Roles of estrogen receptor α in endometrial carcinoma (Review)

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Abstract. Endometrial carcinoma (EC) is a group of endometrial epithelial malignancies, most of which are adenocarcinomas and occur in perimenopausal and postmenopausal women. It is one of the most common carcinomas of the female reproductive system. It has been shown that the occurrence and development of EC is closely associated with the interaction between estrogen (estradiol, E2) and estrogen receptors (ERs), particularly ERα. As a key nuclear transcription factor, ERα is a carcinogenic factor in EC. Its interactions with upstream and downstream effectors and co-regulators have important implications for the proliferation, metastasis, invasion and inhibition of apoptosis of EC. In the present review, the structure of ERα and the regulation of ERα in multiple dimensions are described. In addition, the classical E2/ERα signaling pathway and the crosstalk between ERα and other EC regulators are elucidated, as well as the therapeutic targeting of ERα, which may provide a new direction for clinical applications of ERα in the future.

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Abbreviations: AF, activation function; AhR, arylhydrocarbon receptor; BAG3, BCL2-associated athanogene 3; BAX, BCL2-associated X protein gene; BCL2, B-cell lymphoma/leukemia-2; Cx, connexin; DBD, DNA binding domain; EC, endometrial carcinoma; EFEMP1, epidermal growth factor-containing fibulin-like extracellular matrix protein 1; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; ERE, E2 response element; ERR, ER-related receptor; E2, estrogen/17-β-estradiol; FBXO45, F-box protein 45; FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; FES, 16α-[^{18}F]fluoro-17β-estradiol; FTO, fat mass and obesity-associated protein; GJIC, gap junctional intercellular communication; GPER, G protein-coupled ER; hnRNPK, heterogeneous nuclear ribonucleic protein K; hPEBP4, human phosphatidylethanolamine-binding protein 4; LBD, ligand-binding domain; MMP, matrix metalloproteinase; NPM, nucleophosmin; OLFM4, olfactomedin 4; Pak4, p21-activated kinase 4; PKCα, protein kinase C α; PPARγ, peroxisome proliferator-activated receptor γ; RCAS1, receptor-binding cancer antigen expressed on SiSo cells; RIZ1, retinoblastoma protein-interacting zinc finger gene 1; SPOP, speckle-type POZ protein

Key words: endometrial carcinoma, estrogen, estrogen receptor a, signaling pathway, regulator

Contents

1. Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies and the sixth most common malignant disease worldwide. Its incidence is increasing year on year, and the age of onset is decreasing (1-3). The incidence of EC in developing countries (5.1/100,000 females) is lower than that in developed countries (13.8/100,000 females), but there is little difference in mortality rates between developed (2.63/100,000 females) and developing countries (1.52/100,000 females) (2,4). In addition, the incidence of EC is increasing in numerous developing countries (5). Data on the global burden of cancer in 2020, released by the International Agency for Research on Cancer, indicate that there were 417,000 new cases of EC and 97,000 deaths associated with EC in 2020 (2).

Based on its pathogenesis and biological behavior, EC can be divided into two types: Estrogen/17-β-estradiol (E2)-dependent EC (type I) and non-E2-dependent EC (type II) (3). The majority of type I ECs are endometrioid carcinomas, which are well differentiated, and a few are mucinous adenocarcinomas (6). Type II includes serous carcinoma and clear cell carcinoma (7). The majority of type II ECs do not express estrogen receptors (ERs) and may develop in a hormone-independent manner (7). The etiology of type I EC includes age, obesity, diabetes, hypertension, polycystic ovary syndrome, anovulation, infertility, nonpregnancy, early age at menarche, late age at menopause, ovarian neoplasms, use of

exogenous estrogens and genetic factors (8,9). However, the main mechanism of its pathogenesis is that atypical hyperplasia of the endometrium occurs followed by carcinogenesis under the long-term stimulatory effect of E2 (10). For example, an early age at menarche, a late age at menopause and ovarian tumors all increase the cumulative exposure of the endometrium to E2, thereby increasing the risk of EC (11). In addition, tamoxifen, which is commonly used in the treatment of breast cancer, can act as an ER agonist and cause endometrial hyperplasia, polyps, cancer or sarcoma in the long term after surgery (12). Regarding type II, there is as yet no consensus on the etiology of precancerous lesions, but p53 mutations and the abnormal amplification of HER-2 are the main causes that are currently known (13). Therefore, from the classification criteria of EC, it may be noted that the occurrence and development of EC, particularly that of type I, are closely associated with E2.

E2 binds specifically with ERs to form a hormone-receptor complex, thus exerting its biological functions (14). There are two groups of ERs. One group includes the classical nuclear receptors ERα and ERβ, which are located in the nucleus and exert their functions by regulating the transcription of specific target genes (15). The other group comprises membranous receptors, including the membrane ER and G protein-coupled ER (GPER) family, which mainly play an indirect transcriptional regulatory function through the second messenger system, and in some cases appear to only have local effects in the brain (15,16). These two types of ER have a tissue/cell-specific distribution in the body and are involved in the regulation of various functions such as reproduction, learning, memory and cognition (15,17).

Of all ERs, ERα was the first to be identified, has been most comprehensively researched and is the most well understood (15). ERα is encoded by the *ESR1* gene mapping to 6q25, and its main function is to stimulate and maintain the development of female reproductive organs and the emergence of secondary sexual characteristics (10,18,19). ERα exists not only in the reproductive tract and breast, but also in the liver, bone, cardiovascular system and brain (18,20). Combining immunohistochemistry with fluorescence *in situ* hybridization, Lebeau *et al* (21) detected the expression of ERα in 100% of 43 cases of endometrial hyperplasia, which is a precursor of EC, and 88.5% of 368 cases of EC. Although ERα is oncogenic in EC, patients with ERα-positive EC have an improved prognosis due to the rapid development of hormone therapy (22,23). In sporadic EC, it has been observed that the expression of ERα is strongly associated with a lower histological grade, and more effective response to hormone therapy in ~80% of EC cases (23). Notably, a search of The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/genes/ENSG00000091831) reveals that ESR1 has the highest mutation frequency in EC, at 4.47%. Among these mutations, those of Y537 are the most numerous, suggesting that ESR1 Y537 mutation may be one of the driving factors for the occurrence and development of EC (Table I).

In the present review, the six domains of ERα and regulation of the *ESR1* gene, ERα mRNA and ERα protein are firstly introduced, respectively. Next, the classical E2/ERα signaling pathway and the role of ERα in EC, according to upstream, co-regulatory and downstream factors, are described in detail. Finally, the clinical significance of ERα in EC is discussed, focusing on ERα-targeted therapy and its role as an indicator of good prognosis of EC.

