanced apoptosis is crucial to ensuring good health.'

SLE is mediated by autoantibodies produced by B cells, the most prevalent of which is an autoantibody specific for double-stranded DNA. Working with human cells and transgenic mouse models that express anti-DNA antibodies, Betty Diamond (New York, NY, USA) and her colleagues have shown that estrogen can break B-cell tolerance. Estrogen blocks the destruction of immature autoreactive B cells developing in the bone marrow of mice, and tamoxifen, which is known to be a partial inhibitor of estrogen, does not reverse this effect completely. Diamond's group is following up these results with studies of human cells to learn if the same pathways function in humans and if estrogen regulates human B cells. They are investigating also the genetics underlying hormonally responsive lupus in mice and humans.

Interactions between B cells and T cells in lupus

In SLE, T cells activate and interact with B cells; this interaction is the focus of a

collaboration between Virginia Rider (Pittsburg, KS, USA) and Nabih Abdou (Kansas City, KS, USA). Rider's and Abdou's groups have shown that estrogen increases the expression of calcineurin and CD40 ligand (CD40L) in cultured T cells from women with lupus [5]. T cells from men with lupus, as well as those from normal men and women, do not exhibit this increase in expression. Calcineurin is one of the proteins in the T-cell activation pathway that increases the expression of CD40L on the surface of T cells, leading to increased antibody production by the interacting B cell. This work is believed to be the first description of a molecular link between estrogen-dependent T-cell activation and possible B-cell hyperstimulation through aberrant T-cell–B-cell interactions.

'Estrogen blocks the destruction of immature autoreactive B cells developing in the bone marrow of mice...'

These studies suggest that estrogen receptor antagonists might be a potential therapeutic approach to help some women with lupus. Rider and Abdou are continuing to explore the underlying molecular mechanisms involved in the action of estrogen on human T cells.

Concluding remarks: sex hormones are not the only factor

Many of the speakers warned against generalizing about endocrine mechanisms in SLE and other autoimmune diseases. Echoing and extending that sentiment, Michael Lockshin (New York, NY, USA) urged scientists to look beyond hormones

to explain sex differences in the incidence of lupus and other autoimmune diseases. Lockshin challenged researchers to demonstrate how estrogen models can explain the highly variable sex ratios in incidence between the various autoimmune diseases, and explain why there are no differences in severity between males and females for most autoimmune diseases. 'So far, you cannot explain autoimmunity [only] with estrogen.'

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Regina Vidaver

Society for Women's Health Research, Suite 625, 1828 L St NW, Washington, DC 20036, USA.

e-mail: regina@womens-health.org

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