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Overviews of Stem Cells for Gonadal and Adrenal Steroidogenic Cells

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Abstract: Gonads and adrenal glands are the primary organs for the production of steroid hormones in mammals. Steroid hormones play important roles in development and are essential for the maintenance of homeostasis during adult life. To supply sufficient amounts of hormones, gonads and adrenal glands maintain their functions by replenishment of steroidogenic cells. It has been hypothesized that stem/progenitor cells of steroidogenic cells are important for this phenomenon. In fact, such cells have been recently identified in gonads and adrenal glands. However, steroid hormone production decreases progressively with age, causing problems such as menopausal disorders in women. Although steroid hormones are administered to these patients, induction of steroidogenic cells from stem cells is a potential strategy to prevent menopausal disorders. Here, we review the current knowledge on stem cells that replenish steroid hormone-producing cells in the gonads and adrenal glands. We also discuss induction of steroidogenic cells from stem cells derived from non-steroidogenic organs.

Keywords: Steroid Hormone, Stem Cell, Adrenal, Testis, Ovary

1. Introduction

In mammals, steroid hormones are mainly synthesized in gonads (testes and ovaries) and adrenal glands [1, 2]. Gonads produce sex steroids, androgens and estrogens, for gametogenesis and the development of sex characteristics, while adrenal glands produce corticoids for glucose metabolism, stress responses, and fluid balance. In testes, interstitial Leydig cells are responsible for the production of androgens under luteinizing hormone (LH) stimulation. In ovaries, theca and granulosa cells produce estrogens cooperatively. The former synthesize androgen autonomously, whereas the latter only convert theca cell-derived androgen to estrogen. However, granulosa cells differentiate into progesterone-producing luteal cells during ovulation. In adrenal glands, three layers of the cortex are responsible for steroid hormone production. The outermost layer, the zona glomerulosa, produces mineralocorticoid through regulation by renin-angiotensin. The middle layer, the zona fasciculate, produces glucocorticoid by adrenocorticotropic hormone (ACTH) stimulation. In some primates including humans, adrenal androgens are produced in the inner layer, the zona reticularis [3, 4]. Such organ- and zone-dependent differences in steroid hormone profiles are caused by cell-specific expression of steroidogenic enzymes including cytochrome P450 steroid hydroxylases and hydroxysteroid dehydrogenases (Fig. 1).

Even though gonads and the adrenal cortex produce different steroid hormones, they have a common developmental origin [5-7]. In the early embryo, they are derived from the adrenogonadal primordium (AGP) within the urogenital ridge. The AGP originates mainly from the intermediate mesoderm. As embryogenesis proceeds, it separates into adrenocortical and gonadal primordia that are characterized by chromaffin cell precursors and primordial germ cells (PGCs), respectively, which originate and migrate from other germ layers. Steroidogenic factor-1 (SF-1; also known as Ad4BP) is one of the earliest markers of the appearance of the AGP [5, 8]. Its expression is detectable within primitive urogenital ridges from the stage at which the

AGP is not discernible by morphological criteria. After separation of the AGP into each organ primordium, SF-1 expression levels increase with the initiation of steroidogenesis and are maintained during postnatal life [9]. Because SF-1-knockout mice fail to develop gonads and adrenal glands, this represents a master regulator of the development of primary steroidogenic organs [10-12]. SF-1 is also important for steroidogenesis by regulating the transcription of various steroidogenesis-related genes [12-15]. It belongs to the nuclear receptor (NR) superfamily and constitutes the NR5A subfamily together with liver receptor homolog-1 (LRH-1), which has a very similar structure to SF-1. Consistent with its role, SF-1 expression of primary steroidogenic organs is detectable in adults in the three layers of the adrenal cortex, testicular Leydig cells, ovarian theca and granulosa cells, and to a lesser extent in the corpus lutea [9, 16]. In corpus lutea, LRH-1 is essential for the progesterone production to maintain the pregnancy [17, 18].