2. Structure of ERα

ERα is a transcriptional factor composed of 595 amino acids and six different domains: A, B, C, D, E and F (Fig. 1) (24). The A domain (amino acids 1-37) and B domain (amino acids 38-180) constitute the ligand-independent activation function (AF)-1, which is independent of E2 activation (25). However, this functional region may regulate the transcription of E2-responsive genes by participating in the process of E2-ERα binding (25). In general, the primary function of AF-1 is the recruitment of co-regulatory proteins (26). The C domain (amino acids 181-263), which is also known as the DNA binding domain (DBD), contains a double zinc finger structure that contains four cysteines (27). The ERα homodimer binds to the palindromic GGTCA-nnn-TGACC sequence of target genes via the DBD to promote their transcription (28). Additionally, the binding of DBD and DNA is stabilized due to the action of the D domain (amino acids 264-302) (25). The D domain contributes to the recruitment of nuclear localization signal and co-regulatory proteins by coordinating the function of AF-1 and ligand-dependent AF-2 in ERα (29). Moreover, the D domain has been shown to acts as a hinge between the C domain and E domain (amino acids 303-546) (29). The E domain has several functions, such as binding to E2, receptor dimerization and binding to co-activators or co-inhibitors (28). In addition, the E domain constitutes the ligand-binding domain (LBD), containing AF-2 (28). When AF-2 encounters different types of estrogen, it adopts different conformations and determines which co-activators and/or co-suppressors are required for binding during the transcription of target genes (28). AF-1 and AF-2 coordinate with each other to maximize the transcriptional activity of ERα (25). The function of the F domain (amino acids 547-595) is relatively obscure. However, it has been reported that the F domain may be necessary for transcriptional activation and the functioning of anti-E2 drugs such as 4-hydroxytamoxifen (28,30).

ERβ is similar to ERα in protein structure, and also contains A, B, C, D, E and F domains (20). However, the major difference between ERβ and ERα is in AF-1. The activity of AF-1 of ERβ is relatively low, while that of AF-2 is similar to that of ERα, revealing that they have different effects on various E2-responsive genes at the transcriptional level (31,32). Specifically, when AF-1 and AF-2 are both required for gene transcription, the effect of ERβ is weaker than that of ERα, and they are equivalent if only AF-2 is required (32).

3. Regulation of ERα

The regulation of ERα can be divided into three different aspects: Transcription of *ESR1*, translation of ERα mRNA and post-translational modification of ERα protein (33-35). The different types of regulation of ERα can produce divergent effects, and sometimes even opposite results, particularly in the occurrence and development of EC (36,37). Given that the present review focuses on the roles of ERα in EC, the following sections mainly summarize the regulation of ERα in relation to EC (Table II).

Regulation of the transcription of ESR1. Compared with the translational regulation of ERα mRNA and the

Table I. Mutation sites and frequency of estrogen receptor 1 in gynecological tumors.

Cancer	Frequency, % (n/N)	Missense mutation	Synonymous mutation	Other mutation
Endometrial carcinoma	4.47 (28/512)	Y73H, C188R, Y191H, A207T, D218N, E247K, K257R, R263I, R269H, R300H, E330D, G344D, K416N, S463P, Y537C, Y537N, Y537S, D538G, R548H, A551V, R555C, R555H, S576L, K581T	S341=, L448=, S559=, G586=	V422del, G415_C417del
Cervical cancer	1.74 (5/287)	K206R, I298M	S317=, L372=	G77Lfs*6
Breast cancer	1.24 (12/965)	Q17H, P222S, L370F, E380Q, A593D	G274=, L448=, K472=	P29Sfs*79, I451_I452del,
Ovarian cancer	0.48 (2/418)	P336T, P399R	NA	NA

NA, not applicable.

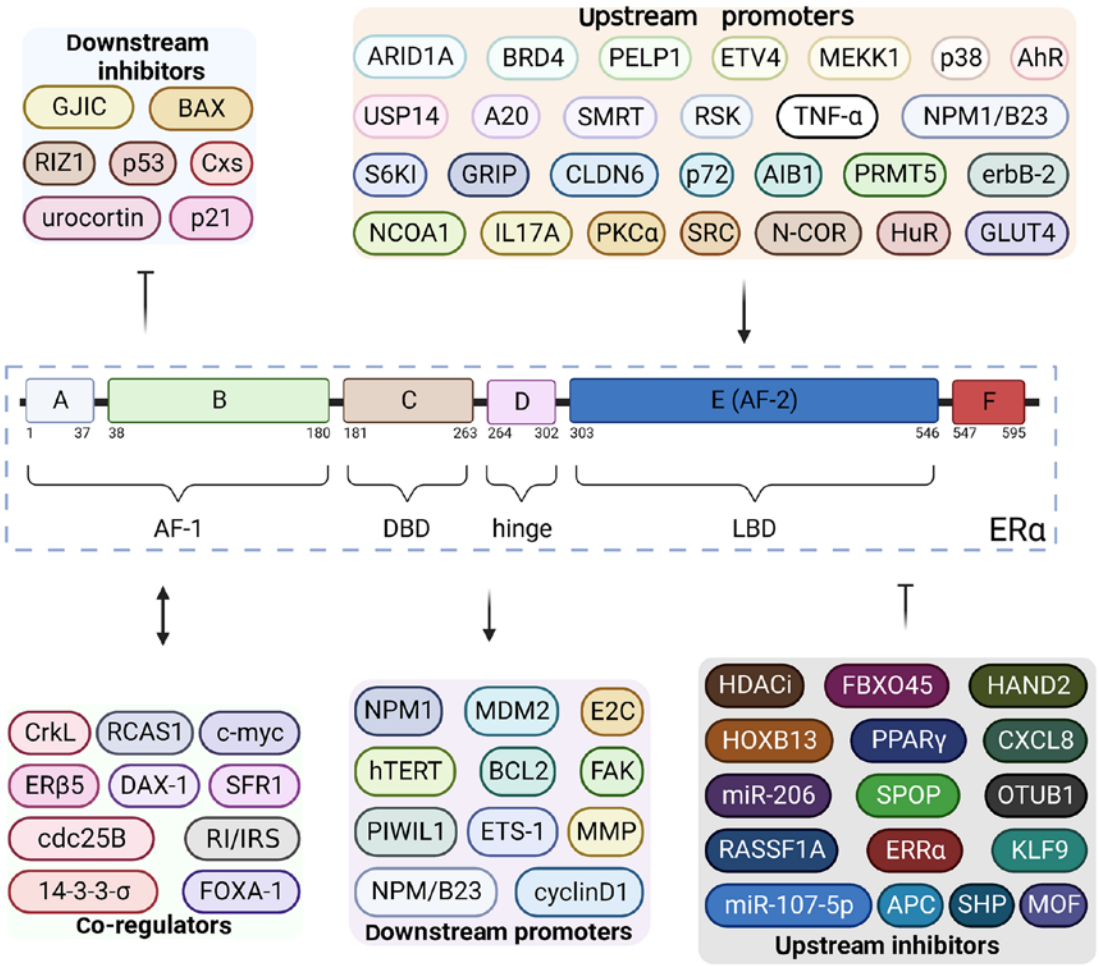

Figure 1. Structure and regulation of ERα. ERα is composed of six domains, A-F, and had upstream, downstream and co-regulators. The upstream and downstream factors include promoters and inhibitors. These regulators can affect the role of ERα in endometrial cancer. ERα, estrogen receptor α.

post-translational modification of ERα protein, the research into the transcriptional regulation of *ESR1* is relatively unclear. However, by the analysis of *ESR1* gene amplification and ERα protein expression in 368 EC tissue microarrays, Lebeau *et al* (21) found that the strong expression of ERα protein was significantly associated with *ESR1* amplification in EC, suggesting that *ESR1* amplification may be a mechanism by which ERα is overexpressed in EC, and could play an important role in the development of a significant proportion of EC cases. Kershah *et al* (38) found that the nuclear receptor co-regulators steroid receptor coactivator (SRC)-1, SRC-2, SRC-3, nuclear receptor corepressor and silencing mediator

Table II. Regulation of ERα in EC.

