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Review Article

Regulation of endometriosis by long non-coding RNA SRA through estrogen receptor: research progress

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Abstract: Endometriosis (EMS) is an estrogen-dependent chronic gynecologic condition that affects approximately 10%-15% of women of childbearing age. Long non-coding RNA SRA (lncRNA SRA) was the first identified non-coding RNA that possesses dual functions: it acts as an RNA scaffold and also encodes the SRAP protein. It participates in estrogen signaling by co-activating estrogen receptors. Recent studies have revealed a distinct expression pattern in ectopic lesions of EMS: lncRNA SRA and ERα are coordinately downregulated, whereas SRAP and ERβ are coordinately upregulated. This inverse correlation highlights a unique dual-function switching mechanism of the SRA/SRAP axis in the pathogenesis of EMS. In this review, we systematically summarize the conserved domain features of lncRNA SRA and its dual roles as an RNA scaffold and a protein-coding transcript. We then dissect the molecular mechanisms by which SRA/SRAP influences the ERα/ERβ balance, thereby modulating cell proliferation, apoptosis, and the inflammatory microenvironment in EMS. Based on current evidence, we propose a dual-function switching model: the EMS microenvironment drives alternative splicing of the SRA gene, shifting the output from lncRNA SRA toward SRAP protein. These two products selectively couple with ERα and ERβ, respectively, and jointly reshape estrogen receptor signaling in ectopic endometrial cells. Furthermore, we discuss the clinical translational potential of the lncRNA SRA/SRAP ratio as both a diagnostic biomarker and a therapeutic target, aiming to provide new insight for precision diagnosis and treatment of EMS.

Keywords: Long non-coding RNA SRA, estrogen receptor, endometriosis

Introduction

Endometriosis (EMS), a common chronic gynecologic disease, refers to the presence of endometrial tissue with growth function outside the uterine cavity lining and the myometrium [1]. EMS affects approximately 10%-15% of reproductive-aged women globally, with a prevalence of 30%-50% among infertile patients. A recent systematic review and meta-analysis incorporating 127 studies and covering nearly 200 million women worldwide has further updated these data, showing that the global prevalence of EMS in the general population is approximately 5% (95% CI, 2%-9%), while the prevalence is as high as 38% (95% CI, 25%-51%) in women with infertility, and 18%-42% in patients with gynecologic symptoms [2]. By pathologic subtype, the prevalence is 6% for peritoneal EMS, 13% for ovarian EMS, and 10% for deep-infiltrating EMS [2]. These findings suggest that the disease burden of EMS has been underestimated, underscoring an urgent need for early diagnostic biomarkers. Typical clinical manifestations of EMS include progressively worsening dysmenorrhea, chronic pelvic pain, painful intercourse, and decreased fertility, which seriously affect the physical and mental health and quality of life of patients [3]. Although the pathogenesis of EMS involves multiple hypotheses, including retrograde menstruation and implantation, coelomic metaplasia, and impaired immune clearance, evidence suggests that abnormal activation of estrogen receptor (ER) signaling is the core factor driving the survival, proliferation, and invasion of ectopic endometrial tissue [4]. The central role of abnormal activation of estrogen signaling pathways in the pathogenesis of EMS is widely recognized. Estrogen regulates target gene transcription through its classical nuclear receptors ERα and ERβ, and rapidly activates downstream kinase

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cascades by membrane receptor-mediated non-genomic signaling. Overexpression of ERβ in EMS is closely related to progesterone resistance, exacerbated inflammation, anti-apoptosis effects, and mitochondrial metabolic reprogramming. Thus, aberrant estrogen signaling is not merely a matter of excessive ligand-receptor activation, but a systemic disorder involving epigenetic modifications, transcriptional co-regulatory factor networks, and cellular metabolic states.

Long non-coding RNAs (lncRNAs) are a class of non-coding transcripts longer than 200 nucleotides, widely involved in various biological processes such as gene expression regulation, chromatin remodeling, and post-transcriptional processing. Steroid receptor RNA activator (SRA) was initially found to co-activate the transcriptional activity of the steroid nuclear receptor family, and it was the first RNA molecule found among nuclear receptor co-activators [5]. Unlike the traditional understanding that lncRNAs function only in the form of RNA, SRA has the ability to encode SRA protein (SRAP), representing a new model of functional complexity for non-coding RNAs [6]. SRA is abnormally expressed in the reproductive system and is closely related to the development and progression of various estrogen-dependent diseases, especially EMS [7]. The research history of SRA itself reflects the evolution of the lncRNA research paradigm. Early studies primarily focused on the co-activation role of SRA as a non-coding RNA in the transcriptional regulation of nuclear receptors. Subsequent findings revealed that SRA also encodes the SRAP protein, rendering it an ideal model for investigating the regulatory pattern of "dual-functional RNA-protein genes". Notably, RNA and protein products of SRA are not entirely functionally independent; instead, they synergistically regulate target gene expression by forming RNA-protein complexes. This complex regulatory pattern provides a new perspective for understanding the functional consequences of abnormal SRA expression in EMS.

Given the crucial role of SRA in regulating estrogen signaling and its emerging implications in EMS, this review aims to examine systematically the molecular structure characteristics and dual-function model of SRA, deeply elucidate the molecular mechanisms of ER signaling pathway abnormalities in EMS, focus on the multidimensional disease-promoting effects (including cell proliferation, apoptosis resistance, inflammation, and adhesion) of the SRA-ERα regulatory axis in EMS, and evaluate the translational and application prospects of SRA as a clinical diagnostic marker and therapeutic target, to provide a theoretical basis for understanding the molecular pathologic mechanism of EMS and the development of novel diagnostic and therapeutic strategies.

The central role of estrogen receptors in endometriosis

Estrogen receptor subtypes and expression distribution

The estrogen receptor (ER) belongs to the nuclear receptor superfamily, including ERα and ERβ subtypes, which are encoded by ESR1 and ESR2 genes located on different chromosomes, respectively [8, 9]. The two ER subtypes are highly homologous in protein structure, especially in the DNA-binding domain (DBD), which is as high as 97%. However, they differ significantly in the LBD and N-terminal transcriptional activation domain (AF-1), leading to a clear functional division between them in ligand affinity, co-regulatory factor recruitment profiles, and target gene profiles [10].

