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Function of steroidogenic factor 1 during development and differentiation of the reproductive system

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Intact reproductive development depends on steroids and other endocrine signals. Although recent discoveries have elucidated important steps of sexual differentiation, the intricate mechanisms that regulate the development of steroid-producing tissues remain elusive. In adults, complex feedback mechanisms determine the hypothalamic and pituitary regulation of steroid hormone biosynthesis. Steroidogenic factor 1 (SF-1), an orphan member of the nuclear receptor superfamily of proteins, plays a critical role in development and differentiation of the endocrine and reproductive systems. This review provides an overview of the function of SF-1, its mechanism of action, and a perspective on the interaction of SF-1 with other determinants of sexual differentiation. Whereas SF-1 is essential for the expression of numerous steroidogenic enzymes, its presence may not correlate with steroidogenic function. Moreover, diverse co-regulators modulate the influence of SF-1 on gene transcription. The significance of these interactions is discussed in the context of reproductive development and function. Other orphan or ligand-dependent nuclear proteins may share similar mechanisms.

The nuclear receptor family of transcription factors plays a central role in many aspects of tissue development and function. This family of proteins includes the steroid hormone receptors, such as receptors for oestrogen, progesterone and androgen, as well as receptors for thyroid hormone, vitamin D and retinoids (Mangelsdorf *et al*., 1995). Providing a link between extracellular lipophilic hormonal cues and transcriptional regulation of gene expression in the nucleus, these receptors are positioned to direct cell proliferation, differentiation and apoptosis. This review focuses on steroidogenic factor 1 (SF-1, also known as Ad4BP), a member of the nuclear receptor family of proteins that shares high homology with the *Drosophila* protein FTZ-F1, a regulator of embryogenesis and metamorphosis in this organism. SF-1 plays a pivotal role in guiding the embryonic development of the reproductive system. Moreover, SF-1 is expressed in steroid-producing tissues in adults, as well as in additional endocrine tissues that govern reproductive function. Thus, deciphering the function of SF-1 is essential for understanding reproductive development, and the mechanisms that influence the production and release of steroid hormones.

Monomeric binding of DNA half-sites by the orphan nuclear receptor SF-1

SF-1 is classified as a nuclear receptor on the basis of its structural homology and functional similarity with many members of this family of proteins (Mangelsdorf *et al*., 1995). Nuclear receptors are composed of several homologous modular domains (Fig. 1). Central to the function of these proteins is the highly conserved DNA-binding domain (DBD, domain C), composed of two zinc-chelating motifs ('zinc fingers'). A variable amino-terminal region (domain A–B) flanks the DBD at its N-terminus. This domain harbours activation function 1 (AF-1), which is responsible for ligand-independent transactivation. C-terminal to the DBD is the hinge region (domain D), which regulates complex interactions among receptors, DNA binding sites, and co-repressive proteins. Domains E–F are located at the C-terminus of the protein. This region contains the ligand-dependent activation or ligand-reversed transcriptional silencing domain (commonly termed activation function 2, AF-2), and also mediates dimerization with other receptors (for review, see Sadovsky and Crawford, 1998).

SF-1 belongs to a subgroup of nuclear receptors that are distinguished by three important features: first, SF-1 is termed an orphan nuclear receptor because, unlike many steroid receptors, a physiological ligand that modulates its activity has not been identified (see below). Second, SF-1 differs structurally from most other nuclear receptors, as it lacks an amino-terminal (A–B) domain (Parker and Schimmer, 1997; Sadovsky and Crawford, 1998), rendering the carboxy-terminal region entirely responsible for gene activation by SF-1 (Fig. 1). Indeed, the extreme carboxy-terminus of SF-1 harbours a sequence of six amino acids, commonly referred to as the AF-2 hexamer, which is highly conserved among numerous steroid receptors. The AF-2 domain of SF-1 is necessary, but insufficient, for transcriptional activation, and residues amino-terminal to AF-2 are required for transcriptional activity (Crawford *et al*., 1997a), as well as for interaction with co-regulators and transcription factors (see below). Third, many nuclear receptors (such as receptors for oestrogen or progesterone) bind their cognate DNA response as