First author/s, year	Regulation	Regulator	Site	Mode	Effect	(Refs.)
Shiozawa *et al*, 2002	Transcriptional regulation	N/A	CpG island	Methylation	Methylation modification of the CpG island negatively correlates with ERα	(40)
Rocha *et al*, 2005		HDACi	Promoter	N/A	Regulates E2/ERα signaling pathway	(33)
Zhang *et al*, 2015		PPARγ	N/A	N/A	Inhibits the ERα mRNA level and thus reduces the metastasis of EC	(43)
Gao *et al*, 2008		ERRα	N/A	N/A	Interferes with ERα transcription	(39)
Kershah *et al*, 2004		SRC-1	N/A	N/A	Increases ERα mRNA	(38)
Kershah *et al*, 2004		SRC-2	N/A	N/A	Increases ERα mRNA	(38)
Kershah *et al*, 2004		SRC-3	N/A	N/A	Increases ERα mRNA	(38)
Kershah *et al*, 2004		N-COR	N/A	N/A	Increases ERα mRNA	(38)
Kershah *et al*, 2004		SMRT	N/A	N/A	Increases ERα mRNA	(38)
Zhang *et al*, 2015	Translational regulation	PPARγ	N/A	N/A	Inhibits ERα protein level and thus reduces the metastasis of EC.	(43)
Hirschfeld *et al*, 2015		HNRNPG	Exon7	N/A	Antagonizes exon7 inclusion by inducing exon7 skipping	(171)
Hirschfeld *et al*, 2015		HTRA2-b1	Exon7	N/A	Promotes exon7 inclusion	(171)
Chen *et al*, 2012		miR-206	3'-UTR	N/A	Inhibits proliferation and invasion, and induces cell cycle arrest	(34)
Bao *et al*, 2019		miR-107-5p	3'-UTR	N/A	Promotes proliferation and invasion	(36)
Liu *et al*, 2014; Song *et al*, 2019		miR-222-3p	3'-UTR	N/A	Promotes proliferation and invasion, and increases raloxifene resistance	(41,42)
Kato *et al*, 1995	Post-translational modification	MAPK	S118	Phosphorylation	Important for the full activity AF-1	(50)
Hermon *et al*, 2008		Phosphorylated p44/42 MAPK	S118	Phosphorylation	Promotes uterine leiomyoma cell growth	(35)
Uchida *et al*, 2020		Phosphorylated AKT S473, phosphorylated AKT T308	S104, S118, S167	Phosphorylation	Regulates the apoptosis of endometrial cells and arterioles	(44)
Vilgelm *et al*, 2006		AKT	S167	Phosphorylation	Promotes the transcriptional activity of ERα and promotes EC	(51)
Kato *et al*, 2014		S6K1, RSK	S167	Phosphorylation	Provides a strong stimulus for the growth of EC	(52)
Lee and Bai, 2002		p38 immunocomplex	T311	Phosphorylation	Promotes the nuclear localization of ERα and the interaction between ERα and steroid receptor co-activators	(53)
Zhang *et al*, 2015		SPOP	AF-2	Ubiquitination	Inhibits the development of EC	(45)
Han *et al*, 2016		FBXO45	NA	Ubiquitination	Inhibits the development of EC	(55)
Ohtake *et al*, 2009		AhR	AF-1	Ubiquitination	Enhances the ubiquitination and degradation of ERα	(54)

Table II. Continued.

First author/s, year	Regulation	Regulator	Site	Mode	Effect	(Refs.)
Stanišić *et al*, 2009		OTUB1	C/D domain	De-ubiquitination	Inhibits the transcriptional activity of ERα and the development of EC	(172)
Su *et al*, 2023		USP14	N/A	De-ubiquitination	Promotes the development of EC	(56)
Lv *et al*, 2019		A20	N/A	De-ubiquitination	Promotes the development of EC	(57)
Wu *et al*, 2019		MOF	N/A	Acetylation	Inhibits the proliferation of EC cells	(37)

A20, ubiquitin-editing enzyme A20; AF, activation function; AhR, arylhydrocarbon receptor; E2, estrogen/estradiol; EC, endometrial carcinoma; ERα, estrogen receptor α; ERRα, estrogen receptor-related receptor α; FBXO45, F-box protein 45; HDACi, histone deacetylase inhibitor; HNRNPG, heterogeneous nuclear ribonucleoprotein G; HTRA2-β1, high-temperature requirement serine protease A2-β1; miR, microRNA; MOF, males absent on the first; N/A, not applicable; N-COR, nuclear receptor corepressor; OTUB1, OUT deubiquitinase, ubiquitin aldehyde binding 1; PPARγ, peroxisome proliferator-activated receptor γ; RSK, ribosomal S6 kinase; S6K1, S6 kinase 1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; SPOP, speckle-type POZ protein; SRC, steroid receptor coactivator; USP14, ubiquitin-specific protease 14; UTR, untranslated region.

of retinoic acid and thyroid hormone receptor significantly increased mRNA expression in EC and were highly correlated with ERα mRNA, indicating that these regulatory factors may be associated with EC. Conversely, it has been suggested that ER-related receptor (ERR)α may regulate ERα-mediated pathways by interfering with *ERα* transcription (39). Also, in EC, methylation of the CpG island of the *ESR1* gene has been found to be negatively associated with ERα expression (40). In addition, histone deacetylase (HDAC) inhibitors directly inhibit the transcription of *ESR1* promoters and thus regulate the E2/ERα signaling pathway (33).

Regulation of the translation of ERα mRNA. Studies on translational regulation have mainly focused on the regulation of ERα mRNA by microRNAs (miRNAs or miRs). Bao *et al* (36) showed that miR-107-5p directly targets ERα mRNA to downregulate the expression of ERα mRNA and protein, thereby promoting tumor proliferation and EC invasion. Similarly, other studies have shown that miR-222-3p downregulates the expression of ERα, thereby promoting the proliferation and invasion of EC and increasing raloxifene resistance (41,42). Furthermore, miR-206 has been reported to inhibit ERα-dependent proliferation, impair the invasion ability of ERα-positive EC cells, and induce cell cycle arrest, indicating that abnormal miR-206 expression may be associated with the occurrence of EC (34). In addition to miRNA, a study by Zhang *et al* (43) confirmed that the stimulation of peroxisome proliferator-activated receptor γ (PPARγ) expression inhibited ERα expression at the mRNA and protein levels, and impaired the ability of Ishikawa cells to migrate and invade. Therefore, activation of PPARγ may enhance the effects of anti-E2 therapy in ERα-positive EC through ERα-mediated ER transactivation (43).

Regulation of the post-translational modification of ERα protein. The post-translational modification of ERα includes phosphorylation, ubiquitination, acetylation, sumoylation, methylation and glycosylation, among which phosphorylation, ubiquitination and acetylation are associated with EC development (37,44-48). Phosphorylation of ERα generally regulates the transcriptional activity of ERα by regulating the interaction between the AF domain and transcription co-activators (Fig. 1) (49). Kato *et al* (50) showed that MAPK-mediated phosphorylation of ERα S118 is necessary for the activity of AF-1, *in vivo and in vitro*. Furthermore, another study demonstrated that the phosphorylation of ERα S118 mediated by MAPK signaling pathway promotes uterine leiomyoma cell growth (35). Vilgelm *et al* (51) found that the deletion of Pten activates AKT in mouse endometrium, which leads to an increase in the phosphorylation of ERα S167, thereby increasing the ability of ERα to activate the transcription of several target genes. Similarly, Kato *et al* (52) found that the mTOR/p70 S6 kinase 1 and MAPK/p90 ribosomal S6 kinase signaling pathways co-regulate the phosphorylation of ERα at S167, and the levels of such phosphorylation are elevated in advanced EC. In the normal endometrium during the menstrual cycle, phosphorylation of ERα at S104, S118 and S167 synergizes with the phosphorylation of AKT at S473, while the phosphorylation of AKT at T308 regulates apoptosis in endometrial cells and arterioles (44). It has also been shown that the p38-MAKP-mediated signaling pathway induces the phosphorylation of ERα T311, which blocks ERα nuclear export and promotes the interaction between ERα and steroid receptor co-activator p160 (53).

