Molecular and Cellular Endocrinology 371 (2013) 154–159

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Beyond steroidogenesis: Novel target genes for SF-1 discovered by genomics

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ARTICLE INFO

Article history:
Available online 17 November 2012

Keywords:
Adrenal cortex
Transcription factors
Nuclear receptors
Genomics

ABSTRACT

Steroidogenic Factor-1 (SF-1) is a nuclear receptor transcription factor that has an essential role in the development of adrenal glands and gonads and in the regulation of steroidogenic gene expression. Recent studies using genomic approaches have revealed that SF-1 also has an important role in regulating proliferation of adrenocortical cells and have revealed its role in the control of a variety of biological processes as diverse as angiogenesis, adhesion to the extracellular matrix, cytoskeleton dynamics, transcriptional and post-transcriptional regulation of gene expression and apoptosis in the adrenal cortex. The identification of the complete set of SF-1 target genes will be of great importance to open new avenues for therapeutic intervention in adrenal diseases.

Contents

1. Introduction

Steroidogenic Factor-1 (SF-1; NR5A1) is a transcription factor that was identified by its capacity to coordinately regulate the expression of steroidogenic P-450 enzymes (Lala et al., 1992; Morohashi et al., 1992). SF-1 is a member of the nuclear receptor superfamily, which is able to bind as a monomer to nuclear receptor half-sites (Wilson et al., 1993). Multilayered regulation of SF-1 activity is achieved by association with positive and negative cofactors, post-translational modifications, phospholipid ligand availability, tissue-specific and epigenetic gene expression regulation and gene dosage (reviewed in Hoivik et al., 2010; Lalli, 2010; Schimmer and White, 2010) (Fig. 1). The expression pattern of SF-1 is restricted to the adrenal cortex and gonads, spleen, pituitary gonadotropes and ventro-medial hypothalamic (VMH) nucleus in the brain (Ikeda et al., 1993). SF-1 binding sites are present in the promoters of virtually all genes involved in the steroidogenic process, including the steroidogenic acute regulatory protein (*StAR*), and mutation of these sites in transient transfection experiments often dramatically impairs reporter gene expression (reviewed in Parker et al., 2002; Hoivik et al., 2010; Schimmer and White, 2010). Based on these data, SF-1 has a recognized role as a global regulator of steroidogenesis in the adrenal cortex and gonads. Further evidence for the essential role of SF-1 as a master

Abbreviations: HPA axis, hypothalamic-pituitary-adrenal axis; VMH, ventromedial nucleus of the hypothalamus; SF-1, Steroidogenic Factor-1.

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http://dx.doi.org/10.1016/j.mce.2012.11.005

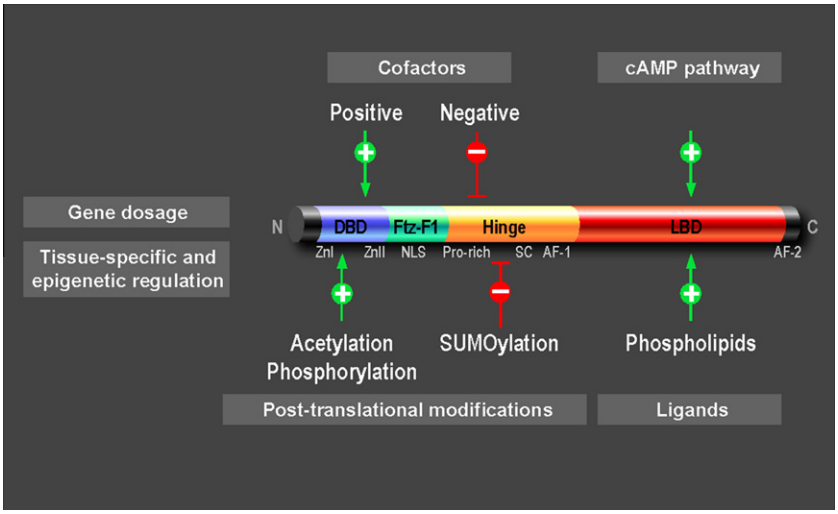

Fig. 1. Structure of the SF-1 protein and mechanisms of control of its transcriptional activity. N,N-terminus of the protein; DBD, DNA binding domain with two zing finger (Zn I and Zn II) motifs; Ftz-F1, Fushi tarazu-F1 domain with a nuclear localization signal (NLS); Hinge, hinge region; Pro-rich, proline-rich region; SC, synergy control region; AF-1, transcriptional activation domain 1; LBD, ligand-binding domain; AF-2, transcriptional activation domain 2; C,C-terminus of the protein. Mechanisms of positive and negative modulation of SF-1 transcriptional activity are indicated.

steroidogenic gene came from experiments showing that its forced expression in embryonic and mesenchymal stem cells is sufficient to activate steroidogenic genes and to initiate steroid expression (Crawford et al., 1997; Tanaka et al., 2007). The phenotype of the *Nr5a1* null mouse (Luo et al., 1994,1995; Sadovsky et al., 1995) indicated for the first time that SF-1 has important functions in adrenal glands and gonads that go beyond steroidogenic gene regulation. The purpose of this article is to review the progress that has recently been made in extending our knowledge about regulation of gene expression in the adrenal cortex by SF-1 involving processes different from steroidogenesis.

