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Steroid Receptor Coactivators as Therapeutic Targets in the Female Reproductive System

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Abstract

The Steroid Receptor Coactivators (SRCs/p160/NCOA) are a family of three transcriptional coregulators initially discovered to transactivate the transcriptional potency of steroid hormone receptors. Even though SRCs were also found to modulate the activity of multiple other transcription factors, their function is still strongly associated with regulation of steroid hormone action and many studies have found that they are critical for the regulation of reproductive biology. In the case of the female reproductive tract, SRCs have been found to play crucial roles in its physiology, ranging from ovulation, implantation, to parturition. Not surprisingly, SRCs' action has been linked to numerous abnormalities and debilitating disorders of female reproductive tissues, including infertility, cancer, and endometriosis. Many of these pathologies are still in critical need of therapeutic intervention and "proof-of-principle" studies have found that SRCs are excellent targets in pathological states. Therefore, small molecule modulators of SRCs' activity could be applied in the future in the treatment of many diseases of the female reproductive system.

Keywords

female reproductive tract; female reproductive tract pathology; cancer; infertility; endometriosis; Steroid Receptor Coactivators

Introduction

Steroid hormone receptors, in particular the estrogen and progesterone receptors (ER α and PR), are crucial functional regulators of female reproductive biology. Apart from being modulated by hormones, their activity, as in the case for all transcription factors, requires their interactions with many transcriptional coregulators. These coregulators, either coactivators or corepressors, form large complexes that engage in the remodeling of chromatin through histone post-translational modifications and link transcription factors to

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the basal transcriptional RNA polymerase II machinery for all subsequent genomic actions [1].

The first discovered coactivator for steroid receptors was the Steroid Receptor Coactivator-1 (SRC-1/NCOA1) [2] which was found to interact with the ligand binding domain of PR and importantly to transactivate the transcriptional activity of PR, ER α , and many other nuclear receptors and transcription factors [2]. Shortly thereafter, the remaining two members of the SRC family were discovered: SRC-2 (NCOA2/GRIP-1/TIF-2) [3, 4] and SRC-3 (NCOA3/pCIP/AIB1) [5–7]. Even though their official nomenclature refers to them as nuclear coactivators, *i.e.*, NCOA, it is important to note that the NCOA name describes a broader group of transcriptional coregulators (NCOA1-7 in humans) while the subgroup of SRCs is a family of three highly homologous coregulators and will therefore be referred to as SRCs throughout this article.

The SRCs account for three out of 19 mammalian proteins that possess a basic helix-loop-helix-Per-Arnt-Sim (bHLH-PAS) domain. bHLH-PAS domain-containing proteins are primarily transcription factors which can bind to DNA by means of this domain. However, up until now SRCs have not been shown to directly interact with DNA, neither via their N-terminal bHLH-PAS domain or other domains, *i.e.*, the central receptor interaction domain (RID) or the C-terminal activation domains 1 and 2 (AD1 and AD2) (Fig. 1). Each of these domains primarily functions as an interaction hub with many other molecules leading to the formation of intricate complexes required for the proper execution of the cell's transcriptional program.

The bHLH-PAS domain, the most conserved domain of SRCs, is called activation domain 3 (AD3) due to its ability to interact with secondary coactivators (*e.g.*, GRIP1-associated coactivator 63 (GAC 63) [8], coiled-coil coactivator A (CoCoA) [9], or Flightless-I (Flii) [10]) and transcription factors such as members of the signal transducer and activator of transcription (STAT) family [11, 12] or tumor protein 53 (TP53) [13]. The central RID domain, on the other hand, has been found to bind to nuclear receptors and contains three LXXLL (L – leucine, X – any amino acid) motifs critical for multiple protein-protein interactions and transactivation of nuclear receptors [14].

As in the case of the N-terminus, the C-terminus of SRCs functions as a recruiter of secondary coregulators. The C-terminal AD-1 domain binds histone acetyl-transferases (HATs): p300 and cyclic AMP-response element binding (CREB) protein binding protein (CBP) [7, 15], which function by acetylating lysine residues of histones causing neutralization of the histones' positive charge and through this mechanism reducing the affinity between histones and negatively charged DNA. This attenuated affinity leads to the opening of chromatin structure allowing the recruitment of the transcriptional machinery [16]. The AD-1 also can bind to transcription factors like NF- κ B [17] or members of the bHLH-PAS family (*e.g.*, AHR and ARNT/HIF-1 β) [18] including SRCs themselves [19, 20].

