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[REVIEW]

Regulation of Steroidogenesis, Development, and Cell Differentiation by Steroidogenic Factor-1 and Liver Receptor Homolog-1

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Steroidogenic factor-1 (SF-1) and liver receptor homolog-1 (LRH-1) belong to the nuclear receptor superfamily and are categorized as orphan receptors. In addition to other nuclear receptors, these play roles in various physiological phenomena by regulating the transcription of target genes. Both factors share very similar structures and exhibit common functions. Of these, the roles of SF-1 and LRH-1 in steroidogenesis are the most important, especially that of SF-1, which was originally discovered and named to reflect such roles. SF-1 and LRH-1 are essential for steroid hormone production in gonads and adrenal glands through the regulation of various steroidogenesis-related genes. As SF-1 is also necessary for the development of gonads and adrenal glands, it is also considered a master regulator of steroidogenesis. Recent studies have clearly demonstrated that LRH-1 also represents another master regulator of steroidogenesis, which similarly to SF-1, can induce differentiation of non-steroidogenic stem cells into steroidogenic cells. Here, we review the functions of both factors in these steroidogenesis-related phenomena.

Key words: steroidogenesis, transcriptional regulation, gonad, adrenal, steroidogenic factor-1, liver receptor homolog-1

INTRODUCTION

Nuclear receptors (NRs) belong to a large superfamily of transcription factors, which are essential for various physiological phenomena (Mangelsdorf et al., 1995; Robinson-Rechavi et al., 2003). They are activated in a lipophilic ligand-dependent manner in response to stimulation by steroid hormones, thyroid hormones, vitamins, and various lipids. In addition to such typical classes, NRs include orphan receptors whose ligands have not been identified. Some orphan NRs are constitutively activated in a ligand-independent fashion; steroidogenic factor-1 (SF-1) and liver receptor homolog-1 (LRH-1) are two such receptors and are members of the NR5A subfamily (SF-1 is NR5A1, and LRH-1 is NR5A2), together with *Drosophila* FTZ-F1 (NR5A3) (Fayard et al., 2004; Lee and Moore, 2008; Parker and Schimmer, 1997; Schimmer and White, 2010) (Fig. 1A). Both transcription factors play important roles in controlling the endocrine functions of various tissues. Of these, the regulation of steroidogenesis is one of the most important roles for both factors. In particular, SF-1 was originally identified as a transcription factor that is essential for the transcription of steroidogenic enzyme genes.

Adrenal glands and gonads are the primary steroidogenic organs in mammals and other amniotes (Miller, 1988; Miller and Auchus, 2011). Organ-derived steroid hormones are involved in various physiological phenomena. Adrenal steroids (glucocorticoid and mineralocorticoid) are essential for glucose metabolism, stress responses, immunity, and fluid/electrolyte balance. Gonadal sex steroids (androgens and estrogens) are important for sex differentiation and reproduction. Ovarian progesterone is necessary for ovulation and pregnancy. Steroid hormones are synthesized from cholesterol, which is delivered to the inner compartments of mitochondria by steroidogenic acute regulatory protein (StAR) (Papadopoulos and Miller, 2012; Stocco, 1997, 2000). Cholesterol is converted to pregnenolone by P450 side chain cleavage enzyme (P450scc/CYP11A1/Cyp11a1), a rate-limiting enzyme in the synthesis of all steroid hormones (Miller, 2008; Papadopoulos and Miller, 2012). Thereafter, tissue-specific P450 hydroxylases and hydroxysteroid dehydrogenases catalyze reactions that produce tissue-specific steroid hormones (Miller, 1988, 2008; Miller and Auchus, 2011).

It is well known that SF-1 and LRH-1 are involved in the

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transcription of steroidogenesis-related genes (Fayard et al., 2004; Lee and Moore, 2008; Parker and Schimmer, 1997; Schimmer and White, 2010; Wang et al., 2001; Yazawa et al., 2014; Yazawa et al., 2011) and that steroidogenesis is markedly influenced by a deficiency of either factor (Duggavathi et al., 2008; Jeyasuria et al., 2004; Pelusi et al., 2008; Zhang et al., 2013). SF-1 is also known to be involved in the development of steroidogenic organs (Luo et al., 1994; Parker and Schimmer, 1997) and the differentiation of steroidogenic cells (Yazawa et al., 2014; Yazawa et al., 2009; Yazawa et al., 2006). For these reasons, SF-1 has long been known as a master regulator of steroidogenesis. More recently, a number of groups, including ours, have shown that LRH-1 is another master regulator for steroidogenesis (Bouguen et al., 2015; Yazawa et al., 2009; Yazawa et al., 2011; Zhang et al., 2013). The present review outlines the discovery of SF-1 and LRH-1 and their roles in steroidogenesis-related phenomena and their functional differences.

