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Role of the steroidogenic acute regulatory protein in health and disease

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Abstract

Steroid hormones are an important class of regulatory molecules that are synthesized in steroidogenic cells of the adrenal, ovary, testis, placenta, brain and skin, and influence a spectrum of developmental and physiological processes. The steroidogenic acute regulatory protein (STAR) predominantly mediates the rate-limiting step in steroid biosynthesis, i.e., the transport of the substrate of all steroid hormones, cholesterol, from the outer to the inner mitochondrial membrane. At the inner membrane, cytochrome P450 cholesterol side chain cleavage enzyme cleaves the cholesterol side-chain to form the first steroid, pregnenolone, which is converted by a series of enzymes to various steroid hormones in specific tissues. Both basic and clinical evidence have demonstrated the crucial involvement of the STAR protein in the regulation of steroid biosynthesis. Multiple levels of regulation impinge on STAR action. Recent findings demonstrate that hormone-sensitive lipase, through its action on the hydrolysis of cholesteryl esters, plays an important role in regulating StAR expression and steroidogenesis which involve the liver X receptor pathway. Activation of the latter influences macrophage cholesterol efflux that is a key process in the prevention of atherosclerotic cardiovascular disease. Appropriate regulation of steroid hormones is vital for proper functioning of many important biological activities, which are also paramount for geriatric populations to live longer and healthier. This review summarizes the current level of understanding on tissue-specific and hormone-induced regulation of STAR expression and steroidogenesis, and provides insights into a number of cholesterol and/or steroid coupled physiological and pathophysiological consequences.

Keywords

STAR protein; steroid biosynthesis; STAR deficiency; lipoid CAH; endometriosis; HSL; LXR; ABCA1; atherosclerosis; aging

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Conflicts of Interest

The authors declare no conflict of interest.

Introduction

The maintenance of normal reproductive development and function, and bodily homeostasis, is dependent on steroid hormones. Although the steroid hormones are diverse, they are synthesized from a common precursor substrate, cholesterol, which can be derived from a number of sources, i.e., *de novo* synthesis of cellular cholesterol, lipoprotein-derived cholesteryl esters (CEs), and hydrolysis of CEs stored in lipid droplets [1–3]. Even so, the conversion of CEs into free cholesterol serves as a crucial step in controlling cholesterol availability for steroidogenesis. Regulation of steroid biosynthesis is primarily mediated by trophic hormones, although multiple intracellular events and signaling pathways have been demonstrated to play permissive roles [3–10]. Hormonal control of steroid biosynthesis occurs within minutes (acute) to hours (chronic) and is mediated by cAMP signaling. The biosynthesis of steroid hormones is initiated upon mobilization of cholesterol from cellular stores to the mitochondrial inner membrane and to the site of cytochrome P450 cholesterol side chain cleavage enzyme (P450scc or CYP11A1) (reviewed in Refs. [6, 10–12]). The precise mechanism by which cholesterol is transported to the mitochondria for steroidogenesis remains unknown; however, considerable evidence suggests the involvement of a dynamic mitochondrial protein complex in this process. These proteins include acyl-CoA synthetase 4, steroidogenic acute regulatory protein (STAR), peripheral benzodiazepine receptor/translocator protein, and AAA domain containing protein 3 [12–20]. Among them, the STAR protein has essentially all of the characteristics to become an acute regulator of steroid biosynthesis in steroidogenic tissues [6, 8, 10, 11, 13, 21–24]. STAR consists of several forms of a newly synthesized 30 kDa protein which has a 37 kDa precursor form containing an N-terminal mitochondrial targeting sequence. In describing STAR's role in cholesterol transport, the preponderance of evidence indicates that the 37 kDa STAR acts on the outer mitochondrial membrane [13, 25]. Alternatively, it has been demonstrated that the 30 kDa phosphorylated form acting on the inner mitochondrial membrane allowing for the transfer of the majority of cholesterol [14].

The compelling evidence for the critical role of STAR in the regulation of steroidogenesis has been demonstrated in patients suffering from lipoid congenital adrenal hyperplasia (lipoid CAH), an autosomal recessive disorder in which both adrenal and gonadal steroid biosyntheses are severely impaired due to mutations in the *STAR* gene [23, 26–29]. Targeted disruption of the *STAR* gene in mouse results in an essentially identical phenotype to that found in lipoid CAH in humans [30–32]. In fact, the STAR protein plays an important role in the regulation of steroid hormones required for life itself, in the case of adrenal steroids, and for maintaining reproductive capacity, in the case of gonadal steroids [3, 4, 6, 8, 21, 25]. Nonetheless, in virtually every system studied, agents that influence STAR expression also influence steroid biosynthesis through endocrine, autocrine and paracrine regulation. Regardless of the regulatory events, studies have demonstrated a tight correlation between the synthesis of STAR protein and the synthesis of steroids in a variety of classical (e.g. adrenal and gonadal) and non-classical (e.g. glial and skin) steroidogenic tissues [3, 6, 33, 34].