Although SRCs act as potent integrators regulated through an extensive post-translational modification (PTM) code (reviewed in [21]) and they serve as a scaffold of nucleating

transcriptional complexes, they also are actively involved in transcription. The AD2 of SRC-1 and -3, but not SRC-2, has been found to exhibit a HAT activity which could contribute to their transcriptional functions [22, 23]. Additionally, AD2 recruits members of the protein arginine N-methyltransferase (PRMT) family critical for the formation of transcriptional complexes, the coactivator-associated arginine methyltransferase-1 (CARM1) [24] and PRMT1 [25].

Over the last 20 years, many factors interacting with SRCs have been discovered, which include nuclear receptors and other transcription factors, co-coactivators, and proteins editing the PTM code of SRCs, unveiling a complex picture of nucleating transcriptional complexes which change their composition depending on specific genes they bind and on a variety of signaling events. Despite their vast functionality, SRCs are still strongly associated with the control of steroid hormone action, so it is not surprising that over time, they have been determined as powerful biological regulators of the female reproductive tract, a quintessential target of hormones. This review will focus on how SRCs control normal function of female reproductive tissues and will also describe how they have been linked with numerous dysfunctions like infertility, endometriosis, and cancer.

Endometrium

Since the initial generation of the SRC-1 knockout mouse model [26] followed by knockouts of the other two coregulators [27, 28] and newer generations of tissue specific knockouts [29] and over-expressor models [30], numerous studies have given tremendous insight into SRC function in the female reproductive tract. One of the most studied tissues from the perspective of the SRCs is the endometrium, the inner lining of the uterus to which a developing embryo must attach and subsequently implant. This tissue is comprised of mesenchymal cells that form the stromal compartment and epithelial cells that line the lumen of the uterus and protrude into the stroma to form endometrial epithelial glands. When the developing embryo attaches to the endometrium, it induces both breakdown of the luminal epithelium and a critical decidual response in the underlying stromal compartment. The decidual response is a prerequisite for embryo implantation and is characterized by rapid proliferation of stromal cells and their subsequent trans-differentiation from a fibroblast to epitheloid phenotype forming the decidua. The decidua both supports the development of the embryo and protects it from the maternal immune system [31–33].

The process of decidualization is tightly regulated by both estrogen and progesterone so, not surprisingly, steroid hormone receptor coregulators have been implicated in its biology. Studies of whole-body and tissue-specific knockout mouse models of SRCs have unveiled that SRC-1 and SRC-2 are critical factors for decidualization. Even though SRC-1 knockout mice are fertile, SRC-1 function is required for PR's transcriptional activity in the endometrial epithelium and stroma [34, 35] and for the establishment of a full decidual response [26].

Deletion of SRC-2, on the other hand, leads to infertility initially thought to be caused only by placental hypoplasia [27]. However, further findings in a tissue-specific knockout mouse model have revealed that SRC-2 is crucial for normal functionality of the endometrium.

Deletion of SRC-2 led to an impairment of embryo attachment and the decidual response (even further exacerbated by concomitant SRC-1 deletion) [29]. Later findings unveiled that SRC-2's reproductive action is associated with its established role as a potent metabolic regulator [36]. Experiments in isolated human endometrial stromal cells uncovered that SRC-2 functions as a transcriptional regulator of expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB-3), an enzyme upregulated during decidualization [37]. PFKFB3 increases the rate of glycolysis by generating fructose-2,6-bisphosphate, an allosteric activator of the glycolytic enzyme 6-phosphofructo-1-kinase (PFK-1) [38, 39]. As a result, upregulation of the glycolytic rate supplies rapidly proliferating decidualizing cells with ATP (the Warburg effect; as in the case of cancer cells) and metabolic intermediates which can be directed towards anabolic pathways for production of biomass needed for the generation of two daughter cells from one dividing mother cell [40].

However from the clinical side, investigation of SRCs in the endometrium have been focused on delineating their expression pattern in abnormal endometrium due to their known oncogenic functions in both female and male tissues, *e.g.*, the mammary gland [5, 41, 42] or prostate [43]. Findings from several groups have shown that SRC-3 and SRC-2 levels are elevated in endometrial hyperplasia and adenocarcinoma [44–46]. These studies primarily focused on establishing the expression of SRC-3 as opposed to SRC-1 and -2 in the malignant endometrium due to the fact that SRC-3 has been discovered to be a gene commonly amplified in breast cancer [5]. Additionally, one study has shown that higher expression of SRC-3 in endometrial tumors correlates with clinical stage and depth of myometrial invasion of tumors and with lower survival of endometrial cancer patients [47].