Under normal physiologic conditions, the tissue distribution of ERα and ERβ exhibits differentiation characteristics. ERα is primarily highly expressed in classic estrogen target organs such as the mammary glands, uterus (especially the endometrium and myometrium), ovaries, and fallopian tubes, and dominates the reproductive functions of estrogen in promoting proliferation and differentiation [11-14]. At the molecular structural level, although ERα and ERβ are highly homologous (97%) in the DBD domain, their differences in the AF-1 domain are less than 20%, which accounts for their significant differences in recruiting co-regulatory factors [15]. The AF-1 domain of ERα possesses ligand-independent transcriptional activation capabilities, while the AF-1 domain of ERβ exhibits extremely weak activity, with its transcriptional activation primarily dependent on the AF-2 domain [15]. These structural differences lead directly to the divergence of the two in terms of their target gene recognition profiles and biologic functions. Regarding ligand binding, ERα has a slightly higher affinity for estra-

diol than ERβ, but ERβ shows a higher binding preference for certain environmental estrogens and phytoestrogens, suggesting that environmental factors may contribute to the pathogenesis of EMS by differentially activating ERβ. ERβ is more widely distributed. Besides high expression in ovarian granulosa cells, it is also significantly expressed in immune cells (T lymphocytes, B lymphocytes, macrophages), cardiovascular endothelial cells, smooth muscle cells, central nervous system neurons, and bone tissues, participating in immune regulation, vascular protection, neuroprotection, and anti-proliferation processes [16]. ERα typically promotes cell proliferation, while ERβ has an anti-proliferative effect [17]. Therefore, the ERα/ERβ ratio may have a significant effect on tissue proliferation and differentiation. Research has found that in endometrial cancer, the ratio of ERα to ERβ expression can serve as a prognostic indicator; a lower ERα/ERβ ratio is associated with poorer clinical outcomes [18]. This research further supports the balancing role of ERα and ERβ in endometrial health.

The functional outputs of ERα and ERβ in target cells are not independent of one another, but depend on the combined effects of their relative expression levels, the ligand microenvironment, the availability of co-regulators, and chromatin status. In normal endometrium, ERα-dominant proliferative signaling and ERβ-mediated differentiation/anti-proliferative signaling form a dynamic balance, which fluctuates periodically with the menstrual cycle. However, in EMS, this delicate balance control mechanism is disrupted. ERβ overexpression not only alters the compositional preference of the nuclear receptor dimers, but also weakens ERα transcriptional output by competing for a limited pool of coactivators (e.g., SRC-1, GRIP1). More importantly, ERβ overexpression induces unique transcriptomic profiles, including upregulation of inflammation-related genes and anti-apoptotic genes, which functionally counteract rather than synergize with the ERα-dominant transcriptional program. Therefore, the inversion of the ERα/ERβ ratio in EMS is essentially a “shift in signal output”, which switches the physiological state dominated by proliferation and periodic differentiation to a pathologic state characterized by exacerbated inflammation, anti-apoptosis, and abnormal cell survival.

Severe imbalance in the ERα/ERβ ratio in EMS

One of the molecular pathologic markers of EMS is the imbalance in the expression of ERα and ERβ in ectopic endometrium, with the degree of imbalance far exceeding the normal cyclical fluctuation range. ERβ expression is very increased in ectopic endometrium, while ERα expression is relatively decreased [19-21]. This alteration leads to an imbalance in the ERα/ERβ ratio. These findings suggest that ERα/ERβ imbalance contributes to ectopic lesion progression.

The divergent expression patterns of ERα and ERβ may be attributed to epigenetic mechanisms, including DNA methylation and miRNA-mediated regulation. Aberrant methylation exists in the promoter region of the ERα gene, thus hindering ERα expression [22]. Although certain miRNAs exhibit variable expression in endometriosis, they may influence disease progression by modulating ERα and ERβ expression [23].

Downstream signaling pathways of ER

Hyperactivation of ER signaling in ectopic endometrium directly promotes proliferation, anti-apoptosis, and invasion. Ligand-activated ERα forms a homodimer, which directly binds to the estrogen response element (ERE) in the promoter region of target genes, or indirectly binds to DNA through interactions with other transcription factors (e.g., AP-1, Sp1). For instance, ERα overexpression upregulates Cyclin D1 and c-Myc transcription, promoting G1/S transition and accelerating cell division [24]. In addition to classical nuclear transcription, membrane-associated ERα, located in the cell membrane and caveola, can mediate rapid non-genomic signaling. Estradiol (E_2) activates downstream kinase cascades within seconds to minutes. A recent study reported that membrane ERα signaling transactivated epidermal growth factor receptor (EGFR), which in turn phosphorylates and activates the MAPK pathway, promoting malignant behavior of cells [25]. Therefore, in EMS, ERα may regulate malignant behaviors such as migration and invasion of endometrial stromal cells through the EGFR/MAPK pathway, thereby contributing to disease progression. Furthermore, overactivation of the ER signaling pathway can induce the release of inflammato-

ry factors (e.g., IL-6, TNF-α), further exacerbating local inflammatory response [4].

Genomic and non-genomic ER signaling are not independent but rather exhibit intricate crosstalk. Membrane ER enhances the transcriptional activity of ERα by activating the MAPK/ERK and PI3K/AKT pathways, which directly phosphorylate the AF-1 domain of ERα (e.g., at Ser118 and Ser167), even in the absence of ligands or at extremely low ligand concentrations. This mechanism is particularly crucial in EMS, as local estrogen levels in ectopic lesions may fluctuate periodically. In addition, the MAPK/ERK pathway can also phosphorylate p160 family coactivators (e.g., SRC-1, TIF2), enhancing their recruitment efficiency and thus amplifying the genomic signaling output of ER. From a functional perspective, this cross-talk constitutes a "signal amplification loop": low-level estrogen stimulation rapidly activates the kinase cascade through the membrane ER, thereby enhancing the transcriptional response of the nuclear ER through phosphorylation modification, rendering ectopic endometrial cells highly sensitive to exogenous estrogen signals. In the context of EMS, this cross-talk loop may be continuously activated, which partly explains why ectopic lesions exhibit highly active ER signaling even when serum estrogen levels are normal.

Molecular structure and dual function of lncRNA SRA

Gene mapping and transcriptional characteristics of SRA

lncRNA SRA is transcribed from the host SRA gene. The SRA gene is located on human chromosome 5q31.3, and its promoter region contains an estrogen response element (ERE), a GC box, and multiple transcription factor binding sites [26]. The ERE element in the SRA gene promoter endows it with the ability to respond directly to estrogen signals, so that SRA is not only a coactivator of the ER signaling pathway but also a target gene of ER, forming a positive feedback regulatory loop. Furthermore, the GC box in the promoter region is a binding site for the Sp1 transcription factor, suggesting that SRA expression is also regulated by growth factors and MAPK signaling. In EMS, abnormal changes in the DNA methylation status and histone modifications (e.g., H3K27ac, H3K4me3) in the SRA gene promoter region may occur, thereby affecting its transcriptional activity and alternative splicing decisions. It is worth noting that changes in the epigenetic status of promoters may not uniformly affect all transcripts, but differentially regulate the production of non-coding and coding isoforms. This hypothesis provides an epigenetic explanation for the paradox of downregulation of lncRNA SRA and upregulation of SRAP in EMS.

