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Review

Distinct functions of steroidogenic factor-1 (NR5A1) in the nucleus and the centrosome

Chia-Yih Wang, Wei-Yi Chen [1], Pao-Yen Lai, Bon-chu Chung *

Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan

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ABSTRACT

Steroidogenic Factor 1 (SF-1, Ad4bp, NR5A1) is a nuclear receptor expressed mainly in the adrenals and gonads. It activates the transcription of genes in steroidogenesis, reproduction, and energy metabolism. In addition, it also regulates the growth and differentiation of adrenogonadal primodial cells. SF-1 resides in the nucleus and the centrosome. SF-1 moves dynamically in the nucleus, and SF-1 location and activity are dynamically regulated by post-translational modification. In the centrosome, SF-1 maintains genomic integrity by controlling centrosome homeostasis. SF-1 prevents centrosome amplification by restricting aberrant activation of centrosomal DNA-PK. Upon SF-1 removal, DNA-PK is activated and centrosomes are amplified. This leads to genomic instability and cell growth defects. These data indicate that SF-1 at both the nucleus and the centrosome contributes to cell growth control, but the mechanisms of SF-1 action in different locations are different.

Contents

Abbreviations: CDK2, cyclin-dependent kinase 2; DNA-PK, DNA-dependent protein kinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; SF-1, Steroidogenic Factor 1 NR5A1, Ad4BP; SUMO, small ubiquitin like modifier; MT, microtubule.

* Corresponding author. Tel.: +886 2 27899215; fax: +886 2 27826085.
E-mail address: mbchung@sinica.edu.tw (B.-c. Chung).
[1] Present address: Laboratory of Biochemistry and Molecular Biology, The Rockefeller University, New York, NY 10065, USA.

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1. Regulation of SF-1 activities for adrenal and gonadal gene control

Steroidogenic Factor 1 (SF-1), also known as Ad4BP or NR5A1, is a member of the nuclear receptor superfamily. It controls the expression of genes involved in steroidogenesis, α- and β- subunit of gonadotropins, MC-2R, intracellular cholesterol carrier (StAR), and others (Val et al., 2003), which are important in the differentiation and control of the hypothalamus–pituitary–adrenal axis. In these cells, SF-1 activates its target genes in response to the stimulation of adrenocorticotropin (ACTH) and gonadotropin (LH and FSH), and intracellular cAMP/PKA signal pathway is a major signaling pathway that transmits the signal from outside stimuli to the nucleus (Schimmer and White, 2010).

Post-translational modification is an important way to modulate the transcriptional activity of SF-1. SF-1 function is activated by phosphorylation of a single Ser residue (Ser-203) by mitogen-activated protein kinase (MAPK) (Hammer et al., 1999). In addition, acetylation of SF-1 also potentiates SF-1 activity (Chen et al., 2005). On the contrary, inhibition of histone deacetylase cause increased ubiquitination of SF-1, leading to its degradation and reduction of steroid secretion (Chen et al., 2007), and conjugation SF-1 by a small ubiquitin like modulator (SUMO) leads to the repression of SF-1 activity (Chen et al., 2004).

SF-1 also interacts with numerous coactivators and co-repressors, including Steroid Receptor Coactivator-1 (SRC-1), Receptor Interacting Protein 140 (RIP140), Nuclear receptor CoRepressor (N-CoR), DEAD-box protein 103 (DP103) and others (Crawford et al., 1997a; Li et al., 1999). However, these co-regulators are all general factors; none of them are specific for SF-1 or steroidogenic tissues. The only SF-1 specific negative regulator is Dax-1. Dax-1 is colocalized with SF-1 in multiple cell lineages (Ikeda et al., 1996); it interacts with SF-1 and inhibits SF-1 activity (Babu et al., 2002). Dax-1 blocks steroid secretion by repressing the expression of steroidogenic genes in these cells (Lalli et al., 1998).

2. Intracellular locations of SF-1

2.1. Dynamic localization of SF-1 in the nucleus

SF-1 is a member of the nuclear receptor family, which can be classified into two major categories according to their subcellular distribution in the absence of cognate ligands. Type I nuclear receptors are located in the cytoplasm and associated with heat shock proteins. Upon ligand binding, these receptors are dissociated from heat shock proteins, translocated into the nucleus, bind to and activate their target genes. This category includes androgen receptor, estrogen receptor, progesterone receptor, and glucocorticoid receptor. In contrast to type I, type II nuclear receptors are located in the nucleus and bind to DNA constitutively. Ligand binding may regulate the interactions between type II nuclear receptors with transcriptional co-regulators, and thus modulate their transcriptional functions. SF-1, RAR and RXR belong to this category.