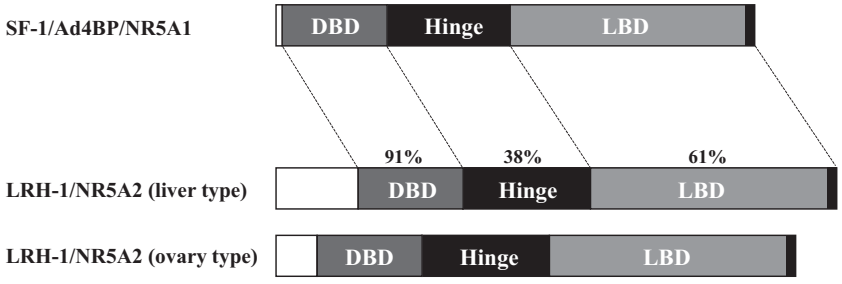

Fig. 1. Schematic structure of SF-1 and LRH-1. DBD, Hinge and LBD represent DNA-binding domain, hinge region and ligand-binding domain, respectively. Black boxes of C-terminus show an AF-2 motif. The percentages indicate the levels of amino-acid identity between each region of human proteins. Ovarian LRH-1 is different from liver form only in N-terminal domain (white boxes).

General characteristics of SF-1 and LRH-1

Early studies demonstrated that the promoter regions of multiple cytochrome P450 steroid hydroxylase genes include an AGGTCA-like motif (Ad4 sequence) that is essential for their transcription in steroidogenic cells (Honda et al., 1990; Rice et al., 1991). Keith Parker and Ken Morohashi independently identified a transcription factor in mouse and bovine adrenal glands that binds to this motif (Lala et al., 1992; Morohashi et al., 1992). Because this transcription factor confers promoter activity to P450 steroid hydroxylase genes in non-steroidogenic cells, they respectively named it steroidogenic factor-1 (SF-1)/adrenal 4-binding protein (Ad4BP). Consistent with this role, detection of SF-1/Ad4BP in adults revealed its expression in the three layers of the adrenal cortex (zona reticularis, zona fasciculata, and zona glomerulosa), testicular Leydig and Sertoli cells, ovarian theca, granulosa cells (GCs), and to a lesser extent in the corpus lutea (Hatano et al., 1994; Ikeda et al., 1993; Kawabe et al., 1999). From these findings Parker and Morohashi concluded that SF-1/Ad4BP is a determining factor for cell-specific expression of cytochrome P450 steroid hydroxylase genes. Consistent with this hypothesis, SF-1/Ad4BP regulates the transcription of all cytochrome P450 steroid hydroxylase genes (Carlone and Richards, 1997; Guo et al., 2003; Hanley et al., 2001; Hu et al., 2001; Lala et al., 1992; Lin et al., 2001; Lynch et al., 1993; Michael et al., 1995; Morohashi et al., 1993; Schimmer and Parker, 1992; Wang et al., 2000; Ye et al., 2009; Zhang and Mellon, 1996) (Table 1). Additionally, the transcription of various steroidogenesis-related genes is regulated by SF-1/Ad4BP, such as cholesterol deliverers (Cao et al., 1997; Caron et al., 1997;

Table 1. Target genes of SF-1 and LRH-1, which are involved in steroidogenesis.