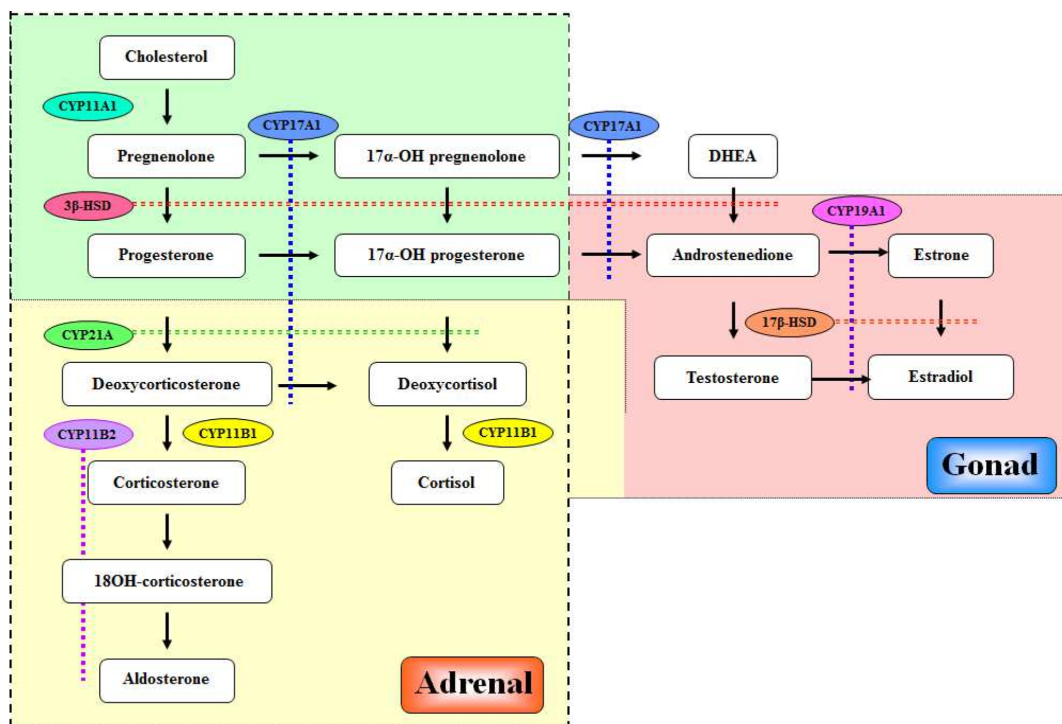

Figure 1. *Steroidogenic pathways in gonad and adrenal.*

Gonads and adrenal glands must continually supply steroid hormones for development as well as maintenance of homeostasis throughout life. Therefore, it is conceivable that steroidogenic cells are replenished from stem/progenitor cell pools. In fact, such stem/progenitor cells have been identified in the adrenal cortex, testes, and ovaries. However, the production of various steroid hormones declines with age. Testicular testosterone production is decreased by a reduction in the steroidogenic capability of aged Leydig cells [19, 20]. In ovaries, the development of granulosa and theca cells does not occur after menopause because of the cessation of new follicle recruitment. Therefore, ovarian androgen and estrogen production ceases in post-menopausal women [21, 22]. In adrenal glands, it is well known that the decline in adrenal androgen production is closely associated with aging [23]. The deficiency of steroid hormones causes various clinical symptoms, resulting in a low quality of life. Although hormone replacement therapy is well established for the treatment of such patients, we and others have attempted to regenerate steroidogenic cells from stem cells for the development of a novel therapy [24]. This article reviews our current knowledge of the stem cells for gonadal and adrenal steroidogenic cells, and recent studies of the differentiation of steroidogenic cells from non-steroidogenic stem cells.

2. Stem Cells of Steroidogenic Cells

2.1. Testicular Leydig Cells and Their Stem Cells

There are two types of Leydig cell populations: fetal and adult. Even though the cells in these two populations share the common characteristic of androgen production, they are different in terms of their origin, ultrastructure, lifespan, and steroidogenic pathways and regulation [25]. Fetal Leydig cells have multiple origins and appear in the interstitial space to induce sex differentiation just after formation of the testis cord [26]. Their main product is androstenedione because they lack any 17β-hydroxysteroid dehydrogenase (HSD) isoforms that catalyze the final step of testosterone synthesis [27, 28]. Androstenedione is a very weak androgen and insufficient to induce virilization. Therefore, Sertoli cells convert androstenedione into testosterone during fetal life [27]. Adult Leydig cells (ALCs) originate from putative stem cells that are non-steroidogenic mesenchymal cells adjacent to seminiferous tubules [29]. They are initiated to differentiate into testosterone-producing cells from the neonatal period. At