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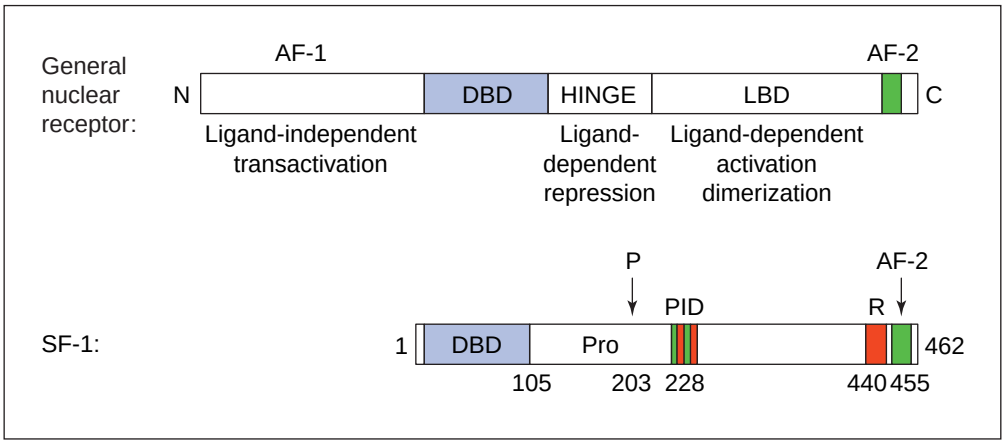

Fig. 1. The structure of steroidogenic factor 1 (SF-1), compared with the general structure of nuclear receptors. In addition to the shared DNA-binding domain (DBD), most receptors contain two activation function (AF) domains. SF-1 lacks a functional AF-1, and its transcriptional activation function resides within its C-terminal region, which harbours the conserved AF-2 hexamer. A repression (R) domain is adjacent to the AF-2 hexamer, and a proximal interaction domain (PID) is located closer to the DBD. The $serine_{203}$ residue is a target for phosphorylation (P). A region C-terminal to the DBD, which includes proline-rich (Pro) sequences, mediates interaction with transcription factor IIB (TFIIB) and c-Jun.

either homodimers, or as heterodimers (in which case the heteropartner is usually the retinoid-X receptor). Each of the two types of receptor dimers binds specific DNA promoter response elements, which are arranged as either a palindrome, a sequence comprising two inverted recognition motifs known as 'half-sites' (such as 5'-AGGTCANNNTGACCT-3'), or a direct repeat of half-sites (such as 5'-AGGTCANAGGTCA-3'). In contrast, SF-1 belongs to a subgroup of receptors that bind to DNA as monomers, requiring only one DNA half-site to bind with high affinity. SF-1 prefers a half-site composed of (C/T)CAAGG(C/T)(C/T)(A/G) sequence. This relatively permissive half-site may explain why numerous promoter targets are activated by SF-1 (Sadovsky and Crawford, 1998 and references therein).