As shown in **Figure 1**, the SRA gene contains 5 exons; among them, exons 1 and 2 are the key regions determining the fate of the RNA product. The primary transcript transcribed from the SRA gene is approximately 0.7-1.5 kb in length and, following complex splicing, gives rise to multiple mature transcript isoforms [27]. Through alternative splicing, it produces two types of mature transcripts: one contains only non-coding exons (i.e., exon 1 → exon 3 → exon 4 → exon 5), forming a long non-coding RNA SRA; the other retains coding exons (i.e., exon 2 → exon 3 → exon 4 → exon 5), which contains an open reading frame of approximately 687 nucleotides that can be translated into functional SRA proteins (SRAPs) through a mechanism mediated by an internal ribosome entry site (IRES) [27, 28]. Thus, the SRA gene exports functional molecules at both the RNA and protein levels through alternative splicing, thereby synergistically regulating the expression of downstream genes. The regulatory mechanisms of SRA alternative splicing decisions are not fully understood, but members of the SR protein family (such as SRSF1 and SRSF9) and the hnRNP family are known to be involved. Differences in the expression profiles and activities of splicing factors under different cell types and pathologic conditions may lead to significant changes in the SRA gene product profile.

Conserved domains of lncRNA SRA and their functional association with ERα

lncRNA SRA molecules fold into multiple evolutionarily highly conserved stem-loop domains through base complementary pairing, which serve as the core structural basis for the biological functions of lncRNA SRAs [28]. lncRNA SRA comprises four major domains: Domain I (D1) contains helices H1, H2, H3, H4, H5, H6, and H7; Domain II (D2) contains helices H10, H11, H12, H13, and H14; Domain III (D3) con-

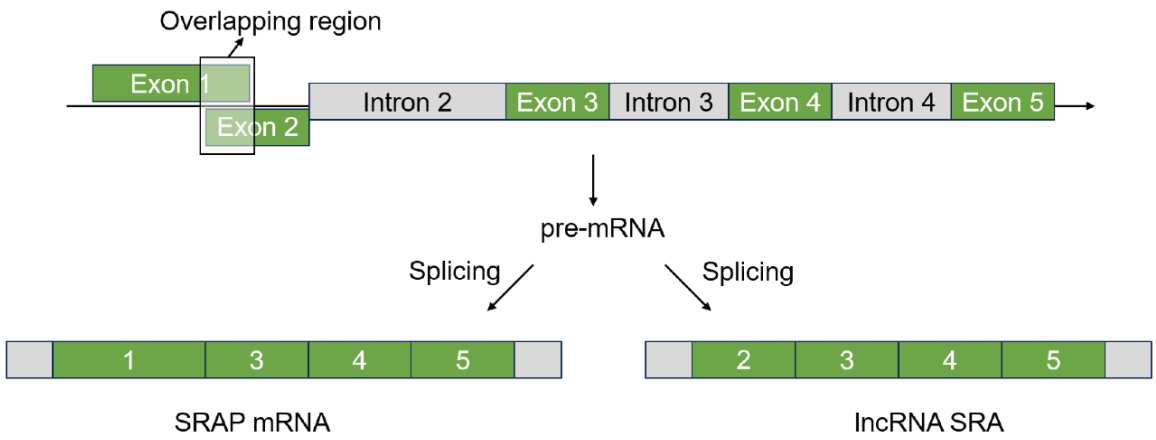

Figure 1. Genomic structure, alternative splicing, and functional products of the human steroid receptor RNA activator (SRA) gene. Schematic representation of the human SRA locus (NG_029333.1) located on chromosome 5q31.3. Genomic organization of the SRA gene. Boxes denote exons (E1-E5), with E1 (1-666 bp) and E2 (621-947 bp) sharing an overlapping region (621-666 bp, indicated by dashed lines), representing alternative 5' untranslated regions driven by distinct promoters. Lines connecting exons represent introns (Intron 2: 948-5909 bp; Intron 3: 6113-6924 bp; Intron 4: 7034-7182 bp).

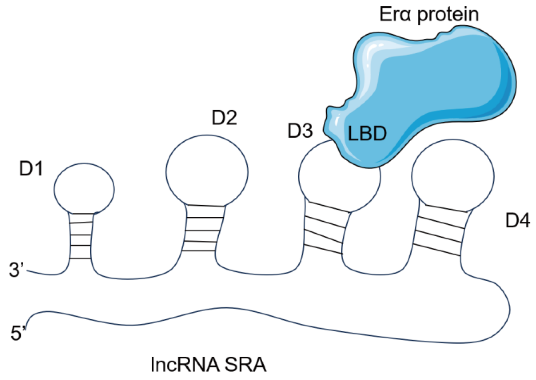

Figure 2. Schematic representation of lncRNA steroid receptor RNA activator (SRA) and Estrogen receptor α (ERα) binding model. lncRNA SRA directly binds to the ligand-binding domain (LBD) of ERα through its conserved D3 structural domain. Upon estradiol (E2) stimulation, ERα undergoes a conformational change that exposes the LBD surface, enabling recognition and binding by the D3 domain of lncRNA SRA.

tains helices H8, H9, H15, H16, H17, H18, H19, H20, and H21; and domain IV (D4) contains helices H22, H23, H24, and H25. Each domain exhibits distinct functional specialization [26, 28]:

(1) Domain III (D3): D3 is the core region where lncRNA SRAs exert their co-activation function. D3 contains four helical structural modules (H15-H18), forming a specific three-dimensional spatial conformation that allows it to be specifically recognized and bound by the ligand-binding domain of the estrogen receptor α. Deletion of the D3 region resulted in a reduction of approximately 60% in ERα-mediated luciferase reporter activity [26], indicating that the D3 region plays a critical role in co-activating ERα transcriptional activity. Within the D3 domain, conserved nucleotide sites in the H15-H18 helix are essential for maintaining the affinity of RNA-protein interactions; mutations at these sites result in a significant decrease in the binding capacity of SRA to ERα, thereby impairing the transcriptional activation of downstream target genes [26]. Therefore, SRA may recognize activated ERα through the H15-H18 structural module of its own D3 domain (**Figure 2**), which may provide a potential structural basis for the development of small-molecule inhibitors that disrupt this RNA-protein interaction.

(2) Domain IV (D4): D4 is rich in RNA-binding protein recognition and binding motifs. p68 (DDX5) and p72 (DDX17) are the most important binding partners for D4, both belonging to the DEAD-box RNA helicase family [29]. By binding to the D4 domain of SRA, p68/p72 forms a stable RNA-protein complex. This interaction is critical for the subcellular localization of the lncRNA SRA. The helicase activity of p68/p72 contributes to the dynamic remodeling of SRA RNA conformation, promoting the assembly and dissociation of the transcription complex. Knocking down p68/p72 or disrupting the interaction between SRA and its site signifi-

cantly reduces the distribution of SRA in the cell nucleus, resulting in a corresponding decrease in transcriptional activity [29]. The diversity of protein partners enables SRA to participate in multi-level gene expression regulation, ranging from transcriptional regulation to RNA processing, and from chromatin remodeling to nucleocytoplasmic transport. In the pathological environment of EMS, the protein profile recruited in the D4 region may undergo changes, thereby affecting the functional output of the SRA.

