INFERTILITY IN MICE WITH NULL MUTATION OF THE EGR-1 TRANSCRIPTION FACTOR

D. L. Russell

Obstetrics and Gynaecology, The University of Adelaide, Adelaide, SA, Australia

Female infertility has been reported in two lines of mice with mutation of the *Egr-1* gene. One underlying cause of this defect is deficient LH production by pituitary gonadotropes. However, Egr-1 is also acutely regulated by both FSH and LH in ovarian granulosa cells (1). A role for this transcription factor in regulating gonadotrophin responsive target genes and ovarian function is hypothesised. Indeed the LH-receptor is a proposed target of Egr-1 regulation, but this has not been investigated in detail *in vivo* and is difficult to reconcile with the pattern of Egr-1 expression.

In this study, the role of Egr-1 within the ovarian follicle was investigated using exogenous gonadotropin replacement in *Egr-1*$^{-/-}$ mice . Adult *Egr-1*$^{-/-}$ female mice superovulated by sequential PMSG and hCG stimulation and mated with proven male breeders failed to produced offspring while 90% of heterozygous females got pregnant and produced litters (7.4 ± 2.9 pups per litter) within 22 days of stimulation. Recovery of oocytes from oviducts of immature superovulated mice revealed a reduced ovulation rate in null females (6.3 ± 3.8 oocytes) compared to their heterozygous (18.0 ± 6.5) and WT (17.8 ± 6.8) littermates. Gross morphology and histology of exogenously stimulated ovaries were indistinguishable from their heterozygous or WT counterparts. Surprisingly, no alteration was detectable in the mRNA expression of previously reported direct Egr-1 responsive genes, namely LH-receptor and membrane prostaglandin E synthase (mPGES). Nor were mRNA for two critical ovulatory genes with putative Egr-1 response elements, ADAMTS-1 or versican V1 altered. Temporal and spatial expression of genes involved in ovarian steroidogenesis, P450scc and Cyp17 and LH-receptor, were indistinguishable from normal littermates during exogenously controled follicular development.

Combined observations of acute Egr-1 induction by gonadotropins, reduced ovulation and complete infertility suggest an important role for Egr-1 in ovarian function. However, genes identified as targets of Egr-1 regulation in other studies proved to be Egr-1 independent in this model.

(1) Russell *et al*. (2003) *Mol. Endo.* **17**, 520.

10.1071/SRB04Ab279