2. SF-1 dosage as a critical regulator of adrenocortical development and growth

The critical role of SF-1 as a developmental regulator became evident by the analysis of the phenotype of *Nr5a1* null mice: *Nr5a1* inactivation causes complete absence of adrenal glands and gonads, with both sexes having female external genitalia (Luo et al., 1994,1995; Sadovsky et al., 1995). It has been shown that an increased apoptotic process in the adrenogonadal primordium starting from E12.0 is responsible for the absence of adrenal and gonadal structures in *Nr5a1* null mice (Luo et al., 1994). Those animals are born normally, but most of them die within few hours after birth because of adrenal insufficiency. Furthermore, in *Nr5a1* null mice the cell number and architecture of the VMH are abnormal, while the pituitary gland selectively lacks gonadotropes and vascular defects are present in the spleen (Ikeda et al., 1995; Shinoda et al., 1995; Morohashi et al., 1999). Remarkably, the different *Nr5a1* expressing tissues have different sensitivity to *Nr5a1* gene dosage, as shown by the fact that experiments aimed to restore SF-1 expression in the *Nr5a1* null background by BAC transgenesis rescued gonadal and spleen defects, but failed to rescue adrenal development (Fatchiyah et al., 2006). A critical role for *Nr5a1* gene dosage in the development of adrenals and gonads is also demonstrated by the finding that *Nr5a1* heterozygous mice have hypoplastic adrenals and gonads, in the presence of decreased corticosterone and increased ACTH plasma levels, especially after stress (Bland et al., 2000). Also in the adult mouse *Nr5a1* dosage is critical for compensatory adrenal growth following unilateral adrenalectomy (Beuschlein et al., 2002). However, a species difference seems to exist in sensitivity to SF-1 dosage. In fact, while adrenals and gonads are both affected by *Nr5a1* haploinsufficiency in mice, in humans the great majority of heterozygote *NR5A1* mutations are associated with disorders of sex development (Lin et al., 2007), premature ovarian failure (Lourenço et al., 2009) or male infertility (Bashamboo et al., 2010). Only a few cases have been described of *NR5A1* mutations that also produce adrenal insufficiency in addition to gonadal defects (Achermann et al., 1999,2002) and a single case of a prepubertal girl where adrenal insufficiency was associated with apparent normal ovarian development (Biason-Lauber and Schoenle, 2000). Follow-up of this case shows lack of ovarian dysfunction even after puberty (A. Biason-Lauber, personal communication). These data suggest that a different threshold of sensitivity to *NR5A1* dosage for adrenal development exists in humans compared to mice. Alternatively, adrenal insufficiency in carriers of heterozygote *NR5A1* mutations may be subtle and difficult to diagnose because of compensatory activation of the HPA axis (although in most reported cases basal ACTH levels were not elevated), similarly to what was shown in *Nr5a1* heterozygote mice (Bland et al., 2000).

The function of SF-1 in the regulation of adrenocortical growth may have a particular relevance to understand the mechanisms of adrenocortical tumorigenesis. Important lessons in this domain have been learnt from pediatric adrenocortical tumors. In these

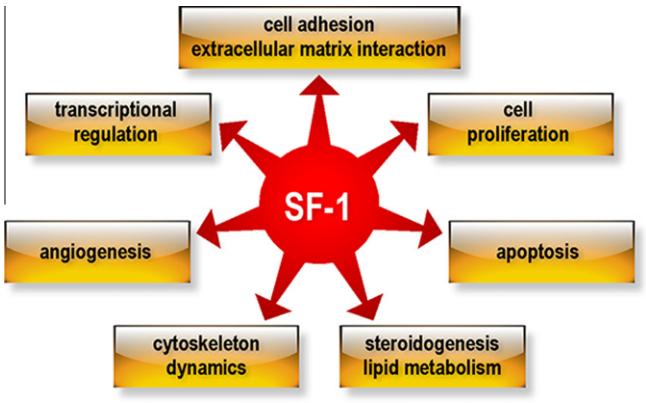

Fig. 2. Examples of gene categories regulated by SF-1 in adrenocortical tumor cells.