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REVIEW

Underlying mechanisms of epithelial splicing regulatory proteins in cancer progression

Ying Liu[1,2] · Yiwen Li[2] · Chengcheng Du[2] · Shouxiang Kuang[2] · Xuehao Zhou[2] · Jinyu Zhang[2] · Xiang Ao[1,2]

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Abstract

Cancer is the second-leading disease-related cause of global mortality after cardiovascular disease. Despite significant advances in cancer therapeutic strategies, cancer remains one of the major obstacles to human life extension. Cancer pathogenesis is extremely complicated and not fully understood. Epithelial splicing regulatory proteins (ESRPs), including ESRP1 and ESRP2, belong to the heterogeneous nuclear ribonucleoprotein family of RNA-binding proteins and are crucial regulators of the alternative splicing of messenger RNAs (mRNAs). The expression and activity of ESRPs are modulated by various mechanisms, including post-translational modifications and non-coding RNAs. Although a growing body of evidence suggests that ESRP dysregulation is closely associated with cancer progression, the detailed mechanisms remain inconclusive. In this review, we summarize recent findings on the structures, functions, and regulatory mechanisms of ESRPs and focus on their underlying mechanisms in cancer progression. We also highlight the clinical implications of ESRPs as prognostic biomarkers and therapeutic targets in cancer treatment. The information reviewed herein could be extremely beneficial to the development of individualized therapeutic strategies for cancer patients.

Keywords ESRPs · EMT · CSC · Biomarker · Therapeutic target

Introduction

Cancer is the second-leading disease-related cause of mortality worldwide after cardiovascular disease. According to the latest statistics from the World Health Organization, approximately 10 million cancer-related deaths occurred in 2020 [1, 2]. Cancer has become one of the major obstacles to extending life expectancy since it is a heterogeneous disease with high incidence and mortality [3, 4]. There have been significant advances in cancer therapeutic strategies owing to progressive research into cancer pathogenesis, but cancer remains a major global public health problem that poses a threat to patients' health and quality of life [5]. When most cancers are detected and diagnosed early, treatment is more effective, and survival improves significantly. However, more than 50% of cancers are still diagnosed at an advanced stage, with a poor 5-year survival rate. This is mainly due to the unknown aspects of the mechanisms involved in cancer progression and a lack of effective approaches for early diagnosis and prognosis assessment in cancer clinical treatment [6]. Therefore, it is crucial to fully elucidate the underlying mechanisms involved in cancer progression and to identify effective therapeutic targets and biomarkers that will aid in the development of individual diagnoses and therapeutic strategies in cancer clinical treatment.

Epithelial–mesenchymal transition (EMT) is a developmental process in which cells shift from an epithelial state to a mesenchymal state. It is involved in various essential physiological and pathological processes, including embryonic development, wound healing, organ fibrosis, and cancer progression [7, 8]. Aberrant EMT activation contributes to cancer progression by modulating many aspects of cancer cell behavior, including metastasis, cancer stem cell (CSC) proliferation, and acquired immune escape [6]. Alternative splicing (AS) is a crucial biological process that produces multiple mRNAs from a single gene [9]. Dysregulation of AS results in disruption of the epithelial cell state, enhancement of metastasis, and extension of survival. In fact, AS

✉ Ying Liu
liuying_hero@163.com; yingliu@qdu.edu.cn

1 Institute for Translational Medicine, The Affiliated Hospital of Qingdao University, Qingdao Medical College, Qingdao University, Qingdao 266021, China

2 School of Basic Medical Sciences, Qingdao Medical College, Qingdao University, Qingdao 266071, China

events in EMT-associated genes have been observed during EMT process. These events play an indispensable role in the regulation of EMT-associated signaling, cytoskeletal remodeling, tumor-initiating capacity, and metastasis [10]. Epithelial splicing regulatory proteins (ESRPs) are identified as core modulators of EMT-related splicing events [9]. ESRPs, including ESRP1 and ESRP2, are members of the heterogeneous nuclear ribonucleoprotein family of RNA-binding proteins and are specifically expressed in epithelial cells [11]. They exert physiological roles by regulating AS events associated with epithelial cell phenotypes [12, 13]. ESRP expression and activity can be modulated via distinct mechanisms, such as non-coding RNAs (ncRNAs) and post-translational modifications (PTMs) [14, 15]. In recent years, numerous studies have demonstrated that ESRPs act as oncoproteins or tumor suppressors to play crucial roles in various cancers, including CRC, breast cancer (BC), and prostate cancer (PCa) [16–18]. Additionally, owing to their aberrant expression pattern, ESRPs have great potential as valuable biomarkers for the early diagnosis and prognostic evaluation of cancer patients.

In this review, we mainly summarize recent advances in the structures, functions, and regulatory mechanisms of ESRPs, with a focus on their critical roles in cancer progression. We also highlight the clinical implications of ESRPs as therapeutic targets or biomarkers for early diagnosis and prognosis. In addition, we explore future research directions aimed at developing ESRP-based therapeutic strategies for cancer patients.

Overview of ESRPs

Structural characteristics of ESRPs

The ESRP family consists of two members that share similar structures and functions: ESRP1 and ESRP2 (also known as RBM35A and RBM35B, respectively) (Fig. 1). The *ESRP1* gene is mapped to human chromosome 8q22.1, and it encodes functional ESRP1 proteins with an estimated molecular weight of 76 kDa and 681 amino acids. The *ESRP2* gene is found on human chromosome 16q22.1, and it produces a nearly 78-kDa ESRP2 protein consisting of 727 amino acids. Both ESRP1 and ESRP2 contain an N-terminal DnaQ-like exonuclease domain and three highly conserved RNA recognition motif (RRM) domains (RRM1–3) that mediate their interactions with RNA and other proteins [19]. The RRM2 and RRM3 domains of ESRP1 mediate its direct interaction with RNA-binding protein with multiple splicing-2, thereby regulating smooth muscle cell plasticity [13]. ESRP1 also has a proline-rich region that is homologous to DAZ-associated protein 2 in its C-terminal region, whereas ESRP2 has a region homologous to FAM70 [19]. The two domains are located in the C-terminal region of ESRPs, and their roles are still inconclusive, requiring further elucidation. In recent years, an increasing number of methods, such as single-particle cryogenic electron microscopy (cryo-EM) and mass spectrometry, have been utilized to investigate the structures and functions of protein [20]. Among them, cryo-EM is being adopted as a mainstream tool in structural biology, which can efficiently detect the high-resolution structure of protein even in the presence of structural and conformational heterogeneity [21]. We believe that the application of cryo-EM in uncovering ESRP structure characteristics will provide more in-depth and comprehensive information for researchers.

Functions of ESRPs

ESRPs are well-studied AS regulators that modulate epithelial-specific AS events associated with epithelial cell phenotypes by directly binding to specific GU-rich sequence elements known as ESRP-binding splicing enhancers and ESRP-binding splicing inhibitors [22]. ESRPs are also involved in the regulation of EMT-related activities, such as cell movement, cytoskeletal dynamics, and intercellular adhesion [9]. Moreover, ESRPs play a fundamental role in the development of various tissues and organs, including the epidermis, face, palate, cochlear, and kidney [23–26]. They are also strongly associated with organogenesis, such as midface morphogenesis

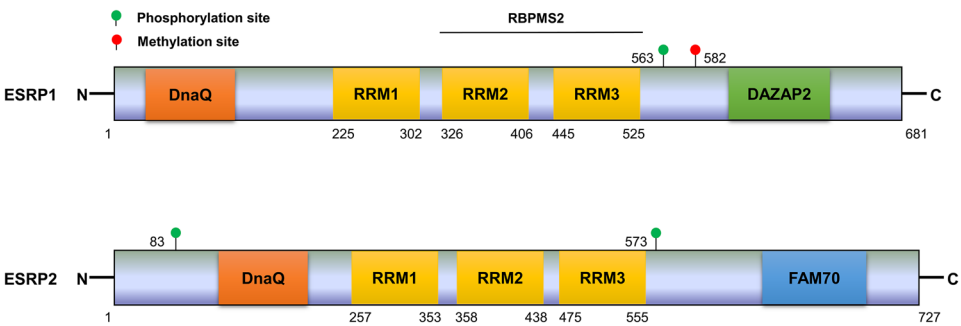

Fig. 1 Structures and PTM sites of human ESRPs. ESRP proteins possess similar conserved structure. The structural domains are indicated in the bar. The well-known PTM sites are shown at the corresponding position. The region containing RRM2 and RRM3 domains mediates the interaction of ESRP1 with RBPMS2

and branching morphogenesis in the lungs and salivary glands [12, 19]. In addition, ESRP1 mediates multiple physiological processes, including spermatogenesis, stomach smooth muscle plasticity, and placentation [13, 27, 28]. The dysregulation of ESRPs has been linked to a variety of diseases, including female infertility, pulmonary fibrosis, alcoholic hepatitis, and cancer [15, 29–31]. Recent studies have suggested that ESRPs play pleiotropic roles in the progression of cancer, but the detailed mechanisms remain unclear [22, 32]. Therefore, further investigations are required to explore their regulatory mechanisms and clinical applications, which may provide new insights into the development of ESRP-based therapeutic strategies for cancer patients.