Ubiquitination of ERα is mainly mediated by speckle-type POZ protein (SPOP), F-box protein 45 (FBXO45) and arylhydrocarbon receptor (AhR) (45,54,55). SPOP specifically recognizes the AF-2 domain of ERα and triggers ERα degradation through the ubiquitin-proteasome system, thereby inhibiting the development of EC (45). Similarly, the E3 ligase FBXO45 inhibits the progression of EC by mediating the ubiquitination and degradation of ERα (55). AhR has been shown

to promote the ubiquitination and degradation of ERα via the assembly of a complex with cullin 4B (CUL4B) (54). In the CUL4B-AhR complex, AhR acts as a substrate recognition subunit that recruits ERα for degradation (54). By contrast, de-ubiquitination meditated by de-ubiquitinating enzymes, including ubiquitin-specific protease 14 and ubiquitin-editing enzyme A20, promotes the transcriptional activity of ERα by inhibiting its degradation, thereby leading to the development of EC (56,57). Regarding the acetylation of ERα, Wu *et al* (37) demonstrated that males absent on the first (MOF), also known as lysine acetyltransferase 8, mediates the acetylation of ERα, maintains the stability of ERα, and regulates the activity of ERα and its target genes. However, the study also indicated that MOF inhibits the proliferation of EC cells (37).

4. Classical E2/ERα signaling pathway

E2 and the ER are known to mediate two types of signaling pathways (58). One of these is mediated by nuclear ERs and is known as the genomic, classical or nuclear signaling pathway, and the other is mediated by membrane ERs and is referred to as the non-genomic, non-classical or extra-nuclear signaling pathway (58,59). Since the present review is focused on ERα, which belongs to the superfamily of nuclear receptors, only the classical E2/ERα signaling pathway is outlined here (Fig. 2).

The classical E2/ERα signaling pathway regulates the transcription of target genes through two different approaches, namely the classical and non-classical approaches, both of which can be divided into three steps, which differ most markedly in the third step (29). First, E2 either diffuses into the cell or is synthesized *in situ* inside the cell (60). Second, E2 enters the nucleus where it binds to and activates ERα to form a homologous or heterodimer of ERα (60). In the classic approach, the third step is that the activated ERα binds to E2 response elements (EREs), which comprise two AGGTCA motifs in a palindromic structure (39). The ERα-ERE complex promotes the formation of transcription initiation complexes and induces the transcription of target genes (39). In addition, *in vivo* pioneer factors initiate chromatin remodeling by opening up the chromatin structure to facilitate the binding of activated ERα with EREs, and co-regulators act synergistically with ERα to enhance or reduce the expression of specific genes, which play an important role in the occurrence and development of EC (61). However, in the third step of the non-classical approach, activated ERα does not directly bind to the promoter region of the target genes (29). Instead, ligand-bound receptor dimers first interact with other transcriptional factors, such as Fos or Jun, for transcriptional activation (29). ERα then binds to enhancer elements such as activating protein 1 and specific protein 1 in the promoter region of target genes to indirectly regulate the transcription of target genes (29).

The classical E2/ERα signaling pathway plays a key role in the occurrence and development of EC. For instance, ERα mediates E2-stimulated IL-6 production, which induces aromatase expression in stromal cells, thereby producing E2 *in situ*, which forms a positive feedback loop by which E2 promotes cancer progression (62). In addition, ERα also binds EREs and co-activators with ERRα (63). However, E2 down-regulates the expression of ERRα at the mRNA and protein levels in Ishikawa cells by a mechanism involving ERα (64). ERRα competes with ERα for the same target gene loci and co-regulators, which interferes with the E2/ERα signaling pathway and thereby potentially suppresses the development of EC (39).

5. Roles of ERα in EC

ERα is generally considered to play a driving role in endometrial malignant transformation, which has three main aspects (Fig. 1) (65). First, upstream regulators of ERα regulate the transcriptional activity of ERα and thus influence the development of EC, especially cell proliferation (66). Second, ERα promotes the occurrence of EC together with other co-regulators (67). Third, ERα mediates EC proliferation, metastasis and apoptosis through its downstream proteins or target genes (68).

Upstream of ERα. Several upstream proteins of ERα participate in the occurrence and development of EC by affecting the transcriptional activity and expression of ERα (Table III). Since the proteins that mediate the post-translational modifications of ERα have been summarized previously in the present review, they are not covered again in this section.

Most of the upstream regulators promote the development of EC by enhancing the transcriptional activity of ERα. For example, the increased expression of co-activators p72 and amplified in breast cancer 1 (AIB1), as well as the interaction between erbB-2 and p72, have been suggested to enhance the interaction between E2 and ERα, thereby inducing the transactivation of ERα in EC; this suggests that transactivation of ERα induced by the overexpression of p72, AIB1 and erbB-2 may be involved in the development of EC stimulated by tamoxifen (69). Similarly, interaction between p21-activated kinase 4 (Pak4) and the E2/ERα signaling pathway has been shown to trigger the proliferation of EC cells (66). Specifically, E2 increases the expression and activation of Pak4 in ERα-positive EC cells via the PI3K/AKT/mTOR signaling pathway, and the accumulation of Pak4 and phosphorylated Pak4 in the nucleus promotes ERα transactivation, which enhances the transcriptional activity of ERα and ERα-dependent gene expression, leading to EC cell proliferation (66). Although these upstream regulators of ERα mainly promote the proliferation of EC, they have also been shown to have some effects on migration (70,71). In addition, protein kinase C α (PKCα) expression stimulates the ligand-independent activation of ER-dependent promoters to enhance the transcriptional capacity of ERα, thereby inducing endometrial proliferation (72). Furthermore, Frigo *et al* (73) showed that p38 promotes the proliferation of EC cells by stimulating ERα-mediated transcription via phosphorylation of the co-activator glucocorticoid receptor-interacting protein 1. With regard to migration, Kojima *et al* (74) demonstrated that claudin 6/Src-family kinase/PI3K-dependent AKT and serum- and glucocorticoid-regulated kinase signaling in EC cells targets ERα Ser518 in a ligand-independent manner to activate the transcriptional activity of ERα, thereby promoting tumor migration. In addition, mitogen-activated protein kinase kinase kinase 1 also induces the transcriptional activity of ERα through the N-terminal kinase of Jun and p38/Hog1, thereby stimulating the excitatory activity of 4-hydroxytamoxifen in the endometrium (75). There are also