this time, fetal Leydig cells are progressively replaced with ALCs, even though the fetal type remains as a minor population in adult testes [30]. ALCs proliferate until puberty for the development of male sexual characteristics. During adult life, Leydig cells are stable populations that are rarely replaced by apoptosis and division. However, it has been demonstrated that stem Leydig cells (SLC) reside in the adult rodent testis. The alkylating agent ethane dimethane sulfonate (EDS) is a selective toxin for ALCs in rats. EDS injection eliminates ALCs completely, following the depletion of testosterone [31]. After a recovery period, ALCs repopulate, and testosterone levels return to normal. It is interesting that aged Leydig cells can be replaced with active Leydig cells in older animals by EDS treatment [32]. Similar to Leydig cells in young animals, the repopulated cells produce testosterone at high levels. In addition, it has been reported that serum testosterone reduction in functional ALC-deficient mice can be recovered by transplantation of a testicular Hoechst-dim side population derived from normal mice into the testicular interstitium [33]. Based on these findings, most researchers have been convinced of the existence of SLCs during the entire lifespan, even though they were impossible to identify because of the lack of a specific cell lineage or surface markers until recently.

In 2006, Hardy and colleagues first purified SLCs from neonatal rat testes by selecting LH receptor (LHR)-negative and platelet-derived growth factor receptor (PDGFR)-α-positive cell populations [34]. These cells expressed c-kit, leukemia inhibitory factor receptor, and GATA4, which are important proteins for Leydig cell development, but they were negative for 3β-HSD and did not produce testosterone. The putative SLCs proliferated in an undifferentiated state for long periods *in vitro* and differentiated into testosterone-producing cells by culture in medium containing thyroid hormone, insulin-like growth factor-1 (IGF-1), and LH. Injection of these cells repopulated 3β-HSD-positive cells in EDS-treated rat testes. Taken together, they concluded that this cell population represented the long-sought SLCs. Following this study, it has been recently reported that PDGFRα-positive peritubular cells exhibit SLC-like characteristics in adult human testes [35]. These cells express not only SLC markers, which were identified in rodents, but also some pluripotency markers (Oct-3/4 and Nanog). In addition, their steroidogenesis can be stimulated with PDGF-BB and forskolin.

2.2. Ovarian Thecal Stem Cells

Theca cells are the ovarian counterpart of testicular Leydig cells. Both cell types share the important characteristic of androgen production in response to LH stimulation [36]. However, the precise origin and the stem cells of theca cells are unclear compared with those of Leydig cells. Theca cells were thought to originate from fibroblast-like progenitor cells within the ovarian stroma [37]. Similar to SLCs, these progenitor cells are non-steroidogenic cells and unresponsive to LH [38, 39]. They are recruited around a follicle with two or more layers of granulosa cells. As follicle growth proceeds, theca cells proliferate and differentiate into steroidogenic cells. They mainly produce androstenedione, the precursor of estrogen until luteinization. Because theca and follicle cells are not present in aged ovaries, the existence of stem cells for theca cells was unclear.

Recently, Ogura and colleagues identified thecal stem cells in neonatal mouse ovaries [40]. Using methods for isolation of germline stem cells from testes [41], they purified colony-forming fibroblast-like cells that were weakly positive for alkaline phosphatase staining. Although these cells could self-renew in culture for a long period, the purified cells were not ovarian germline stem cells because they were deficient for markers of germ cells. However, further analyses demonstrated that these cells were thecal stem cells. They expressed theca cell markers, such as Ptch1 and Gli3, and differentiated into androstenedione-producing cells in vitro by treatment with LH, IGF-1, stem cell factor, and granulosa cell-conditioned medium, and co-culture with granulosa cells. Furthermore, these stem cells were recruited to areas surrounding follicles by intraovarian transplantation.

2.3. Adrenocortical Stem Cells

In early studies, the existence of stem/progenitor cells was suggested in the adult adrenal cortex [42-45]. Regeneration of the adrenal cortex was reported in various experimental models. Unilateral adrenalectomy induces compensatory growth of the remaining cortex [46]. Transplantation of the adrenal cortex regenerates a functional adrenal cortex in recipients [47, 48]. In this model, the zonated cortex can only regenerate from the adrenal capsule and adherent cortical cells after enucleation by removal of the cortex and medulla [48]. These findings strongly indicate localization of adrenocortical stem cells within this region.

