

β -catenin and gonadotropins: A mechanistic tale of two sites of action

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Normal reproductive function in mammals requires precise transcriptional control of the genes encoding LH in the anterior pituitary. In turn, secreted LH regulates gonadal function in part by exerting transcriptional control of steroidogenesis. In both the pituitary and the gonad, the orphan nuclear receptor SF-1 plays a central role regulating transcription of genes encoding LH and those encoding steroidogenic enzymes. In this presentation, new data will be presented indicating that β -catenin interacts functionally with SF-1 to mediate GnRH regulated transcription of the *Lhb* gene and LH-regulated transcription of key steroidogenic enzymes.

With respect to *Lhb* gene transcription, we have discovered that mutation of residues in SF-1 that define a binding pocket for β -catenin abolished the synergy of SF-1 and Egr-1 on the *Lhb* promoter. Together these data suggest that β -catenin is a component of higher-order complex that imparts transcriptional regulation of the *Lhb* gene.

In addition, we can also link β -catenin to transcriptional regulation of steroidogenesis in granulosa cells. In the gonad, SF-1 is critical for basal and cAMP-induction of key steroidogenic enzymes. As for the *Lhb* gene, mutation of the β -catenin interaction domain of SF-1 significantly reduced basal *STAR*, *P450scc*, and *P450aro* mRNA levels in the human KGN granulosa cell line, suggesting that β -catenin is a critical cofactor for SF-1 in both gonadotropes and granulosa cells.

In addition to its effects on SF-1, β -catenin has traditionally been shown to coactivate transcription for the TCF/Lef family in Wnt signaling cascades. Intriguingly, emerging reports suggest TCF isoforms can coregulate genes requiring SF-1, but lacking TCF response elements in their promoter regulatory regions. Thus, competition for shared coactivators such as β -catenin may be one mechanism regulating gene expression by these transcription factors. Consistent with this, we have also observed stimulation of a TCF promoter reporter construct by GnRH and LH, in L β T2 and KGN cells respectively, revealing unexpected regulation of TCF-dependent transcription by peptide hormone signaling cascades. Accordingly, current efforts within our laboratory are focused on determining the hormonal signaling mechanisms underlying β -catenin regulation, and its role as a coactivator of gene expression at multiple levels of the reproductive axis.