Whereas STAR plays an indispensable role in controlling steroid biosynthesis, a complete understanding of the regulation of its expression and function in steroidogenesis is not

available. Recent findings have demonstrated that hormone-sensitive lipase (HSL), a neutral cholesteryl ester hydrolase (NCEH), plays a vital role in regulating STAR expression in adrenal and gonadal cells [3, 9, 35]. Of note, HSL catalyzes the hydrolysis of CEs in steroidogenic tissues and macrophages. In addition, the hydrolysis of CEs has been shown to be influenced by several enzymes, including acyl coenzyme A:cholesterol acyltransferase-1, neutral CE hydrolase 1 (also known as KIAA1363 or arylacetamide deacetylase-like 1), carboxylesterase 3, and CE hydrolase (identical to either human liver carboxylesterase 1 or macrophage serine esterase 1) [36–41]. Studies have demonstrated that regulation of HSL mediated STAR expression and steroid biosynthesis involves the liver X receptor (LXR) pathway [3, 9, 34]. Oxysterols act as ligands for LXRs (LXRα and LXRβ; also known as NR1H3 and NR1H2, respectively), which are members of the nuclear receptor superfamily of ligand activated transcription factors [42, 43]. LXRs form obligate heterodimers with retinoid X receptors (RXRs), which also dimerize with retinoid acid receptors (RARs), and regulate the transcription of a number of genes involved in cholesterol utilization, metabolism, and balance, including sterol regulatory element-binding proteins (SREBPs), ATP-binding cassette transporter 1 (ABCA1), and STAR [9, 42–44]. In this review, we will summarize the significant findings that have been made with regards to expression of the STAR protein and, thus, steroid biosynthesis, and their relevance to a number of endocrinological health issues and/or relevant abnormalities.

STAR protein and regulation of steroidogenesis

Steroid biosynthesis in response to trophic hormones is a *de novo* protein synthesis requiring process that is regulated by the delivery of cholesterol from the outer to the inner mitochondrial membrane. A large body of evidence indicates that the intramitochondrial transport of cholesterol is primarily mediated by the STAR protein, a rapidly synthesized mitochondrial phosphoprotein whose expression, activation, and extinction is mediated by protein kinase A (PKA), PKC, as well as a host of other signaling pathways that produce both acute and chronic effects on steroidogenesis [3, 4, 6, 11, 33]. The first step in the steroid biosynthetic pathway is the conversion of cholesterol to pregnenolone by the action of CYP11A1 in the inner mitochondria (Figure 1). Pregnenolone exits the mitochondria and then it is converted to various steroid hormones in specific tissues. STAR is mostly associated with steroid producing tissues, suggesting its critical role in a number of cholesterol and/or steroid led events. Since STAR plays an indispensable role in steroid biosynthesis, the mechanism surrounding the regulation of this gene is extremely important. It has been demonstrated that expression of the *STAR* gene is regulated in a tissue-, stimulus-, and species-specific manner that involve both positive and negative regulatory events [45–48]. There is a wealth of information indicating that regulation of steroid biosynthesis is mediated by mechanisms that enhance transcription, translation, or activity of STAR [6, 11, 45, 47, 49–51]. In accordance with this, transcriptional and/or translational inhibition of STAR expression results in a marked decrease, but not abolished, in steroid synthesis [8, 9, 47, 52]. This suggests that other proteins, in addition to STAR, play important roles for the intramitochondrial transport of cholesterol in controlling steroidogenesis. Molecular modeling, structure-based thermodynamics and biophysical studies suggest that StAR, upon binding cholesterol, interacts with an import complex at the

surface of the mitochondria for the transfer of cholesterol [53–55]. Molecular events associated with transcriptional and/or translational regulation of STAR have been previously reviewed by us [6, 11, 45, 47] and others [24, 48, 56–58], and will not be elaborated upon in great detail here.

Analysis of STAR protein sequences across different species exhibits considerable homology and demonstrates the presence of PKA phosphorylation sites [51, 59, 60]. Two PKA phosphorylation sites have been identified at Ser56/57 and Ser194/195, in mouse and human respectively, and mutations in these sites (Ser→Ala) demonstrated the importance of the latter in biological activity of STAR [59]. As such, phosphorylation of STAR is a plausible mechanism for the optimal cholesterol transferring ability of the STAR protein in steroid biosynthesis [9, 35, 51, 61, 62].

It is unequivocal that the cAMP/PKA signaling cascade is the major pathway regulating STAR expression and steroid biosynthesis; however, many studies have demonstrated the involvement of cAMP/PKA-independent events in these processes [3, 5, 11, 61, 63–66]. For example, whereas LH/hCG is the main regulator of various Leydig cell functions, including steroidogenesis, there is a large body of evidence indicating that the steroidogenic responsiveness of Leydig cells can be modulated by circulating peptides and locally produced factors. Indeed, several extracellular factors and/or signaling have been shown to enhance STAR expression and steroid production without altering intracellular cAMP/PKA levels. These include growth factors, macrophage derived factors, arachidonic acid and its metabolites, mitogen-activated protein kinase/extracellular signal-regulated kinase cascades, chloride ions, and calcium messenger systems [9, 51, 61, 67–70]. It should be noted, however, that the induction of cAMP/PKA-independent steroid biosynthesis (in the absence of STAR phosphorylation) is quite modest when compared to cAMP/PKA/STAR phosphorylation-dependent signaling. Therefore, phosphorylation of StAR is a potential mechanism between cAMP/PKA-independent and cAMP/PKA-dependent steroid biosynthesis, and point to the involvement of crosstalk in these signaling pathways. Even though cAMP/PKA-independent effects of various factors on steroidogenesis are quite small, many of them are capable of potentiating the steroidogenic response of gonadal and adrenal cells to gonadotropins and/or cAMP analogs. In fact, cAMP/PKA-independent pathways could be very important in modulating local regulation of steroid synthesis in various steroidogenic tissues. Consequently, the importance of cAMP/PKA-independent factors has been demonstrated in controlling a number of testicular and/or ovarian functions, including developmental and reproductive events [3, 6, 11, 61, 63, 71, 72].