Molecular mechanisms of ESRP regulation

ESRP expression and activity are regulated by various mechanisms at different layers, including transcription, post-transcriptional, and post-translational layers (Fig. 2). In this section, we present the main modes of ESRP regulation under physiological and pathological conditions, with a particular focus on their regulation in cancer.

Genetic alterations contribute to ESRP regulation

Gene mutation is one of the crucial factors affecting protein expression and activity. Almost all cancers depend on mutations

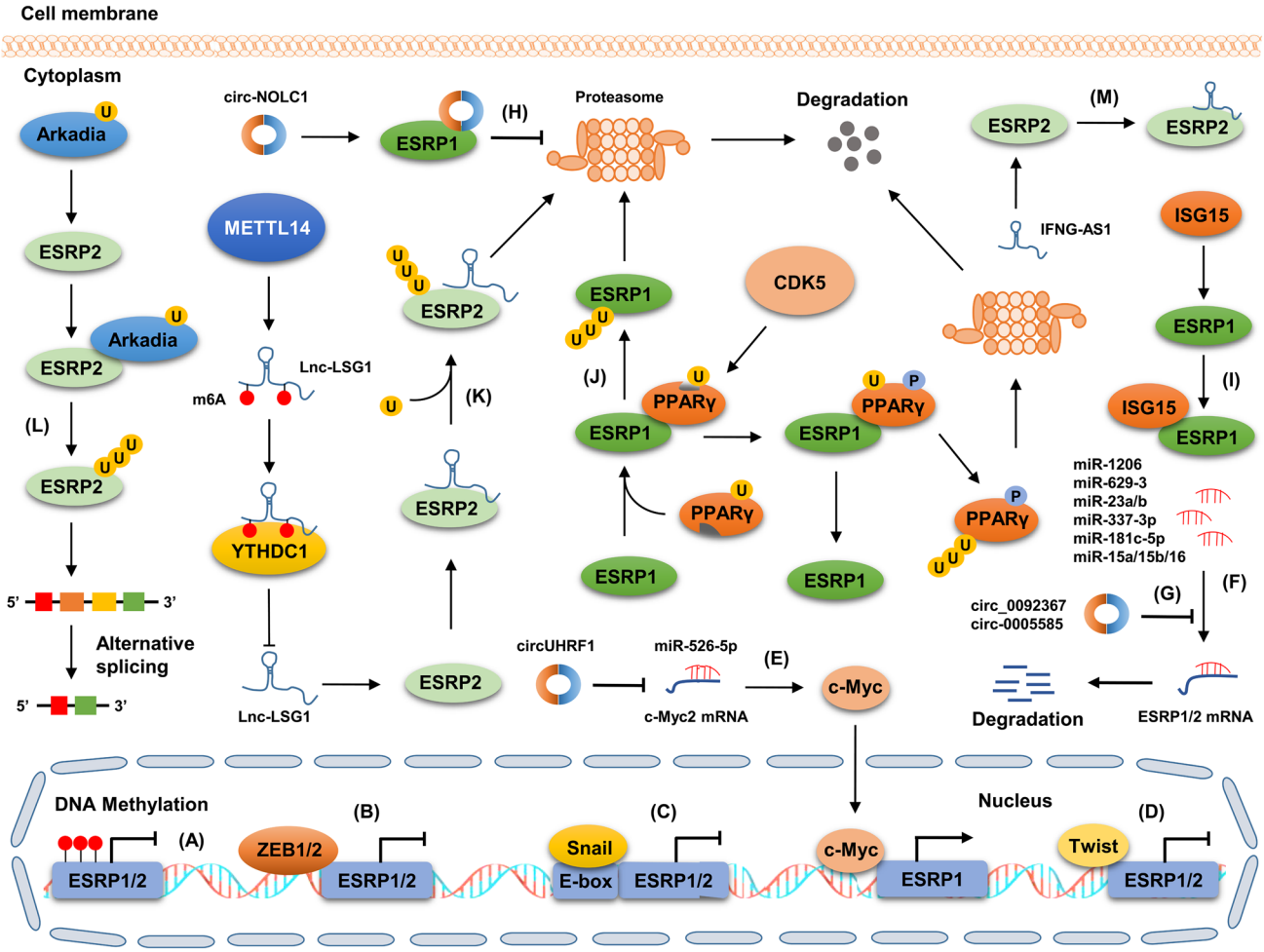

Fig. 2 Regulation of ESRPs. The expression and activity of ESRPs are regulated at different layers, including transcription, post-transcription, and post-translation. (**A**–**D**) DNA methylation, ZEB1/2, Snail, and Twist inhibit ESRP1/2 expression at the transcription level. (**E**) CircUHRF1 enhances the transcriptional activity of ESRP1 by upregulating c-Myc via sponging miR-526-5p. (**F**) MiRNAs facilitate ESRP1/2 degradation by targeting the 3′UTR of their mRNAs. (**G**) CircRNAs modulate ESRP1/2 expression by sponging miRNAs. (**H**) Circ-NOLC1 inhibits ESRP1 degradation by directly binding to it. (**I**) ISG15 enhances ESRP1 stability by promoting its ISGylation. (**J**) PPARγ facilitates ESRP1 degradation in an ubiquitin-dependent manner. CDK5 inhibits the binding of PPARγ to ESRP1 by phosphorylating PPARγ, leading to the enhancement of ESRP1 stability and the ubiquitin-dependent degradation of PPARγ. (**K**) Lnc-LSG1 promotes the ubiquitin-dependent degradation of ESRP2 by binding to ESRP2. METTL14 facilitates ESRP2 m^6A modification and suppresses the interaction between Lnc-LSG1 and ESRP2 in an YTHDC1-dependent manner. (**L**) Arkadia enhances the AS function of ESRP2 by promoting its polyubiquitination. (**M**) IFNG-AS1 modulate ESRP2 functions by interacting with it

in key genes, which endow cancer cell with a selective advantage [33]. Mutations in *ESRP* genes have been observed in CRC and BC [34–36]. Ivanov et al. identified a specific frameshift mutation in the coding region of the *ESRP1* gene in CRC cell lines with microsatellite instability (MSI). This mutation resulted in rapid degradation of the mutated *ESRP1* transcript by a mechanism termed nonsense-mediated decay. Further analysis revealed that this mutation existed in approximately 50% primary CRC tumors with MSI but not in CRC cell lines with microsatellite stability, indicating the stronger selective pressure for the *ESRP1* gene inactivation in MSI-positive CRC [34, 37]. Li et al. analyzed specific high-frequency gene mutations in circulating tumor cells isolated from metastatic BC patients and found that *ESRP1* mutations were only observed in the visceral metastases but not in other metastasis sites, such as the brain, viscus, bone, and soft tissue, suggesting that *ESRP1* mutations may possess potential as a predictive biomarker of visceral metastases for BC patients [35]. In addition, Horvath et al. generated an *ESRP2* (R353Q) variant through site-directed mutagenesis. They showed that the R353Q substitution in ESPR2 reduced its ability to bind to fibroblast growth factor receptor (*FGFR*)*-2* pre-mRNA in BC cell lines [36]. Gene duplication is one of major events resulting in high protein expression [38]. *ESRP1*-containing gene duplication of the 8q22 region has been observed in PCa. Gerhauser et al. revealed that the duplications of *ESRP1* gene existed in 17% of early-onset PCa cases, and *ESRP1* duplications were significantly correlated with increased mRNA and indicators of more aggressive disease (e.g., higher Gleason score and higher Ki67 index). Interestingly, these aggressive indicators were also correlated with increased ESRP1 protein levels [39]. Moreover, a copy number gain of 8q22 region (including ESRP1) was observed in BC patients, and the amplification of *ESRP1* was closely associated with poor survival of BC patients [40].

