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TNF-alpha as a Paracrine Factor in the Testis

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Functions of the testis, which is composed of many different cell types, are controlled by cell-cell communication. The cell-cell communication in the testis is mediated by autocrines and paracrines. Many substances including growth factors and cytokines have been suggested as such regulators. Here, we present that TNF-α, a proinflammatory cytokine, works as a paracrine to modulate gene expression in the testis.

Mullerian inhibiting substance (MIS), also known as anti-Mullerian hormone (AMH), is essential in normal sex differentiation and reproductive function. MIS expression in the testis is restricted to Sertoli cells and is high in fetal to prepubertal mice, but becomes low in pubertal to adult mice. Previous studies have suggested that MIS expression is regulated by meiotic germ cells, although the substance responsible for this cell-cell communication remains unknown. The cytokine TNF-α is produced in meiotic germ cells, while TNF-α receptor is detected in Sertoli cells. Furthermore, NF-κB, a downstream mediator of the TNF-α signaling cascade, is expressed at a high level in Sertoli cells and has been implicated in the regulation of mammalian spermatogenesis. These previous studies let us hypothesize that TNF-α may be the inhibiting substance that is secreted from meiotic germ cells and represses MIS expression in Sertoli cells, possibly through NF-κB activation.

The present study demonstrates that the cytokine TNF-α is a strong candidate for such a germ cell inhibiting substance and how its signaling represses the expression of MIS in Sertoli cells. TNF-α inhibited MIS expression in testis organ cultures and TNF-α -/- testes showed high and prolonged MIS expression. Furthermore, in transient transfection assays TNF-α suppressed the MIS promoter that was activated by SF-1, one of the major transcription factors that regulate MIS expression. The modulation of SF-1 transactivation by TNF-α is through the activation of NF-κB, which subsequently interacts with SF-1 and represses its transactivation. The physical association of NF-κB with SF-1 was shown by yeast two-hybrid protein interaction, GST-pull down, and coimmunoprecipitation analyses. ChIP assays also revealed that endogenous NF-κB as well as SF-1 is recruited to the MIS promoter upon TNF-α signaling. SF-1-bound NF-κB subsequently recruits HDACs to inhibit the SF-1-activated gene expression. These results may identify, for the first time, the responsible substance and its action mechanism underlying the repression of MIS expression by meiotic germ cells in the testis. Furthermore, the regulatory mechanism of SF-1 transactivation by NF-κB, which is defined in this study, adds yet another level to the already complex regulation of gene expression controlled by SF-1.