Non-functional STAR protein, Lipoid CAH, and physiological consequences

Mutations in the *STAR* gene results in a protein that is non-functional and inactive, resulting in lipoid CAH, the rarest and most severe form of CAH [8, 26–28]. This potentially life-threatening disorder is characterized by an inborn error of steroid hormone biosynthesis resulting in near complete inability of the newborn to synthesize steroids. Clinical manifestations of lipoid CAH include a marked adrenocortical insufficiency, hypergonadotropic hypogonadism, and severe salt wasting, and affected newborns die shortly after birth as a result of glucocorticoid and mineralocorticoid deficiencies.

Individuals afflicted with lipoid CAH are phenotypically female irrespective of chromosomal sex, have large adrenals containing high CE and cholesterol levels, and also have cholesterol deposition in steroidogenic cells [8, 26, 27, 73–77]. Affected individuals (who fail to metabolize cholesterol in mitochondria of the adrenal glands and gonads) die shortly after birth due to glucocorticoid and mineralocorticoid insufficiencies; however, appropriate hormone replacement therapy results in the survival of lipoid CAH patients to adulthood. Analysis of the *STAR* gene isolated from testicular tissue of lipoid CAH patients demonstrated the presence of nonsense and deletion mutations, which demonstrated initial proof of this disease and the critical role of STAR in steroid biosynthesis [23]. Whereas overexpression of wild type STAR in monkey kidney COS-1 cells (rendered steroidogenic by transfection with the P450scc system) increased steroid production, cells expressing mutant STAR were completely inactive in promoting steroidogenesis [23, 26, 78]. Therefore, expression of the STAR protein was an obligatory requirement for intracellular trafficking of cholesterol and that lipoid CAH represents a natural knockout of STAR with consequences consistent with the role of STAR on steroid biosynthesis.

Molecular genetic analyses have identified approximately three-dozen mutations in the *STAR* gene producing lipoid CAH and include nonsense and missense mutations, splicing errors, and frameshifts causing deletions/insertions [27, 28, 32, 76, 77, 79]. Notably, two patients diagnosed with lipoid CAH lacked mutations in the *STAR* gene. However, these patients have heterozygous mutations in the *CYP11A1* gene, allowing afflicted individuals to survive longer periods without hormone replacement therapy. Thus, haploinsufficiency of *CYP11A1* can lead to a late onset form of lipoid CAH or these patients may harbor mutations in other gene(s) whose function is dependent on STAR action. Noteworthy, however, CAH can be induced by the deficiency of one of four steroidogenic enzymes involved in cortisol biosynthesis, i.e., 21-hydroxylase, 11-hydroxylase, 3β-hydroxysteroid dehydrogenase, and 17α hydroxylase/17,20-lyase [29, 80–82]. All of the STAR mutations identified in lipoid CAH are found in the C-terminus of the STAR protein, alter its structure/function, and result in a biologically inactive non-functional STAR that lacks the ability to deliver cholesterol to CYP11A1 in supporting steroidogenesis. While a correlation between STAR mutations and lipoid CAH is documented, molecular analyses of female subjects led to the formulation of the two hit model [8, 26, 28, 76]. The first hit is caused by the inability of STAR to transfer cholesterol to the inner mitochondrial membrane for acute steroid synthesis due to mutations in the *STAR* gene. However, cells can continue to make small amounts of steroid by a STAR independent mechanism, which allows for the survival of some lipoid CAH patients for 1 to 2 months without treatment [26, 83]. The second hit results in the prolonged and massive accumulation of lipids in affected cells that eventually interferes with normal cellular processes and results in death of cells. Thus, the feminization occurring at puberty with lipoid CAH is due to the small amount of STAR independent steroids synthesized by ovarian follicles recruited during each cycle. Since STAR is not present in the granulosa cells of preovulatory follicles, the first hit cannot occur. In the second hit, which utilizes a STAR-independent process, recruited follicles synthesize small amounts of estrogen but ultimately accumulate excessive amounts of lipids resulting in destruction of the follicle prior to luteinization and progesterone production [26, 76, 84–86]. Factors responsible for the production of small amount of steroids include members of the

START (STAR-related lipid-transfer) domain family (that have been reported to be involved in steroidogenesis) and oxysterols [43, 87–92].

Further insights into these mechanisms have been documented with targeted disruption of the *STAR* gene in a mouse model [30, 31, 93]. Similar to lipoid CAH in humans, STAR null mice have female external genitalia, fail to grow normally and die shortly after birth as a result of adrenocortical insufficiency. The adrenal glands were smaller in STAR knockout mice than those of wild type littermates and demonstrated profound morphological anomalies in the cortex [8, 30, 31]. Moreover, mice lacking the *STAR* gene had multiple abnormalities in adrenal and gonadal functions caused by the massive lipid accumulation in these tissues. Serum corticosterone and aldosterone levels were low with elevated ACTH and corticotropin-releasing hormone levels, representing impaired adrenal steroid production and loss of feedback regulation at the hypothalamic-pituitary level. Despite the dramatic effects of the absence of STAR on adrenal and gonadal steroid formation, prepubertal serum testosterone levels in STAR null mice did not differ from wild type littermates [30]. The physio-pathological characteristics of STAR knockout mice were similar to those seen in lipoid CAH in humans, supporting the two hit model, demonstrating the consequences of a non-functional STAR, and reinforcing the crucial role of this protein in the regulation of steroid biosynthesis (reviewed in Refs. [6, 8, 26–28]).

STAR expression and its correlation to estrogen dependent disorders

As mentioned above, the STAR protein predominantly regulates steroid biosynthesis. It is well known that estrogen, derived from a number of sources, plays a central role in the pathogenesis of gynecological disorders and/or cancers, i.e., endometriosis and, endometrial, breast, and ovarian cancers [94–97]. The key enzyme for biosynthesis of estrogens is aromatase cytochrome P450 (P450arom, the product of CYP19 gene) that catalyzes the conversion of androstenedione and testosterone to estrone and estradiol [94, 98]. Consequently, aromatase inhibitors (that eliminate and/or block estrogen production) have been successfully used for prevention and treatment of these diseases.