(3) Domain I (D1) and Domain II (D2): D1 and D2 are considered to be involved in the interaction between lncRNA SRA and other co-regulators, including steroid receptor co-activator 1(SRC-1), p300/CBP acetyltransferase, etc. On this basis, SRA acts as a central hub, integrating multiple transcriptional co-regulators to synergistically enhance the expression of ERα target genes [5, 29, 30]. The linker regions between various domains may exhibit certain flexibility, allowing the SRA to undergo conformational transitions between different functional states. Although regions D1 and D2 do not directly bind to ERα like D3, they play an indispensable role in maintaining the overall three-dimensional conformation of the SRA. A structural study demonstrated that helical structures within D1 and D2 stabilize the active conformation of D3 through long-range interactions [28]. Therefore, deletions or mutations in D1 or D2 may indirectly weaken the co-activation function of SRA by affecting the overall structure.

RNA scaffold function: organizer of the ERα transcriptional co-activator complex

lncRNA SRAs, as RNA scaffold molecules, provide a spatial platform for the assembly of multi-protein transcription complexes. lncRNA SRA forms a complex with the TrxG and PRC2 complex and is involved in transcriptional regulation [31]. SRA can bind to RNA helicase p68, stabilizing the formation of the TrxG complex and further supporting its role as a scaffold molecule [32]. Stimulated by ER signal, ERα undergoes a conformational change upon binding to estradiol, exposing the coactivator binding surface of the ligand-binding domain (LBD). SRA recognizes and binds to activated ERα by its D3 domain, while simultaneously recruiting co-activators using other domains to form a hierarchical transcriptional complex. This RNA scaffold mechanism enables spatiotemporal coordination of multi-step reactions. SRA integrates receptor recognition, chromatin modification, and transcription machinery recruitment onto a single molecular platform, eliminating the random nature of individual components diffusing and searching within the nucleus, thus significantly enhancing signal response speed and transcription efficiency. Following SRA knockout, the transcriptional activation of ERα target genes (such as TFF1/pS2 and GREB1) is significantly delayed, and peak transcription levels are markedly reduced, supporting its role as an accelerator of transcriptional kinetics [29].

The RNA scaffold function of lncRNA SRA and the coding function of SRAP protein are not two independent “functional modules”; instead, they constitute a dynamic molecular switch system. In this system, the product of the SRA gene (RNA or protein) guides the ERα signal toward different transcriptional output directions through a differential interaction network. When lncRNA SRA is the major product, the RNA molecule directly binds to ERα through its D3 domain and simultaneously recruits co-activators such as p68/p72 and SRC-1, forming a transcriptional activation complex with RNA as its core backbone, thereby promoting the expression of cell cycle-related genes. When SRAP protein expression is elevated, the RNA-protein complex formed by SRAP and lncRNA SRA may exhibit different target gene preferences, i.e., “enhanced activation of proliferation-related genes and inhibition of differentiation-related genes”. Therefore, the two products of the SRA gene together constitute a “functional output regulation module”, whose overall output depends on the relative ratio of lncRNA SRA to SRAP and the composition of the complex formed by the two. This conceptual framework of the “RNA-protein complex” transcends the traditional dichotomy between “RNA function” and “protein function” and more accurately reflects how SRA genes actually function within cells.

Encoding function: discovery and co-regulation of SRAP proteins

What distinguishes SRA from the vast majority of lncRNAs is its ability to encode proteins. SRA isoforms containing the coding sequence pro-

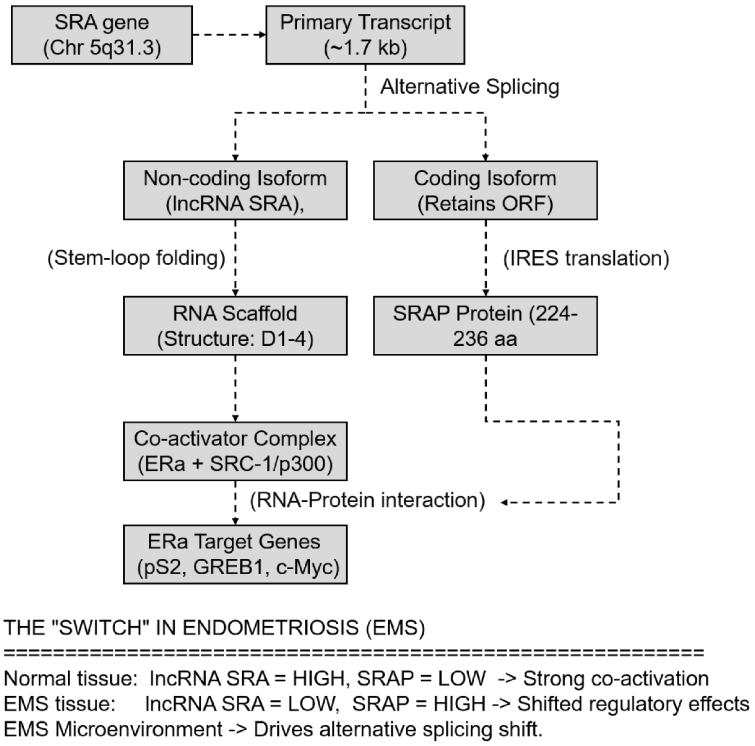

Figure 3. Dual-function switching model of lncRNA SRA/SRAP. SRA, Steroid receptor RNA activator; SRAP, Steroid receptor RNA activator protein; EMS, Endometriosis; ERα, Estrogen receptor α; ORF, Open reading frame; GREB1, Growth regulating estrogen receptor binding 1; D1-4, Domain 1 to 4; SRC-1, Steroid receptor coactivator 1; IRES, Internal ribosome entry site.

duce a protein product of approximately 224-236 amino acid residues, i.e., steroid receptor RNA-activating protein (SRAP), through an internal ribosome entry site (IRES)-mediated translation initiation mechanism [33]. Studies on the function of SRAPs have revealed a complex synergistic regulatory relationship between them and SRA RNAs. SRAP does not function alone; instead, it forms an RNA-protein complex with lncRNA SRA, jointly participating in transcriptional regulation. This complex exhibits the gene-specific regulation of ERα target genes [6]: for cell cycle-related genes such as c-Myc and Cyclin D1, SRAPs enhance the co-activation effect of SRA RNAs; while for certain differentiation-related target genes, SRAPs may exert a negative regulatory effect. SRAP itself does not contain any known functional domains; its function depends entirely on binding to lncRNA SRA. This “unconditional dependence” relationship is relatively rare in proteins, which complicates the functional study of SRAP. Any observed SRAP function is likely attributable to the SRAP-lncRNA-SRA complex, rather than a function performed independently by the SRAP. Therefore, when studying the function of SRAP, the presence and activity of lncRNA SRA must be considered simultaneously.