function in steroidogenesis	target genes	expression in steroidogenic organs	references
cytochrome P450 steroid hydroxylase	CYP11A1	adrenal, testis, ovary	SF-1 [Hu et al., 2001] LRH-1 [Kim et al., 2005; Yazawa et al., 2010]
	CYP11B1	adrenal, testis, ovary	SF-1 [Wang et al., 2000; Ye et al., 2009] LRH-1 [Wang et al., 2001]
	CYP11B2	adrenal	SF-1 [Lala et al., 1992; Ye et al.,, 2009]
	CYP17A1	testis, ovary, adrenal	SF-1 [Zhang and Mellon, 1996; Hanley et al., 2001; Lin et al., 2001] LRH-1 [Yazawa et al., 2009, 2011]
	CYP21A	adrenal	SF-1 [Schimmer and Parker, 1992]
	CYP19A1	ovary, testis	SF-1 [Lynch et al., 1993; Carone and Richards, 1997] LRH-1 [Pezzi et al., 2004]
cholesterol deliverer	SR-BI	testis, ovary, adrenal	SF-1 [Cao et al., 1997] LRH-1 [Schoojans et al., 2002]
	StAR	testis, ovary, adrenal	SF-1 [Sugawara et al., 1996; Caron et al., 1997] LRH-1 [Kim et al., 2004]
hydroxysteroid dehydrogenase	3β-HSD	testis, ovary, adrenal	SF-1 [Leers-Sucheta et al., 1997] LRH-1 [Peng et al., 2003]
electron transporter	Cytochrome b5	testis, ovary, adrenal	SF-1 [Huang et al., 2005]
	FDX1	testis, ovary, adrenal	SF-1 [Imamichi et al., 2013] LRH-1 [Imamichi et al., 2013]
	FDXR	testis, ovary, adrenal	SF-1 [Imamichi et al., 2014]

Sugawara et al., 1996), hydroxysteroid dehydrogenase (Leers-Sucheta et al., 1997), and electron transporters (Huang et al., 2005; Imamichi et al., 2013, 2014) (Table 1).

LRH-1 was first discovered in mouse liver as a transcription factor that regulates the transcription of α-fetoprotein (Becker-Andre et al., 1993; Galarneau et al., 1996). LRH-1 functions in the control of glycolysis as well as cholesterol and bile acid homeostasis by regulating the transcription of various genes, such as glucokinase (Oosterveer et al., 2012), SR-BI (Schoonjans et al., 2002), CYP7A1, and CYP8B1 (Goodwin et al., 2000; Lu et al., 2000). In addition to liver, LRH-1 is highly expressed in tissues of endodermal origin (pancreas and intestine), and involved in metabolism, inflammation, and stem cell renewal (Benod et al., 2011; Botrugno et al., 2004; Coste et al., 2007; Fayard et al., 2003; Fernandez-Marcos et al., 2011; Lazarus et al., 2012). LRH-1 is also expressed in testicular Leydig cells and ovarian GCs, and regulates the transcription of steroidogenesis-related genes (Peng et al., 2003; Pezzi et al., 2004; Yazawa et al., 2009; Yazawa et al., 2010). In particular, expression levels of LRH-1 are more abundant in ovary than in any other tissue (Bookout et al., 2006; Kanno et al., 2014). Recently, it was shown that the ovarian LRH-1 represents a unique isoform, which has a truncated N-terminal domain (Kawabe et al., 2013) (Fig. 1). Although the functional difference between both isoforms is not clear, their expression is controlled by completely distinctive transcriptional regulation (Kawabe et al., 2013; Zhang et al., 2001). LRH-1 can replace SF-1 in progesterone production of the corpus luteum (CL) to maintain pregnancy (Zhang et al., 2013). It is also expressed in embryonic stem (ES) cells and regulates the expression of central self-renewal factors, Oct-3/4 and Nanog (Gu et al., 2005; Mullen et al., 2007; Wagner et al., 2010). Interestingly, LRH-1 enhances the efficiency of reprograming somatic cells into induced pluripotent stem (iPS) cells (Guo and Smith, 2010; Heng et al., 2010; Wang et al., 2011).

SF-1/Ad4BP and LRH-1 belong to the same NR subfamily and share many structural and functional characteristics. Both proteins contain the structural domains of typical NRs, a zinc finger DNA-binding domain, intervening hinge region, and a carboxyl-terminal putative ligand-binding domain, although SF-1 lacks the N-terminal domain containing an AF-1 motif (Fig. 1). It has been proposed that the long hinge region exhibits AF-1-like activation activity (Hammer et al., 1999; Li et al., 1999). Because their DNA-binding domains are particularly similar (Fig. 1), SF-1 and LRH-1 effectively recognize the same DNA sequence, YCAAGGYCR (Y represents a pyrimidine, and R represents a purine), in regulatory elements of target genes (Fayard et al., 2003). Both factors thus commonly regulate the transcription of the same genes. This phenomenon is also applicable to steroidogenesis-related genes, including cytochrome P450 steroid hydroxylases (Kim et al., 2005; Pezzi et al., 2004; Wang et al., 2001; Yazawa et al., 2009; Yazawa et al., 2010; Yazawa et al., 2011), cholesterol deliverers (Kim et al., 2004; Schoonjans et al., 2002), hydroxysteroid dehydrogenase (Peng et al., 2003) and electron transporter (Imamichi et al., 2013) (Table 1). Thus, in addition to SF-1, it is conceivable that LRH-1 also works as a determining factor in cell-specific expression of steroidogenesis-related genes. In support of this notion, SF-1 and LRH-1 share common functions in other phenomena, such as transcriptional regulation of Oct-3/4 (Barnea and Bergman, 2000; Gu et al., 2005) and the generation of iPS cells (Guo and Smith, 2010; Heng et al., 2010).