Using genetic lineage tracing models, Laufer and colleagues showed that adrenocortical cells are derived from stem/progenitor cells in the capsule [49]. The hedgehog signaling pathway plays important roles in development and maintenance by these stem/progenitor cells. After separation from gonadal primordia in the AGP, relatively undifferentiated cells ($SF\text{-}1^{+}/Cyp11b1/2^{-}$) of the adrenal primordia express Sonic hedgehog (Shh). These cells transduce the signal to the overlying non-steroidogenic mesenchymal cells ($SF\text{-}1^{-}$) for expression of a downstream molecule, Gli1. The Gli1-expressing cells migrate to the adrenocortex to generate all layers of steroidogenic cells during postnatal life. In addition, their descendants provide Shh-expressing cells. Conditional Shh knockout in mouse adrenal glands causes a thin capsule and cortex. These studies strongly suggest that capsular mesenchymal cells serve as stem/progenitor cells of the adrenal cortex via Shh signaling from subcapsular layers. Additionally, Hammer and colleagues reported that adult capsular cells are composed of two distinct populations, Gli1- or Tcf21-expressing cells [50]. Each population serves as progenitor cells for steroidogenic and stromal cells, respectively.

3. Induction of Steroidogenic Cell Using Stem Cells Derived From Non-Steroidogenic Organs

In addition to identification of stem cells in steroidogenic organs, we and others have attempted to induce steroidogenic cells from non-steroidogenic stem cells [24, 51-53]. Among various types of stem cells, mesenchymal stem cells (MSCs) are the most appropriate candidates for induction of steroidogenic cells. MSCs are multipotent adult stem cells of mesodermal origin, the same origin as steroidogenic cells [54, 55]. They can differentiate into adipocytes, chondrocytes, and osteoblasts both *in vivo* and *ex vivo*. MSCs can generate cells of all three germ layers, at least in vitro. Although MSCs were originally discovered in bone marrow (BM-MSCs), they have also been isolated from various tissues [56].

To investigate the potential of MSCs to differentiate into steroidogenic cells, BM-MSCs from green fluorescent protein (GFP)-transgenic rats were transplanted into prepubertal testes (adult Leydig cells initiate to differentiate from SLCs), followed by tracking of their fates [51]. At 3 weeks post-transplantation, GFP-positive cells were localized to the interstitium between seminiferous tubules, which were also positive for various steroidogenic enzymes including Cyp11a1, 3β-HSD, and Cyp17a1. These results indicate that MSCs have the capacity to differentiate into steroidogenic Leydig cells *in vivo*. In addition, in vitro studies demonstrated that small populations of murine BM-MSCs can spontaneously differentiate into Leydig-like cells. A human *CYP11A1* promoter-driven GFP reporter, which consisted of the promoter region that drives reporter gene expression selectively in adrenal and gonadal steroidogenic cells [57], was transfected into BM-MSCs to detect cell populations committed to the steroidogenic lineage. In some transfected cell lines, GFP fluorescence was detected in very small populations that were positive for Cyp11a1. These cells also expressed several Leydig cell markers including 3β-HSD and LHR. These observations further support the in vivo findings indicating that MSCs have the capacity to differentiate into steroidogenic cells.

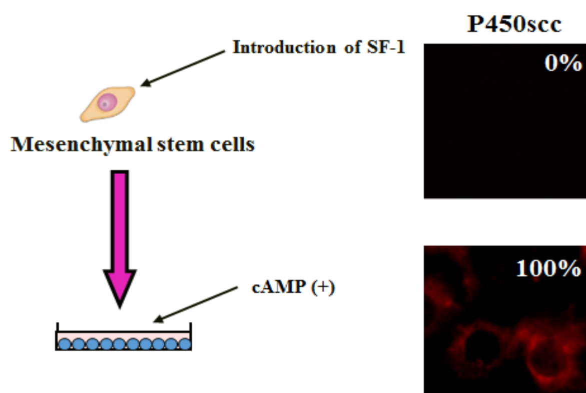

Figure 2. *MSCs are efficiently differentiated into steroidogenic cells by introduction of SF-1 and cAMP-treatment.*