Role of SF-1 during development and sexual differentiation

The homology of SF-1 to the *Drosophila* protein FTZ-F1, a known developmental regulator in the fruit fly, as well as the robust expression of SF-1 in steroid-producing cells (see below), indicates that SF-1 is an important regulator of mammalian steroidogenic tissues. Indeed, several laboratories (Luo *et al*., 1994; Sadovsky *et al*., 1995; Shinoda *et al*., 1995) have used targeted gene disruption to generate SF-1 null ('knock-out') mice. These studies indicate that SF-1 plays an important role at many stages of reproductive development (Fig. 2). Specifically, SF-1-deficient mice are born at a normal Mendelian frequency, establishing that SF-1 is not essential for prenatal survival. SF-1 null mice have neither adrenal glands, nor male or female gonads. Whereas adrenocortical and gonadal precursor cells assemble in the urogenital ridge before embryonic day 12, they subsequently undergo apoptosis (Luo *et al*., 1994). All SF-1 null mice die within 1 week after birth, probably as a result of adrenal insufficiency, since the mice can be rescued by administration of exogenous steroids (Ikeda *et al*., 1995). These studies shed light on the understanding of mammalian sexual differentiation, since the presence of a Y chromosome, and consequently the production of SRY, determine development of the undifferentiated gonad into testis (Parker *et al*., 1999; Swain and Lovell-Badge, 1999). Furthermore, production of sex hormones and ultimate sexual phenotype are determined by unique cells within the differentiated gonad. In the testis, Sertoli cells within testicular cords produce Müllerian inhibitory substance (MIS), which causes regression of Müllerian (paramesonephric) structures, and peritubular Leydig cells produce testosterone, which influences the development of the Wolffian (mesonephric) duct into vas deferens, seminal vesicles and epididymis, as well the formation of the external genitalia (Parker *et al*., 1999). In the absence of MIS, differentiation proceeds towards the default pathway of Wolffian duct regression, and Müllerian duct differentiation into the Fallopian tubes, uterus and upper third of the vagina, as well as development of female external genitalia (Parker *et al*., 1999). As gonads fail to develop in SF-1 null mice, genotypically male SF-1 null mice lack MIS and testosterone, and exhibit a female phenotype (Luo *et al*., 1994; Sadovsky *et al*., 1995). MIS promoter is stimulated directly by SF-1 (see below) and SF-1 is essential for expression of a MIS-promoter transgene (Shen *et al*., 1994; Giuili *et al*., 1997). This finding indicates that the absence of SF-1 contributes to MIS deficiency and subsequent pseudohermaphroditism in the SF-1 null males. However, using selective disruption of the SF-1 site within the endogenous mouse MIS promoter, Arango *et al*. (1999) demonstrated that the SF-1 binding site in the MIS promoter is dispensable for male mouse development, even though MIS expression in the SF-1 site mutants was relatively reduced. In contrast, SOX9, an SRY-related high mobility group (HMG) transcription factor (for review, see Swain and Lovell-Badge, 1999 and references therein) is absolutely essential for MIS expression and Müllerian duct regression. The

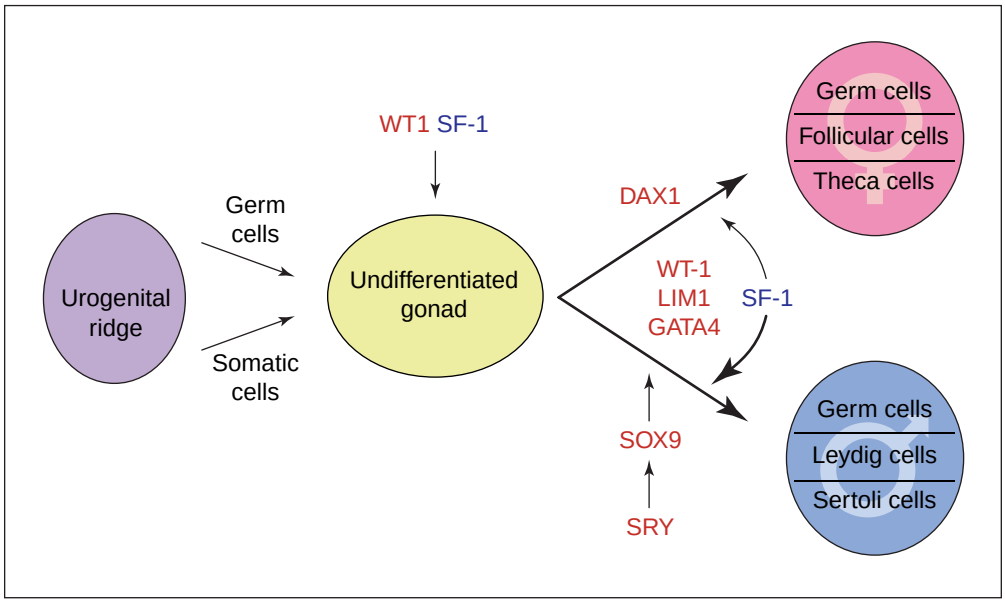

Fig. 2. A model for the function of steroidogenic factor 1 (SF-1) in regulation of gonadal and adrenal development and differentiation. Whether SF-1 is essential for induced expression of steroidogenic enzymes remains to be established. Several proteins that play a role in sex determination, including WT-1, DAX1, SRY, SOX9, LIM1 and GATA4, may modulate the activity of SF-1 (for review, see Swain and Lovell-Badge, 1999).

induction of MIS promoter by SOX9 is potentiated by SF-1 through direct interaction with SOX9 (De Santa Barbara *et al*., 1998) and WT1 (see below).

