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STEROIDOGENIC FACTOR 1: A KEY MEDIATOR OF ENDOCRINE DEVELOPMENT AND FUNCTION

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1. Initial characterization of SF-1

Through concerted analyses of the mouse cytochrome P450 steroid hydroxylases, we defined promoter elements that regulated their coordinate expression within steroidogenic cells. Several of these elements interacted with the same cell-selective DNA-binding protein, designated steroidogenic factor 1 (SF-1). The cloning and characterization of cDNA and genomic clones encoding SF-1 demonstrated that SF-1 is an orphan member of the nuclear hormone receptor family. Promoter analyses in transfected steroidogenic cells suggested that SF-1 is a key determinant of the cell-selective expression of the cytochrome P450 steroid hydroxylases.

To explore the roles of SF-1 in endocrine function, we used in situ hybridization to examine its sites of expression. In adult mice, SF-1 was expressed in the adrenal cortex, testicular Leydig cells, and theca and granulosa cells of the ovary-all known to express the steroidogenic cytochromes P450. During embryonic development, SF-1 was expressed in both male and female mouse embryos as the intermediate mesoderm condensed to form the urogenital ridge in early stages of gonadogenesis.

With the onset of testes differentiation, SF-1 levels increased in the interstitial region (i.e. androgen-producing Leydig cells) and the testicular cords (i.e. Müllerian-inhibiting substance-synthesizing Sertoli cells). Strikingly, SF-1 transcripts in ovaries decreased coincident with sexual differentiation, suggesting that persistent SF-1 expression may impair female sexual differentiation. Besides the gonads and adrenals, SF-1 transcripts also were detected in the anterior pituitary and hypothalamus, suggesting that SF-1 regulates the endocrine axis at other levels.

2. Analyses of SF-1 knockout mice

To examine its roles in vivo, we used targeted gene disruption to make SF-1 knockout mice. The absence of SF-1 was associated with a dramatic phenotype-adrenal and gonadal agenesis and male-to-female sex reversal-establishing essential roles for SF-1 in the development of the steroidogenic tissues. The earliest stages of gonadogenesis occurred without SF-1, but the gonads regressed via programmed cell death when sexual differentiation would normally occur. The SF-1 knockout mice also showed that SF-1 is essential for pituitary expression of multiple gonadotrope-specific genes, linking SF-1 to a second level of the reproductive axis. Finally, SF-1 also is essential for the integrity of the ventromedial hypothalamic nucleus (VMH). Thus, SF-1 globally regulates reproduction at all three levels of the hypothalamic-pituitary-gonadal axis.

The striking effect of the SF-1 knockout on the VMH is intriguing, as this nucleus has been implicated in appetite regulation and female reproductive behavior. Analysis of VMH development-using the modified SF-1 transcript as a lineage marker-suggested that SF-1-expressing neurons migrated into the appropriate region of the diencephalon, but then disappeared between E17.5 and postnatal day 1. SF-1 deficiency specifically affects the VMH, with absent estrogen receptor (ER) positive cells in the ventrolateral portion of the VMH, but normal ER expression in the adjacent arcuate. These data suggest that SF-1-directly or indirectly-plays important roles in cell migration and/or proliferation in the mediobasal hypothalamus.

3. Characterization of SF-1 target genes

We and others have identified a number of target genes through which SF-1 modulates endocrine development. The cytochrome P450 steroid hydroxylases were the first group of genes shown to be activated by SF-1. SF-1 also regulates a number of genes that play critical roles in endocrine differentiation and function, including: Müllerian Inhibiting Substance (Sertoli cells), the steroidogenic acute regulatory protein (steroidogenic cells of the adrenal cortex and gonads); the alpha subunit of glycoprotein hormones (pituitary gonadotropes), the HDL receptor SR-B1 (adrenocortical cells, Leydig cells and ovarian theca cells).

Although these studies provide important insights into SF-1 function, they do not fully account for the phenotype of SF-1 knockout mice, as mutations or targeted disruptions of each of these genes have been reported-none of which causes complete loss of the primary steroidogenic organs.

While it remains possible that the collective effect of absent expression of multiple target genes of SF-1 has more severe effects than single mutations, this finding suggests that additional target genes of SF-1 mediate its critical roles in organogenesis.

4. Characterization of the human SF-1 gene

The essential roles of SF-1 in mice raised the question of whether SF-1 plays similar roles in humans. We first mapped the human gene to chromosome 9q33-34. Unfortunately, this region has not been implicated in genetic syndromes that match the phenotype predicted from SF-1 knockout mice (e.g., adrenal insufficiency with 46, XY sex reversal). To set the stage to identify human SF-1 mutations associated with endocrine diseases, we determined the sequence of the human SF-1 gene, showing that SF-1 was highly conserved between mice and humans. Finally, we established that the expression pattern of SF-1 in human embryos closely resembled that previously defined in mice. These findings strongly suggested that SF-1 plays similar essential roles in human endocrine development. Definitive proof for this model came when Jameson and colleagues reported a human patient with adrenal insufficiency and 46, XY sex reversal associated with a de novo mutation of SF-1 that abrogated DNA binding. Intriguingly, SF-1 in humans shows haploinsufficiency, as the second allele of SF-1 lacked any detectable mutations. This finding suggests that the dosage of SF-1 expression may be more critical in humans than in mice.