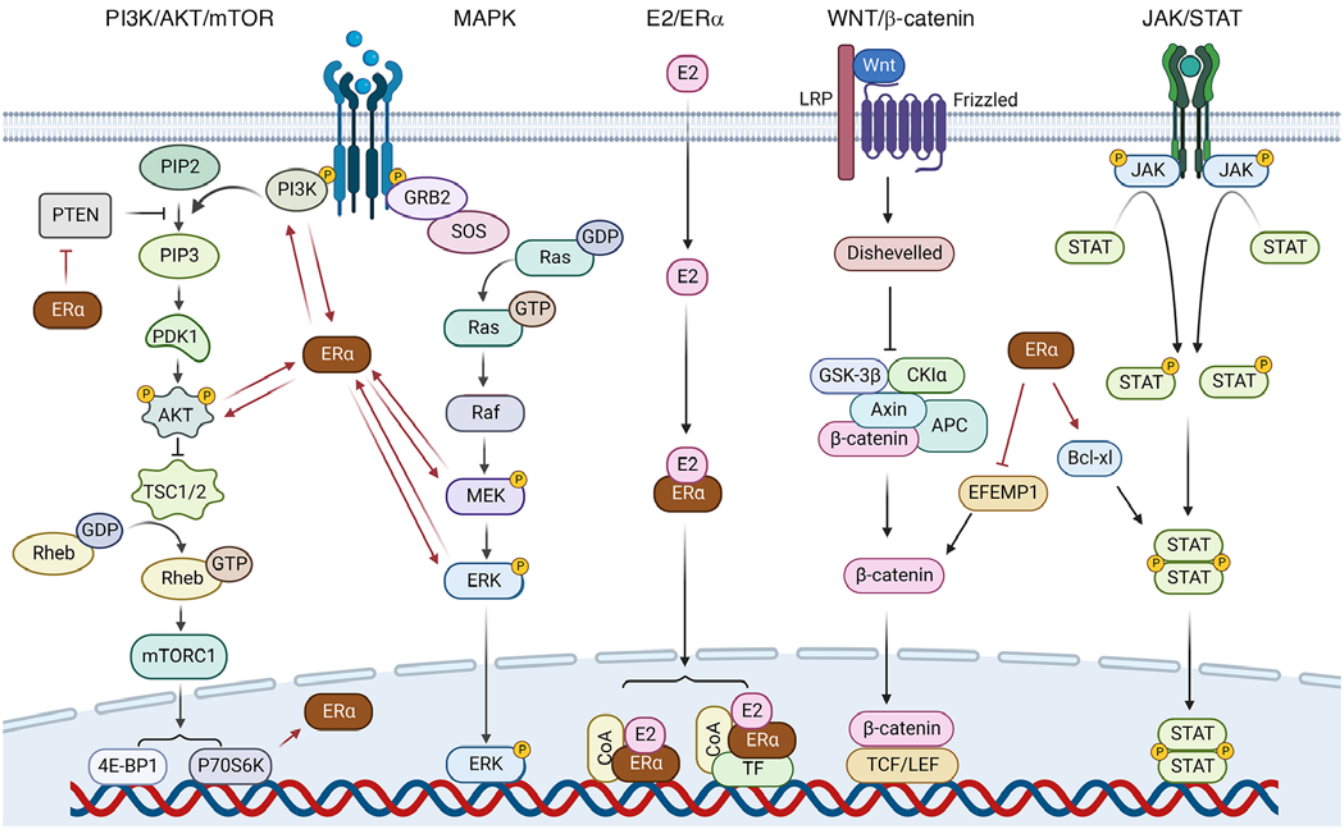

Figure 2. Signaling pathways associated with ERα. ERα is mainly involved in the E2/ERα signaling pathway, which includes classical and non-classical approaches. In addition, ERα regulates the PI3K/AKT/mTOR, MAPK, WNT/β-catenin and JAK/STAT signaling pathways. ERα, estrogen receptor α; E2, estrogen/estradiol.

negative upstream regulators that inhibit the transcription of ERα and thus inhibit EC development. For example, the activation of Pten and subsequent inhibition of AKT have an inhibitory effect on several ERα-dependent pathways, which suppresses the development of EC (76). Moreover, Velard *et al* (77) demonstrated that Krüppel-like factor 9 inhibited the transcriptional activity of ERα in endometrial epithelial cells, and suggested that it acts at a node of the ERα genomic pathway to negatively regulate the proliferation of EC.

Another means by which upstream regulators regulate ERα is by affecting the expression of ERα. For example, Cheng *et al* (78) found that interleukin 17A induced the proliferation and metastasis of EC cells by promoting the expression of ERα. Likewise, human antigen R has been reported to increase the expression of ERα protein in Ishikawa cells, thereby promoting proliferation and inhibiting apoptosis (79). In addition, hyperglycemia-induced glucose transport protein 4 expression has been shown to increase the secretion of vascular endothelial growth factor (VEGF) and the expression of its receptor VEGFR via the upregulation of ERα, leading to accelerated epithelial-mesenchymal transition (EMT) in EC (80). Conversely, the inhibition of ERα expression delays the development of EC. For example, the downregulation of ERα by RAS association domain family 1 subtype A induces EC cell apoptosis and inhibits EC growth (81). However, some upstream regulators have been suggested to promote the development of EC by inhibiting ERα expression. For example, Tanwar *et al* (82) showed that reduced adenomatous polyposis coli activity in mouse uterine stromal cells led to transformation of the cells to a myofibroblast phenotype, which reduced ERα expression and induced EC. In addition, another study demonstrated that chemokine C-X-C motif chemokine ligand 8 (CXCL8) promoted the development of EC via the inhibition of ERα expression (83). Specifically, CXCL8 secreted by tumor-associated macrophages was shown to downregulate the expression of ERα in EC cells via homeobox 13, which was associated with the invasive ability of the cells (83).

Co-regulators of ERα. ERα contributes to the occurrence and development of EC via interactions with several proteins, such as receptor-binding cancer antigen expressed on SiSo cells (RCAS1), and by crosstalk with signaling pathways including the MAPK signaling pathway and insulin/insulin receptor signaling pathway (Table III) (84-87). For example, ERα and ERβ5 have been found to be co-expressed in the nuclei of endometrial adenocarcinoma cells, and to form heterodimers that enhance the hormone sensitivity of Ishikawa cells, thereby promoting the development of EC (88). Moreover, Bircan *et al* (89) demonstrated by immunohistochemical analysis that ERα expression was positively correlated with c-myc expression, suggesting that c-myc expression may contribute to the development of EC through ERα. With regard to specific effects, ERα has been suggested to influence the proliferation, invasion and metastasis of EC cells through interaction with various proteins or signaling pathways (86,90).

Table III. Upstream mediators, co-regulators and downstream mediators of ERα.