The ventromedial hypothalamic nucleus, a region implicated in control of sexual behaviour, also fails to develop in SF-1 null mice (Ikeda *et al*., 1995; Shinoda *et al*., 1995). In addition, the expression of β-subunit of LH and FSH in SF-1 –/– mice is diminished, but can be restored by administration of gonadotrophin-releasing hormone (Ikeda *et al*., 1995). These studies demonstrate that SF-1 is a critical component of the events that guide the formation and function of endocrine tissues within the reproductive system. Crawford *et al*. (1997b) transfected SF-1 into the pluripotent embryonic stem (ES) cells, which normally do not express SF-1, to define further the role of SF-1 in development and differentiated function. The ectopic expression of SF-1 led to differentiation of ES cells toward a steroidogenic cell lineage, demonstrated by expression of P450scc in a manner inducible by cAMP and retinoic acid, and the consequent production of progesterone (Crawford *et al*., 1997b). The identity of SF-1-dependent genes that usher the development of urogenital tissues is not yet known, and it is likely that SF-1 recruits additional transcription factors in a cascade of events that results in a steroidogenic cell phenotype.

The identification of the first function-perturbing SF-1 mutation in humans provided further support for a developmental role of SF-1 in endocrine and reproductive development. An amino acid substitution within the first zinc finger of SF-1 led a genotypically 46, XY patient to exhibit primary adrenal failure within the first 2 weeks of life, associated with streak-like gonads and normal Müllerian structures (Achermann *et al*., 1999). Menstruation was restored with administration of oestradiol and progesterone. This observation underscores the obligatory role of SF-1 in adrenal and gonadal development in humans.

Expression and function of SF-1 in reproductive tissues

Since the identification and cloning of SF-1, numerous investigators have examined the expression of SF-1 *in vivo*, and its function *in vitro*. During mouse development, SF-1 is expressed in the urogenital ridge as early as embryonic day 9.5, coinciding with the development of steroidogenic tissues, and before aggregation into separate adrenocortical and bipotential gonadal anlagen (Ikeda *et al*., 1994). In the fetal adrenal, SF-1 is expressed in steroidogenic cells within the outer cortical region. After embryonic day 12.5, SF-1 is expressed in both male and female gonads. Specifically, SF-1 is detected in the interstitial regions of developing testes, as well as in testicular cords and seminiferous tubules. The intensity of testicular SF-1 expression in embryonic life exceeds its expression in the ovary, which exhibits a diffuse pattern of SF-1 expression (Ikeda *et al*., 1994; for review, see Parker and Schimmer, 1997). In the developing brain, SF-1 is expressed in hypophyseal precursors at embryonic days 13.5–14.5, before the appearance of FSHβ and LHβ transcripts (Ingraham *et al*., 1994). SF-1 is also expressed in hypothalamic primordia, which develop into the ventromedial hypothalamic nucleus. A small amount of SF-1 is also detected in mouse and human placenta (Sadovsky *et al*., 1995; Bamberger *et al*., 1996). In mature mice, SF-1 is highly expressed in endocrine tissues related to steroidogenesis and reproduction: the three layers of the adrenal cortex, testicular Leydig and Sertoli cells, and ovarian granulosa and theca cells (for review, see Morohashi and Omura, 1996; Sadovsky and