One of the most common, inherited, chronic, and estrogen-dependent gynecological disorder of complex multifactorial etiology is endometriosis. This disease is defined by the presence of endometrial glands and stroma within pelvic peritoneum and other extrauterine tissues and is associated with pelvic pain and infertility [99, 100]. It is well established that estrogen from the ovaries is critical for maintenance of endometriosis, which affects approximately 5–10% in reproductive-aged women and 40–50% with infertility [101–104]. Endometriotic tissue expresses STAR, CYP11A1, aromatase, and other steroidogenic enzymes, thereby producing estrogen from cholesterol *de novo* [99, 105–107]. However, normal endometrium is not steroidogenic. Studies have shown that both mouse and rat peritoneal macrophages produce 25-hydroxycholesterol (25-HC; an endogenous metabolite of cholesterol) that can serve as a substrate for inducing STAR expression and steroid production in different steroidogenic tissues [108–110]. Hence, macrophages in the peritoneal cavity might be involved in providing 25-HC to endometriotic cells, thus increasing the estrogen load to the lesions. Studies have also reported that altered expression and DNA binding activity of a

number of transcription factors involved in controlling steroidogenic genes are responsible for the abnormalities connected with endometriosis [94, 98, 104].

We observed recently that both oxysterols (22R-, 25- and 27-HC) and peritoneal fluids (collected from woman without or with endometriosis of stages from I through IV; Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center; IRB# L13-033) were capable of increasing STAR expression and pregnenolone synthesis in human endometrial stromal (ATCC, Manassas, VA) cells (Manna PR et al., unpublished observations). In addition, *STAR* mRNA expression was found to be strikingly higher in stage IV endometriosis when compared with control endometrium. It is likely that 25-HC derived estrogen plays an important role in endometriosis, has the ability to induce non-steroidogenic cells to become steroidogenic, and is elevated in women with endometriosis. As such, determination of 25-HC in the peritoneal fluid and/or blood of patients with endometriosis could be a novel noninvasive procedure for diagnosing this disorder. Collectively, there are two sources of estrogen stimulating the endometriotic tissue, one from the ovary and the other from the lesions themselves. Regardless of estrogen sources, drugs that inhibit the production or action of estrogen have been shown to reduce the severity of endometriosis [104, 111–113].

Role of HSL-LXR signaling on STAR mediated physiological events

HSL, a multifunctional enzyme, by catalyzing the hydrolysis of CEs, plays an important role in a number of physiological processes [3, 9, 38, 114, 115]. Notably, HSL is the primary NCEH in steroidogenic tissues, and disruption of *HSL* in mice results in a marked attenuation of NCEH activity in the adrenals and testes accompanied with profound morphological alterations in these tissues [3, 9, 38, 39, 116, 117]. Male, but not female, mice homozygous for the mutant HSL allele were sterile [38]; thus, the inactivation of HSL mainly affected spermatogenesis and not oogenesis. HSL null male mice exhibit several testicular anomalies, including decreased weight, vacuolated seminiferous tubules, reduced spermatids, and sterility [38, 117–119]; however, circulating steroid hormone levels were normal in these mice. The mechanism responsible for persistent steroidogenesis in HSL null mice, resulting in little to no HSL/NCEH activity, remains unclear, and may involve one or more compensatory event(s), including acyl-coenzyme A:cholesterol-acyltransferase activity and/or *de novo* cholesterol synthesis.

Hormonal control of HSL activity is chiefly mediated by phosphorylation of several serine (Ser) residues i.e. Ser563, Ser565, Ser600, Ser659, and Ser660 (sequences corresponding to rat HSL), by cAMP-dependent PKA as well as other kinases [9, 120–122]. Previously, we have demonstrated that activation of cAMP/PKA signaling enhances phosphorylation of HSL at Ser660 and Ser563, concomitant with its increased hydrolytic activity, and these events are tightly connected with STAR expression and steroid biosynthesis in gonadal and adrenal cells [3, 9]. In keeping with this, deficiency of HSL decreases STAR and steroid levels, demonstrating that HSL plays a vital role in regulating the steroidogenic response. However, the interaction of HSL with a number of proteins, including STAR and perilipin (a lipid droplet associated protein), in trafficking of intracellular cholesterol from lipid droplets into the mitochondria thereby supporting steroidogenesis has been demonstrated [2, 123].

Whether members of the START domain family, specifically STARD3 (also called as MLN64, metastatic lymph node 64) and STARD4-STARD6, interact with HSL and influence cholesterol trafficking, metabolism and balance requires additional investigation.

Lipoprotein-derived selective uptake of CEs, via the scavenger-receptor class B type 1 ((SR-B1, a high-density lipoprotein (HDL) receptor)), provides most of the cholesterol for steroidogenesis in rodents, with lesser contributions from low-density lipoprotein (LDL) and *de novo* synthesis [1, 61, 124, 125]. Receptor-mediated endocytic uptake of lipoprotein-derived CEs is processed via the LDL receptor in the human systems [126, 127]. The roles of the Niemann Pick C1 (NP-C1) and NP-C2 proteins in cholesterol trafficking via LDL receptor-mediated endocytosis and cleavage of CEs by lysosomal acid lipase have also been reported [128–130]. Nonetheless, a striking correlation between hormonal induction of SR-B1 expression and steroid synthesis has been reported in different steroidogenic cells. High levels of HSL and SR-B1 are also linked with constitutive expression of STAR and steroid production in R2C rat Leydig cells [124]. It is worth mentioning that knock-down of HSL decreases SR-B1, cholesterol, and STAR levels in gonadal and adrenal cells, representing a direct connection between HSL action and STAR expression [3, 9, 124]. Alternatively, overexpression of HSL increases not only the efficacy of LXR ligands on STAR transcription and steroid biosynthesis but also the LXR target genes, SREBP-1c and ABCA1 (Figure 2), demonstrating the involvement of LXR signaling in controlling HSL mediated steroidogenesis.