Regulation of ESRPs at the transcription level

DNA methylation is one of the most widely studied epigenetic modifications that can modulate gene expression at the transcriptional level by attracting proteins involved in gene suppression or inhibiting the binding of transcription factor (TF) to DNA [41, 42]. Aberrant methylation of ESRP promoters has been observed in several cancer types, including ovarian cancer (OC), BC, gastric cancer (GC), and Wilms tumor (WT) [43–46]. Teles et al. discovered that 62% of GC samples had both concomitantly demethylated *ESRP1* promoters and *ESRP1* amplification and the demethylation of the *ESRP1* promoters had a close correlation with high RNA expression in GC cells [45]. Jeong et al. revealed that OC cells that expressed high *ESRP1* or *ESRP2* levels exhibited DNA hypomethylation of CpG sites in the *ESRP1* or *ESRP2* promoter region, whereas cells that expressed low *ESRP1* or *ESRP2* levels exhibited DNA hypermethylation of CpG sites. Treatment with 5-aza-2′-deoxycytidine (a DNA methylation inhibitor) significantly upregulated the *ESRP1* transcript levels in the low-*ESRP1* OC cells. However, treatment of 5-aza-2′-deoxycytidine significantly elevated the *ESRP2* transcript levels in the low-*ESRP2* OC cells [43]. Legge et al. demonstrated that *ESRP2* expression was inhibited by DNA methylation in WT. They discovered that treatment of 5-aza-2′-deoxycytidine reactivated *ESRP2* expression in the WT cell lines [46]. Furthermore, Ashok et al. demonstrated that CpG islands on the *ESRP1* promoter in BC cells are heavily methylated under hypoxia, as opposed to normoxia, resulting in reduced E2F1 recruitment on the *ESRP1* promoter. Consistent with this findings, BC cells treated with 5-aza-2′-deoxycytidine decreased the methylation level of the E2F1 binding site and restored E2F1 binding on the *ESRP1* promoter [44]. These studies indicate that methylation in gene promoter is one of the major mechanisms to regulate *ESRP* expression. DNA methylation is a dynamic reversible process mediated by a series of methylases (e.g., DNMT1, DNMT2, and DNMT3a) and demethylases (e.g., ALKBH1 and ALKBH4). Thus, the identification of methylases and demethylases for *ESRP* genes is an important direction in future studies.

EMT-associated TFs that regulate ESRP expression at the transcriptional level are known as members of the zinc finger E-box-binding homeobox (ZEB), Snail, and Twist families [47–49]. For example, Gemmill et al. discovered that the mRNA level of *ZEB1* in non-small-cell lung cancer (NSCLC) cells was negatively associated with *ESRP1* and *ESRP2* mRNA levels [50]. Larsen et al. showed that ZEB1 significantly inhibited *ESRP1* expression by directly interacting with its promoter region, resulting in the facilitation of malignant transformation in human bronchial epithelial cells and carcinogenesis, invasion, and metastases in NSCLC cell lines [51]. Reinke et al. revealed that Snail downregulated ESRP1 by binding to E-boxes in the *ESRP*1 promoter, thereby enhancing the EMT process in human mammary epithelial cells [48]. Moreover, Cui et al. demonstrated that the activation of Twist by TGFβ1 in NSCLC cells was accompanied by ESRP1 downregulation [49]. In another study by Dave et al., Twist was found to upregulate *ZEB1* expression by directly binding to its promoter via cooperating with Snail1 in mouse mammary epithelial cells [51]. These data indicate that Twist may indirectly decrease ESRP1 levels through induction of *ZEB1* expression. Taken together, these findings strongly suggest that *ESRP* expression can be modulated by various factors at the transcription level. These upstream regulators apply extra layers of control to the biological roles of ESRPs. Therefore, in-depth investigations that identify upstream regulators of ESRPs and clarify their regulatory mechanisms may bring great benefits to the development of ESRP-based therapeutic strategy.

Contribution of ncRNAs to posttranscriptional ESRP regulation

NcRNAs are unique functional RNA transcripts that regulate gene expression at the transcriptional, RNA processing, and translational levels in almost all biological processes [52, 53]. Furthermore, ncRNAs can be divided into several categories based on their size, structure, and function: microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and piwi-interacting RNAs [54–57]. Numerous studies have suggested that ncRNAs contribute to the posttranscriptional regulation of ESRPs in cancer progression (Table 1).

MiRNAs are a class of small ncRNAs (18–25 nucleotides) that can regulate gene expression at the post-transcriptional level by suppressing messenger RNA (mRNA) translation or by facilitating mRNA degradation [67–69]. ESRPs have been shown to be targets of miRNAs in multiple cancer types. For example, Pan et al. showed that *ESRP1* was a direct target gene of miR-337-3p. MiR-337-3p suppressed *ESRP1* expression by binding to its 3′-untranslated region (3′UTR) region, resulting in the inhibition of viability, migration, invasion, and EMT process in BC cells [58]. In our previous work, we discovered that hsa-miR-181c-5p was a potential upstream regulator of ESRP1. Hsa-miR-181c-5p may exert its antitumor function in BC by targeting ESRP1 in BC [11]. In addition, Yue et al. demonstrated that miR-629–3 inhibited *ESRP2* expression by targeting its 3′UTR in laryngeal cancer cells. Further analysis revealed that SP1 was a direct upstream TF for miR-629-3p and a downstream effector of MYCT1. MYCT1 suppressed the EMT and migration of laryngeal cancer cells through the SP1/miR-629-3p/ESRP2 pathway [63]. CircRNAs are a group of covalently closed single-stranded RNA molecules that modulate cancer progression by altering the expression of their target genes [70–72]. Multiple circRNAs can regulate ESRPs. For example, circ-NOLC1 overexpression was found to increase ESRP1 expression at both protein and mRNA levels, whereas circ-NOLC1 knockdown yielded the opposite effect. Functional analysis revealed that circ-NOLC1 promoted the proliferation, migration, and invasion ability of OC cells by directly interacting with ESRP1 [61]. Moreover, circRNAs can serve as miRNA sponges to alter ESRP1 expression [73, 74]. Yu et al. showed that circ_0092367 was downregulated in pancreatic cancer (PC) tissues and cell lines. Circ_0092367 acted as a sponge to suppress the levels of miR-1206, thereby upregulating ESRP1 expression, resulting in the inhibition of EMT and enhancement of gemcitabine sensitivity in PC cells [62]. In

Table 1 NcRNAs targeting ESRPs in cancer

Cancer types	ncRNAs	ESRPs	Function of the interaction	References
BC	miR-337-3p	ESRP1	Overexpression of miR-337-3p inhibited the viability, migration, invasion, and EMT of BC cells by directly targeting ESRP1	[58]
	hsa-miR-181c-5p	ESRP1	ESRP1 was a potential downstream target of hsa-miR-181c-5p in BC	[11]
	miR-101-5p	ESRP1	Overexpression of miR-101-5p suppressed proliferation, migration, and invasion, in BC cells by targeting ESRP1, GINS1, High Mobility Group Box 3, Tumor Protein D52, Serine/Arginine-Rich Splicing Factor Kinase 1, Vang-like protein 1, and Mago Homolog B	[59]
	LncRNA Esrp2-as	ESRP2	Knockdown of Esrp2-as in BC cells was found to promote cell motility and inhibit proliferation by downregulating ESRP2	[60]
OC	circ-0005585 miR-23a/b miR-15a/15b/16	ESRP1	Circ-0005585 overexpression significantly increased ESRP1 levels by sponging miR-23a/b and miR-15a/15b/16, leading to the inhibition of migration in epithelial OC cells and promotion of colonization	[14]
	circ-NOLC1	ESRP1	Overexpression of circ-NOLC1 in epithelial OC cells promoted cell proliferation, migration, and invasion ability by upregulating CDK1 and RhoA via binding to ESRP1	[61]
PC	circ_0092367 miR-1206	ESRP1	Overexpression of circ_0092367 inhibited EMT phenotypes and enhanced gemcitabine sensitivity in PC cells by upregulating ESRP1 via sponging miR-1206	[62]
Laryngeal cancer	miR-629-3p	ESRP2	MiR-629-3p was found to inhibit ESRP2 expression by directly targeting its 3′UTR	[63]
Cervical cancer	hsa_circ_0001495	ESRP2	Hsa_circ_0001495 was involved in carcinogenesis of cervical cancer by interacting with ESRP2 and acting as a sponge by competing for miRNAs with TBL1XR1	[64]
PA	lncRNA IFNG-AS1	ESRP2	ESRP2 was a target of IFNG-AS1 in PA. IFNG-AS1 contributed PA progression by interacting with ESRP2	[65]
ccRCC	Lnc-LSG1	ESRP2	Lnc-LSG1 promoted ESRP2 degradation by facilitating ESRP2 ubiquitination via directly binding to ESRP2 in ccRCC cells	[66]