First author/s, year	ERα	Regulator	Result	Effect on EC	(Refs.)
Zhao *et al*, 2008	Upstream	p72 and AIB1	Enhances ERα transactivation	Promotes development	(69)
Zhao *et al*, 2008		p72 and erbB-2	Enhances ERα transactivation	Promotes development	(69)
Su *et al*, 2017		Pak4	Enhances ERα transactivation	Promotes proliferation	(66)
Mei *et al*, 2021		PRMT5	Enhances ERα transcriptional activity	Promotes development	(173)
Kojima *et al*, 2021		CLDN6	Enhances ERα transcriptional activity	Promotes development	(74)
Tong *et al*, 2019		NCOA6	Enhances ERα transcriptional activity	Promotes development	(174)
Gori *et al*, 2011		TNF-α	Enhances ERα transcriptional activity	Promotes development	(175)
Hu *et al*, 2020		ARID1A	Enhances ERα transcriptional activity	Promotes development	(176)
Thorne *et al*, 2013		PKCα	Enhances ERα transcriptional activity	Promotes proliferation	(72)
Frigo *et al*, 2006		p38	Enhances ERα transcriptional activity	Promotes proliferation	(73)
Nagarajan *et al*, 2014		BRD4	Enhances ERα transcriptional activity	Promotes proliferation	(70)
Vadlamudi *et al*, 2004		PELP1	Enhances ERα transcriptional activity	Promotes proliferation	(71)
Rodriguez *et al*, 2020		ETV4	Enhances ERα transcriptional activity	Promotes proliferation	(177)
Lee *et al*, 2000		MEKK1	Enhances ERα transcriptional activity	Mediates the agonistic activity of 4-hydroxytamoxifen on EC	(75)
Kojima *et al*, 2021		AKT and SGK signaling pathway	Enhances ERα transcriptional activity	Promotes migration	(74)
Velarde *et al*, 2007		KLF9	Inhibits ERα transcriptional activity	Inhibits proliferation	(77)
Lian *et al*, 2006		Pten	Inhibits ERα transcriptional activity	Inhibits development	(76)
Ring *et al*, 2017		MEK	Inhibits ERα transcriptional activity	Inhibits development	(178)
Fukuda *et al*, 2015		HAND2	Inhibits ERα transcriptional activity and promotes ERα degradation	Inhibits development	(179)
Lin *et al*, 2016		NPM1	Inhibits ERα transcriptional activity and expression	Induces resistance to hormone therapy	(135)
Klinge *et al*, 2002		SHP	Inhibits ERα transcriptional activity and dimerization	Inhibits proliferation	(180)
Gu *et al*, 2018		GLUT4	Enhances ERα expression	Promotes EMT	(80)
Cheng *et al*, 2020		IL-17A	Enhances ERα expression	Promotes proliferation and metastasis	(78)
Wang *et al*, 2014		HuR	Enhances ERα expression	Promotes proliferation and inhibits apoptosis	(79)
Tanwar *et al*, 2021		APC	Inhibits ERα expression	Inhibits development	(82)
Tong *et al*, 2016		CXCL8	Inhibits ERα expression	Promotes invasion and metastasis	(83)
Nan *et al*, 2018		RASSF1A	Inhibits ERα expression	Promotes apoptosis and inhibits proliferation	(81)

Table III. Continued.

First author/s, year	ERα	Regulator	Result	Effect on EC	(Refs.)
Collins *et al*, 2020	Co-regulator	ERβ5	Forms a heterodimer with ERα	Promotes development	(88)
Wincewicz *et al*, 2011		STAT3 and BCL-xL	Interacts with STAT3 and BCL-xL	Promotes development	(112)
Feng *et al*, 2013		SFR1	Interacts with ERα	Promotes development	(181)
Wu *et al*, 2003		Cdc25	Interacts with ERα	Promotes development	(182)
Bircan *et al*, 2005		c-myc	Interacts with ERα	Promotes development	(89)
Padmanabhan *et al*, 2011		CrkL	Interacts with ERα	Promotes proliferation	(183)
Saito *et al*, 2005		DAX-1	Interacts with ERα	Inhibits proliferation	(87)
Wang *et al*, 2014		FOXA1	Interacts with ERα	Inhibits proliferation	(91)
Zhou *et al*, 2008		RCAS1	Interacts with ERα	Promotes metastasis	(84)
Tian *et al*, 2019		Insulin/insulin receptor signaling pathway	Crosstalk with ERα	Promotes development	(85)
Zhang *et al*, 2019		EGFR/ERK signaling pathway	Crosstalk with ERα	Promotes development and resistance to chemotherapy	(86)
Nakayama *et al*, 2005		14-3-3σ	Synergistic effect with ERα	Promotes proliferation and inhibits apoptosis	(90)
Chen *et al*, 2020	Downstream	PIWIL1	Upregulates PIWIL1	Promotes proliferation	(92)
Zhang *et al*, 2012		BCL2	Upregulates BCL2	Promotes proliferation	(95)
Chao *et al*, 2013		NPM	Upregulates NPM	Promotes proliferation	(96)
Hu *et al*, 2020		Cyclin D1	Upregulates cyclin D1	Promotes proliferation	(97)
Zhang *et al*, 2012		BAX	Downregulates BAX	Promotes proliferation	(95)
Hu *et al*, 2020		p21	Downregulates p21	Promotes proliferation	(97)
Saito *et al*, 2004		GJIC	Downregulates GJIC	Promotes proliferation	(98)
Mizumoto *et al*, 2002		MMP-1, -7, -9	Upregulates MMP-1, -7, -9	Promotes invasion and metastasis	(102)
Mizumoto *et al*, 2002		ETS-1	Upregulates ETS-1	Promotes invasion and metastasis	(102)
Flamini *et al*, 2011		FAK	Upregulates FAK	Promotes invasion and metastasis	(93)
Liu *et al*, 2020		E2C	Upregulates E2C	Promotes invasion and metastasis	(103)
Yang *et al*, 2016		EFEMP1	Downregulates EFEMP1	Promotes invasion and metastasis	(106)
Owens *et al*, 2017		RIZ1	Downregulates RIZ1	Promotes invasion and metastasis	(108)
Yang *et al*, 2017		Urocortin	Downregulates urocortin	Promotes invasion and metastasis	(107)
Abe *et al*, 2011		AKT	AKT nuclear localization	Inhibits apoptosis	(111)
Sayeed *et al*, 2007		p53	Downregulates p53	Inhibits apoptosis	(94)
Sulkowska *et al*, 2015		Cx43	Downregulates Cx43	Influences apoptosis	(113)
Sulkowska *et al*, 2015		Cx26	Downregulates Cx26	Influences apoptosis	(113)
Abe *et al*, 2021		miR-29b	Downregulates miR-29b	Induces drug resistance	(114)
Abe *et al*, 2021		BAG3	Upregulates BAG3	Induces drug resistance	(114)
Abe *et al*, 2021		Mcl-1	Upregulates Mcl-1	Induces drug resistance	(114)

Table III. Continued.

First author/s, year	ERα	Regulator	Result	Effect on EC	(Refs.)
Ali *et al*, 2000		Angiogenic factor	Downregulates angiogenic factor	Inhibits cancer blood vessel formation	(148)
Suga *et al*, 2007		MDM2	Downregulates p21	Promotes development	(184)
Duan *et al*, 2014		OLFM4	Downregulates OLFM4	Inhibits development	(147)
Boggess *et al*, 2006		hTERT	Promotes hTERT gene transcription and telomerase activation	Promotes malignant transformation	(185)
Chen *et al*, 2018		miR-200c	Upregulates miR-200c	Promotes proliferation and inhibits apoptosis	(100)
Chen *et al*, 2018		Pten	Downregulates Pten	Promotes proliferation and inhibits apoptosis	(100)
Zhou *et al*, 2014		NPM1	Upregulates NPM1	Promotes proliferation, inhibits differentiation and inhibits apoptosis	(3)
Hou *et al*, 2014		p58α	Activates the PI3K/AKT/mTOR signaling pathway	Promotes proliferation, migration and invasion	(68)
Zhu *et al*, 2016; Zhang *et al*, 2012		PI3K/AKT/mTOR signaling pathway	Nuclear localization and nuclear accumulation of FTO	Promotes proliferation, invasion and metastasis	(99, 104)
Jing *et al*, 2019		PI3K/AKT/mTOR signaling pathway	Upregulates KIF5B	Promotes metastasis	(186)