LXRs bind to oxysterol ligands, activate transcription of many genes, including STAR, and play essential roles in regulating intracellular cholesterol trafficking and balance [9, 43, 131]. Oxysterols are involved in STAR expression and steroidogenesis. Mice lacking LXRs (both α and β) display reduced fertility, underscoring the importance of these receptors in reproduction [132, 133]. In keeping with this, we have shown that silencing of LXRα/β diminishes cAMP/PKA responsive HSL activity, accompanied with decreased expression and phosphorylation of STAR and steroid biosynthesis in mouse Leydig cells [9]. An increase in HSL levels modulates the steroidogenic response mediated by LXR ligands, suggesting HSL dependent steroidogenesis entails enhanced oxysterol production. HSL is also capable of increasing ABCA1 protein expression. Recent findings provide evidence that LXRs interact/cooperate with RXRs/(RARs) and result in synergistic activation of cAMP/PKA mediated STAR expression and steroid synthesis [9, 35]. Additionally, it has been demonstrated that retinoids (vitamin A and its derivatives), especially all-trans retinoic acid (atRA) and 9-cis RA (which primarily act through RXRs and RARs), by interacting with an LXR-RXR/RAR heterodimeric motif in the *STAR* promoter, plays an important role in transcriptional regulation of the *STAR* gene [34, 35]. Retinoids are hormone-like molecules that exert a multifaceted array of effects on development, differentiation, reproduction, and epidermal homeostasis [35, 134–140]. Retinoid signaling enhances HSL activity, and HSL mediated up-regulation of StAR expression involves the LXR regulatory pathway [3, 9, 35]. Based on these observations, it is plausible that regulation of HSL-LXR-RXR/RAR by retinoid signaling may have important implications on prevention of many complications and diseases.

Role of STAR in macrophage cholesterol efflux and its relevance to atherosclerosis

The deposition of excess lipids/CEs in the arterial walls is a hallmark of atherosclerosis in which macrophages play a vital role to form the foam cells. Atherosclerosis is the most prevalent event within cardiovascular diseases and is the leading cause of morbidity and mortality worldwide. Accumulating evidence indicates that stimulation of CE hydrolysis following overexpression of HSL correlates with ABCA1 expression in macrophages, a crucial event in cellular lipid transport and atherosclerosis [141–145]. ABCA1, a key protein in cholesterol efflux, transports cellular cholesterol from macrophages to apolipoprotein A1 (Apo-A1). The importance of ABCA1 has been documented by its absence in patients afflicted with Tangier disease, which is linked to HDL deficiency and premature atherosclerosis [146]. Removal of excess CEs from macrophage-derived foam cells is critical for the progression of atherosclerotic lesions [145, 147–149]. Studies have shown that overexpression of STAR increases macrophage cholesterol efflux and decreases intracellular lipids and the secretion of inflammatory factors [148, 149].

LXR-RXR/RAR and their heterodimerization partners, especially lipid homeostasis-related transcription factors, SREBPs (particularly SREBP-1c) and peroxisome proliferator-activated receptors (PPARs), are targets for intervention in atherosclerosis [144, 150–152]. Our recent findings demonstrate that retinoids strikingly increase cAMP/PKA responsive STAR and steroid levels in a variety of steroidogenic cell models [9, 34, 35]. These results suggest that retinoid signaling is capable of enhancing cholesterol clearance from cells, an approach that may be effective in limiting plaque stability and progression of atherosclerotic cardiovascular disease. Consistent with this, in a recent study [153] we have reported that retinoids enhance cholesterol efflux to Apo-A1 in mouse RAW 264.7 macrophages, and this effect was further augmented in the presence of cAMP/PKA signaling (Figure 3). Besides, macrophages overexpressing HSL increased the hydrolysis of CEs resulting in a depletion of CE content and elevated *StAR* mRNA expression. Concurrently, HSL overexpression was capable of enhancing the efficacy of RAR and LXR ligands on StAR and ABCA1 protein levels [153]. These findings imply that an increase in HSL levels promotes oxysterol production, which, in turn, activates LXR and results in up-regulation of retinoid mediated macrophage cholesterol efflux. In support of this, previous studies have demonstrated the role of LXRs and PPARs in the control of cholesterol trafficking in macrophages [142, 154]. Taken together, it is plausible that LXR activation enhances plasma membrane cholesterol trafficking and efflux, and modulates cholesterol esterification, thus contributing to the effects of retinoids in controlling cholesterol balance for limiting/stabilizing atherosclerotic cardiovascular disease. An understanding of the process of macrophage foam cell formation and its connection to HSL-LXR regulated events will help develop novel therapeutic interventions for atherosclerosis.