Inveolvement of SF-1 and LRH-1 in the development and steroidogenesis of gonads and adrenal glands

The requirement for SF-1 in the development of steroidogenic organs has been demonstrated in vivo using various gene-targeted models. SF-1-knockout (KO) mice die of glucocorticoid deficiency shortly after birth, and exhibit male-to-female sex reversal in external genitalia (Luo et al., 1994; Sadovsky et al., 1995). These phenotypes are caused by the complete loss of gonads and adrenal glands. Although gonadal and adrenal development initiate without SF-1, they regress via apoptotic cell death during the subsequent developmental stage, possibly due to an abnormality in glycolysis and the pentose phosphate pathway (Baba et al., 2014). In SF-1-KO mice, because the gonads disappear prior to the production of anti-Müllerian hormone and testosterone, which are necessary for the induction of male sexual differentiation, the internal and external urogenital tracts are of the female type, even in genetic males. Heterozygous KO mice also show a decrease in adrenal gland volume, which is associated with an impairment of corticosterone production in response to stress (Bland et al., 2004; Bland et al., 2000; Fatchiyah et al., 2006). These KO mouse models demonstrate that SF-1 functions as a master regulator in the development of steroidogenic organs in vivo. Consistent with the phenotypes of KO mice, patients with mutations in the SF-1 gene exhibit gonadal and adrenal defects (Achermann et al., 1999; Ferraz-de-Souza et al., 2011; Hasegawa et al., 2004; Lourenco et al., 2009). In addition to steroidogenic organs, SF-1 gene mutations and KO result in defects of the pituitary gonadotroph (Ingraham et al., 1994; Shinoda et al., 1995; Zhao et al., 2001), ventromedial hypothalamus (Ikeda et al., 1995; Shinoda et al., 1995; Zhao et al., 2008), and spleen (Morohashi et al., 1999; Zangen et al., 2014).

In tissue-specific KO models, it has been shown that SF-1 plays important roles in steroidogenesis and other homeostatic processes following organ development. In Leydig cell-specific KO mice, there are marked decreases in testicular Star and Cyp11a1 expression, indicating a defect in testosterone production (Jeyasuria et al., 2004). Consistent with this hypothesis, the testes fail to descend (an androgen-dependent developmental process) and are hypoplastic. In GC-specific KO mice, there are numerous ovarian defects (Pelusi et al., 2008). In these mice, the ovaries are hypoplastic, adults are sterile, and ovaries show reduced numbers of oocytes. Gonadotropin-induced estrogen and progesterone production are also markedly reduced in this model. These findings show that SF-1 expression is essential in steroidogenic organs throughout life.

Total ablation of LRH-1 causes a severe reduction of Oct-3/4 expression levels and an embryonic lethal phenotype at around embryonic day 6.5–7.5 (Gu et al., 2005; Pare et al., 2004). The functions of LRH-1 in vivo have additionally been revealed by examination of heterozygous and tissue-specific KO models. In heterozygous Lrh-1 KO mice, the abnormalities of gonadal steroidogenesis are exhibited

in both males and females (Labelle-Dumais et al., 2007; Volle et al., 2007). In males, testicular testosterone production is decreased by a reduction in the expression of steroidogenesis-related genes such as Star, Cyp11a1, and Hsd3b (Volle et al., 2007). Accordingly, the epididymides and seminal vesicles of these mice have smaller weights than those of wild-type mice. In females, there is a reduction in the progesterone production of luteal cells, resulting in a subfertile phenotype (Labelle-Dumais et al., 2007). The importance of LRH-1 in female reproduction was further strengthened by Murphy and colleagues using GC- and CL-KO models (Bertolin et al., 2014; Duggavathi et al., 2008; Zhang et al., 2013). GC-KO mice are infertile because of anovulation and impairment of progesterone production due to failure of luteinization (Bertolin et al., 2014; Duggavathi et al., 2008). However, even though CL-KO mice ovulate normally, they are infertile because of implantation failure caused by a deficiency in progesterone production (Zhang et al., 2013). Thus, in addition to SF-1, LRH-1 is also necessary for steroidogenesis in some tissues during postnatal life.

