OVARIAN RESEARCH IN THE POST GENOMIC ERA: ANALYSES OF GDF-9 AND OTHER PARACRINE SIGNALING PATHWAYS

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Recent publication of the genomic sequences for human and multiple model organisms allows the elucidation of the evolutionary origins of human genes. Because of the coevolution of polypeptide ligands and their cognate receptors, analysis of human genomic sequences allows one to predict the pairing of these elements. Based on a genomic approach, we identified the known BMPRII and ALK5 as the receptors for GDF-9 (1,2) and elucidated downstream signaling Smad molecules in ovarian follicles. We also identified LGR7 and LGR8 as receptors for relaxin and INSL3 respectively (3,4). Based on the known production of INLS3 by testicular Leydig cells and ovarian theca cells, we investigated the expression of the INSL3 receptor, LGR8, in male and female gonads. Of interest, LGR8 expression was found exclusively in oocytes in the ovary and male germ cells in the testis. We further found that LH stimulates INSL3 transcripts in ovarian theca and testicular Leydig cells. INSL3, in turn, binds LGR8 expressed in germ cells to initiate meiotic progression of arrested oocytes in preovulatory follicles *in vitro* and *in vivo* and to suppress male germ cell apoptosis *in vivo* (5). In contrast to its stimulation of cAMP production by somatic cells, INSL3 interacts with germ cells to activate the inhibitory G protein, thus leading to decreases in cAMP production. Our data demonstrate the importance of the INSL3–LGR8 paracrine system in mediating gonadotropin actions in gonads. We have set up an ovarian gene database (Ovarian Kaleidoscope database at http://ovary.stanford.edu) in which more than 1 600 ovarian gene pages can be accessed online and searched by gene name, function, mutation phenotype, expression pattern, cellular location and other parameters. Database analysis of polypeptide ligand and receptor genes provides a functional genomic paradigm for the identification of novel ligands and receptors in the ovary. To assist ovarian researchers in the analyses of their DNA array datasets, a Microarray Data Interpreter has been set up in the OKdb to facilitate searches and comparisons of known and novel genes in the ovary.

(1) *Biol. Reprod.* 2002. (2) *Mol. Endocrinol.* 2004. (3) *Science* 2002. (3) *J. Biol. Chem.* 2002 (4) Kawamura *et al. PNAS* 2004.