The synergistic mechanism between SRAPs and the lncRNA SRAs may involve the stabilization of RNA conformation. SRAP binding may induce or stabilize specific active conformations of lncRNA SRAs, thereby enhancing their affinity for ERα and coactivators [34]. Another possibility is that SRAP itself acts as an adaptor protein, bridging lncRNA SRA with other transcription factors or chromatin-modifying enzymes, thus expanding the functional scope of the SRA complex.

Differential expression and dual functional switching of lncRNA SRA/SRAP in EMS

lncRNA SRA and SRAP exhibit completely opposite expression patterns. Compared to normal endometrial tissue, expression of the lncRNA SRA is downregulated in endometriotic lesions, while SRAP expression is upregulated [7]. The above evidence suggests that the expression levels of lncRNA SRA gradually decrease from normal endometrium to ectopic cysts and then to the tissue surrounding the lesion; the EMS microenvironment may have driven the alternative splicing of the SRA gene to shift from producing non-coding lncRNA to producing SRAP protein.

Based on the above expression differences and literature reports, we propose a dual-function switching model of lncRNA SRA/SRAP (**Figure 3**). This model illustrates that the SRA gene produces two classes of isoforms by alternative splicing. In normal cells, the non-coding lncRNA functions as an RNA scaffold with coactivator activity, whereas in the EMS microenvironment, splicing shifts towards the production of SRAP protein. This explains the paradoxical observation of decreased lncRNA SRA expression but increased SRAP expression in

ectopic lesions. This switch may be driven by inflammatory signals (e.g., TNF-α, IL-6), oxidative stress, or epigenetic changes in the EMS microenvironment, but the specific molecular mechanisms remain to be elucidated.

Potential mechanisms by which the SRA-ER axis regulates endometriosis

Regulation of cell proliferation and apoptosis balance by the lncRNA SRA-ER axis

For ectopic endometrial cells to survive outside the uterine cavity and establish lesions, they must simultaneously possess both accelerated proliferation and resistance to apoptosis. lncRNA SRA plays a crucial role in balancing cell proliferation and apoptosis by regulating ERα signaling.

Regarding the promotion of cell proliferation, a study indicated that knocking down the SRA gene in stromal cells of ovarian endometriosis significantly inhibited cell proliferation, an effect accompanied by a decrease in ERα levels and an increase in ERβ levels [7]. This result reveals two key insights: first, the overall function of SRA1 gene products (whether lncRNA SRA or SRAP) is indispensable for maintaining the survival and proliferation of ectopic endometrial cells; second, interfering with the SRA/SRAP balance can alter the ERα/ERβ ratio, thereby affecting the cell proliferation phenotype.

In terms of inhibiting apoptosis, the lncRNA SRA-ER axis suppresses apoptotic signaling through multiple mechanisms. In recurrent spontaneous abortion, lncRNA SRA correlates with BCL-2 expression [35], suggesting a regulatory role through through the BCL-2 family pathway. Another mechanism involves the ceRNA function of the SRA. In a β-cell apoptosis model, lncRNA SRA has been shown to function as a ceRNA that sponged miR-146b to activate the IRAK1/LDHA signaling axis; in the inflammatory microenvironment induced by EMS, this axis may induce the expression of apoptosis-related proteins such as cIAP1/2 through NF-κB cross-activation, further influencing intracellular anti-apoptotic effects [36]. These findings from other cellular contexts provide clues for the anti-apoptotic role of the lncRNA SRA-ER axis, but their relevance to EMS pathogenesis remains to be experimentally validated.

lncRNA SRA-ER-NF-κB axis and local inflammation

EMS is a typical chronic inflammatory disease, and the formation of an immune-inflammatory microenvironment in ectopic lesions is a driving factor for the sustained progression. Current evidence suggests that ER can directly interact with the p65 subunit of NF-κB, thereby enhancing p65's transcriptional activity; simultaneously, it can also activate the IKK complex via the PI3K/AKT pathway, promoting the phosphorylation and proteasomal degradation of IκBα, releasing p65/p50 into the nucleus [37-39]. In a study on metabolic syndrome, the SRA gene was found to be significantly positively correlated with IL-6 [40]. In obesity and insulin resistance models, SRA expression significantly correlates with TNF-α [41]. These two findings suggest that SRA has pro-inflammatory potential in other inflammatory conditions. TNF-α and IL-6 are downstream target genes of the NF-κB pathway. Given that SRA is a transcriptional coactivator of ER, we hypothesize that SRA may indirectly enhance the NF-κB pathway by increasing ER transcriptional activity, thereby upregulating the expression of downstream pro-inflammatory factors in ectopic endometrial tissue. However, direct evidence for SRA involvement in ER-NF-κB protein-protein interactions is currently lacking. In addition, the ERα-NF-κB interaction is bidirectional: ERα coactivates NF-κB transcription, while NF-κB activation reciprocally modulates ERα activity. In ectopic lesions of EMS, overexpression of ERβ may alter the balance of ERα-NF-κB interaction by competitively binding to NF-κB.

Inflammatory factors such as TNF-α have been shown to activate the NF-κB pathway through a positive feedback mechanism, thereby altering the expression of other NF-κB target genes [42]. Building upon this, we further propose a hypothetical positive feedback inflammatory loop: in ectopic lesions, persistently high levels of inflammatory factors such as TNF-α and IL-6 may, in turn, influence the transcription and alternative splicing of the SRA gene through the NF-κB pathway, altering the ratio of lncRNA SRA to SRAP, thereby regulating the output

Table 1. Comparison of SRA expression, major functions, and signaling pathways in estrogen-dependent disease

Disease	lncRNA SRA expression	SRAP expression	Major biological functions	Signal pathways involved	References
EMS	Downregulated	Upregulated	Promoting cell proliferation and inhibiting apoptosis; enhancing inflammation; promoting adhesion and invasion	ERα/ERβ signaling, NF-κB, ceRNA (miR 146b/IRAK1/LDHA), BCL-2 family	[7, 35, 36]
Breast cancer	Upregulated	Limited reports; primarily focusing non-coding types	Promoting tumor proliferation and progression as an ERα co-activator	p38 MAPK, Notch, and TNF-α signaling pathways	[5]
Cervical cancer	Upregulated	Not clear	Enhancing cell proliferation, migration, and invasion	Not specified; possibly involving EMT and proliferation pathways	[50]
Ovarian cancer	Upregulated	Not clear	Mediating cell migration, invasion, and tumor progression	Not specified	[51]

Note: SRA, Steroid receptor RNA activator; SRAP, Steroid receptor RNA activator protein; EMS, Endometriosis; ERα, Estrogen receptor α; ERβ, Estrogen receptor β; NF-κB, Nuclear factor κB; IRAK1, Interleukin-1 receptor-associated kinase 1; LDHA, Lactate dehydrogenase A; BCL-2, B-cell lymphoma 2; MAPK, Mitogen-activated protein kinase; TNF-α, Tumor necrosis factor-α; EMT, Epithelial-mesenchymal transition.

intensity of ER signaling. Notably, this feedback model is currently still a hypothesis pending experimental verification. This hypothesis provides a new theoretical framework for understanding the chronicity and progressive development of EMS: inflammatory signals further exacerbate ER signal imbalance by altering the splicing pattern of the SRA, and such ER signaling imbalance in turn amplifies inflammatory output through NF-κB, thereby forming a self-sustaining vicious cycle. The existence of this feedback loop explains why EMS lesions, once established, are difficult to spontaneously resolve and tend to develop resistance to conventional anti-inflammatory or anti-estrogen therapies.