Importantly, SRC-2 and SRC-3 levels have been found to be increased in the endometrium of women with polycystic ovary syndrome (PCOS) [48–50]. PCOS is characterized by anovulation which results in the appearance of cystic ovaries but also by metabolic syndrome, elevated miscarriage rate [51], and an increased risk of developing endometrial cancer [52]. These descriptive findings suggest that the increase in SRC-2/3 levels may be a causal factor for endometrial abnormalities leading to both infertility and cancer. This postulate is further supported by discoveries made in a transgenic mouse model in which human SRC-2 was expressed at much higher levels than endogenous mouse SRC-2 in PR-positive cells of the endometrium [30]. Through the use of this mouse model, it has been demonstrated that increased levels of SRC-2 lead to endometrial dysfunction represented by both a decreased ability of the endometrium to undergo a decidual response and an exacerbated reaction to estrogen leading to severe cystic hyperplasia. Additionally in the case of SRC-3, increased endometrial tumor incidence has been reported in a mouse model of SRC-3 over-expression driven by the MMTV promoter [41]. These findings indicate that SRC-2 and -3 could be exceptional targets for endometrial cancer treatment because the increased levels of SRC-2 and SRC-3 in endometrial cancer are not only a correlative occurrence but also have been found to be causally linked to the development of this malignancy.

Another endometrial pathology that has been recently linked to SRCs' action is endometriosis. Endometriosis is a disease which is characterized by the survival and growth of endometrial tissue outside the uterus primarily in the pelvic area. It is one of the most

common gynecological diseases with up to 10% of women in the US suffering from its symptoms which include infertility and severe pelvic pain [53]. This disease is highly estrogen-dependent and is accompanied by a major inflammatory response. Apart from surgical removal of endometriotic lesions, the main therapeutic approach is continuous treatment with progestins to inhibit the proliferation of this ectopic tissue which is not always effective [53]. Therefore, investigation of steroid hormone signaling in this disease is critical to identify new therapeutic targets.

Initial findings implicating SRCs' roles in this disease were contradictory. While one group found that the levels of SRC-1 are slightly increased in ectopic endometrial lesions when compared to eutopic endometrium [54], another found an opposite trend [55]. An explanation to these findings could be provided by the recent discovery of a novel isoform of SRC-1 [56]. This isoform is generated by cleavage of SRC-1 by matrix metalloproteinase 9 (MMP9), a protease upregulated in endometriotic tissues [57], which results in the generation of a 70 kDa protein containing the C-terminus of SRC-1. The truncated SRC-1 can block TNF α -induced apoptosis by inhibiting cytoplasmic caspase-8, thereby promoting the survival of cells in ectopic lesions. Importantly, the isoform still retains its AD1 and AD2 domains which could allow the transactivation of transcription factors critical for endometriosis development and progression like estrogen receptor β (ER β) and steroidogenic factor 1 (SF-1/NR5A) [56]. Targeting the truncated SRC-1 in endometriosis therapy could be an alternative approach to progesterone treatments which in many cases are inadequate [58].

Myometrium

Another uterine compartment, whose function is regulated by SRCs, is the myometrium. This smooth muscle tissue, found adjacent to the endometrium, plays a critical function in parturition. During pregnancy, high levels of progesterone maintain the myometrium in a quiescent state allowing the uterus to expand for the developing and growing fetus [59]. In mice at the onset of labor, progesterone levels drop leading to activation of uterine contractility which allows delivery of the offspring [60]. In humans however, progesterone levels remain high during and after labor [61]. Therefore, a mechanism of so called "functional progesterone withdrawal" was hypothesized to exist to induce the onset of labor [59]. An explanation for this phenomenon may be that progesterone responsiveness is affected not by modulating the levels of progesterone or PR but by modulating the activity or levels of PR's coactivators. In fact, studies have shown that levels of SRC-2, along with SRC-3 and CBP are decreased in the myometrium during labor [62]. Interestingly, this decrease in coactivator levels may be regulated by progesterone through a novel membrane-bound G protein-coupled progesterone receptor [63]. In uterine smooth muscle cells, SRC-2 levels were shown to be reduced by tumor necrosis factor- α (TNF- α) which has been implicated in induction of preterm labor [64]. Notably, SRC-2 also has been implicated in the induction of labor itself. Studies have shown that SRC-2 can transactivate estrogen-related receptor α (ERR α) at the promoter of surfactant protein A (SP-A) in the lungs of the fetus which can lead to induction of myometrial contractions [65]. Therefore modulation of SRC-2 activity to prevent preterm labor would have to be approached with great caution and directed specifically towards the myometrium.