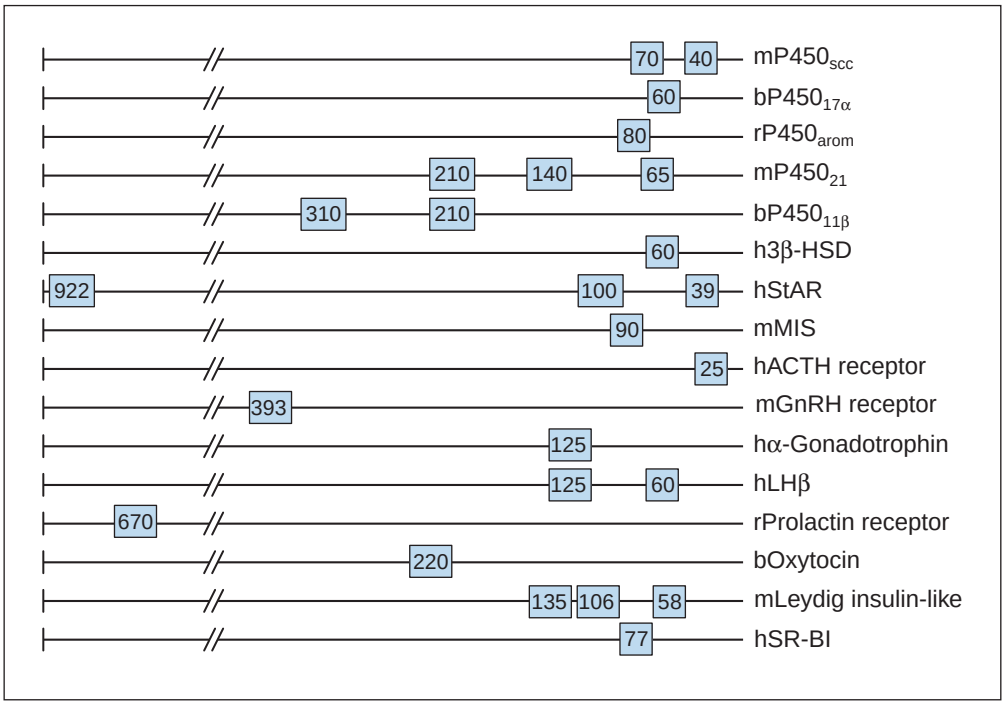

Fig. 3. Promoter elements that mediate the effect of steroidogenic factor 1 (SF-1) on important endocrine and reproductive targets. Promoter from other species may harbour SF-1 sites at different locations. HSD: hydroxysteroid dehydrogenase; StAR: steroidogenic acute regulatory protein; MIS: Müllerian inhibitory substance; ACTH: adrenocorticotrophic hormone; SR-BI: scavenger receptor B-1.

Crawford, 1998). Because of the marked cyclic changes in the ovary during reproductive life, the expression of SF-1 in this organ is of particular interest. Indeed, in the human ovary, SF-1 is not detected in the primordial or primary follicle; it is detected sporadically in preantral granulosa and theca cells, even before the expression of steroidogenic enzymes (Morohashi and Omura, 1996). SF-1 expression is associated with growth of the antral follicles, in which it is expressed in both granulosa and theca interna cells. The expression of SF-1 in women is maintained in the corpus luteum, as well as in the atretic follicle, but not in the corpora albicans. A similar pattern is observed in cyclic female rats, in which the amount of SF-1 is increased in preovulatory follicles, and is only minimally reduced in corpora lutea (for review, see Parker and Schimmer, 1997; Sadovsky and Crawford, 1998).

SF-1 is expressed in ovarian tumours, such as Sertoli–Leydig and granulosa cell tumours (Sadovsky and Crawford, 1998). In contrast, SF-1 is not expressed in the hormonally inert ovarian fibromas and thecomas. In the adrenal cortex, SF-1 is expressed in equal intensity in all three layers. SF-1 expression is maintained in both adrenocortical adenoma and aldosteronoma, as well as in poorly differentiated adrenocortical carcinomas (Sadovsky and Crawford, 1998; Parker *et al*., 1999). SF-1 is also expressed in non-functional adrenal adenomas. Together, these data indicate that SF-1 expression may be essential for the steroidogenic phenotype, yet its presence may not correlate with steroidogenic function.

