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## JOURNAL ARTICLE

# Direct and indirect effects of murine interleukin-2, gamma interferon, and tumor necrosis factor on testosterone synthesis in mouse Leydig cells

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It was recently observed that treatment of patients with a high dosage of human interleukin (IL-2) resulted in suppression of plasma concentrations of testosterone. A murine model was developed to assess the direct and indirect effects of murine IL-2 and the secondarily released cytokines, gamma interferon (INF gamma), and tumor necrosis factor (TNF alpha), on testosterone production in isolated Leydig cells. Pretreatment for 24 hours with IL-2 (100 to 500 IU/ml) or INF gamma (100 to 1000 IU/ml) significantly decreased testosterone production in response to luteinizing hormone (LH;  $P < 0.02$  and  $0.005$ , respectively). The combinations of INF gamma with either TNF alpha or IL-2 produced enhanced suppressive effects on Leydig cell testosterone production. Steroidogenic precursors (22-hydroxycholesterol, 17 alpha-hydroxypregnenolone, and dehydroepiandrosterone) restored testosterone secretion to control levels after preincubation with INF gamma or TNF alpha. In contrast, the inhibition of testosterone synthesis produced by either IL-2 or INF gamma plus TNF alpha could be reversed by 17 alpha-hydroxypregnenolone and dehydroepiandrosterone, but not by 22-hydroxycholesterol ( $P < 0.01$ ). Dibutyryl cyclic adenosine monophosphate was also ineffective in reversing the inhibitory effects of these cytokines on synthesis. Although IL-2 directly inhibited synthesis in isolated Leydig cells, it stimulated testosterone production ( $P < 0.005$ ) in minced murine testes. This suggests that IL-2 releases regulatory factors from other cells that were able to overcome the direct inhibitory effect of IL-2. This stimulatory effect was not caused by INF gamma and TNF alpha because INF gamma alone or with TNF alpha inhibited ( $P < 0.005$ ) testosterone production in minced testes. (ABSTRACT TRUNCATED AT 250 WORDS)

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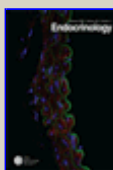
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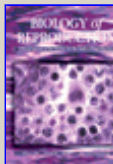
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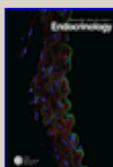
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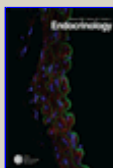
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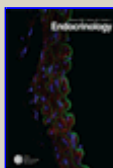
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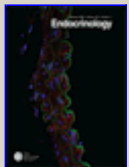
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