CONNECTIVE TISSUE DISEASES

Shedding light on SLE autoimmunity

The findings of a study published in *Arthritis and Rheumatism* could help unravel the complex relationship between reproductive hormones and systemic lupus erythematosus (SLE) autoimmunity. Researchers from the University of Washington have shown that the administration of depot medroxyprogesterone acetate (DMPA), a common human contraceptive agent, reduces mortality associated with the development of glomerulonephritis in a mouse model of lupus.

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“Estrogens and prolactin are thought to contribute to SLE in genetically predisposed individuals by promoting survival of autoreactive B cells and activation of dendritic cells,” explains the study’s lead investigator Grant Hughes. “By contrast, the role of progesterone, a known immunomodulatory steroid, has not been well studied.” The investigators hoped that an effect of progesterone treatment in lupus-prone mice could help shed light on the progesterone deficiency that is commonly seen in patients with SLE.

“In order to increase the chances of observing an effect,” says Hughes,

“we began treating animals before disease onset, using high-physiologic concentrations of hormone.” Premorbid (6-week-old) female NZB/NZW mice were administered vehicle or 2 mg or 10 mg of DMPA as a long-acting subcutaneous dose every 6 weeks. After 39 weeks of treatment, the investigators observed a significant reduction in mortality in mice treated with DMPA. All of the animals that had been treated with 10 mg DMPA, and the majority of those given the lower dose of the agent, survived until the end of the study period; by contrast, just one-third of the control animals remained alive at 39 weeks.

“This effect has not been reported in female NZB/NZW mice treated with other forms of progesterone,” observes Hughes. Moreover, levels of proteinuria, a marker of glomerulonephritis activity that in mice is closely followed by death, were reduced in DMPA-treated animals compared with controls, suggesting that the prolonged survival times were associated with attenuation of glomerulonephritis by DMPA.

The investigators then sought to determine whether differences in the animals’ serum autoantibody responses could explain the reduced mortality seen in DMPA-treated mice. They found that DMPA treatment suppressed serum levels of IgG2a anti-double-stranded DNA (dsDNA), whereas serum IgG1 anti-dsDNA levels were elevated, despite

an overall reduction in the total serum IgG1 subclass level. These observations led the investigators to suggest that one way in which DMPA exerts its effect is through blockade of the nephritogenic type 1 T-helper (T_H1)-associated antibodies, IgG2a while increasing the protective T_H2 -associated antibody IgG1. “When the results of this study are compared with the known effects of estrogen treatment in the same model, a compelling pattern emerges,” says Hughes. “In NZB/NZW mice, estrogen enhances an already strong tendency to produce IgG2a anti-DNA antibodies; progesterone has the opposite effect.” The balance of estrogen and progesterone could, therefore, be important in determining whether or not a genetically susceptible individual develops glomerulonephritis.

As well as explaining the potential significance of reduced progesterone levels in patients with SLE, these findings could strengthen the rationale for the use of progestin-containing contraceptives as a potential therapeutic option. “Many clinicians who care for patients with SLE already favor progestin-only forms of hormonal birth control over those containing estrogen, which are linked to an increase in SLE; our findings provide mechanistic support for that practice,” says Hughes.

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