Because strict regulation of SRC-2/3 levels in the myometrium is crucial for the maintenance of pregnancy, it was not surprising that coactivators have been linked to myometrial pathology. One of the most common diseases associated with the myometrium are uterine fibroids/leiomyoma. Even though the majority of these fibroids are benign, they can cause infertility [66] and excessive menstrual bleeding which can lead to anemia [67]. Although, one study has not shown any differences in expression of SRCs between primary cells isolated from healthy myometrium and uterine fibroids [68], another one revealed that SRC-1 levels are increased in leiomyomas when compared to healthy tissue [69]. Additionally, the gene encoding SRC-1 flanks a recurrent translocation in leiomyomas, t(1;2)(p36;p24) [70]. Unfortunately, the functional significance of this translocation is currently not known. Analysis of the translocation site, however, suggested possible introduction of novel transcription initiation sites which could deregulate SRC-1 expression.

Currently, the most common treatment options for leiomyomas are gonadotropin-releasing hormone (GnRH) agonists, which can have serious side-effects because of induction of a postmenopausal state [71]. Progestin-releasing intrauterine devices on the other hand are only a symptomatic treatment option [72]. Therefore other targeted therapeutic options involved in hormonal regulation of this tissue should be explored and whether SRC-1 is a driver of this disease and could serve as one of the potential targets should be further investigated.

Cervix

In the developed world, cervical cancer is becoming progressively more manageable due to well established screening programs. However in the developing world, this disease is the number one cancer of female reproductive tissues with a high mortality rate affecting mainly socially disadvantaged women [73]. Very limited information is available about the expression of SRCs in cervical cancer. One study has found that SRC-3 levels are not differently expressed in healthy cervical tissue and cervical cancer, but SRC-3 expression has been correlated with lymph node involvement [74]. Moreover, the 20q12 genomic region encoding SRC-3 has been found to be amplified in cervical cancer cell lines, however, this would not correlate with an increase in SRC-3 mRNA expression [75].

The primary risk factor for development of cervical cancer is infection with human papillomavirus (HPV), particularly with two subtypes, 16 and 18, which leads to the expression of the HPV E6 and E7 viral oncogenes. The E7 oncogene from high-risk HPV has been discovered to bind to SRC-1 causing its translocation from the nucleus into the cytoplasm leading to downregulation of SRC-1-mediated transcription [76]. Specific target genes affected by this change in SRC-1's subcellular localization have not been determined in this study. The E6 protein, on the other hand, has been shown to compete with SRC-1 and NF- κ B for binding to CBP at the interleukin-8 (IL-8) promoter which results in downregulation of expression of this chemokine. The reduction of IL-8 was hypothesized to attenuate the immune response leading to persistent infection induced by HPV [77].

When translocated into the cytoplasm, SRC-1's non-nuclear actions should also be considered as a plausible mechanism for cervical cancer development. This theory becomes

even more credible in the light of known cytoplasmic functions of the short SRC-1 isoform found in endometriotic lesions [56] as discussed earlier. Similarly as in the case of endometriosis, non-genomic actions of SRC-1 could lead to modulation of signaling pathways causing the survival of cells and the development and progression of cervical cancer. However, the possible role of SRC-1 in cervical cancer and its possible interaction with E6/7 must be further investigated to determine its potential as a therapeutic target in this disease.

Ovary

The most common cause of infertility is chronic anovulation, *i.e.*, the lack of oocyte release during menstrual cycles. There are multiple types of anovulation and most of them are of hormonal or metabolic etiology [78]. The most common type is normogonadotropic normoestrogenemic in nature and within these cases most of them are associated with PCOS [78], the most frequent endocrine disorder of women of reproductive age. The standard method to induce ovulation in these women is clomiphane citrate administration. Unfortunately, 15% to 40% of PCOS patients are resistant to this treatment [79] and new therapeutic approaches are needed.