Molecular analysis revealed that SF-1 regulates the expression of many of the genes that encode steroidogenic enzymes and other regulators of endocrine function (Parker and Schimmer, 1997; Sadovsky and Crawford, 1998). These genes harbour SF-1 response elements within their proximal promoter (Fig. 3). Examples include the gene for P450scc, a key rate-limiting enzyme in the steroid hormone biosynthetic pathway, as well as the genes for P450c17, P450c21, P450c11, P450arom and 3β-hydroxysteroid dehydrogenase (for review, see Morohashi and Omura, 1996; Parker and Schimmer, 1997). SF-1 also regulates the promoter of steroidogenic acute regulatory protein (StAR), a mitochondrial protein essential for transport of cholesterol to the inner mitochondrial membrane (Sugawara *et al*., 1997). Similarly, SF-1 enhances the activity of adrenocorticotrophic hormone (ACTH) receptor promoter in adrenocortical cells (Cammas *et al*., 1997). In testicular Sertoli cells, SF-1 is required for expression of Müllerian inhibitory substance (MIS) (Shen *et al*., 1994; Giuili *et al*., 1997) and MIS-II receptor (Barbara *et al*., 1998) whereas, in Leydig cells, it regulates the expression of insulin-like hormone, which is essential for intra-abdominal testicular descent and, consequently, spermatogenesis and germ cell maturation (Zimmermann *et al*., 1998; Nef and Parada, 1999). SF-1 also regulates the expression of the gene for the high density lipoprotein receptor SR-B1, which mediates the uptake of lipoprotein-derived lipids, the substrate for steroidogenesis in the adrenal gland and gonads (Cao *et al*., 1997), as well as the α_2-macroglobulin gene (Dajee *et al*., 1998). In bovine granulosa cells, SF-1 regulates the expression of the oxytocin and prolactin receptor genes (Wehrenberg *et al*., 1994; Hu *et al*., 1997). In the pituitary, SF-1 is expressed in pituitary gonadotropes, in which it transcriptionally activates the α-subunit of

gonadotrophins, as well as LHβ (Barnhart and Mellon, 1994; Halvorson *et al*., 1996) and the human gonadotrophin-releasing hormone receptor (Ngan *et al*., 1999). Taken together, these findings indicate that SF-1 is required for basal promoter activity in diverse endocrine and reproductive tissues and, consequently, optimal gene expression (Parker and Schimmer, 1997). In this context, the physiological significance of SF-1 stimulation of the promoter for the transcriptional repressor small heterodimer partner (SHP) (Lee *et al*., 1999) remains to be determined.

In addition to the tissues detailed above, SF-1 also exhibits widespread expression in the brain, including the cortex, hippocampus, caudate and subthalamic nuclei, thalamus, hypothalamus and the spinal cord. It is also expressed in the spleen and other lymphoid tissues (Parker and Schimmer, 1997). Further studies are required to elucidate the role of SF-1 in modulating development or function of these non-steroidogenic tissues. However, the mechanisms that guide tissue-specific expression of SF-1 are largely unknown. Several elements within the proximal promoter of SF-1 appear important for the expression of SF-1 in steroidogenic cell lines. These elements include an E-box, which is required for activity of SF-1 promoter, as well as a binding element for CAAT-binding factor and for the ubiquitous Sp1 (Woodson *et al*., 1997). An autoregulatory loop, in which SF-1 enhances its own transcription, has also been described by Morohashi and Omura (1996) and Nomura *et al*. (1996). The role of these sites in guiding tissue-specific expression of SF-1 remains to be determined.

The use of SF-1 null mice for examination of the role of SF-1 in the maintenance or regulation of steroidogenic enzyme gene expression in the mature organs *in vivo* is hampered by the absence in these mice of the main steroid-producing organs. Despite this absence, SF-1 null mice express P450scc in the placenta and have normal embryonic serum corticosteroid concentrations (Sadovsky *et al*., 1995). Similarly, SF-1 is also expressed in the gut and skin, and P450scc is expressed in these tissues even in SF-1 null mice (Keeney *et al*., 1995). These findings underscore the need to define the role of SF-1 in tissue-specific regulation of its target proteins.

Molecular regulation of SF-1 activity

The temporal and spatial expression of target genes for SF-1 vary during development and throughout adult life. Although SF-1 is not the sole regulator of these genes, a central role for SF-1 would require tight regulation of the expression and activity of SF-1. As described above, changes in SF-1 expression are not sufficient to account for the delicate modulation of its gene targets. It is possible that a constant concentration of SF-1 is required for basal expression of these genes, and that additional tissue-specific factors influence their temporal expression, cooperatively or independently of SF-1.