STAR expression and its correlation to aging

Complex endocrine changes, affecting the morphology and function of a multitude of organs, occur as life progresses from adulthood into senescence. This aging process results in a decline of various hormones and, as a consequence, affects a number of physiological

functions [155–160]. The occurrence of hormone deficiencies (or endocrinosenescence) is constituted to be the major cause of human senescence and it is associated with numerous complications and disabilities [156, 160–162]. Endocrinosenescence includes growth hormone/insulin-like growth factor-1 axis (somatopause), hypothalamic-pituitary gonadal axis (hypogonadism), testosterone (andropause), estradiol (menopause), and dehydroepiandrosterone (adrenopause) [159, 160, 163–166]. The manifestations of these deficiencies include, but are not limited to, inefficient hypothalamic-pituitary-thyroidal-adrenal-gonadal (HPTAG) axes, neurodegenerative disorders, diminished eyesight, impaired memory and cognitive function, decreased muscle mass and bone density, decreased steroid biosynthesis, sexual dysfunction and depression, increased risk in cardiovascular disease, and skin disorders [65, 139, 155, 159, 162, 167, 168]. These conditions profoundly affect geriatric populations worldwide within the context of a substantial rise in life expectancy. Preservation of hormonal balance is the key to proper functioning of various biological activities during aging. We have demonstrated that retinoids, especially RAs, up-regulate STAR expression and steroid biosynthesis in adrenal, gonadal, glial, and epidermal cells [34, 35], indicating that retinoid signaling is capable of influencing a number of cholesterol/steroid coupled physiological activities that are frequently impaired in geriatric populations.

Aging is an inevitable heterogeneous phenomenon involving the whole organism and results in a decline of the central nervous system and the endocrine system [156, 169–172]. The maintenance of a well-balanced endocrine circadian rhythmicity is critical to health. Age-associated hormonal imbalance, involving a reduction in the steroidogenic output, is linked to numerous health complications along with a host of pathologies [138, 173–177]. There is increasing evidence that aging is connected to the progressive accumulation of dysfunctional mitochondria and oxidative damage, which modulate the immune system and contribute to increased morbidity and mortality [177–181]. With aging, excessive production of free radicals and reactive oxygen species (ROS) occurs in the mitochondria, which affects the function of the HTPAG axis auto-regulating system. The increase in free radicals is inversely correlated with antioxidant capacity in the central nervous system and its associated glands [179, 182]. It is conceivable that an imbalance between production of free radicals/ROS and protective antioxidant systems, affecting cellular oxidative damage, might induce age-related complications and diseases [179, 180, 182]. Previous studies have reported that ROS disrupts mitochondria and decreases in STAR expression and steroidogenesis in a variety of steroid producing cells, and is tightly connected with age-related decline in steroid biosynthesis [177, 178, 183, 184]. As such, oxidative damage induced by ROS is deleterious to the functional efficiency of various cellular processes and is implicated in the pathogenesis of numerous conditions including age-related complications and disabilities.

Physiological aging results in most of the phenotypic changes observed in skin. The latter forms an essential barrier between the external environment and the biological milieu, and it is tightly networked to central regulatory systems [34, 139, 176, 185–187]. Several lines of evidence demonstrate that regulation of glucocorticosteroidogenesis in the skin is similar to those operating in classical steroidogenic tissues [188–191]. Human skin cells express STAR, synthesize cholesterol, and possess the functional biochemical apparatus for the synthesis of glucocorticoids, androgens, and estrogens, which play vital roles in epidermal

homeostasis [139, 188, 190, 192–194]. It should be noted that in human skin CYP11A1 can also use 7-dehydrocholesterol (precursor to cholesterol and vitamin D) as an alternative substrate leading to production of 7Δ-steroids [176, 195]. Expression levels of STAR and aromatase have been correlated with androgen and estrogens in male and female skin tissues, respectively, demonstrating the relevance of STAR and sex steroids in homeostasis of the human skin [194]. In contrast, malfunction in skin cholesterol synthesis, involving a global reduction in steroids, is associated with down-regulation of epidermal differentiation, leading to many skin complications/disorders [34, 139, 187, 193, 196]. We and others have demonstrated that expression of *STAR* mRNA is decreased or aberrant in several inflammatory skin diseases, including eczema, intertrigo, atopic dermatitis, signifying that steroid biosynthesis is disrupted in these diseased conditions [34, 139, 197–199].

As mentioned above, retinoids influence an array of functions, ranging from vision to reproduction to homeostasis [35, 139, 199–202]. The therapeutic and preventive effects of retinoids in numerous skin conditions and diseases, including premature skin aging, skin cancer prevention, squamous cell carcinoma, and skin rejuvenation and hyperpigmentation have long been established [137, 191, 203–205]. Retinoid metabolism and signaling also decreases in a variety of complications and diseases [138, 140, 168, 206]. The systemic administration of RAs has been shown to reverse most reproductive and developmental blocks in vitamin A deficient (VAD) rats and mice, demonstrating that retinoid signaling rescues reproductive defects as well as steroidogenesis in VAD animals [201, 207, 208]. An unanswered question is if retinoids are able to reverse the decline in steroid biosynthesis in target tissues and thereby restore steroid coupled impaired biological activities that particularly evolve during aging. It has been shown that retinoids, especially RAs, elevate expression of steroidogenic enzymes, STAR, and steroid biosynthesis in a variety of target tissues [35, 209–213]. Recently, we observed that retinoids were capable of enhancing and/or restoring STAR expression and pregnenolone synthesis in isolated epidermal keratinocytes of elderly (64–83 years) individuals (Manna PR et al., unpublished observations). These de-identified human skin tissues were obtained upon various surgeries from the Department of Dermatology clinic, Texas Tech University Health Sciences Center (IRB# L14-085). This implies that retinoid signaling is capable of reversing the decline in steroid biosynthesis and relevant skin complications and disorders in aging populations. Hence, it is conceivable that therapeutic strategies involving the use of retinoids will have benefits in the restoration of many impaired physiological activities that are important for healthy aging. Future studies on tissue-specific regulation of retinoid mediated restoration of cholesterol/steroid dependent events provide better understanding on many important physiological and/or patho-physiological processes.