Differentiation of stem cells into steroidogenic cells by SF-1 and LRH-1

In support of the phenotypes of gene-targeted models, we have demonstrated that SF-1 and LRH-1 induce differentiation of non-steroidogenic stem cells into steroidogenic cells (Miyamoto et al., 2011; Yazawa et al., 2014; Yazawa et al., 2009; Yazawa et al., 2010; Yazawa et al., 2011; Yazawa et al., 2006; Yazawa et al., 2008) (Fig. 2). Among the various types of stem cells, we focused on mesenchymal stem cells (MSCs). MSCs are multipotent somatic stem cells that originate in the mesoderm, as is the case with steroidogenic organs. They are defined as adherent fibroblast-like cells that can differentiate into osteoblasts, adipocytes, and chondrocytes (Fig. 2), although they can also generate cells of all three germ layers, at least in vitro (Gojo and Umezawa, 2003; Prockop, 1997; Toyoda et al., 2007). MSCs were originally isolated from bone marrow (BM-MSCs) by Friedenstein et al. (Friedenstein et al., 1976), and have been identified in fat, placenta, umbilical cord blood, and other tissues (Hass et al., 2011; Kode et al., 2009). Because they may be a source of connective tissue lineages in vivo, it is plausible that MSCs are present in most organs throughout the body.

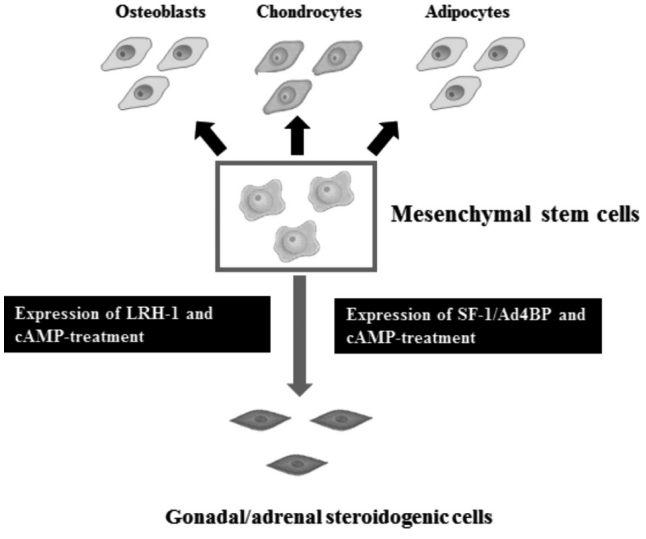

Fig. 2. Induction of gonadal and adrenal steroidogenic cells from multipotent MSCs. With aid of cAMP, both SF-1 and LRH-1 independently have a capacity to differentiate MSCs into steroidogenic cells.

To explore the potential to differentiate into steroidogenic cells, rat BM-MSCs were transplanted into immature testes at the same stage that adult Leydig cells begin to differentiate from stem/progenitor mesenchymal cells (Yazawa et al., 2006). After several weeks, transplanted MSCs had colonized the interstitial spaces of recipient testes and expressed Leydig cell markers, such as Cyp11a1, Hsd3b1, and Cyp17a1. Using a promoter-sorting approach with the human CYP11A1 promoter (genome sequences that regulate cell-specific expression of the CYP11A1 gene in gonadal and adrenal steroidogenic cells), we demonstrated that some isolated mouse BM-MSCs spontaneously differentiate into cells expressing steroidogenic enzymes (Yazawa et al., 2006). These results indicate that MSCs have a capacity to differentiate into steroidogenic cells both in vivo and in vitro. In addition, stable transfection of SF-1 and cAMP treatment induces differentiation of all mouse MSCs into Cyp11a1-positive steroidogenic cells. These cells express various steroidogenic enzymes, and produce progesterone and testosterone. This method can also differentiate human BM-MSCs into cortisol-producing cells in response to adrenocorticotropic hormone stimulation, which are similar to the zona fasciculata cells of the adrenal gland. Additionally, BM-MSCs transform to steroidogenic cells by adenovirus-mediated transient expression of SF-1 (Mizutani et al., 2010; Tanaka et al., 2007; Wei et al., 2012; Yanase et al., 2006). These studies are consistent with the concept that SF-1 is a master regulator for steroidogenesis. In addition to SF-1, introduction of LRH-1 also efficiently induces the differentiation of BM-MSCs into steroidogenic cells without SF-1 (Yazawa et al., 2009; Yazawa et al., 2011). In LRH-1-itroduced cells, expression levels of steroidogenic enzymes and steroid hormone productions were comparable with those in SF-1-introduced cells, suggesting that LRH-1 could be another master regulator in steroidogenesis. In fact, such situations likely occur in CL and intestinal epithelial cells (IECs). These cells synthesize progesterone or glucocorticoid, and although the expression of SF-1 is nearly undetectable (Mueller et al., 2007; Peng et al., 2003; Ramayya et al., 1997), LRH-1 is highly expressed (Mueller et al., 2007; Peng et al., 2003). It is thus conceivable that steroidogenesis of CL and IECs is depend solely on LRH-1, a hypothesis that is supported by the disordered steroidogenesis of these cells in conditional KO mice (Coste et al., 2007; Zhang et al., 2013).