another study, miR-23a/b and miR-15a/15b/16 were identified as upstream regulators for ESRP1 and downstream targets of circ-0005585. Circ-0005585 overexpression in epithelial OC cells upregulated ESRP1 levels by sponging miR-23a/b and miR-15a/15b/16, thereby triggering AS events of a series of genes, including *EPB41L5*, *RAC1*, and *FLNB* [14]. ESRP1 was also an indirect target of circUHRF1. CircUHRF1 upregulated c-Myc by sponging miR-526b-5p, thereby promoting ESRP1 transcription in oral squamous cell carcinoma (OSCC) cells. Interestingly, ESRP1 could reversely facilitate the circularization and biogenesis of circUHRF1 by targeting flanking introns [75]. LncRNAs are a class of endogenous ncRNAs with more than 200 nucleotides in length. They participate in a wide range of physiological and pathological processes by interacting with DNA, RNA, or proteins [76]. LncRNAs are crucial regulators of ESRP2 during cancer progression. Lu et al. demonstrated that ESRP2 was a target protein of lncRNA IFNG-AS1 in pituitary adenoma (PA). IFNG-AS1 directly interacted with ESRP2 via its first 960 bp. Functional analysis revealed that IFNG-AS1 exerted its oncogenic role in PA progression through its binding to ESRP2 [65]. In another study, Lnc-LSG1 was found to directly bind to ESRP2 proteins and facilitated ubiquitin-dependent degradation in clear cell renal cell carcinoma (ccRCC) cells. Methyltransferase 14 (METTL14) was identified as an upstream modulator of lnc-LSG1, which enhanced ESRP2 stability by increasing N6-Methyladenosine (m^6A) levels of lnc-LSG1 [66]. Furthermore, silencing lncRNA Esrp2-as significantly decreased ESRP2 protein levels without affecting their mRNA expression in BC cells [60].

These findings strongly suggest that the expression and activity of ESRPs are closely regulated by a complicated network consist of miRNAs, lncRNAs, and circRNAs during cancer progression. ESRP dysregulation induced by the disorder of this regulatory network may play a major role in accelerating cancer progression. Therefore, an improved understanding of the mechanisms of ncRNAs involved in ESRP regulation will provide new insights into the development of ESRP-based therapeutic strategies for cancer patients.

Regulation of ESRPs by PTMs

PTMs are chemical modifications of proteins that occur after translation, and they are vital for proteins to maintain their proper biological functions, structure, function, stability, and subcellular localization [77]. According to a growing body of evidence, ESRPs are potential substrates of several PTMs, including ubiquitination, ISGylation, phosphorylation, and methylation [66, 78, 79]. Ubiquitination is a common PTM in which ubiquitin is covalently attached to substrate proteins to alter their stability, cellular localization, and biological activity [80]. The most common function of ubiquitination is to mediate protein degradation in a proteasome-dependent manner [81]. Bei et al. discovered that peroxisome proliferator–activated receptor-gamma (PPARγ) specifically ubiquitinated ESRP1 in triple-negative BC (TNBC) cells and facilitated its ubiquitin-dependent degradation. The E3 ubiquitin ligase activity of PPARγ could be switched by cyclin-dependent kinase 5 (CDK5) protecting ESRP1 from ubiquitin-dependent degradation [82]. Shen et al. demonstrated that Lnc-LSG1 overexpression in ccRCC cells significantly increased the ubiquitination levels of ESRP2 and downregulated its expression through the proteasome pathway. The stability of ESRP2 was enhanced by METTL14, which decreased ESRP2 ubiquitination by disturbing the interaction between ESRP2 and Lnc-LSG1 [66]. Moreover, Mizutani et al. demonstrated that Arkadia could act as an E3 ligase to mediate the polyubiquitination of ESRP1 and ESRP2 in ccRCC cells. The Arkadia-mediated ubiquitination occurred on Lys27 of ubiquitin molecules. Functional analyses further revealed that the ubiquitination of ESRP2 by Arkadia enhanced the splicing function of ESRP2 without changing its protein stability [83]. ISGylation is a type of ubiquitination-like PTM that can alter the stability and activity of substrate proteins [84]. Qu et al. demonstrated that ESRP1 was modified by ISG15 (an ubiquitin-like protein) in lung adenocarcinoma (ADC) cells and that the ISGylation of ESRP1 retarded its degradation [85]. In addition, bioinformatics analysis revealed the presence of several types of PTM sites, including phosphorylation and methylation, in the protein sequence of ESRPs, suggesting that ESRPs may be potential targets of these PTMs. Extensive investigations are required to further understand the mechanisms of PTMs in ESRP regulation. Collectively, these studies indicate that the functions of ESRPs are tightly controlled by a series of PTMs via different enzymatic reactions. ESRP dysregulation triggered by PTM system disorder may be a key mechanism driving tumorigenesis and development. Therefore, understanding the regulatory mechanism of PTMs on ESRP functions may provide novel insights for the designing of ESRP-based therapeutic strategies for cancer patients.

Implications of ESRPs in cancer progression

ESRP dysregulation contributes to cancer progression by regulating various cellular processes, such as proliferation, apoptosis, invasion, metastasis, EMT, and drug resistance (Fig. 3). However, the detailed mechanisms remain unclear. A deeper understanding of the roles of ESRPs in cancer progression may provide novel insights into the development of effective therapeutic strategies for cancer patients. Herein, we summarize recent findings on the implication of ESRPs in cancer progression (Table 2).

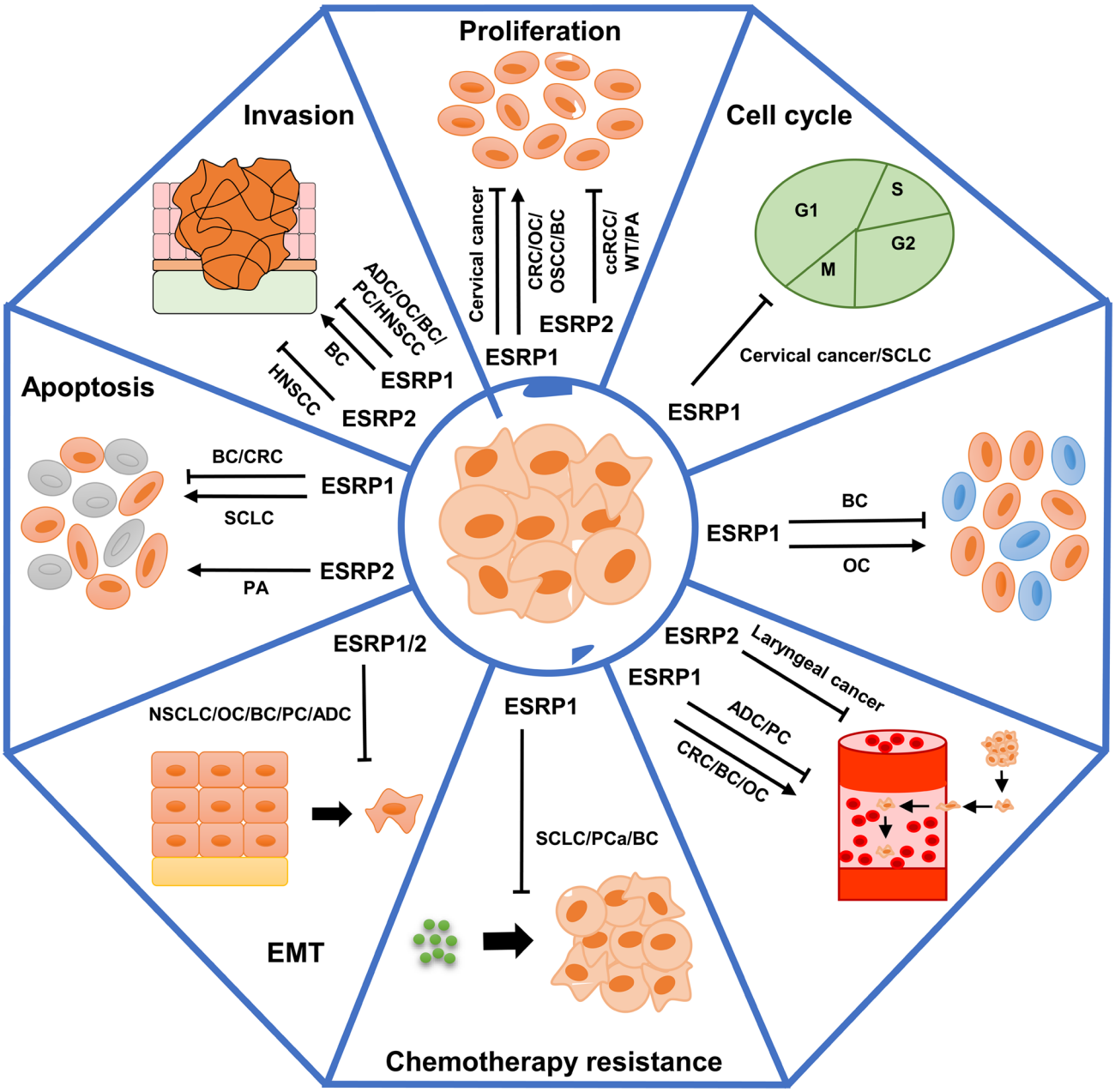

Fig. 3 Role of ESRPs in cancer progression. ESRP1 and ESRP2 act as oncogenes or tumor suppressors to regulate biological behaviors of cancer cells, including cell proliferation, apoptosis, cell cycle, invasion, metastasis, EMT, stemness, and drug resistance