For successful oocyte maturation and release to occur, cross-talk between the developing oocyte and remaining cells of the ovarian follicle, the thecal and cumulus cells, is critical. Recently, it has been found that cumulus cells isolated from mature follicles of patients with PCOS have downregulated levels of SRC-1 and, similarly as in the case of the endometrium of PCOS patients, upregulated levels of SRC-2 and SRC-3 when compared to cumulus cells from healthy subjects [80]. The changes in the coactivator expressions could partially explain the diminished competence of oocytes from women with this syndrome. However it is important to notice that these changes are also accompanied by significant alterations in expression of components of growth factor (GF) signaling which could also be a factor underlying the dysfunctionality of oocytes of women with PCOS [80]. Whether these two pathways, *i.e.*, GF signaling and SRCs, are dependent on each other remains to be further elucidated.

As previously underscored, levels of SRCs have to be fine-tuned for their proper functionality. Hence, it was not surprising that absence of SRC-3 in a whole-body knockout mouse model led to delayed puberty and diminished ovulation [28]. Additionally, deletion of SRC-3 caused a decrease in estrogen production, the primary source of which are the ovaries. Unfortunately, due to the fact that in this model SRC-3 is absent in all tissues including the hypothalamic–pituitary–gonadal axis and that the block of ovulation could be rescued by standard superovulatory hormone treatments [28], it is unclear whether the ovarian phenotype can be clearly ascribed to lack of SRC-3 in ovarian cells. Therefore, ovarian-specific knockout models of SRC-3 are needed to fully investigate its function in this reproductive organ. However taking into account that the SRC-3 whole body knockout mice are of general good health, SRC-3 can be considered as a compelling target for inhibition in cases where delayed onset of puberty is a desired outcome as it is in the case of youth with gender identity disorder (GID). Suppression of puberty leads to attenuation of secondary sex characteristics and therefore gives GID patients more time for reflection over

their gender identity before deciding about what medical treatments and procedures to undergo [81]. Targeting of SRC-3 could be an alternative approach to the standard therapy delaying the onset of puberty, which is treatment with GnRH agonists and which unfortunately in some cases due to its costliness is inaccessible to patients [81].

In the instance of ovarian cancer, the most deadly female reproductive cancer in the developed world, the findings related to SRC-3 are less ambiguous and suggest that SRCs could be a potential therapeutic target in this malignancy. At the time of SRC-3's discovery, it was found that it is amplified in ovarian cancers [5]. Even amplification of a region adjacent to the gene encoding SRC-3 was linked to poor prognosis [82]. During immortalization of primary ovarian epithelial cells, amplifications of SRC-3 also occurred recapitulating *in vivo* events [83]. Additionally, levels of this coactivator have been found to be elevated in serous, mucinous, and granulosa cell ovarian tumors compared to healthy controls [84]. In a US study, it has been discovered that ovarian cancer patients who express SRC-3 with shorter polyglutamine tracts have a much poorer prognosis [85], however the opposite correlation has been found for the Chinese Han population [86]. The functional implications of the polyglutamine tract polymorphism of SRC-3 are not clear at this point. It may be associated with SRC-3's transactivational activity, as it has been discovered in the case of the androgen receptor, which loses its transcriptional function proportionally to the length of its polyglutamine repeats [87]. Therefore, this SRC-3 polymorphism has to be further studied to fully understand its significance in ovarian cancer biology.

SRCs as Targets in Female Reproductive Dysfunction

Currently, the common approach in developing novel therapeutic compounds is to target the activity of molecules, mostly receptors and enzymes that due to their ability to bind ligands/substrates with high affinity and specificity are considered “druggable”. Great progress has been achieved over the last decades in developing directed therapies which promoted the successful generation of many drugs. The number of Pubmed citations including the term “targeted therapy” has been growing almost exponentially since the mid-1990s. However, especially in the case of cancer therapeutics, approaching one target in one cellular pathway at a time can apply highly selective pressure which then leads to development of resistance through numerous other pathways.

SRCs serve as hubs converging many signaling pathways and this is reflected by downstream generation of a transcriptional output that depends on the cellular and extra-cellular environment/signals. SRCs have been shown to interact with and be modified by a myriad of posttranslationally-modifying enzymes, *e.g.*, kinases, phosphatases (MAPK, PKA, IKK, PP, PP2A [88–90]), ubiquitin ligases, and ubiquitin conjugating enzymes [91–93] which modulate their stability and transcriptional activity. Additionally, even though SRCs have been primarily linked to the regulation of steroid hormone receptors, they also function as coregulators of many other transcription factors as described in the Introduction. Therefore, the ability to modulate many pathways simultaneously predisposes SRCs to be exceptional targets for inhibition or even activation for therapeutic purposes because of a lesser chance of developing resistance. Until now, three inhibitors targeting SRC function have been described. Two of them, gossypol [94] and bufalin [95], inhibit SRC-1 and SRC-3

and another one, verrucarin A [96], targets SRC-3 and to a lower but still notable extent – SRC-1 and -2.