Because GFP-positive and -negative cells could be completely separated into SF-1-positive and -negative fractions, respectively, it is probable that SF-1 can dictate the MSC fate for steroidogenic cells. In fact, murine BM-MSCs can efficiently differentiate into steroidogenic cells after stable expression of SF-1 using plasmids or retroviruses and cAMP treatment (Fig. 2). SF-1 by itself induces morphological changes in BM-MSCs, such as accumulation of numerous lipid droplets, although these cells hardly express steroidogenic enzyme genes or produce steroid hormones at detectable levels. However, SF-1-expressing cells become strongly positive for Cyp11a1 after cAMP treatment . These cells express many other steroidogenesis-related genes (SR-BI, StAR, 3β-HSD, and other P450 steroid hydroxylases) and autonomously produce steroid hormones including androgen, estrogen, progestin, glucocorticoid, and aldosterone. Notably, this approach differentiates human BM-MSCs into cortisol-producing cells in response to ACTH, which are very similar to fasciculata cells in the adrenal cortex. Adenovirus-mediated transient expression of SF-1 also differentiates BM-MSCs into steroidogenic cells with the capacity for *de novo* synthesis of various steroid hormones [53]. In addition to BM-MSCs, these methods can induce differentiation of MSCs derived from various tissues such as adipose, umbilical cord blood, and the uterus [24, 52, 58, 59]. However, these methods are not applicable to embryonic stem (ES) cells, embryonal carcinoma cells, or terminally differentiated cells such as fibroblasts and adipocytes. These studies clearly demonstrate that MSCs are suitable stem cells for differentiating steroidogenic cells. This inference is supported by the fact that, after pre-differentiation into MSCs, ES cells can also be subsequently differentiated into steroidogenic cells using SF-1 [60].

4. Conclusion

It has long been proposed that stem/progenitor cells play important roles in the development and maintenance of steroidogenic cells in the gonads and adrenal glands. Although such stem cells have been recently identified in human and rodents, further studies are necessary to understand the biology of these stem cells in steroidogenic organs. Induction systems for deriving steroidogenic cells from MSCs could be useful tools for studies in this field. Such systems might also provide an opportunity for developing novel treatments of steroidogenesis deficiencies in aging patients.

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References

[1] W. L. Miller, Molecular biology of steroid hormone synthesis. Endocr Rev, 1988, 9, pp. 295-318.

[2] W. L. Miller, R. J. Auchus, The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev, 2011, 32, pp. 81-151.

[3] W. E. Rainey, Y. Nakamura, Regulation of the adrenal androgen biosynthesis. J Steroid Biochem Mol Biol, 2008, 108, pp. 281-286.

[4] P. J. Hornsby, Adrenarche: a cell biological perspective. J Endocrinol, 2012, 214, pp. 113-119.

[5] O. Hatano, A. Takakusu, M. Nomura, K. Morohashi, Identical origin of adrenal cortex and gonad revealed by expression profiles of Ad4BP/SF-1. Genes Cells, 1996, 1, pp. 663-671.

[6] K. Morohashi, The ontogenesis of the steroidogenic tissues. Genes Cells, 1997, 2, pp. 95-106.

[7] P. Val, J. P. Martinez-Barbera, A. Swain, Adrenal development is initiated by Cited2 and Wt1 through modulation of Sf-1 dosage. Development, 2007, 134, pp. 2349-2358.

[8] Y. Ikeda, W. H. Shen, H. A. Ingraham, K. L. Parker, Developmental expression of mouse steroidogenic factor-1, an essential regulator of the steroid hydroxylases. Mol Endocrinol, 1994, 8, pp. 654-662.

[9] O. Hatano, K. Takayama, T. Imai, M. R. Waterman, A. Takakusu, T. Omura, K. Morohashi, Sex-dependent expression of a transcription factor, Ad4BP, regulating steroidogenic P-450 genes in the gonads during prenatal and postnatal rat development. Development, 1994, 120, pp. 2787-2797.

[10] X. Luo, Y. Ikeda, K. L. Parker, A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. Cell, 1994, 77, pp. 481-490.

[11] K. L. Parker, B. P. Schimmer, Steroidogenic factor 1: a key determinant of endocrine development and function. Endocr Rev, 1997, 18, pp. 361-377.

[12] B. P. Schimmer, P. C. White, Minireview: steroidogenic factor 1: its roles in differentiation, development, and disease. Mol Endocrinol, 2010, 24, pp. 1322-1337.

[13] D. S. Lala, D. A. Rice, K. L. Parker, Steroidogenic factor I, a key regulator of steroidogenic enzyme expression, is the mouse homolog of fushi tarazu-factor I. Mol Endocrinol, 1992, 6, pp. 1249-1258.