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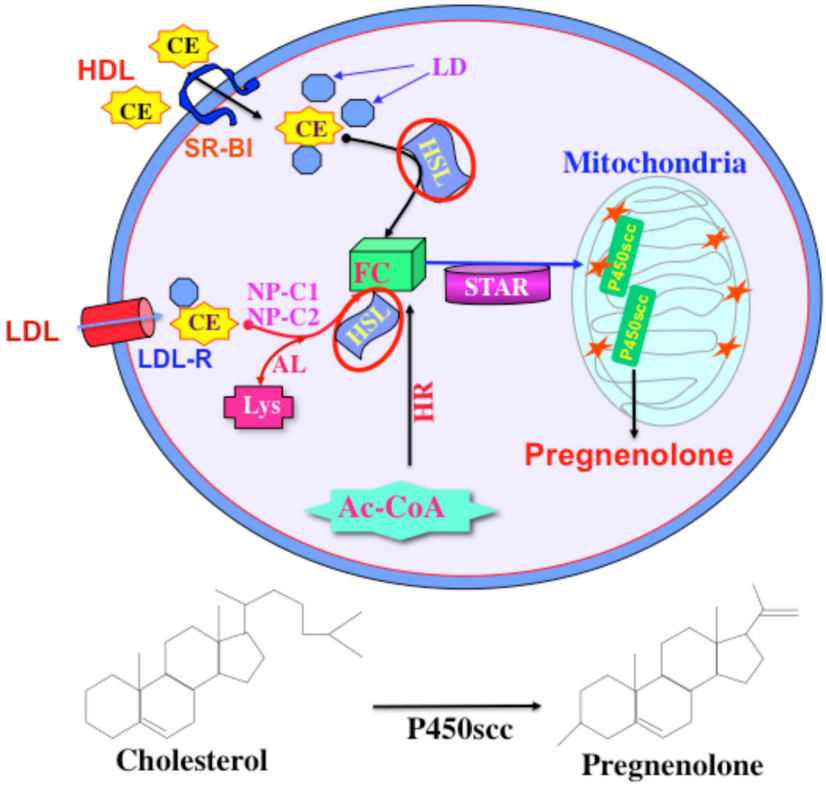

Fig. 1.

A model illustrating CE metabolism and its relevance to steroidogenesis. Cholesterol utilized for steroidogenesis is derived from a number of sources. The hydrolysis of CEs stored in lipid droplets is an important source of cholesterol for optimum steroid biosynthesis. HSL is a multifunctional enzyme that is responsible for NCEH activity. Circulating lipoprotins (HDL or LDL) bind to SR-B1 and release CEs into the cells. In rodents, free cholesterol (FC) utilized for steroid synthesis is mostly obtained via HDL mediated CE internalization and followed by cleavage by HSL. Receptor-mediated uptake of lipoprotein-derived CEs is processed via the LDL receptor in the human systems. *De novo* synthesis of cholesterol from acetyl-coenzyme A (AC-CoA) provides also FC for steroid synthesis. The STAR protein regulates steroid biosynthesis by controlling the transport of cholesterol from the outer to the inner mitochondrial membrane. Conversion of cholesterol to pregnenolone is the first enzymatic step in steroid hormone biosynthesis (bottom panel). Pregnenolone is then converted to various steroid hormones by a series of enzymes in specific tissues. LD, lipid droplets; AL, acid lipase; NP-C1 and C2, Niemann Pick C1 and C2; Lys, lisosome; HR, HMG-Coenzme A reductase. Revised and represented with permission from Molecular Human Reproduction (3).