As is the case for BM-MSCs, MSCs derived from other tissues can be differentiated into steroidogenic cells using the above methods (Gondo et al., 2008; Wei et al., 2012; Yazawa et al., 2014; Yazawa et al., 2010). However, these methods are not applicable to pluripotent stem cells, such as ES cells, iPS cells, and embryonal carcinoma cells, because SF-1 and LRH-1 are cytotoxic to these cells (Yazawa et al., 2011; Yazawa et al., 2006). In an early study, Crawford et

al., also reported that even though ectopic expression of SF-1 only rarely induces ES cells to express the Cyp11a1 gene, these cells do not synthesize steroid hormone due to the lack of cholesterol transporter (Crawford et al., 1997; Yazawa et al., 2006). These phenomena are likely because of the properties of LRH-1 that are important for Oct-3/4 expression in these cells (Gu et al., 2005). Oct-3/4 expression levels must be constant in order to maintain the undifferentiated status of pluripotent stem cells (Niwa et al., 2000). Overexpression of LRH-1 (or ectopic expression of SF-1) can markedly affect the expression levels of Oct-3/4 (Gu et al., 2005; Heng et al., 2010). Therefore, it is reasonable to conclude that these factors cause difficulties for the direct induction of steroidogenic cells from pluripotent stem cells. However, mouse ES cells do differentiate into adrenal cortex-like cells when they are pre-differentiated into MSCs by pulse treatment with retinoic acid before expressing SF-1 (Yazawa et al., 2011). These results indicate that MSCs are very useful tools for inducing steroidogenic cells using NR5A subfamily proteins. Our results also suggest that pluripotent stem cells can differentiate into steroidogenic cells by these factors after pre-differentiation into the mesodermal lineage. Consistent with this hypothesis, it was demonstrated by Sonoyama et al. that human ES and iPS cells can differentiate into cortisol-producing cells by the expression of SF-1 only after pre-differentiation into mesodermal cells (Sonoyama et al., 2012). In addition, Jameson and colleague reported that pre-selection or EB formation is necessary to differentiate SF-1-introduced mouse ES cells into sex steroid-producing cells (Jadhav and Jameson, 2011).

CONCLUSION

NR5A subfamily proteins are essential for various phenomena associated with steroidogenesis. SF-1 and LRH-1 activate the transcription of steroidogenesis-related genes by binding to the same DNA sequences of their regulatory regions. SF-1 is a master regulator for the development of gonads and adrenal glands as well as for steroidogenesis following organogenesis. Conversely, LRH-1 is unlikely to be involved in the development of these tissues, although it has been shown to be important for gonadal steroidogenesis. Both factors induce the differentiation of non-steroidogenic stem cells into steroidogenic cells. It is thus clear that SF-1 and LRH-1 have common functions in steroidogenesis, although future studies should resolve the differences between them. For example, as mentioned above, the localization and expression levels of SF-1 and LRH-1 are quite different in steroidogenic tissues. Additionally, although both factors are expressed in Leydig cells and GCs simultaneously, a deficiency of either factor cannot be compensated by another factor. These findings suggest that both factors have unique functions. In GCs, it is noteworthy that ovarian estrogen production is reduced by repression of aromatase expression in SF-1 GC-KO mice (Pelusi et al., 2008), but it is unaffected in LRH-1 GC-KO mice (Duggavathi et al., 2008). Further studies are necessary to reveal the functions of SF-1 and LRH-1 in steroidogenesis.

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