AIB1, amplified in breast cancer 1; APC, adenomatous polyposis coli; ARID1A, AT-rich interactive domain-containing protein 1A; BAG3, BCL2-associated athanogene 3; BAX, BCL2-associated X protein gene; BCL2, B-cell lymphoma/leukemia-2; BCL-xL, BCL-extra large; BRD4, bromodomain-containing protein 4; cdc25, cell division cycle 25; CLDN6, claudin 6; Cx, connexin; CrkL, CRK like protein; CXCL8, C-X-C motif chemokine ligand 8; DAX-1, dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; EFEMP1, epidermal growth factor-containing fibulin-like extracellular matrix protein 1; EC, endometrial carcinoma; ERα, estrogen receptor α; EGFR, epidermal growth factor receptor; ETV4, ETS variant transcription factor 4; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; FOXA1, Forkhead-box A1; FTO, fat mass and obesity-associated protein; GJIC, gap junctional intercellular communication; GLUT4, glucose transport protein 4; HAND2, hand- and neural crest derivatives-expressed 2; hTERT, human telomerase reverse transcriptase; HuR, human antigen R; IL-17A, interleukin 17A; KLF9, Krüppel-like factor 9; Mcl-1, myeloid cell leukemia 1; MDM2, E3 ubiquitin-protein ligase Mdm2; MEKK4, mitogen-activated protein kinase kinase kinase 1; miR, microRNA; MMP, matrix metalloproteinase; NCOA6, nuclear receptor co-activator 6; NPM, nucleophosmin; OLFM4, olfactomedin 4; Pak4, p21-activated kinase 4; PELP1, proline-, glutamate- and leucine-rich protein 1; PIWIL1, Piwi-like RNA-mediated gene silencing 1; PKCα, protein kinase C α; PRMT5, protein arginine methyltransferase 5; RASSF1A, RAS association domain family 1 subtype A; RCAS1, receptor-binding cancer antigen expressed on SiSo cells; RIZ1, retinoblastoma protein-interacting zinc finger gene 1; SFR1, SWI5 dependent homologous recombination repair protein; SGK, serum- and glucocorticoid-regulated kinase; SHP, short heterodimer partner.

Nakayama *et al* (90) observed an inverse correlation between ERα and 14-3-3σ, and speculated that these proteins have a synergistic effect that promotes EC proliferation and prevents apoptotic signal transduction in high-grade and middle-advanced endometrial adenocarcinoma. Furthermore, Zhou *et al* (84) demonstrated that the co-expression of RCAS1 and ERα may be involved in the development and metastasis of EC. Crosstalk between ERα and the MAPK signaling pathway has been suggested to be associated with the phenotypic plasticity of EC cells triggered by chronic 2,2',4,4'-tetrabromodiphenyl ether exposure, which promoted EC tumor growth and attenuated the resistance of EC cells to chemotherapy (86). Similarly, crosstalk between the E2/ERα signaling pathway and the insulin/insulin receptor signaling pathway has been demonstrated to activate downstream PI3K/AKT/mTOR and MAPK signaling pathways, thereby contributing to occurrence and development of EC (85).

However, interactions between ERα and certain other proteins may inhibit EC cell proliferation (87,91). For example, Saito *et al* (87) suggested that an orphan nuclear receptor known as dosage-sensitive sex reversal adrenal hypoplasia congenita critical region on the X chromosome gene 1 inhibits the proliferation and progression of EC by interacting with ERα in EC cells. Additionally, ERα and Forkhead-box A1, which is a tumor suppressor, have been demonstrated to interact in EC cells, and to inhibit the proliferation of EC cells (91).

Downstream of ERα. In addition to the upstream and co-regulators of ERα, downstream proteins or target genes are also involved in the promotion of EC development by ERα. These mainly contribute to three aspects: Proliferation, metastasis and invasion, and anti-apoptosis (Table III) (92-94).

Proliferation. ERα has been shown to induce the proliferation of EC cells via the promotion or inhibition of downstream substrates. For example, Chen *et al* (92) found that in EC cells, ERα binds to a half-ERE on the promoter of the gene encoding the stem cell protein Piwi-like RNA-mediated gene silencing 1 (PIWIL1), thereby upregulating the expression of PIWIL1 (92). The authors also found that upregulated PIWIL1 promoted the proliferation of EC cells, and that this effect was closely associated with hypomethylation of the *PIWIL1* promoter (92). Similarly, ERα activates the promoter of the B-cell lymphoma/leukemia-2 (*BCL2*) gene to increase the transcription of BCL2, and also downregulates the expression of BCL2-associated X protein gene (BAX) via several miRNAs, thus leading to an imbalance of the BCL2/BAX ratio that promotes the proliferation of EC (95). In addition, in primary cultured human endometrial adenocarcinoma cells, E2 has been demonstrated to upregulate the expression of nucleophosmin 1 (NPM1) in a dose-dependent manner through ERα-mediated signaling rather than via ERβ, with the upregulation of NPM1 promoting the growth and proliferation of the cells and inhibiting their differentiation and apoptosis (3). It has also been shown that the E2/ERα signaling pathway inhibits the formation of an NPM-alternate reading frame complex, resulting in increased levels of NPM protein, which promote the proliferation of endometrial tissues and tumors (96). Additionally, ERα up- and downregulates the expression levels of cyclin D1 and p21, respectively, which induces dysregulation of the cell cycle and triggers the proliferation of EC cells (97). Furthermore, ERα has also been indicated to downregulate gap junctional intercellular communication (GJIC) mediated by the formation of gap junctions by connexins (Cxs), which is important in cell growth, differentiation, homeostasis and morphogenesis (98). Saito *et al* (98) showed that the activation of ERα by E2 stimulated cell growth and inhibited GJIC by inhibiting the expression of Cxs, leading to the proliferation of EC cells.

ERα can also promote the proliferation of EC cells via the activation of certain downstream signaling pathways (Fig. 2). For example, Hou *et al* (68) found that ERα overexpression promotes the phosphorylation of p85α, the regulatory subunit of PI3K, which activates the PI3K/AKT/mTOR signaling pathway, thereby increasing the proliferation, migration and invasion of EC cells. Moreover, another study demonstrated that the activation of ERα by E2 induces the nuclear localization and accumulation of fat mass and obesity-associated protein (FTO) through the PI3K/AKT/mTOR signaling pathway, which increases the proliferation of EC cells (99). Furthermore, the E2/ERα signaling pathway has been shown to increase the expression of miR-200c and decrease the expression of Pten, leading to activation of the PI3K/AKT/mTOR signaling pathway, thus promoting the proliferation of EC cells and inhibiting their apoptosis (100). Moreover, when stimulated by E2, cytoplasmic ERα forms a complex with protein kinase 2-α, which mediates the phosphorylation of Pten and promotes EC cell proliferation (101).

Invasion and metastasis. Invasion and metastasis are also affected by ERα through its downstream substrates, either directly or indirectly. In a Transwell experiment, Mizumoto *et al* (102) found that stimulation with E2 increased the invasive ability of Ishikawa cells, while the expression levels of matrix metalloproteinase (MMP)-1, -7 and -9 and the transcriptional factor ETS-1 were also enhanced. These results indicate that the activation of ERα stimulates EC cell invasiveness and tumor progression by promoting the expression of MMPs (102). In endometrial stromal cells and Ishikawa cells, E2 has been shown to promote cytoskeletal and membrane remodeling by the activation of focal adhesion kinase, thus increasing the motility and invasion of the cells (93). Furthermore, E2 upregulates the expression of ubiquitin-binding enzyme E2C via ERα in EC, which downregulates the expression of p53 and its downstream effector p21, thus promoting EC metastasis and invasion (103). In addition to playing a role in proliferation, the activation of FTO via E2/ERα also stimulates the invasion of EC cells through the PI3K/AKT/mTOR and MAPK signaling pathways (104). However, Wik *et al* (105) found that ERα-negative tumors are also associated with EMT, which is linked to the PI3K/AKT/mTOR signaling pathway. In addition to the aforementioned substrates, ERα also inhibits epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (EFEMP1), retinoblastoma protein-interacting zinc finger gene 1 (RIZ1) and urocortin to promote EC cell mobility (106-108). Using chromatin immunoprecipitation and dual-luciferase reporter assays, Yang *et al* (106) demonstrated that the E2/ERα signaling pathway downregulated EFEMP1 expression in EC cells by the direct binding of ERα to the EFEMP1 promoter. Given that EFEMP1 was also shown to inhibit EMT and the migration of EC cells via inhibition of the WNT/β-catenin signaling pathway, it was suggested that EFEMP1 may be an excellent candidate for EC therapy (106). The activation of ERα reduces the expression of urocortin, a protein that inhibits EC cell migration; therefore, the E2/ERα pathway may promote EC cell invasion and metastasis via this mechanism (108). Furthermore, RIZ1 has been shown to inhibit the migration and invasion of EC cells *in vivo* and *in vitro* (107). Yang *et al* (107) showed that E2 downregulated the expression of RIZ1 in EC cells, which promoted the development of EC. They also found that the selective ERα antagonist ICI182780 reversed this effect, suggesting that a potential mechanism by which RIZ1 promotes EC involves the E2/ERα signaling pathway (107).