The first molecule discovered to inhibit the action of SRCs was gossypol which has been found in luciferase-based assays to decrease the stability and the transcriptional transactivation ability of SRC-1 and SRC-3 but not other coregulators like p300 or CARM1. Importantly, gossypol has been shown to interact directly with the RID (Fig. 1) of SRC-3 and inhibited specifically the viability of cancer but not normal cells [94]. The other two known inhibitors of SRCs, bufalin [95] and verrucarin A [96], on the other hand have not been shown to interact directly with SRCs but they were still able to specifically inhibit their activity. Most notably, one of these inhibitors, bufalin, has also been proven using a nanoparticle-based delivery system to be capable of inhibiting breast tumor growth *in vivo* in a xenograft mouse model.

Although at this point, these inhibitors only serve as “proof-of-principle” molecules, they indicate that cancer cells with elevated levels of SRCs can be targeted selectively. Additionally, such drugs can also sensitize cancer cells to chemotherapeutic agents as in the case of gossypol which sensitizes lung cancer cells to the MEK inhibitor AZD6244 [94] or bufalin – to the AKT inhibitor MK-2206. Given the vast functionality of SRCs in the female reproductive tract, particularly their increased levels in pathological states, targeting coactivators in these tissues could be of significant value, especially considering that many treatments could be administered locally, *e.g.*, through intrauterine devices.

It is also important to note that out of the three published inhibitors of SRCs, only one has been found to bind to its target directly [94]. The development of additional small molecule inhibitors (SMIs) that interact with SRCs would be of great value especially considering the multi-domain structure of these coregulators. Designing screens to develop SMIs targeting a specific domain could enable the inhibition of specific protein-protein interactions, for example not only block the binding of SRCs with nuclear receptors through their RID domain but also with the many factors mentioned in the Introduction that bind to the three AD domains. Even though when it comes to the case of cancer where the primary goal of these small molecule inhibitors is the overall downregulation of SRCs' activity, finding small molecules that can specifically bind to different domains of SRCs could even lead to the discovery of activating compounds that could be tested as treatments of other pathologies in which SRCs are involved like infertility.

Conclusions

SRCs have been initially found as transcriptional coregulators of steroid hormone receptors and even though they coregulate many other transcription factors, they are still strongly associated with archetypical functions of steroid hormone action including the biology of the female reproductive tract. Through the use of transgenic mice and *in vitro* models, SRCs have been shown to regulate female reproduction from ovulation, implantation, to parturition. In light of their diverse roles, it is not surprising that SRCs also have been found to be deregulated in many pathologies of female reproductive tissues as in the case of upregulation in endometrial cancer or amplification in ovarian cancer. The findings in

healthy and abnormal tissues are summarized in Fig. 2. Even though SRCs were considered classically undruggable targets, screens of small molecules have shown that the identification of inhibitors of SRCs' action is possible and it is important to note that similar approaches can be used to find specific activators of these coregulators. The future will entail finding whether implementation of modulators of SRCs function in the treatment of female reproductive pathology is possible. Even though more insight is needed into the molecular functions of SRCs in reproduction and its associated diseases, today's knowledge about these powerful multi-functional coregulators indicates that they are promising molecules to exploit from a clinical perspective in the future.

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Highlights

- SRCs regulate female reproductive biology, from ovulation to parturition.
- Deregulation of SRCs may be causal in the development of reproductive pathologies.
- Modulators of SRCs could be used to treat diseases of the female reproductive system.

Fig. 1. Schematic representation of the functional domain structure of SRCs

LXXLL – leucine-X-X-leucine-leucine (X=any amino acid); bHLH – basic helix loop helix domain; PAS-A and PAS-B – Per/ARNT/Sim domain A and B; Q-rich – glutamine-rich sequence; poly-Q – poly-glutamine tract; poly-Q-IM – poly-glutamine interaction motive; AD-1, -2, and -3 – activation domain 1, 2, and 3; RID – receptor interaction domain.

Fig. 2. SRCs' functions in female reproductive physiology and pathology

Schematic representation of the female reproductive tract with descriptions of known involvements of SRCs in of each tissue in normal biology (on the left) and pathology (on the right).