The lncRNA SRA-ER axis modulates ECM homeostasis and the adhesive capacity of ectopic cells by regulating ICAM-1 and VCAM-1 expression [25, 43, 44]. Following adhesion, ectopic endometrial cells significantly upregulate MMP-9, which degrades the basement membrane and ECM, thereby promoting invasion [45, 46]. Subsequently, the lncRNA SRA-ER axis may promote invasion [19, 47-49].

Evidence supporting the pathogenic role of the lncRNA SRA-ER axis in estrogen-dependent tumors

Although EMS is classified as a benign gynecologic disease, its clinical characteristics of "benign metastasis and malignant behavior", along with a risk of approximately 1% malignant transformation, make it biologically similar to malignant tumors. The role of lncRNA SRA in gynecologic tumors has been reported, providing insight into the pathogenic mechanisms of SRA while also highlighting the unique expression patterns of SRA in EMS.

In breast cancer, lncRNA SRA expression serves as a novel prognostic biomarker for patients with ER-positive breast cancer; the p38 MAPK, Notch, and TNF-α signaling pathways involved in this process play critical roles in the pathogenesis of estrogen-dependent breast cancer [5]. A study based on 100 clinical samples indicated that lncRNA SRA was significantly overexpressed in cervical cancer tissues, and high lncRNA SRA expression was an independent prognostic factor for overall survival; furthermore, lncRNA SRA overexpression enhanced cell proliferation, migration, and invasion [50]. In ovarian cancer, lncRNA SRA mediated the migration, invasion, and progression of ovarian cancer cells, and high expression of lncRNA SRA was a significant predictor of overall survival and progression-free survival [51].

It is worth noting that EMS exhibits distinct differences from the aforementioned tumors in terms of SRA expression patterns. Therefore, the pathogenic mechanism of the SRA gene may be highly dependent on the disease context and splicing pattern. In EMS, SRAP may play a major pathogenic role, which contrasts with the pathogenic pattern dominated by lncRNA SRA in tumors. This provides a molecular-

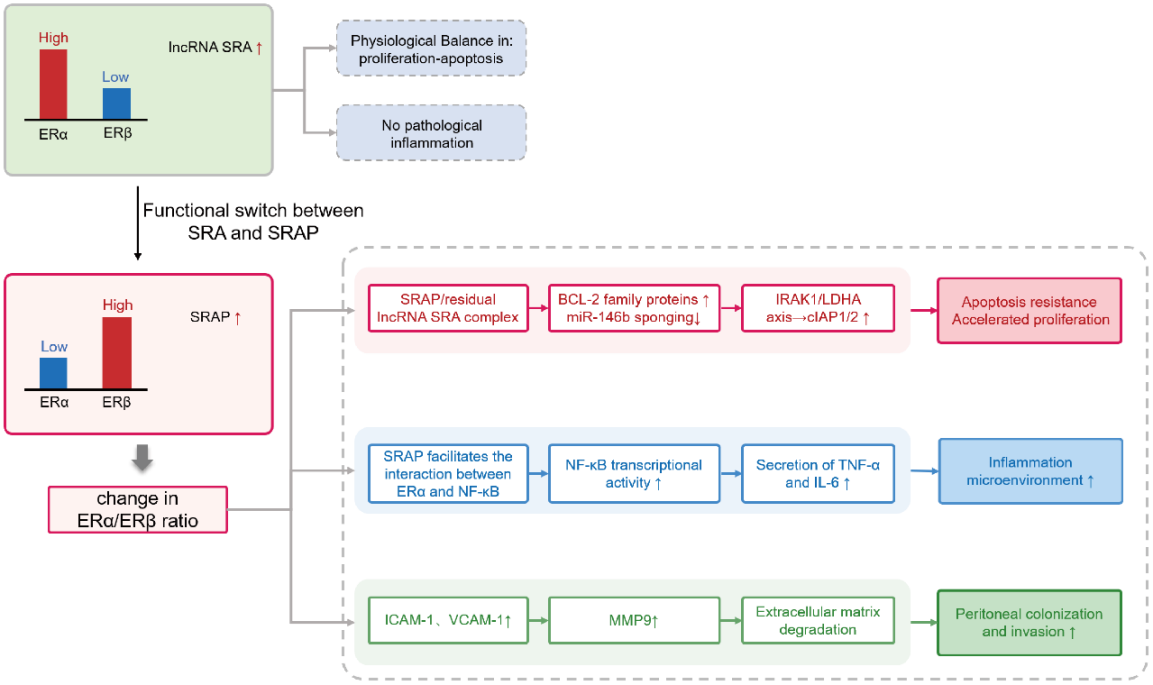

Figure 4. Pathogenic signaling network of SRA/SRAP dual-function switching and comparison of ERα/ERβ ratios. SRA, Steroid receptor RNA activator; SRAP, Steroid receptor RNA activator protein; ERα, Estrogen receptor α; ERβ, Estrogen receptor β; NF-κB, Nuclear factor κB; IRAK1, Interleukin-1 receptor-associated kinase 1; LDHA, Lactate dehydrogenase a; BCL-2, B-cell lymphoma 2; TNF-α, Tumor necrosis factor-α; IL-6, Interleukin-6; ICAM-1, Intercellular adhesion molecule 1; VCAM-1, Vascular cell adhesion molecule 1; MMP9, Matrix metalloproteinase 9.

level explanation for the "tumor-like" yet not entirely tumor-equivalent biological behavior of EMS. The expression trends, major functions, and involved signaling pathways of SRA across these estrogen-dependent diseases are summarized and compared in **Table 1**.

In summary, the SRA/SRAP dual-function switching model integrates the proliferation, anti-apoptosis, inflammatory feedback, and adhesion/invasion pathways regulated by the SRA-ER axis in EMS, while also exhibiting the typical inversion of the ERα/ERβ ratio observed in ectopic lesions. This integrated mechanism network is shown in **Figure 4**.