[14] K. Morohashi, S. Honda, Y. Inomata, H. Handa, T. Omura, A common trans-acting factor, Ad4-binding protein, to the promoters of steroidogenic P-450s. J Biol Chem, 1992, 267, pp. 17913-17919.

[15] T. Yazawa, Y. Imamichi, K. Miyamoto, M. Khan, J. Uwada, A. Umezawa, T. Taniguchi, Regulation of Steroidogenesis, Development and Cell Differentiation by Steroidogenic Factor-1 and Liver Receptor Homolog-1. Zoological Science, (in press)

[16] K. Kawabe, T. Shikayama, H. Tsuboi, S. Oka, K. Oba, T. Yanase, H. Nawata, K. Morohashi, Dax-1 as one of the target genes of Ad4BP/SF-1. Mol Endocrinol, 1999, 13, pp. 1267-1284.

[17] C. Zhang, M. J. Large, R. Duggavathi, F. J. DeMayo, J. P. Lydon, K. Schoonjans, E. Kovanci, B. D. Murphy, Liver receptor homolog-1 is essential for pregnancy. Nat Med, 2013, 19, pp. 1061-1066.

[18] K. Bertolin, J. Gossen, K. Schoonjans, B. D. Murphy, The orphan nuclear receptor Nr5a2 is essential for luteinization in the female mouse ovary. Endocrinology, 2014, 155, pp. 1931-1943.

[19] H. Chen, R. S. Ge, B. R. Zirkin, Leydig cells: From stem cells to aging. Mol Cell Endocrinol, 2009, 306, pp. 9-16.

[20] M. C. Beattie, L. Adekola, V. Papadopoulos, H. Chen, B. R. Zirkin, Leydig cell aging and hypogonadism. Exp Gerontol, 2015, pp.

[21] S. Jabara, L. K. Christenson, C. Y. Wang, J. M. McAllister, N. B. Javitt, A. Dunaif, J. F. Strauss, 3rd, Stromal cells of the human postmenopausal ovary display a distinctive biochemical and molecular phenotype. J Clin Endocrinol Metab, 2003, 88, pp. 484-492.

[22] F. Labrie, All sex steroids are made intracellularly in peripheral tissues by the mechanisms of intracrinology after menopause. J Steroid Biochem Mol Biol, 2015, 145, pp. 133-138.

[23] P. J. Hornsby, Aging of the human adrenal cortex. Sci Aging Knowledge Environ, 2004, 2004, pp. re6.

[24] T. Yazawa, Y. Imamichi, K. Miyamoto, A. Umezawa, T. Taniguchi, Differentiation of mesenchymal stem cells into gonad and adrenal steroidogenic cells. World J Stem Cells, 2014, 6, pp. 203-212.

[25] R. Habert, H. Lejeune, J. M. Saez, Origin, differentiation and regulation of fetal and adult Leydig cells. Mol Cell Endocrinol, 2001, 179, pp. 47-74.

[26] P. J. O'Shaughnessy, P. J. Baker, H. Johnston, The foetal Leydig cell-- differentiation, function and regulation. Int J Androl, 2006, 29, pp. 90-95; discussion 105-108.

[27] Y. Shima, K. Miyabayashi, S. Haraguchi, T. Arakawa, H. Otake, T. Baba, S. Matsuzaki, Y. Shishido, H. Akiyama, T. Tachibana, K. Tsutsui, K. Morohashi, Contribution of Leydig and Sertoli cells to testosterone production in mouse fetal testes. Mol Endocrinol, 2013, 27, pp. 63-73.

[28] P. J. O'Shaughnessy, P. J. Baker, M. Heikkila, S. Vainio, A. P. McMahon, Localization of 17beta-hydroxysteroid dehydrogenase/17-ketosteroid reductase isoform expression in the developing mouse testis--androstenedione is the major androgen secreted by fetal/neonatal leydig cells. Endocrinology, 2000, 141, pp. 2631-2637.

[29] H. B. Siril Ariyaratne, S. Chamindrani Mendis-Handagama, D. Buchanan Hales, J. Ian Mason, Studies on the onset of Leydig precursor cell differentiation in the prepubertal rat testis. Biol Reprod, 2000, 63, pp. 165-171.

[30] J. B. Kerr, C. M. Knell, The fate of fetal Leydig cells during the development of the fetal and postnatal rat testis. Development, 1988, 103, pp. 535-544.