Expression profiles of ESRPs in cancer

The expression patterns of ESRPs have been analyzed in various cancer tissues and cell lines. Warzecha et al. performed a high throughput cDNA expression screening using epithelial and mesenchymal BC (ZR75, SKBR3, MCF7, BT-549, and MDA-MB-231), PCa (LNCaP and Du145), and OC (OVCAR3 and OVCAR5) cell lines. The epithelial cancer cells had at least a tenfold higher expression of both ESRP1 and ESRP2 than the mesenchymal cancer cells [123]. Ishii et al. discovered that ESRP1 and ESRP2 were expressed in both normal epithelium and OSCC samples and that the two proteins were upregulated during OSCC carcinogenesis. However, ESRP1 and ESRP2 expression was downregulated in the invasive OSCC samples. They also discovered that the head and neck squamous cell carcinoma (HNSCC) cell lines had higher ESRP1 expression than the cervical carcinoma cell line (HeLa cells), but no significant difference in ESRP2 expression was observed between the HNSCC cell lines and HeLa cells [124]. Moreover, Teles

Table 2 Roles of ESRPs in different types of cancer

Cancer types	ESRPs	Key message(s)	References
BC	ESRP1	High ESRP1 expression is closely associated with poor prognosis in ER^+ BC patients. Knockdown of ESRP1 in tamoxifen-resistant BC cells inhibited lipid metabolism and oxidoreductase processes by downregulating FASN, SCD1, and PHGDH	[17]
	ESRP1	ESRP1 promoted the biogenesis of circANKS1B, a circRNA that fascinated invasion and metastasis in BC	[86]
	ESRP1	Knockdown of ESRP1 in BC cells enhanced CSC properties by shifting AS from CD44v to CD44s	[87]
	ESRP1	The upregulation of ESRP1 in BC was mediated by increased E2F1 levels and CpG hydroxymethylation of the E2F1 binding motif	[44]
	ESRP1	Downregulation of ESRP1 by miR-337-3p suppressed viability, migration, invasion, and EMT in BC cells	[58]
	ESRP1	ESRP1 overexpression was associated with poor prognosis in BC patients. Furthermore, hsa-miR-181c-5p was a potential upstream regulator of ESRP1	[11]
	ESRP1	The downregulation of ESRP1 by hypoxia in BC cells increased hMENAΔ11a (a pro-metastatic isoform) levels by trigging skipping of hMENA exon 11a, leading to the enhancement of EMT	[88]
	ESRP1	High levels of ESRP1, ESRP1/HAS2, and ESRP1/ZEB1 were closely associated with poor prognosis in multiple BC datasets	[89]
	ESRP1	ESRP1 overexpression in BC cells enhanced PB sensitivity by inhibiting ANKRD1, ETS1, and KIAA1199 expression	[90]
	ESRP1	ESRP1 promoted or inhibited lung metastasis of BC cells by increasing or decreasing the CD44v/CD44s ratio in BC cells	[91]
	ESRP1	ESRP1 was found to upregulate CD44v expression Knockdown of ESRP1 in CD44v(+) cells resulted in an isoform switch from CD44v to CD44s, leading to decreased cell surface expression of xCT and inhibition of lung colonization	[92]
	ESRP1	Overexpression of ESRP1 in invasive mesenchymal BC cells resulted in a phenotypic switch characterized by changes in the cytoskeletal architecture, re-expression of hMENA(11a), and a reduction in cell invasion	[93]
	ESRP1	ESRP1 regulated the EMT phenotype of BC cells by controlling the CD44 isoform switch	[94]
	ESRP2	Knockdown of lncRNA Esrp2-as in BC cells decreased ESRP2 levels without influencing mRNA expression, resulting in an altered transcriptional profile correlated with extracellular matrix, cell motility, and decreased proliferation	[60]
	ESRP2	A rare substitution in ESRP2 (R353Q) impaired its binding to FGFR2 pre-mRNA in BC	[36]
	ESRP2	ESRP2 expression was downregulated in NMuMG cells by δEF1 and SIP1, which directly bound to the ESRP2 promoter. Overexpression of ESRPs in TGF-β-treated BC cells resulted in restoration of the epithelial splicing profiles and attenuation of certain phenotypes of EMT	[47]
	ESRP1 ESRP2	The ratio between ESRP1 or ESRP2 and RBFOX2 significantly downregulated during EMT and was positively associated with the EMT-specific phenotype in BC cells. Moreover, low ESRP1/RBFOX2 ratio was significantly correlated with a higher risk of metastasis ($p < 0.005$) in early BC patients	[95]
OC	ESRP1	Overexpression of circ-NOLC1 significantly upregulated ESRP1 at both protein and mRNA levels. Knockdown of ESRP1 abolished the oncogenic effect of circ-NOLC1 in epithelial OC cells	[61]
	ESRP1	Circ-0005585 upregulated ESRP1 by sponging miR-23a/b and miR-15a/15b/16. ESRP1 overexpression inhibited epithelial OC cell migration, but facilitated colonization by altering AS of EPB41L5 and RAC1. Moreover, high ESRP1 expression was associated with immune-suppression in tumor immune microenvironment	[14]
	ESRP1	High ESRP1 expression in OC patients was associated with poor prognosis. Knockdown of ESRP1 in epithelial OC cells significantly promoted migration and invasion by trigging isoform switching from CD44v to CD44s	[96]
	ESRP1	ESRP1 mediated the upregulation of CD44s during TGFβ1-induced EMT	[97]
	ESRP1	ESRP1 was associated with platinum resistance in OC	[98]
	ESRP1 ESRP2	The levels of ESRP1 and ESRP2 mRNA significantly increased in serous OC. High expression of ESRP1 promoted metastasis in OC by facilitating colonization of OC cells via the mesenchymal-epithelial transition process	[99]
	ESRP1 ESRP2	The expression of ESRP1 and ESRP2 was negatively associated with DNA methylation in OC cells. ESRP1 overexpression in mesenchymal OC cells facilitated proliferation and inhibited migration by inducing the expression of epithelial cell-specific variant of CD44 and ENAH	[43]

Table 2 (continued)

