36. IFN-GAMMA AND UTERINE EPITHELIAL RESPONSIVENESS TO TGF-BETA

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Positive pregnancy outcomes are critically dependant on an immunologically receptive environment in the female reproductive tract. Seminal fluid is important in generating maternal immune tolerance to paternal transplantation antigens, and TGF-beta 1 has been identified as the key factor in seminal fluid, which initiates this process (1). IFN-gamma is a potent immune modulator known to interfere with TGF-beta 1 signalling in other cell systems, and IFN-gamma is often present in high levels in the semen of partners of women suffering recurrent miscarriage (2). Modulation of uterine epithelial cell responsiveness to TGF-beta 1 by IFN-gamma was investigated using an in vitro cell culture model. Uterine epithelial cells were harvested from estrous female mice and exposed to a range of doses of TGF-beta 1 or beta 3 and IFN-gamma either individually or in combination. GM-CSF and IL-6 were measured as an indication of responsiveness to TGF-beta, using specific bioassays. Addition of TGF-beta 1, beta 2 or beta 3 alone resulted in a 4-fold and 2-fold increase in GM-CSF and IL-6 production, respectively, and the response was dose-dependent. IFN-gamma elicited a dose-dependent inhibition of up to 75% in GM-CSF production but did not affect IL-6 production. When cytokines were added in combination, both TGF-beta 1 and beta 3 overcame the inhibitory effect of IFN-gamma. Similarly, when penicillin - a known IFN-gamma binding molecule - was added to the culture system, the inhibitory effects of IFN-gamma were neutralised. We conclude that there is a mutually antagonistic relationship between TGF-beta and IFN-gamma in semen. High concentrations of IFN-gamma in semen may act to inhibit the immune tolerance-inducing properties of TGF-beta during early pregnancy. The findings support the use of exogenous TGF-beta as a therapeutic strategy in treating miscarriage in women.

(1) Robertson SA, Ingman WV, O'Leary S, Sharkey D and Tremellen KT (2002) *J. Reprod. Immunol.* **57**, 109–128. (2) DJ Sharkey, KP Tremellen, GA Dekker, SA Robertson (2002) *Reprod. Fertil. Dev.* Suppl. **14**, 81.

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