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Gonadotropin-Mediated Regulation of the Murine VEGF Expression in MA-10 Leydig Cells

HEIDI SCHWARZENBACH, GOPA CHAKRABARTI, HANS JOACHIM PAUST AND AMAL K. MUKHOPADHYAY

From the Institute for Hormone and Fertility Research, University of Hamburg, Grandweg 64, D-22529 Hamburg, Germany.

Correspondence to: Dr Amal K. Mukhopadhyay, Agelab, Falkenried 88, D-20251 Hamburg, Germany (e-mail: am{at}agelabpharma.de).

Presence of vascular endothelial growth factor (VEGF) is not only limited to cells directly involved in angiogenesis but has also been demonstrated in steroidogenic cells like testicular Leydig cells. Because Leydig cells are subjected to regulation by gonadotropic hormones and produce steroid hormones, we have investigated here the effects of human chorionic gonadotropin (hCG) or steroid hormones on VEGF expression in cultured mouse tumor Leydig cells (MA-10 cells) and have then analyzed the underlying molecular mechanisms. Northern blot analysis and enzyme-linked immunosorbent assays revealed increases in VEGF mRNA and protein levels, respectively, over 3-20 hours in MA-10 cells after stimulation with hCG or 8-Br-cAMP. Although MA-10 cells lack the classical progesterone receptor, progesterone was able to stimulate VEGF expression. Promoter analyses and antibody supershift experiments suggested that the proximal region is able to constitutively bind the transcription factors Sp1 and Sp3. Mutations of 2 potential Sp1 binding sites in the proximal region showed the requirement of these motifs for stimulation of VEGF by hCG and 8-Br-cAMP. The distal cytosine-rich sequence interacts with so far-unidentified faster migrating factors. Following stimulation with hCG or 8-Br-cAMP, the binding of these proteins was increased in the complexes formed in the proximal and distal regions. VEGF expression in Leydig cells is regulated by gonadotropin via a cAMP-dependent mechanism, and the transcription factors Sp1 and Sp3 appear to be involved in the activation of the promoter. Progesterone also appears to play a role in the regulation of VEGF, acting presumably via a nonconventional receptor that remains to be characterized yet.

Key words: Testes, angiogenesis, vascular permeability, growth factor, progesterone, nongenomic steroid action.

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