[31] J. B. Kerr, K. Donachie, F. F. Rommerts, Selective destruction and regeneration of rat Leydig cells in vivo. A new method for the study of seminiferous tubular-interstitial tissue interaction. Cell Tissue Res, 1985, 242, pp. 145-156.

[32] H. Chen, I. Huhtaniemi, B. R. Zirkin, Depletion and repopulation of Leydig cells in the testes of aging brown Norway rats. Endocrinology, 1996, 137, pp. 3447-3452.

[33] K. C. Lo, Z. Lei, V. Rao Ch, J. Beck, D. J. Lamb, De novo testosterone production in luteinizing hormone receptor knockout mice after transplantation of leydig stem cells. Endocrinology, 2004, 145, pp. 4011-4015.

[34] R. S. Ge, Q. Dong, C. M. Sottas, V. Papadopoulos, B. R. Zirkin, M. P. Hardy, In search of rat stem Leydig cells: identification, isolation, and lineage-specific development. Proc Natl Acad Sci U S A, 2006, 103, pp. 2719-2724.

[35] L. Landreh, K. Spinnler, K. Schubert, M. R. Hakkinen, S. Auriola, M. Poutanen, O. Soder, K. Svechnikov, A. Mayerhofer, Human testicular peritubular cells host putative stem Leydig cells with steroidogenic capacity. J Clin Endocrinol Metab, 2014, 99, pp. E1227-1235.

[36] J. M. Young, A. S. McNeilly, Theca: the forgotten cell of the ovarian follicle. Reproduction, 2010, 140, pp. 489-504.

[37] J. A. Parrott, M. K. Skinner, Kit ligand actions on ovarian stromal cells: effects on theca cell recruitment and steroid production. Mol Reprod Dev, 2000, 55, pp. 55-64.

[38] C. T. Huang, S. R. Weitsman, B. N. Dykes, D. A. Magoffin, Stem cell factor and insulin-like growth factor-I stimulate luteinizing hormone-independent differentiation of rat ovarian theca cells. Biol Reprod, 2001, 64, pp. 451-456.

[39] M. Orisaka, T. Mizutani, K. Tajima, S. Orisaka, K. Shukunami, K. Miyamoto, F. Kotsuji, Effects of ovarian theca cells on granulosa cell differentiation during gonadotropin-independent follicular growth in cattle. Mol Reprod Dev, 2006, 73, pp. 737-744.

[40] A. Honda, M. Hirose, K. Hara, S. Matoba, K. Inoue, H. Miki, H. Hiura, M. Kanatsu-Shinohara, Y. Kanai, T. Kono, T. Shinohara, A. Ogura, Isolation, characterization, and in vitro and in vivo differentiation of putative thecal stem cells. Proc Natl Acad Sci U S A, 2007, 104, pp. 12389-12394.

[41] M. Kanatsu-Shinohara, K. Inoue, J. Lee, M. Yoshimoto, N. Ogonuki, H. Miki, S. Baba, T. Kato, Y. Kazuki, S. Toyokuni, M. Toyoshima, O. Niwa, M. Oshimura, T. Heike, T. Nakahata, F. Ishino, A. Ogura, T. Shinohara, Generation of pluripotent stem cells from neonatal mouse testis. Cell, 2004, 119, pp. 1001-1012.

[42] E. M. Walczak, G. D. Hammer, Regulation of the adrenocortical stem cell niche: implications for disease. Nat Rev Endocrinol, 2015, 11, pp. 14-28.

[43] A. C. Kim, G. D. Hammer, Adrenocortical cells with stem/progenitor cell properties: recent advances. Mol Cell Endocrinol, 2007, 265-266, pp. 10-16.

[44] A. C. Kim, F. M. Barlaskar, J. H. Heaton, T. Else, V. R. Kelly, K. T. Krill, J. O. Scheys, D. P. Simon, A. Trovato, W. H. Yang, G. D. Hammer, In search of adrenocortical stem and progenitor cells. Endocr Rev, 2009, 30, pp. 241-263.

[45] M. A. Wood, G. D. Hammer, Adrenocortical stem and progenitor cells: unifying model of two proposed origins. Mol Cell Endocrinol, 2011, 336, pp. 206-212.

[46] F. Beuschlein, C. Mutch, D. L. Bavers, Y. M. Ulrich-Lai, W. C. Engeland, C. Keegan, G. D. Hammer, Steroidogenic factor-1 is essential for compensatory adrenal growth following unilateral adrenalectomy. Endocrinology, 2002, 143, pp. 3122-3135.