Several mechanisms may affect the function of SF-1 in hormonally active tissues, independent of its level of expression. An intermittently available ligand may bind SF-1 and regulate transcriptional activity in a manner similar to the role of steroids in gene activation by steroid receptors. Indeed, 25-OH-cholesterol, an endogenous oxysterol, enhances the transcriptional activation function of SF-1 (Lala *et al*., 1997). Similar to the ligand-mediated activation of other steroid receptors, this effect of 25-OH-cholesterol requires intact AF-2 hexamer. Whether this compound acts as a direct ligand for SF-1 and regulates its activity *in vivo* remains to be determined. Post-translational modifications are also pertinent in the regulation of the activity of SF-1. For example, phosphorylation of SF-1 at $serine_{203}$ was shown to be important for the transcriptional activity of SF-1 (Hammer *et al*., 1999). Furthermore, the transcriptional capacity of SF-1 is enhanced by protein kinase A (Carlone and Richards, 1997), and a phosphorylated form of SF-1 can be detected in rat granulosa cells after treatment with either FSH or cAMP *in vitro*. Indeed, cAMP signalling has been shown to synergize with SF-1 activity in several targets. Gonadotrophins and ACTH use cAMP as a second messenger, and it is possible that transcriptional activation by SF-1 and signalling by cAMP converge on target promoters without a direct modification of SF-1. For example, studies using the promoter for either P450scc or mouse StAR failed to show a requirement for SF-1 in cAMP-dependent gene induction (Chau *et al*., 1997). The influence of cAMP on some of these promoters may represent stimulation of additional proteins (such as CREB, Sp1 or C/EBPβ) which, in turn, interact functionally with SF-1 (Carlone and Richards, 1997; Reinhart *et al*., 1999).

SF-1 activity is modulated by interaction with co-regulatory proteins known to alter the transcriptional activity of other nuclear proteins. Steroid receptor co-activator 1 (SRC-1) binds SF-1 and potentiates its activity *in vitro* (Crawford *et al*., 1997a; Ito *et al*., 1998). Mutation of either AF-2 or proximal interaction domain abrogates this interaction (Crawford *et al*., 1997a). Furthermore, SRC-1 recruits the transcriptional integrator CBP/p300 to the promoter-bound complex, and further potentiates SF-1 activity (Ito *et al*., 1998). Another protein shown to potentiate the activity of SF-1 is multiprotein bridging factor 1 (MBF-1), which bridges between DNA-bound transcriptional regulators and the basal transcription machinery (Kabe *et al*., 1999). Finally, a region C-terminal to the DBD of SF-1, which includes proline-rich sequences (see Fig. 1), mediates interaction with transcription factor IIB (TFIIB) and c-Jun (Li *et al*., 1999).

DAX-1 is another member of the nuclear receptor superfamily, which, like SF-1, is expressed in the gonads, adrenal cortex, hypothalamus and pituitary. DAX-1 maps to the Xp21 region of the human X chromosome and has been implicated in sex determination. Mutations in DAX-1 gene have been shown to cause X-linked adrenal hypoplasia congenita (AHC), and hypogonadotrophic hypogonadism, reminiscent of the phenotype of SF-1 null mice (for review, see Swain and Lovell-Badge, 1999, and references therein). A mouse mutated in DAX-1 (also known as Ahch) gene exhibits male hypogonadism, sterility due to abnormal maintenance of spermatogenesis, presence of multiple ovarian oocytes in the female, and abnormal degeneration of the fetal zone in the adrenal cortex (Yu *et al*., 1998). DAX-1 and SF-1 interact physically, and this interaction is mediated by two discrete domains within the C-terminal region of SF-1 (Ito *et al*., 1997; Crawford *et al*., 1998) (see Fig. 1). In addition, SF-1 upregulates the activity of the DAX promoter (Vilain *et al*., 1997). These data indicate that the activities SF-1 and DAX-1 converge in steroidogenic tissue development, and that each is required for inducing the steroidogenic phenotype. However, DAX-1 recruits the co-repressor N-Cor to inhibit SF-1-mediated transcriptional activation (Crawford *et al*., 1998), and DAX-1/Ahch mutations that lead to AHC or its variants abrogate the repression of SF-1 by DAX-1 (Crawford *et al*., 1998;