Although being constitutively located in the nucleoplasm, SF-1 also moves around the nucleus according to its status of post-translational modifications (Chen et al., 2004, 2005; Fan et al., 2004). SUMO conjugation appears to repress SF-1 activity as the mutations of SUMO acceptor sites, K119 and K194, enhance gene activation by SF-1. One possibility for this repressive effect is that SUMO-conjugated SF-1 is localized to the PML nuclear speckles, in which SF-1 is sequestrated from nucleoplasm and becomes associated with its repressors, such as DP103 (Lee et al., 2005), thus achieving transcriptional repression (Fig. 1).

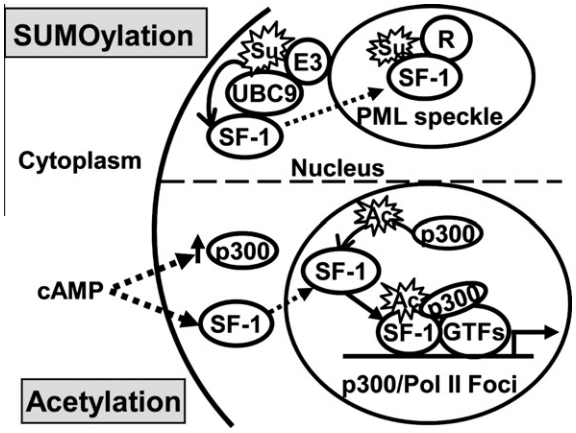

Fig. 1. SF-1 moves around the nucleus exerting different functional states. SF-1 can be conjugated by SUMO by the activity of UBC9 and E3 SUMO ligase. After sumoylation, SF-1 moves to the PML nuclear speckle that contains transcriptional repressor (R), and its activity is repressed. In contrast, SF-1 can be acetylated by p300, which is stimulated by cAMP. Upon acetylation, SF-1 moves to transcriptionally active loci containing p300, RNA polymerase II (Pol II), and general transcription factors (GTFs). This association activates SF-1 activity, leading to transcriptional activation. su: SUMO molecule.

SF-1 is acetylated at the KQQKK sequence at the Ftz-F1 box and activated by p300 (Chen et al., 2005). Upon cAMP stimulation, the nuclear localization of SF-1 is reorganized from a diffuse distribution into discrete transcriptionally active foci that contain RNA polymerase II, p300 (Chen et al., 2005) and GCN5 (Fan et al., 2004) (Fig. 1). As the acetyl transferase activity of p300 is not required for this translocation, SF-1 is probably recruited to these transcriptionally active loci as a result of physical interactions with its co-regulators, such as p300 or GCN5. Moreover, p300-mediated acetylation of SF-1 at the FTZ-F1 domain increases its binding to p300, suggesting that acetylation is involved in retaining SF-1 in the transcriptionally active foci and thus facilitating the transcription of target genes (Chen et al., 2005).

Although the phosphorylation of SF-1 at Ser-203 is involved in transcriptional regulation, this modification has not been reported to change its subcellular localization (Hammer et al., 1999; Lewis et al., 2008). Furthermore, SF-1 is ubiquitinated, which induces the degradation of SF-1 like most other proteins (Chen et al., 2007). Therefore ubiquitination does not appear to regulate the subcellular distribution of SF-1 directly.

2.2. SF-1 is also located in the centrosome

As described above, SF-1 is constitutively localized in the nucleus where it functions as DNA-binding transcription factor. In addition, it is also located in the centrosome. Immunofluorescence staining of endogenous or ectopic SF-1 shows that SF-1 is colocalized with γ-tubulin, the marker for the centrosome, indicating that SF-1 is a centrosomal protein in mouse adrenocortical Y1, mouse testicular Leydig MA-10, and human adrenocortical H295 cells (Lai et al., 2011). Centrosomal localization of SF-1 is further confirmed by sucrose gradient fractionation of centrosome in Y1 cells (Lai et al., 2011). Many other chromatin-interacting transcription factors, including SP1, RUNX3, and TP53, also reside in the centrosome in similar assays (Astrinidis et al., 2010; Chuang et al., 2012; Shinmura et al., 2007). Thus SF-1 is not unique in this aspect.

Centrosome is a small cytoplasmic non-membrane-bounded organelle, which is composed of a pair of centrioles and the surrounding pericentriolar material. The centriole is a pair of microtubule cylinders, serving as the docking site for centrosome duplication; and the pericentriolar material contains γ-tubulin ring

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