The effect of transforming growth factor beta1 null mutation on murine reproductive function

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ABSTRACT

Transforming growth factor beta 1 (TGFβ1) is a multifunctional cytokine implicated in gonad and secondary sex organ development, spermatogenesis and ovarian function, immunoregulation of pregnancy, embryo implantation and placental development. The TGFβ1 null mutant mouse offers the unique opportunity to study the role of TGFβ1 in vivo. TGFβ1 null mutant males are 100% infertile. When housed with normal females they do not deposit sperm or induce pseudopregnancy. Serum testosterone levels in adult TGFβ1 null mutant mice is decreased by 75%, caused by factors upstream of testis function as testosterone production can be induced by exogenous gonadotrophins. In the majority of TGFβ1 null mice, spermatogenesis proceeds normally and in vitro fertilisation experiments have shown the sperm are viable. Behavioural studies revealed that TGFβ1 null mutant males display mounting behaviour and while some intromit, ejaculation never occurs. Nitric oxide synthase enzymes were not induced in the penis of TGFβ1 null males in response to gonadotrophin, and this may be the cause of impaired sexual performance. Neither replacement of testosterone during perinatal development and/or adulthood, nor treatment with sildenafil citrate restored sexual function. Female TGFβ1 null mice also have severe fertility deficiencies. These mice suffer three distinct reproductive lesions (1) failure of 50% of the females to mate with normal stud males, (2) in females that do mate, failure of preimplantation embryo development leading to 80% infertility and (3) failure to nurture pups in the small proportion of females that produce live litters. Ovarian function is severely impaired in TGFβ1 null mutant females and is likely to be the principle cause of reproductive failure. The number of ovulations is reduced by 40% and each corpora lutea produces less progesterone leading to a 75% decrease in serum progesterone during early pregnancy. Embryos from TGFβ1 null mutant females on day 3.5 post coitum were developmentally arrested in the morula stage. Embryos from superovulated null mutant mice fertilised with normal sperm and cultured in vitro also failed to develop to blastocysts. Together, these studies suggest that preimplantation embryo developmental failure is the result of a lesion in oocyte development in the ovary prior to ovulation. These studies demonstrate that TGFβ1 is indeed a critical factor in many aspects of murine reproductive function.