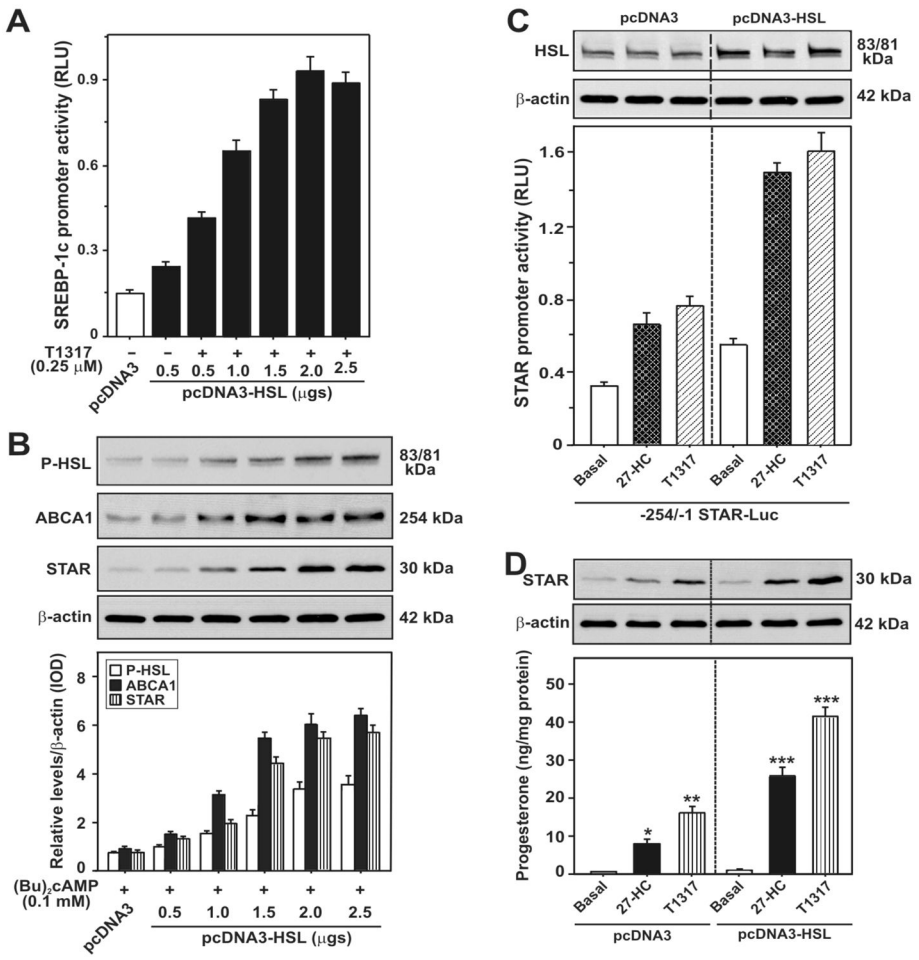

Fig. 2.

Overexpression of HSL on 27-HC and/or T1317 and $(Bu)_2$cAMP stimulated SREBP-1c and STAR promoter activity, and HSL, P-HSL, ABCA1, and STAR and steroid levels. MA-10 cells were transfected with pcDNA3-HSL at either increasing (0.5–2.5 μg; A and B) or fixed (2.0 μg; C and D) amounts of cDNAs, within the context of either the −2.7 kb/+1 bp SREBP-1c (A) or −254/−1 bp STAR (C) promoter-driven luciferase reporter plasmid, in the presence of pRL-SV40. Following 36h of transfection, cells were treated without or with 27-HC (0.25 μM) and T1317 (0.25 μM) for an additional 6h. Luciferase activity in the cell lysates was determined and expressed as SREBP-1c (A) and STAR (C) promoter activity, RLU (luciferase/renilla). Cells were also processed for immunoblotting (B). Representative immunoblots illustrate HSL, P-HSL, ABCA1, and STAR in different groups using 20–30 μg of total cellular protein (B–D). Immunoblots shown are representative of four independent experiments. β-actin expression was assessed as a loading control (C and D). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ vs. basal. (Revised and represented following copyright permission, "this research was originally published in The Journal of Biological Chemistry, Manna PR, Cohen-Tannoudji J, Counis R, Garner CW, Huhtaniemi I, Kraemer FB, Stocco DM, Mechanisms of action of hormone-sensitive lipase in mouse Leydig cells: its role in the

regulation of the steroidogenic acute regulatory protein. J. Biol. Chem., 2013, 288(12): 8505–18. © the American Society for Biochemistry and Molecular Biology").

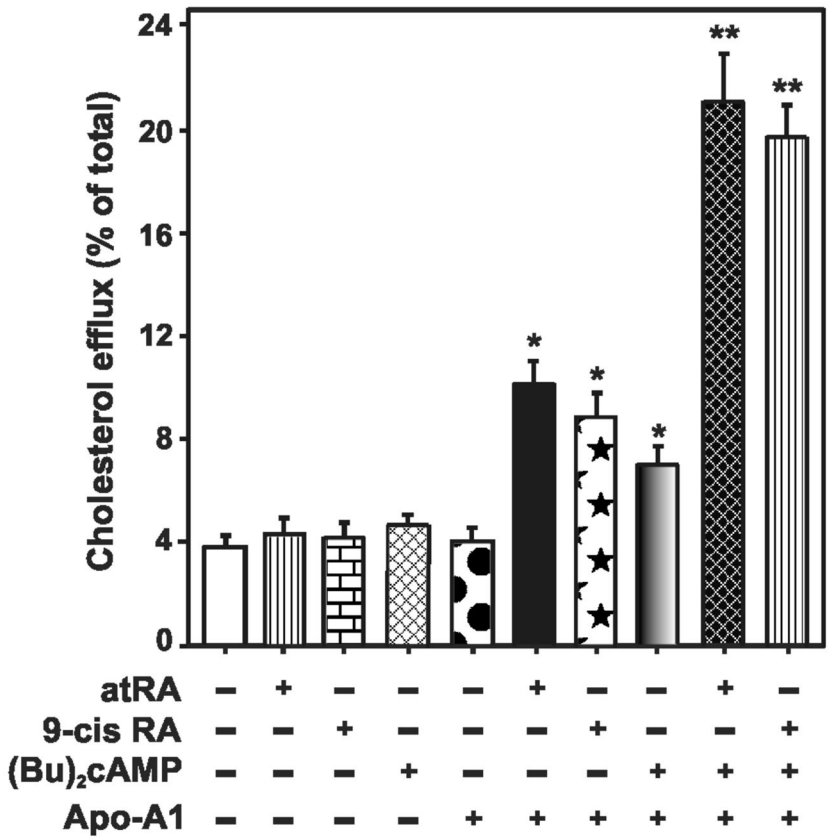

Fig. 3.

Effects of atRA and 9-cis RA on $(Bu)_2$cAMP stimulated macrophage cholesterol efflux. Mouse RAW 264.7 macrophages were labeled with ^{3}H-cholesterol for 24h. Macrophages were then treated without or with atRA (10 μM), 9-cis RA (10 μM), $(Bu)_2$cAMP (0.1 mM), or their combination, for 12h, in the absence or presence of Apo-A1 (20 mg/ml), as indicated. Following treatments, media and cells from different groups were collected separately and counted in a liquid scintillation counter, and cholesterol efflux was calculated as the percentage of radioactivity recovered in the media over total (cells plus media) radioactivity. Data represent the mean ± SE of 4 independent experiments. *, $p < 0.05$; **, $p < 0.01$; vs. control. Revised and represented with permission from Biochemical Biophysical Research Communication (153).