

Molecular regulation of gonadotropin receptor expression: Relationship to sterol metabolism. K.M.J.Menon, Lei Wang, Anil K.Nair, Helle Peegel, Bindu Menon and Nathan Kolderman, Departments of Ob/Gyn and Biological Chemistry, University of Michigan, Ann Arbor, MI, 48109, U.S.A.

Post-transcriptional mechanism plays an important role in the regulation LH/hCG receptor (LHR) expression in the ovary. We have identified a specific LHR mRNA binding protein that selectively binds to the polypyrimidine rich bipartite sequence in the coding region of the LHR mRNA and accelerates its degradation. This process has been shown to be one of the mechanisms that is responsible for the loss of the steady state levels of LHR mRNA following the preovulatory LH surge or the down regulation of the receptor in response to the administration of a pharmacological dose of LH or hCG. The *trans* factor, designated as the LHR mRNA binding protein (LRBP), was purified and its identity was established as being mevalonate kinase, an enzyme involved in cholesterol biosynthesis. Depletion of mevalonate kinase by treating cultured luteal cells with 25-hydroxycholesterol totally abrogated LHR mRNA down regulation. The expression of mevalonate kinase is induced in response to cholesterol depletion resulting from increased LH-induced steroidogenic activity. Examination of the crystal structure of mevalonate kinase coupled with mutagenesis of the critical residues in the catalytic site revealed that the catalytic site is in close proximity to the LHR mRNA binding site. Further studies revealed that mevalonate kinase causes LHR mRNA degradation by acting as a translational suppressor by forming an untranslatable ribonucleoprotein (RNP) complex which is then targeted for degradation. An examination of possible interacting partners of mevalonate kinase in yeast 2 hybrid screen using a cDNA library constructed from LHR down regulated ovary revealed 2 proteins, ribosomal protein S20 and ubiquitin conjugating enzyme (UBCE 2i). These proteins might serve as intermediary molecules in translational suppression and LHR mRNA degradation. (Supported by NIH grant R37 HD 06656)