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Immature rat ovaries become revascularized rapidly after autotransplantation and show a gonadotropin-dependent increase in angiogenic factor gene expression

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Abstract

When the ovaries of 23-day-old juvenile rats are transplanted to an ectopic site, they recover within 1 week the ability to control gonadotropin secretion via steroid negative feedback. Vascular corrosion casting followed by scanning electron microscopy revealed that the transplanted ovary becomes profusely revascularized within 48 h after transplantation. Vascular ingrowth was accompanied by a 40- to 60-fold increase in expression of the genes encoding two angiogenic factors, vascular endothelial growth factor (VEGF) and transforming growth factor-beta 1 (TGF beta 1), as assessed by RNA blot hybridization of the corresponding mRNAs. Although TGF beta 3 mRNA levels also increased, no changes in the levels of mRNAs encoding other putative angiogenic factors, such as TGF alpha, basic fibroblast growth factor, and TGF beta 2, were observed. Hybridization histochemistry demonstrated that in intact ovaries, VEGF mRNA is mainly expressed in granulosa cells of the cumulus oophorus and thecal cells of large antral follicles. Transplantation is followed by an increase in mRNA abundance and a dramatic shift in cellular localization, so that the mRNA becomes predominantly expressed in cells of the outer ovarian cortex. In intact ovaries, low levels of TGF beta 1 mRNA were detected in thecal-interstitial cells; after transplantation, its expression also became more predominant in the ovarian outer cortex, but this change was not as marked as in the case of VEGF. Because ovarian autotransplantation is followed by a rapid increase in serum gonadotropin levels, experiments were conducted to determine the importance of this rise in the activation of VEGF and TGF beta 1 gene expression. After transplantation, some animals were treated with the LHRH antagonist Nal-Glu LHRH (50 micrograms/rat, once a day for 2 days) to prevent the posttransplantation rise in serum gonadotropins. Quantitation of VEGF and TGF beta 1 mRNA by RNase protection assay 48 h later showed that suppression of gonadotropin secretion diminished the increase in both VEGF and TGF beta 1 gene expression. Concomitant treatment with PMSG (8 IU/rat, single injection), which mainly bypasses the suppression of endogenous FSH levels, restored the TGF beta 1 mRNA response, but had no effect on VEGF mRNA. The results suggest that the increase in gonadotropin secretion following ovarian transplantation contributes to revascularization of the graft by up-regulating the gene expression of two major angiogenic factors.