Cancer types	ESRPs	Key message(s)	References
PC	ESRP1	ESRP1 mediated the inhibition of circ_0092367 on EMT and gemcitabine resistance in PC. Circ_0092367 increased ESRP1 levels by sponging miR-1206	[62]
	ESRP1	ESRP1 was a direct target of miR-23a in PC cells. ESRP1 overexpression blocked the enhancement of miR-23a on EMT process of PC cells	[100]
	ESRP1	PC patients with high ESRP1 expression exhibited longer survival compared with those with low ESRP1 expression. ESRP1 overexpression in PC cells inhibited growth, migration, invasion, and metastasis by altering FGFR-2 expression pattern	[101]
	ESRP1	AS events of ESRP1 were significantly associated with overall survival in PC patients	[102]
	ESRP1	ESRP1 mediated the regulation of ZEB1 on CD44s splicing in PC	[103]
Cervical cancer	ESRP1	Overexpression of ESRP1 induced G1-phase cell cycle arrest of cervical cancer cells by decreasing the stability of the cyclin A2 mRNA via binding to GGUGGU sequence in the 3′UTR of the cyclin A2 mRNA, leading to the inhibition of cervical cancer cell proliferation	[104]
	ESRP2	ESRP2 mediated the effects of hsa_circ_0001495 on the proliferation and NOTCH signaling in cervical cancer cells	[64]
	ESRP1 ESRP2	ESRP1 and ESRP2 mediated the downregulated of FGFR2b induced by 16E5 in cell models of transfected human keratinocytes as well as in cervical epithelial cells containing episomal HPV16	[105]
ccRCC	ESRP2	ESRP2 inhibited ccRCC tumor growth by coordinating with Arkadia. Moreover, Arkadia was found to mediate the polyubiquitination and splicing function of ESRP2 by directly binding to it	[83]
	ESRP2	Lnc-LSG1 facilitated ESRP2 degradation in ccRCC cells by directly binding to it in an ubiquitin-dependent manner	[66]
GC	ESRP1	*ESRP1* was frequently amplified and demethylated in GC, leading to upregulation of ESRP1. Moreover, *ESRP1* amplification was closely associated with a significant decreased expression of FGFR2-IIIc	[45]
PCa	ESRP1	PC patients in ESRP1-high group exhibited significantly worse biochemical recurrence-free survival and recurrence-free survival compared with patients in ESRP1-low group ($p<0.05$). Moreover, ESRP1 was a significantly risk factor for cancer-specific survival ($p=0.034$) and for biochemical recurrence ($p=0.049$) in PC	[106]
	ESRP1	ESRP1 downregulation was observed in taxane-exposed metastatic castration-resistant PC patients. High ESRP1 expression was independently associated with longer PSA progression-free survival ($p<0.001$) and radiologic-progression-free survival ($p=0.001$) in docetaxel-treated patients and shorter PSA progression-free survival ($p=0.041$) in the cabazitaxel-treated patients	[107]
	ESRP2	ESRP2 expression in clinical PC is inhibited by androgen deprivation therapy, which may thus inadvertently impaired epithelial splice process	[18]
	ESRP1 ESRP2	The suppression of ESRP1 and ESRP2 in PC cells can inhibit androgen receptor-antagonist-driven cancer invasion	[108]
	ESRP1 ESRP2	The expressions of ESRP1, ESRP2, and combined ESRP1/ESRP2 were independent prognostic biomarkers in PCa treatment, with a potential for routine application	[109]
	ESRP1	ESRP1 was independently associated with biochemical recurrence-free survival in PC patients, indicating the potential of ESRP1 as a prognostic biomarker in PCa	[110]
CRC	ESRP1	The ESRP1 oncogenic role in CRC cells at least partially was mediated by RAC1b	[111]
	ESRP1	High ESRP1 expression stimulated growth of cancer epithelial cells and facilitated CRC progression	[112]
	ESRP1	Knockdown of ESRP1 in CRC cells facilitated cell death by inducing caspase-independent cell death via modulation of CD44 AS	[113]
	ESRP2	ESRP2 mediated the proto-oncogene MYC by regulating the splicing of the *ITGA6* integrin gene in CRC cells	[114]
	ESRP1 ESRP2	Expression of ESRP1 and ESRP2 was significantly associated with favorable overall survival ($p=0.0186$ and 0.0408)	[37]
SCLC	ESRP1	ESRP1 might be a molecular driver of SCLC transformation of TKI resistance	[115]
	ESRP1	Overexpression of ESRP1 enhanced SCLC drug sensitivity, and induced cell apoptosis and cell cycle arrest	[116]
NSCLC	ESRP1	ESRP1 was an independent prognostic factor for NSCLC patients. The expression of ESRP1 was negatively regulated by Twist. Moreover, TGFβ1 increased Twist levels while decreased ESRP1 levels	[49]
	ESRP1	ESRP1 was inhibited by ZEB1 in human bronchial epithelial cells, resulting in the upregulation of a mesenchymal splice variant of CD44 and a more invasive phenotype	[51]

Table 2 (continued)

Cancer types	ESRPs	Key message(s)	References
	ESRP1	ESRP1 was suppressed by EML4-ALK activity. ALK tyrosine kinase inhibitors treatment upregulated ESRP1 and E-cadherin. ESRP1 knockdown impaired E-cadherin upregulation upon ALK inhibition	[117]
ADC	ESRP1	ESRP1 upregulated ISG15 by CREB, lending to the inhibition of EMT in lung ADC. ISG15 facilitated ISGylation of ESRP1 and slowed ESRP1 degradation	[85]
	ESRP1	ESRP1 suppressed the invasion and metastasis of lung ADC	[118]
	ESRP1	Knockdown of ESRP1 resulted in increased Rac1b messenger RNA (mRNA) and inhibition of ZEB1 in lung ADC	[119]
Melanoma	ESRP1	Low expression of ESRP1 was associated with better overall survival in cutaneous malignant melanoma patients. ESRP1 was involved in the regulation of ribosome metabolism, drug metabolism, and chemical carcinogenesis tumor–associated macrophage polarization, dendritic cell infiltration, Treg cells, and T cell exhaustion	[120]
	ESRP1	ESRP1 was identified as an informative biomarker for immunotherapy in melanoma	[121]
	ESRP1 ESRP2	ESRP1 and ESRP2 were associated with CD44v6 expression in primary melanoma, and ESRP1 knockdown significantly downregulated CD44v6 expression	[122]
Laryngeal cancer	ESRP2	The expression of ESRP2 was significantly negatively associated with metastasis in patients with laryngeal cancer. MiR-629-3p could inhibit ESRP2 expression by directly targeting its 3′UTR	[63]
PA	ESRP2	ESRP2 was a target of IFNG-AS1 in PA. Overexpression of ESRP2 abolished the oncogenic effects of IFNG-AS1 in PA cells	[65]

et al. detected the expression pattern of ESRP1 in GC samples using The Cancer Genome Atlas datasets and revealed that ESRP1 is overexpressed in tumor samples compared to normal samples (p-value ranging from 8.93×10^{-6} to 9.46×10^{-3}) [45]. Furthermore, Polar et al. demonstrated that acquired tamoxifen-resistant BC cells had significantly higher ESRP1 expression at the mRNA and protein levels than parental endocrine therapy-sensitive control cells ($p = 0.0001$) [17]. Collectively, these findings demonstrate that aberrant ESRP expression may be a hallmark of cancer progression and that ESRP expression is plastic during the invasion and metastasis of cancer cells. The differential expression patterns of ESRPs in distinct cell types endow them with potential as tumor biomarkers or therapeutic targets. A thorough understanding of ESRP expression patterns in cancer progression will contribute to the development of better diagnostics and treatments for cancer patients.

Roles of ESRPs in cancer proliferation and apoptosis

Proliferation maintenance and apoptosis evasion are considered representative hallmark capabilities of cancer cells. These cellular processes involve complicated mechanisms that have not been fully understood. ESRP1 has been reported to play an oncogenic role by facilitating proliferation and/or suppressing apoptosis in various cancers, including CRC, BC, OC, and OSCC [43, 58, 112, 125]. ESRP1 expression has also been found to be significantly upregulated in these cancer types. Fagoonee et al. discovered that ESRP1 overexpression facilitated CRC cell proliferation and transformation by activating FGFR-2 and the PI3K/AKT signaling pathway [112]. Jeong et al. revealed that DNA hypomethylation of CpG sites in the *ESRP1* promoter resulted in high ESRP1 expression, and its overexpression promoted proliferation in OC cells [43]. Zhao et al. discovered that ESRP1 facilitated the circularization and biogenesis of circUHRF1, thereby promoting proliferation in OSCC cells [125]. However, low ESRP1expression was observed in cervical carcinoma and small cell lung cancer (SCLC), indicating that ESRP1 could play an anti-tumoral role in these cancers [104, 116]. Chen et al. demonstrated that ESRP1 could inhibit proliferation in cervical carcinoma cells by directly regulating the cell cycle. Mechanistically, ESRP1 overexpression induced G1-phase arrest of the cervical carcinoma cells by decreasing cyclin A2 levels via direct binding to its 3′UTR. ESRP1 overexpression also upregulated CDC20 in cervical carcinoma cells, resulting in cyclin A2 degradation [104]. ESRP1 overexpression was also found to induce cellular apoptosis and cell cycle arrest in SCLC cells. The knockdown of ESRP1 resulted in the opposite effect [116].

Several studies have suggested that ESRP2 acts as a tumor suppressor in cancer progression [46, 83]. Legge et al. demonstrated that ESRP2 was significantly downregulated in WT tissues by DNA hypermethylation. Consistent with this, DNA methyltransferase inhibition reactivated ESRP2 expression in WT cells. The overexpression of ESRP2 significantly suppressed the proliferation of the WT cells in vitro and inhibited tumor growth of orthotopic xenografts in vivo [46]. Mizutani et al. demonstrated that ESRP2 repressed cellular proliferation and tumor growth in ccRCC by cooperating with Arkadia [83]. ESRP2 has also been found to mediate the regulation of lncRNA IFNGAS1 during the proliferation and apoptosis of PA cells [65].