Clinical translational potential of lncRNA SRA

Potential of novel biomarkers for EMS

Early diagnosis of EMS remains a major clinical challenge, with a current average diagnostic delay of 7-10 years from symptom onset. Delayed diagnosis results in long time suffering from pain and other symptoms and missed optimal therapeutic window in patients, leading to progression from mild to more severe disease in some patients. Although laparoscopic combined with pathological examination is the gold standard, its invasive nature limits the widespread application of screening and early diagnosis. Therefore, there is an important clinical need to search for non-invasive or minimally invasive biomarkers with high sensitivity.

Given the divergent expression patterns of lncRNA SRA and SRAP in EMS, we propose using the SRA/SRAP ratio as a novel biomarker [7]: rather than merely measuring the expression level of lncRNA SRA alone, it is the ratio of lncRNA SRA to SRAP (or the SRA/SRAP functional switching index) that should be evaluated. We infer that, compared to normal endometrium, the SRA/SRAP lncRNA ratio was significantly reduced in endometriotic lesions. This ratio change may be a better indicator of the pathological state of EMS than the expression level of a single molecule. Current serum biomarkers, such as CA125, show suboptimal sensitivity and specificity for EMS diagnosis, and are easily affected by factors such as the

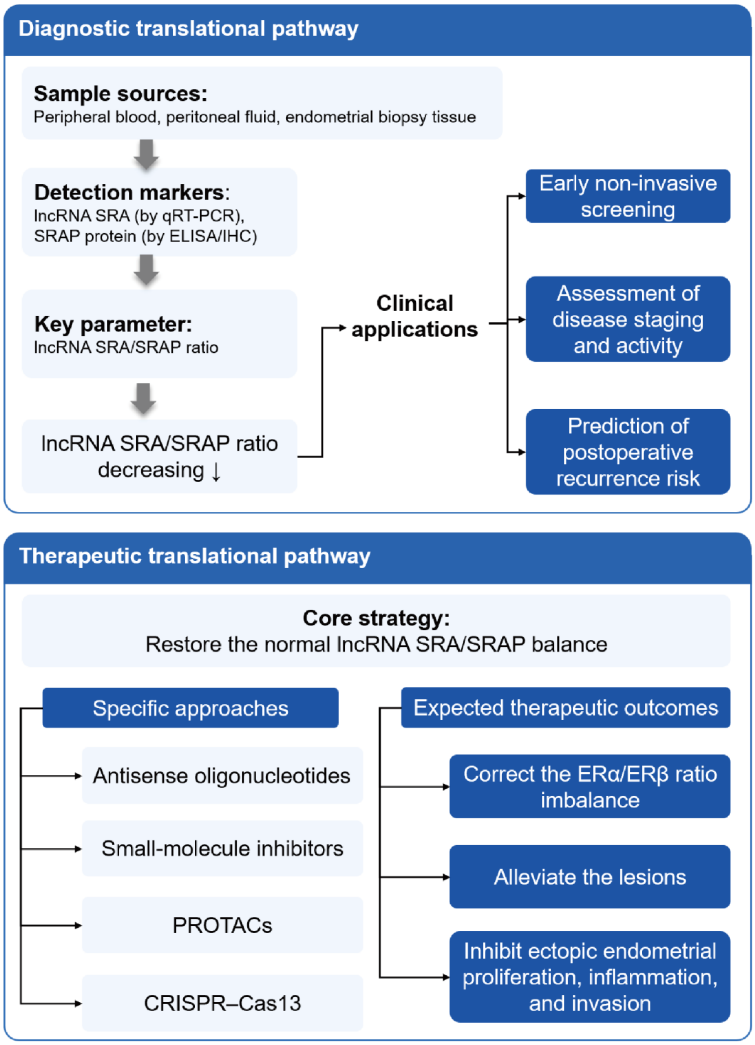

Figure 5. Clinical translational potential of SRA/SRAP as diagnostic biomarkers and therapeutic targets in endometriosis.

menstrual cycle, pelvic inflammatory disease, and ovarian tumors. In contrast, the SRA/SRAP ratio, as a functional indicator reflecting disease-specific molecular pathological states (ER signaling imbalance), may have higher pathologic relevance. More importantly, changes in the SRA/SRAP ratio may occur in the early stages of the disease, even before the formation of radiologically detectable lesions, as ER signal imbalance is a core driver of EMS pathogenesis rather than a late-stage event. However, it is important to recognize that the technical challenges involved in detecting lncRNAs and protein biomarkers in peripheral blood are far greater than those associated with traditional ELISA methods, and the stability of the biomarkers, the reproducibility of the assays, and their cost-effectiveness all require systematic evaluation. Therefore, the SRA/SRAP ratio is more likely to serve as a supplement rather than a replacement for existing biomarkers such as CA125. Particularly, combined detection with CA125 may improve the diagnostic efficiency for early-stage EMS.

However, applying this biomarker to clinical examination still faces many challenges. The immunohistochemistry or ELISA assays for SRAP have not yet been standardized; and whether circulating (serum/peritoneal fluid) lncRNA SRA and SRAP can accurately reflect the expression pattern in lesions remains to be verified. Prospective, multi-center, large-cohort studies are urgently needed. The translational roadmap from SRA/SRAP molecular switching to clinical application, encompassing both diagnostic and therapeutic avenues, is summarized in **Figure 5**. In addition, the detection of lncRNAs SRA and SRAP in serum or peritoneal fluid is also confronted with the issue of stability. lncRNAs are readily degraded by RNases in body fluids, and their levels may be affected by various factors such as the menstrual cycle and hormone level fluctuations. Establishing standardized sample collection, processing, and testing procedures is a prerequisite for clinical translation.

Therapeutic strategies targeting lncRNA SRA/SRAP functional switching

Inhibiting the overall expression of the SRA gene reduces the proliferation of ectopic endometrial stromal cells and promotes apoptosis, suggesting that the SRA gene product is essential for the survival of ectopic endometrial cells; however, simultaneous knockdown of the lncRNA SRA and SRAP may lead to com-

pensatory elevation of ERα, resulting in uncertain therapeutic outcomes [7].