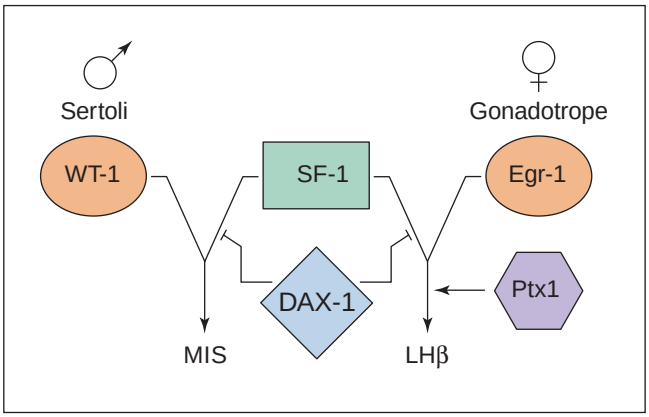

Fig. 4. The analogous interaction between steroidogenic factor 1 (SF-1) and either WT-1 or Egr-1 in the regulation of Müllerian inhibitory substance (MIS) and LHβ, respectively. A synergistic interaction between SF-1 and WT-1 is essential for MIS production by Sertoli cells. An analogous synergy between SF-1 and Egr-1, which is modulated by Ptx1, is essential for LHβ production by pituitary gonadotropes. The synergy of SF-1 with either WT-1 or Egr-1 is repressed by DAX-1.

Reutens *et al.*, 1999). Further studies are needed to decipher the complex interaction of SF-1 and DAX-1.

The activity of two important genes in the reproductive system, MIS and LHβ, are transcriptionally regulated through synergistic interaction of SF-1 and closely related zinc-finger transcription factors (Fig. 4). Wilm's tumour 1 (WT-1), a protein essential for normal renal and gonadal development, interacts directly with SF-1 in Sertoli cells to stimulate production of MIS, which produces Müllerian duct regression (Nachtigal *et al.*, 1998). The influence of SF-1–WT1 synergy on MIS is modulated by DAX-1. Similarly, Egr-1 is required for LHβ synthesis in gonadotropes and, thus, for female fertility (Lee *et al.*, 1996). The binding of both SF-1 and Egr-1 to their respective response elements within the LHβ promoter is essential for LHβ gene expression (Halvorson *et al.*, 1996; Dorn *et al.*, 1999). Whereas the dynamic regulation of LHβ by GnRH depends on SF-1–Egr-1 synergy, it is likely that Egr-1 plays a more important role in mediating GnRH effect, because: (a) GnRH stimulates the expression of Egr-1 and not SF-1; (b) overexpression of Egr-1 was sufficient to stimulate LHβ expression in a gonadotrope line; and (c) GnRH administration to SF-1-null mice restores gonadotrophin expression (Ikeda *et al.*, 1995; Dorn *et al.*, 1999). Although direct protein–protein interaction between SF-1 and Egr-1 has been described (Tremblay and Drouin, 1999), the exact mechanism of this interaction remains to be established. Lastly, the effect of SF-1 on LHβ is modulated by additional proteins, such as the pituitary protein Ptx1 (Tremblay and Drouin, 1999).

Conclusion

The data presented in this review establish the critical role of SF-1 in reproductive and endocrine development and function. These processes are regulated by an intricate system of hormones and transcription factors, which determine not only the formation of hormone-producing organs, but also the temporal and spatial expression of diverse hormones. Although understanding of the structure and expression of SF-1 have markedly improved, the complete mechanism of gene activation by SF-1 has not yet been deciphered. Moreover, the developmental targets for SF-1 during gonadal and adrenal formation remain elusive. It is clear that SF-1 binding to its promoter targets is not a simple on–off switch, but rather a critical component among several, which cooperate to provide precise regulation of gene expression. Understanding the mechanism of SF-1 action will shed light on reproductive and adrenal physiology, and is likely to provide clues to the aetiology of abnormal sexual differentiation and reproductive dysfunction.

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