

Dr. Mary Hunzicker-Dunn is the recipient of the 2005 SSR Research Award. This prestigious award, funded by Organon NV, is given for scientific accomplishments during the past six years. Dr. Hunzicker-Dunn is an outstanding researcher who has made numerous contributions to the field of signal transduction that have enhanced our understanding of how the gonadotropin receptors signal to promote follicular maturation and is preeminently worthy of this award. Below is a research summary provided by Dr. Hunzicker-Dunn, focusing on the last six years of her distinguished career.



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Dr. Hunzicker-Dunn has made seminal contributions to our understanding of signal transduction pathways activated by the gonadotropins. During the past six years, she and her laboratory have published 31 papers in premier journals, e.g. *Biology of Reproduction*, *Journal of Biological Chemistry*, and *Proceedings of the National Academy of Sciences*. Her research has been recognized by her peers, as evidenced by her invited presentations at the Endocrine Society Meeting and at numerous universities, service on NIH study sections, and current responsibility as one of the associate editors for *Molecular Endocrinology*.

One of the major accomplishments of the Hunzicker-Dunn laboratory in the last six years was to elucidate the cellular mechanism by which the LH receptor becomes desensitized. In particular, they not only convincingly demonstrated that desensitization of the LH receptor does not involve receptor phosphorylation, but also proved the involvement of the proteins ARNO, ARF6, and arrestin in this pathway. This research is considered to be a major breakthrough because it is in contrast to the popular belief that G protein-coupled receptors are generally desensitized by receptor phosphorylation, as in the case of the adrenergic receptors. Thus, this body of work has settled the controversy regarding the requirement for receptor phosphorylation by this gonadotropin receptor to promote desensitization. Following this new paradigm for phosphorylation-independent desensitization of the LH receptor, other groups appear to be re-examining desensitization of other G protein-coupled receptors including the adrenergic receptors, to determine the roles of ARNO, ARF and arrestin in regulating the coupling of these receptors to their cognate G proteins. This is an area in which reproductive biology has played the pioneering role and led the general field of cell biology and biochemistry.

The Hunzicker-Dunn laboratory has also made impressive strides towards elucidating the signaling pathway by which the FSH receptor directs follicular development. One of the key substrates that this lab has identified as being downstream of the FSH receptor and its signaling intermediate protein kinase A (PKA) is histone H3. This lab, in collaboration with Larry Jameson, demonstrated that FSH stimulates the phosphorylation and acetylation of histone H3 on Ser10 and Lys14, respectively, under cellular conditions in which granulosa cells differentiate but do not proliferate. While histone H3 phosphorylation on Ser10 has long been recognized as a marker for mitosis, the notion that H3 phosphorylation marks regions for transcriptional activation was novel and potentially universal, since the Ser10 phosphorylation site on histone H3 can be phosphorylated not only by PKA but also by a number of protein kinases including those downstream of growth factor receptors. Indeed, the demonstration of H3 phosphorylation in a 1999 publication and its phosphorylation and acetylation coupled with activation of immediate early target FSH genes in a 2001 publication by the Hunzicker-Dunn laboratory was some of the first evidence that histone H3 modifications were directly linked with activation of target genes. The epigenetic field is now filled with papers describing histone modifications under various experimental paradigms.

Dr. Hunzicker-Dunn's group has gone on to identify a previously unrecognized target gene activated by FSH, that of the A-kinase anchoring protein microtubule associated protein 2D (MAP2D). The family of MAP2 proteins, which consists of MAP2A, 2B, 2C, and 2D was thought to be predominately associated with neuronal cells. The discovery by the Hunzicker-Dunn lab that MAP2D, and not the other members of this family, is selectively induced in granulosa cells by FSH and persists into corpora lutea following ovulation suggests that this protein plays a key role in final follicular maturation.

Additionally in the past 6 years, this laboratory has identified the cellular pathway by which FSH signals to activate the extracellular regulated mitogen-activated protein kinases, or ERKs. They discovered that all of the components in this signaling cascade were already activated in untreated granulosa cells, and yet FSH was able to activate ERK. This conundrum was solved when this laboratory demonstrated that FSH signals into the ERK cascade at the level of ERK itself by regulating the association of an inhibitory protein tyrosine phosphatase with ERK. By catalyzing the phosphorylation of this phosphatase, PKA promotes the dissociation of the inhibitory phosphatase from ERK, allowing ERK activation via a tonic pathway which is not presently understood. Using chemical inhibitors of the ERK pathway, FSH-stimulated ERK activation appears to be crucial not only for the ability of FSH to induce a select group of FSH target genes, including MAP2D. This group has also shown that FSH signals into the phosphatidylinositol-3 kinase (PI-3 kinase) pathway to regulate translation. One of the proteins whose translation is increased in response to FSH is the transcription factor hypoxia inducible factor-1 (HIF-1). They have shown that HIF-1 activation is necessary for FSH to activate a number of target genes, including that for the LH receptor, inhibin- $\alpha$ , and vascular endothelial growth factor (VEGF). This was the first evidence that FSH regulated expression and activation of this transcription factor.

Overall, Dr. Hunzicker-Dunn's laboratory has provided a body of work in the past six years that begins to define the cellular mechanisms by which the gonadotropic hormones regulate ovarian function.