These findings suggest that ESRP dysregulation contributes to cancer progression by influencing cell proliferation and apoptosis processes. However, the regulatory mechanisms of ESRPs involved in these processes remain largely uncharted. Complex signaling pathways (e.g., PI3K/AKT, MAPK, and Wnt/β-catenin) and a variety of regulators (e.g., Bcl-2 and FADD) have been shown to participate in cell proliferation and apoptosis [126]. Identifying their downstream effectors may be an important direction to elucidate the underlying mechanisms of ESRPs in the regulation of cell proliferation and apoptosis during cancer progression.

Roles of ESRPs in cancer EMT

EMT is an evolutionarily conserved developmental process characterized by the upregulation of mesenchymal markers (e.g., vimentin, N-cadherin) and the downregulation of epithelial markers (e.g., E-cadherin) [77]. Aberrant activation of EMT has been shown to enhance the metastatic behavior and drug resistance of tumor cells [6]. ESRPs are known to play a role in the regulation of EMT during cancer progression by altering isoform switching of EMT-associated genes, such as FGFRs and clusters of differentiation-44 (CD44) [101]. FGFRs are major regulators in numerous biological processes, and their isoform switching from the epithelial (FGFR2IIIb) to the mesenchymal (FGFR2IIIc) type has been shown to promote EMT and enhance aggressiveness during cancer progression [127]. Warzecha et al. demonstrated that ESRP1 and ESRP2 mediated the AS of FGFR2 by binding to its intronic splicing enhancer/intronic splicing silencer-3 element located between exons IIIb and IIIc, causing the upregulation of FGFR2IIIb (epithelial variant) [123]. In another study, the downregulation of ESRP1 and ESRP2 by HPV16 E5 was found to trigger an isoform switching from FGFR2IIIb to FGFR2IIIc, facilitating EMT progression in human keratinocytes [105].

CD44 is a transmembrane glycoprotein that can be spliced alternatively into standard isoforms (CD44s) and variant isoforms (CD44v). CD44s plays a crucial role in promoting EMT during cancer progression [127]. Larsen et al. revealed that ESRP1 facilitated the AS of CD44 variable exons by binding to the GU-rich element present in CD44 pre-mRNA. The downregulation of ESRP1 by ZEB1 decreased the CD44v levels and increased the CD44s levels, enhancing the EMT process in lung cancer cells [51]. Chen et al. showed that ESRP1 knockdown promoted the EMT process in epithelial OC cells by triggering an isoform switching from CD44v to CD44s [96]. Several other researchers also discovered that ZEB1 downregulated ESRP1 in BC and PC cells, resulting in CD44 splice isoform switching and increased CD44s levels [89, 103]. Taken together, all these findings support the hypothesis that ESRPs inhibit the EMT process by altering the isoform switching of EMT-associated genes during cancer progression. However, the exact mechanisms involved in ESRP regulation during EMT require further elucidation, which may provide new insights for the development of ESRP-based therapeutics strategies for cancer patients.

Roles of ESRPs in cancer invasion and metastasis

Invasion and metastasis are remarkable hallmarks of cancer that are closely associated cancer-related deaths. Metastasis is a complicated, multistep process that is crucial for the dissemination of cancer cells to anatomically distant organ sites. Invasion is the first step toward metastasis [42]. Recent studies have suggested that ESRPs are crucial regulators of invasion and metastasis during cancer progression. For example, ESRP1 overexpression has been negatively associated with metastasis in lung ADC patients. The knockdown of ESRP1 enhances the invasion of lung ADC cells [118]. In another study, decreased ESRP1 expression was found to significantly promote the migration and invasion of epithelial OS cells, both in vivo and in vitro [96]. Furthermore, Deng et al. demonstrated that ESRP1 overexpression inhibited the migration of epithelial OC cells by triggering a switch from mesenchymal to epithelial phenotypes via the AS of EPB41L5 and RAC1 [14]. However, ESRP1 exhibits pro-metastatic function in several cancer types, including CRC, BC, and OSCC. In a previous study, ESRP1 was found to facilitate the ability of CRC cells to generate macrometastases in mouse livers [112]. ESRP1 overexpression also enhanced the metastatic ability of 4T1 BC cells in another study [92]. Moreover, ESRP1 enhances cancer cell invasion and metastasis by promoting the biogenesis of oncogenic circRNAs [86, 125]. Conversely, ESRP2 mainly plays an inhibitory role in cancer cell metastasis. Yue et al. demonstrated that ESRP2 expression was negatively associated with metastasis in laryngeal cancer patients [63]. ESRP2 has also been found to inhibit the motility of HNSCC cells by altering cell–cell adhesion through the regulation of the expression of EMT-associated TFs [124]. These studies strongly suggest that ESRPs play vital roles in cancer progression by modulating invasion and metastasis. Although the detailed mechanisms involved in these processes are still unclear, ESRPs have exhibited great potential as targets for the development of pharmacological drugs in cancer treatment. Elucidating their underlying mechanism in cancer invasion and metastasis would help to precisely utilize ESRP-based therapeutics in particular type of cancer.

Roles of ESRPs in regulating CSC stemness

CSCs are a small subpopulation of cells within tumors that possess self-renewal and differentiation abilities, and they are recognized as the main cause of metastasis and

recurrence during cancer treatment [128]. Understanding the underlying mechanisms involved in the regulation of CSC stemness could lead to the identification of new therapeutic targets for cancer patients. According to a growing evidence, ESRP1 plays a crucial role in cancer progression by regulating CSC stemness. CD44 is a well-known CSC marker [129]. Zhang et al. showed that high ESRP1 expression significantly inhibited the promotion of CD44 in CSC stemness in BC. Mechanistically, ESRP1 increased the CD44v levels by triggering an isoform switch from CD44s to CD44v, causing the CSC characteristics to be impaired. ESRP1 knockdown also shifted the AS of CD44 from CD44v to CD44s, resulting in an enhancement in the CSC traits [87]. In another study, ESRP1 was found to efficiently promote the lung metastasis of $CD44v^+$ BC stem-like cells in mice in a cystine transporter xCT-dependent manner. ESRP1 knockdown in the $CD44v^+$ BC cells decreased xCT expression in the cell surface by upregulating CD44v, resulting in lung metastasis inhibition [92]. In addition, Bhattacharya et al. revealed that TGFβ1-induced ESRP1 downregulation increased the CD44s levels in OC cells, resulting in enhanced stem-like features and drug resistance [97]. The crucial α6β1 variant that drives CSC function in TNBC is called α6β1 integrin. Goel et al. demonstrated that the downregulation of ESRP1 by VEGF/NRP/GLI signaling increased the α6Bβ1 levels, thereby enhancing the self-renewal ability of breast CSCs [130]. Although some advances have been made, the underlying mechanisms of ESRPs involved in the regulation of CSC stemness remain largely unknown. Further studies are required to elucidate the exact roles and mechanisms of ESRPs in CSC stemness modulation, which may provide novel insights for the development of strategies based on targeting ESRPs for cancer patients.

Roles of ESRPs in cancer drug resistance

Chemotherapy remains the standard treatment option for all stages of cancer, and it can efficiently improve the short-term survival of patients. However, the emergence of drug resistance significantly restricts the role of chemotherapy in extending patients' life span [131]. The mechanisms underlying drug resistance are extremely complicated and remain largely uncharted. ESRP1 has been reported to be involved in the modulation of drug resistance in various cancers, including SCLC, PCa, and BC [62, 90, 116]. For example, Zheng et al. discovered that ESRP1 was much more downregulated in SCLC tissues than in adjacent control tissues. ESRP1 overexpression enhanced drug sensitivity in the SCLC cells, whereas ESRP1 knockdown had the opposite effect. Mechanistically, ESRP1 reversed the drug resistance of the SCLC cells by suppressing the TGF-β/Smad signaling pathway via a change in CARM1 AS [116]. Yu et al. demonstrated that ESRP1 could mediate the inhibition of circ_0092367 on the gemcitabine resistance of PCa cells. Circ_0092367 upregulated ESRP1 by sponging miR-1206, which enhanced the sensitivity of the PCa cells to gemcitabine [62]. ESRP1 has also been identified as a key regulator of phenylbutyrate (PB) sensitivity in BC cells. ESRP1 overexpression in the PB-resistant BC cells enhanced their sensitivity to PB by reducing the expression of PB resistance-related genes, such as ANKRD1, ETS1, and KIAA1199 [90]. In addition, Polar et al. revealed that the knockdown of ESRP1 in tamoxifen-resistant estrogen receptor $(ER)^+$ BC cells reduced the expression of fatty acid synthase, stearoyl-CoA desaturase 1, and phosphoglycerate dehydrogenase by influencing lipid metabolism and oxidoreductase processes, indicating that ESRP1 can play a role in preventing tamoxifen resistance in ER^+ BC [17]. All these findings strongly suggest that ESRP1 is involved in the regulation of cancer drug resistance, but the underlying mechanisms are still largely unknown. An in-depth investigation into the ESRP mechanisms involved in cancer drug resistance will be significantly beneficial to the development of new drugs to treat chemoresistant tumors and ESRP-based therapeutic strategies for patients who have a poor response to chemotherapy.