[47] R. D. Perrone, H. H. Bengele, E. A. Alexander, Sodium retention after adrenal enucleation. Am J Physiol, 1986, 250, pp. E1-12.

[48] A. S. Belloni, G. Neri, F. G. Musajo, P. G. Andreis, M. Boscaro, D. D'Agostino, P. Rebuffat, D. P. Boshier, G. Gottardo, G. Mazzocchi, et al., Investigations on the morphology and function of adrenocortical tissue regenerated from gland capsular fragments autotransplanted in the musculus gracilis of the rat. Endocrinology, 1990, 126, pp. 3251-3262.

[49] P. King, A. Paul, E. Laufer, Shh signaling regulates adrenocortical development and identifies progenitors of steroidogenic lineages. Proc Natl Acad Sci U S A, 2009, 106, pp. 21185-21190.

[50] M. A. Wood, A. Acharya, I. Finco, J. M. Swonger, M. J. Elston, M. D. Tallquist, G. D. Hammer, Fetal adrenal capsular cells serve as progenitor cells for steroidogenic and stromal adrenocortical cell lineages in M. musculus. Development, 2013, 140, pp. 4522-4532.

[51] T. Yazawa, T. Mizutani, K. Yamada, H. Kawata, T. Sekiguchi, M. Yoshino, T. Kajitani, Z. Shou, A. Umezawa, K. Miyamoto, Differentiation of adult stem cells derived from bone marrow stroma into Leydig or adrenocortical cells. Endocrinology, 2006, 147, pp. 4104-4111.

[52] S. Gondo, T. Okabe, T. Tanaka, H. Morinaga, M. Nomura, R. Takayanagi, H. Nawata, T. Yanase, Adipose tissue-derived and bone marrow-derived mesenchymal cells develop into different lineage of steroidogenic cells by forced expression of steroidogenic factor 1. Endocrinology, 2008, 149, pp. 4717-4725.

[53] T. Tanaka, S. Gondo, T. Okabe, K. Ohe, H. Shirohzu, H. Morinaga, M. Nomura, K. Tani, R. Takayanagi, H. Nawata, T. Yanase, Steroidogenic factor 1/adrenal 4 binding protein transforms human bone marrow mesenchymal cells into steroidogenic cells. J Mol Endocrinol, 2007, 39, pp. 343-350.

[54] S. Gojo, A. Umezawa, Plasticity of mesenchymal stem cells--regenerative medicine for diseased hearts. Hum Cell, 2003, 16, pp. 23-30.

[55] D. G. Phinney, D. J. Prockop, Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair--current views. Stem Cells, 2007, 25, pp. 2896-2902.

[56] J. A. Kode, S. Mukherjee, M. V. Joglekar, A. A. Hardikar, Mesenchymal stem cells: immunobiology and role in immunomodulation and tissue regeneration. Cytotherapy, 2009, 11, pp. 377-391.

[57] M. C. Hu, S. J. Chou, Y. Y. Huang, N. C. Hsu, H. Li, B. C. Chung, Tissue-specific, hormonal, and developmental regulation of SCC-LacZ expression in transgenic mice leads to adrenocortical zone characterization. Endocrinology, 1999, 140, pp. 5609-5618.

[58] T. Yazawa, Y. Inaoka, R. Okada, T. Mizutani, Y. Yamazaki, Y. Usami, M. Kuribayashi, M. Orisaka, A. Umezawa, K. Miyamoto, PPAR-gamma coactivator-1alpha regulates progesterone production in ovarian granulosa cells with SF-1 and LRH-1. Mol Endocrinol, 2010, 24, pp. 485-496.

[59] X. Wei, G. Peng, S. Zheng, X. Wu, Differentiation of umbilical cord mesenchymal stem cells into steroidogenic cells in comparison to bone marrow mesenchymal stem cells. Cell Prolif, 2012, 45, pp. 101-110.

[60] T. Yazawa, S. Kawabe, Y. Inaoka, R. Okada, T. Mizutani, Y. Imamichi, Y. Ju, Y. Yamazaki, Y. Usami, M. Kuribayashi, A. Umezawa, K. Miyamoto, Differentiation of mesenchymal stem cells and embryonic stem cells into steroidogenic cells using steroidogenic factor-1 and liver receptor homolog-1. Mol Cell Endocrinol, 2011, 336, pp. 127-132.