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Testosterone Acts Directly on CD4⁺ T Lymphocytes to Increase IL-10 Production¹

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Males are less susceptible than females to experimental autoimmune encephalomyelitis and many other autoimmune diseases. Gender differences in cytokine production have been observed in splenocytes of experimental autoimmune encephalomyelitis mice stimulated with myelin proteins and may underlie gender differences in susceptibility. As these differences should not be limited to responses specific for myelin proteins, gender differences in cytokine production upon stimulation with Ab to CD3 were examined, and the mechanisms were delineated. Splenocytes from male mice stimulated with Ab to CD3 produced more IL-10 and IL-4 and less IL-12 than those from female mice. Furthermore, splenocytes from dihydrotestosterone (DHT)-treated female mice produced more IL-10 and less IL-12 than those from placebo-treated female mice, whereas there was no difference in IL-4. IL-12 knockout mice were then used to determine whether changes in IL-10 production were mediated directly by testosterone vs indirectly by changes in IL-12. The results of these experiments favored the first hypothesis, because DHT treatment of female IL-12 knockout mice increased IL-10 production. To begin to delineate the mechanism by which DHT may be acting, the cellular source of IL-10 was determined. At both the RNA and protein levels, IL-10 was produced primarily by CD4⁺ T lymphocytes. CD4⁺ T lymphocytes were then shown to express the androgen receptor, raising the possibility that testosterone acts directly on CD4⁺ T lymphocytes to increase IL-10 production. In vitro experiments demonstrated increased IL-10 production following treatment of CD4⁺ T lymphocytes with DHT. Thus, testosterone can act directly via androgen receptors on CD4⁺ T lymphocytes to increase IL-10 gene expression.

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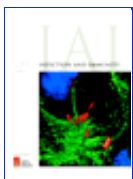
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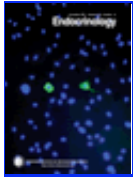
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