Clinical applications of ESRPs in cancer treatment

ESRPs as promising cancer biomarkers

Clinically, it is vital to evaluate the prognostic status and therapeutic efficiency of cancer patients in order to adjust their therapeutic strategies in time. However, patient outcomes remain poor because of the lack of effective assessment methods after treatment [131]. Some protein biomarkers, such as CEA, AFP, and P-gp, have been used in cancer treatment, but their unsatisfactory specificity and sensitivity limit their further application [132, 133]. Therefore, the identification of novel prognostic biomarkers with high specificity and sensitivity is urgently required.

ESRPs have significant potential as biomarkers for cancer prognosis and treatment because of their aberrant expression profiles (Table 3). For example, our previous study showed that the mRNA levels of ESRP1 were significantly upregulated in nine clinical cohorts from Oncomine databases ($p = 1.21 \times 10^{-13}$). The high expression of ESRP1 was closely associated with basal A ($p < 0.00001$) and hormone receptor-sensitive ($p = 0.03125$) subtypes of BC. Furthermore, the high expression of ESRP1 was found to be significantly correlated with poor prognosis in patients with ER-positive ($p = 0.0024$), ER-negative ($p = 0.027$), basal ($p = 0.00076$), luminal A ($p = 0.0024$), lymph node-positive ($p = 0.004$), and $Her2^-$ ($p = 6.2 \times 10^{-5}$) subtypes of BC [11]. These data

Table 3 ESRPs as biomarkers in cancer

Cancer types	ESRPs	Function	Clinical values	References
SCLC	ESRP1	Drug resistance biomarker	ESRP1 was significantly downregulated in SCLC tissues and its expression was positively associated with overall survival. ESRP1 overexpression enhanced drug sensitivity of SCLC	[116]
NSCLC	ESRP1	Prognostic biomarker	ESRP1 was an independent prognostic biomarker for NSCLC, particularly when combined with Twist. The expression of ESRP1 and Twist was positively associated in lung tissues ($p < 0.001$)	[49]
PCa	ESRP1	Prognostic biomarker	ESRP1 was independently associated with biochemical recurrence-free survival in PCa patients	[110]
	ESRP1 ESRP2	Prognostic biomarker	The expressions of ESRP1, ESRP2, and combined ESRP1/ESRP2 were identified as independent prognostic biomarkers	[109]
Melanoma	ESRP1	Informative biomarker	The expressions of ESRP1-low, -truncated, and -full-length may serve as informative biomarkers for immunotherapy in melanoma	[121]
BC	ESRP1	Prognostic biomarker	Low ESRP1/RBFOX2 ratio was significantly associated with a higher risk of metastasis ($p < 0.005$) in early BC patients (AUC 0.8375; 95% CI 0.6963–0.9787)	[95]
	ESRP1	Prognostic biomarker	In clinical BC samples, expression of ESRP1 and CD44v, rather than CD44s or total CD44, was positively associated with distant metastasis	[91]
CRC	ESRP1 ESRP2	Prognostic biomarker	Expression of ESRP1 and ESRP2 was significantly associated with favorable overall survival ($p = 0.0186$ and 0.0408). Moreover, prognostic value of ESRP1 is independent of the pathological stage and microsatellite instability	[37]

strongly suggest that ESRP1 is a valuable prognostic biomarker for various BC subtypes, including ER-positive, ER-negative, basal, luminal A, lymph node-positive, and Her2. Fici et al. discovered that the ratio between ESRP1 and RBFOX2 in BC cells decreased during the EMT process and low ESRP1/RBFOX2 ratio was significantly correlated with a higher risk of metastasis ($p < 0.005$) in early BC patients. Moreover, the ratio of ESRP1/RBFOX2 exhibited fairly high specificity in discriminating between tissues from BC patients with no evidence of disease and BC patients with metastatic disease with area under the curve of 0.8375 [95]. These data indicate that the ESRP1/RBFOX2 ratio has significant potential as a new prognostic biomarker for BC. Additionally, Cui et al. discovered that low ESRP1 expression was significantly associated with poor differentiation ($p = 0.01$), tumor stage ($p = 0.042$), and distant metastasis ($p = 0.012$) in NSCLC patients, indicating that ESRP1 plays a prognostic role in NSCLC [49]. The expression of ESRP1 and/or ESRP2 has also demonstrated potential as an independent prognostic biomarker in PCa [109]. Taken together, these findings strongly indicate the potential value of ESRPs as prognostic biomarkers for distinct types of cancer. However, recent studies are still small-scale and in lack of sufficient data support. Large patient cohorts are required to further validate their application as biomarkers in cancer treatment.

Therapeutic potential of ESRPs in cancer

ESRP dysregulation contributes to cancer progression by regulating the various biological behaviors of cancer cells. High ESRP1 expression has been found to promote cellular proliferation, invasion, and metastasis and to inhibit apoptosis in various cancer types, including CRC, BC, OC, and OSCC [43, 58, 112, 125]. However, several other studies have revealed that it inhibits proliferation in cervical carcinoma and induces cellular apoptosis and cell cycle arrest in SCLC [6, 101]. Low ESRP2 expression facilitates cellular proliferation, invasion, metastasis, and EMT and suppresses apoptosis in WT, ccRCC, PA, and HNSCC cells [46, 65, 83, 124]. These studies strongly suggest that ESRPs play vital roles in many aspects of cancer progression. ESRPs have significant potential as therapeutic targets in cancer treatment because of their unique features, such as induction of cell cycle arrest, inhibition on EMT progress, and anti-chemoresistant capability. Since ESRPs are specific targets of a variety of ncRNAs, such as miR-337-3p, circ-0005585, and IFNG-AS1 [14, 58, 65], the therapeutic regulation of ESRP-targeting ncRNAs is considered a promising strategy for improving cancer intervention. Moreover, some endogenous proteins, such as ZEB1/2, Snail, and Twist, have been shown to modulate the expression and activity of ESRPs [47–49]. Targeting these proteins may be another effective strategy for overcoming cancer. In addition, screening natural products or synthesizing novel chemotherapeutic drugs that target ESRPs is also a promising therapeutic strategy for cancer patients. These findings emphasize the importance of ESRPs as promising therapeutic targets or therapeutic agents for cancer patients. However, cancer treatments that target ESRPs are still in the pre-clinical stage. In-depth studies and sufficient clinical data support are required to translate ESRP-based therapeutic strategies into clinical use.

Conclusion and perspective

Cancer is one of the leading malignant diseases worldwide, causing millions of deaths each year. Cancer pathogenesis is extremely complicated and remains largely unknown. Therefore, understanding the mechanisms that regulate cancer progression will aid in the identification of biomarkers and therapeutic targets that will be useful in the development of individual therapeutic strategies for cancer patients. ESRPs are core regulators of the AS of mRNA, and their activity and expression are tightly controlled by an intricate network of ncRNAs and PTMs. ESRPs have been observed to have aberrant expression patterns in various cancer types [45, 123, 124]. Moreover, ESRP dysregulation contributes to cancer progression by regulating a variety of cellular processes, including proliferation, apoptosis, invasion, metastasis, and EMT. They also play crucial roles in the regulation of CSC stemness and the development of drug resistance [87, 116]. ESRPs have great potential as biomarkers and/or therapeutic targets in cancer treatment because of these unique characteristics. Therefore, targeting ESRPs is a promising therapeutic strategy for cancer patients. However, there are still some unsolved challenges that limit the use of ESRPs in cancer treatment. For example, ESRPs have been shown to play crucial roles in normal physiological processes such as tissue development, organogenesis, and spermatogenesis. Targeting ESRPs may trigger a series of uncharted physiological and pathological reactions. Therefore, it is urgent to elucidate the underlying mechanisms of ESRPs in cancer progression before they can be used in formal clinical application. Nevertheless, recent studies have shown that ESRPs have great potential as prognostic biomarkers and therapeutic targets for cancer treatment. Further investigation into their mechanisms in cancer progression could significantly aid in the development of ESRP-based therapeutic strategies for cancer patients.

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