More precise strategies might modulate SRA alternative splicing to selectively suppress SRAP production while maintaining or enhancing lncRNA SRA levels. One conceptually attractive approach involves antisense oligonucleotides (ASOs) designed to block splice sites around intron 1, whose retention or excision is a critical determinant of the coding/non-coding isoform ratio. In theory, local or systemic administration of such ASOs might shift the SRA/SRAP balance; however, to date no published study has tested this isoform-selective ASOs strategy in any endometriosis animal model. Significant challenges remain, including poor delivery efficiency to lesions, low tissue uptake, and off-target effects, necessitating further optimization of chemical modifications and the development of lesion-targeting delivery systems such as lipid nanoparticles. In addition, the D3 domain (H15-H18 helix) of lncRNA SRA, which serves as the functional interface for specific ERα binding, represents a potential "RNA-protein interaction pocket" for virtual screening of small-molecule inhibitors. If SRAP is confirmed as a major pathogenic molecule, small molecules targeting the SRAP-effector protein interface could also be explored. From a medicinal chemistry perspective, targeting lncRNA-protein interactions (RPIs) represents an emerging drug discovery paradigm distinct from conventional enzyme- or receptor-targeted approaches. RPI inhibitors typically do not compete for ligand binding; instead, they interfere with the assembly or stability of RNA-protein complexes through allosteric modulation. Specifically, regarding the interaction between SRA D3 and ERα LBD, the RPI interface has these 2 potential advantages: First, this interaction selectively regulates the transcriptional activation function of ERα rather than completely blocking its activity, thus avoiding side effects such as endometrial atrophy caused by complete inhibition of ER signaling; second, the H15-H18 helix in the D3 domain contains multiple highly conserved nucleotide sequences, providing a specific binding pocket for small molecules. However, very few RPI small-molecule inhibitors have been reported to date, and most are in the early preclinical stages; their binding affinities (typically in the μM range) fall far short of the requirements for drug development. In addition, the flexibility of RNA molecules poses both computational and experimental challenges for structure-based drug design. Therefore, therapeutic strategies targeting the SRA-ER interaction are still in the conceptual exploration stage and are far from clinical application.

The Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated protein 13 (Cas13) system is a newly emerging RNA editing tool in recent years [52-54]. Unlike CRISPR-CRISPR associated protein 9 (Cas9), which targets DNA, Cas13 specifically recognizes and cleaves single-stranded RNA, efficiently knocking down lncRNA SRAs without permanently modifying the genome, thus avoiding the risks of off-target mutations and long-term safety concerns [55, 56]. The CRISPR-Cas13 system can specifically knock down lncRNA SRA without cleaving the SRAP-encoding isoform, achieving subtype-selective intervention. Proteolysis-targeting chimeras (PROTAC) technology is commonly used for protein degradation. PROTAC technology can recruit E3 ubiquitin ligases to promote SRAP ubiquitination and degradation, thereby specifically eliminating SRAP while preserving lncRNA SRA.

The mechanisms, targets, current evidence, advantages, and challenges of these strategies are summarized in **Table 2**.

Summary and prospect

Main limitations of current research

The current research still has the following main limitations. First, most studies have small sample sizes ($n < 50$) and single-center retrospective designs, with inadequate control for bias and confounders. Large-scale, multi-center, prospective cohort studies across diverse populations are lacking. Therefore, the generalizability and robustness of the conclusions remain to be confirmed. Second, the underlying mechanisms by which lncRNA SRA regulates EMS have not yet been fully elucidated. Most existing studies adopt a global knockdown strategy targeting the entire SRA1 gene, which fails to distinguish the independent functions of lncRNA SRA and SRAP individually. While this approach is useful for proof-of-concept studies, it cannot determine whether reduced lncRNA SRA or increased SRAP primar-

Table 2. Overview of potential treatment strategies targeting SRA/SRAP in endometriosis

Strategy	Mechanism of action	Target molecule	EMS model evidence	Advantages	Challenges
ASOs	Blocking exon splicing and inhibiting SRAP-encoding isomers	SRA precursor mRNA	None	Isoform selectivity; retention of lncRNA SRA	Lesion-targeted delivery; off-target splicing
Small molecules	Blocking SRA D3-ERα binding or SRAP functional interface	D3-ERα/SRAP	None	Potentially available for oral use	Unknown druggability regarding RNA-protein interface
PROTAC	Recruiting E3 ligases to degrade SRAP	SRAP	None	Absolute SRAP specificity; retention of lncRNA SRA	Lack of high-affinity SRAP ligands; complex pharmacokinetics
CRISPR-Cas13	sgRNA targeting non-coding isoforms to specifically cleave lncRNA SRA	Non-coding lncRNA SRA	None	Transcription selectivity; no genome alteration	Bystander cleavage; delivery and immunogenicity

Note: SRA, Steroid receptor RNA activator; SRAP, Steroid receptor RNA activator protein; EMS, Endometriosis; ASOs, Antisense oligonucleotides; ERα, Estrogen receptor α; D3-ERα, Domain 3 of estrogen receptor α; PROTAC, Proteolysis-targeting chimeras; CRISPR-Cas13, Clustered regularly interspaced short palindromic repeats-CRISPR associated protein 13.

ily drives EMS pathology. In addition, the functional differences of SRA in different cell types (epithelial cells vs. mesenchymal cells vs. immune cells) have not yet been systematically studied. Current understanding largely focuses on its role as a classical coactivator of ERα, while key issues such as the interactions between lncRNA SRA and other non-coding RNAs, the dynamic switching mechanism of the lncRNA SRA/SRAP dual functions, and the genome-wide epigenetic remodeling effects, remain to be systematically elucidated. Third, clinical translational research is severely lagging behind. Standardized procedures and diagnostic thresholds for serum SRA testing have not yet been established, and drug development targeting SRA remains at the laboratory research stage, with virtually no accumulation of key druggability evaluation data.

Future research directions

To address the limitations mentioned above, future research should focus on the following directions. At the mechanistic level, separate overexpression and knockout systems for lncRNA SRAs and SRAPs should be established to elucidate their independent functions and synergistic/antagonistic relationships in ectopic endometrial cells; trans-acting factors (such as the splicing factor SRSF family) that regulate the alternative splicing of the first intron of SRA should be identified; and the upstream signals triggered by the EMS microenvironment that induce splicing alternation should be elucidated. Furthermore, it is necessary to integrate multi-omics technologies such as RNA-seq, ChIP-seq, and single-cell sequencing to map systematically the genome-wide regulatory network of SRA in ectopic endometrium, elucidating its ceRNA interaction network and cell type-specific functions. Regarding clinical validation, a quantitative association between the ratio of lncRNA SRA/SRAP and the ERα/ERβ ratio, as well as disease staging in ectopic lesions, should be established through a multicenter cohort study to assess the predictive value of this ratio for the risk of postoperative recurrence. In terms of therapeutic translation, ASOs or small molecule compounds targeting the first intron splicing site of SRA may be explored to verify whether they can correct ER signaling imbalance by restoring the normal production ratio of lncRNA SRA/SRAP, and their therapeutic effects in EMS animal models may be evaluated.

Future research should go beyond measuring lncRNA SRA expression to elucidate how its functional switch between coding and non-coding isoforms modulates ERα/ERβ signaling in EMS pathogenesis. In addition, whether the therapeutic goals can be achieved by intervening in this transformation is also a key issue to be addressed in subsequent research. Integrating SRA, ER, and EMS into a unified mechanistic framework is key to advancing this field from phenomenological description to mechanistic interpretation.

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Disclosure of conflict of interest

None.

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