Anti-apoptosis. There have been only a few studies on ERα in terms of anti-apoptosis and drug resistance. It has been shown that by directly binding to p53, ERα inhibits the transcriptional activation of *p53*, which downregulates the inhibitory effect of p53 on survivin (94). Survivin inhibits apoptosis through a variety of mechanisms, including directly binding to and inhibiting caspase-3 and caspase-9 (109). In a study of Ishikawa and HEC-265 cells, Chuwa *et al* (110) found that E2 significantly induced the co-expression of ERα and survivin in EC cells, which reduced the apoptosis of these cells. In addition, during the G1 phase of EC, the E2/ERα signaling pathway has been shown to promote the translocation of phosphorylated AKT into the nucleus and thereby inhibit the apoptosis of EC cells (111). Moreover, it has been suggested that ERα may enhance the interaction between

STAT3 and the apoptosis regulator BCL-extra large, which is crucial for the development of endometrioid adenocarcinoma (112). Furthermore, ERα expression has been indicated to influence the pro-apoptotic or anti-apoptotic effects of abnormally expressed Cx43 and Cx26 in EC (113). Regarding drug resistance, Abe *et al* (114) found that ERα upregulates the expression of BCL2-associated athanogene 3 (BAG3) in EC cells, inhibits the expression of miR-29b, and increases the expression of Mcl-1, which is a downstream mediator of BAG3. In addition, the authors also found that ERα overexpression improves the survival of EC cells in the presence of cisplatin, suggesting that ERα may enhance the resistance of EC cells to anticancer drugs via the overexpression of BAG3 (114).

6. Clinical application

ERα is used as a therapeutic target for EC, and several drugs targeting ERα are currently being applied for the treatment of EC. In addition, ERα has a role as a good prognostic indicator for EC (Table IV) (12,115).

Selective ER modulators including tamoxifen and raloxifene are the most intensively studied anti-ERα agents in EC. Tamoxifen affects the interaction of ERα with co-regulatory factors and alters the DNA binding characteristics of ERα in EC tissue (116). Tamoxifen contributes to the proliferation and carcinogenesis of EC via the promotion of ERα transcriptional activity through the constitutional activation of MAP kinase signaling (117). Moreover, SRC kinase promotes the role of tamoxifen in EC through the AKT kinase-induced phosphorylation of ER S167, thereby stabilizing ER promoter interactions and increasing ERα signaling (118). However, despite increasing the risk of EC, tamoxifen is also an effective low-toxicity drug for the treatment of advanced or relapsing EC (119). Tamoxifen exerts excitatory or antagonistic effects on ERα through the tissue-specific expression of co-activators and -inhibitors of receptors (119). The development of EC associated with tamoxifen has been suggested to be due to the MAPK signaling pathway increasing the transcriptional activity of ERα through AF-1 (117). It was these negative effects of tamoxifen that drove the development of raloxifene (120). Raloxifene not only has the same mechanism as tamoxifen to inhibit ERα and inhibit the proliferation of EC, but also induces mitochondria-mediated apoptosis of EC (120). The selective ER downregulator ICI-182780 and genistein significantly reduce the expression level of ERα induced by E2 (121). Boisen *et al* (122) found that ICI-182780 binds to ERα to inhibit E2, and also competently binds to the LBD of ERα and induces ERα degradation through the ubiquitin-proteasome system. However, in primary EC, splicing variants and point mutations present in the LBD are associated with hormone-independent ERα activity, which can produce ligand-independent or anti-E2 therapy resistance (123). Similar to ICI-182780, clomiphene citrate has been shown to reduce the ERα protein level via induction of ubiquitin-proteasome system without affecting the ERα mRNA level in Ishikawa cells (124). Arsenic trioxide, however, inhibits both ERα mRNA and protein expression in a dose-dependent manner by promoting the rapid phosphorylation of p42/p44 in the MAPK signaling pathway, thereby exhibiting an anti-EC effect (125). The natural dietary flavonoid kaempferol effectively targets ERα-mediated oncogenic signaling pathways to induce the death of EC cells, not only via the inhibition of ERα and survivin proteins, but also by the induction of p53 (110). Metformin exhibits an inhibitory effect on the E2-induced enhanced proliferation of Ishikawa cells that is weakened or partially reversed in *ESR1* knockout cells, indicating that ERα mediates the inhibitory effect of metformin on the proliferation of EC cells (97). It has been suggested that this effect may be attributed metformin reducing the expression of ERα at the protein and mRNA levels, resulting in a reduction in the expression of the ERα-target genes keratin-19 and WNT-1 (126). Compared with anti-ERα treatment alone, the dual targeting of ERα and ERRα in the treatment of EC has an improved therapeutic effect, because this maximizes the growth inhibitory and pro-apoptotic effect on EC cells (127). DY131, a selective ERRγ agonist, inhibits the growth of ERα-positive EC cells but promotes the growth of ERα-negative EC cells (128). In addition, melatonin has been shown to enhance the anti-EC effect of chemotherapy, particularly paclitaxel, by the inhibition of ERα expression in Ishikawa cells (129). Furthermore, a combination of S-farnesylthiosalicylic acid and medroxyprogesterone acetate was demonstrated to inhibit growth and increase cell death in type II EC cells by decreasing the mRNA expression of the ERα-mediated progesterone receptor (PR), *c-fos* and *ps2*/trefoil factor 1 (130).

A number of very promising targets and drugs for the treatment of EC have been identified. Miki *et al* (131) showed that heterogeneous nuclear ribonucleic protein K (hnRNPK) immunoreactivity in normal endometrium in the proliferative phase was higher than that in the secretory phase, and the expression levels of both ERα and hnRNPK were higher in benign endometrial tissue than in EC. In both normal and cancerous tissues, the median hnRNPK immunoreactivity was significantly increased in cases with high ERα, which was significantly associated with improved disease-free survival (DFS) and overall survival (131). Based on these results, it was proposed that hnRNPK interacts with ERα to regulate changes in the endometrium during the menstrual cycle, thus having the ability to inhibit the malignant behavior of EC (131). Krakstad *et al* (132) found that the GPER protein is significantly associated with ERα in GC, and a loss of GPER in patients with ERα-positive GC is associated with a poor prognosis. Additionally, using bioinformatics they found that HDAC inhibitors may be promising drugs for the treatment of ERα-positive EC with GPER deletion (132). Although E2 activates NPM via ERα, increased NPM expression inhibits ERα (133). Since strategies to promote ERα re-expression may allow patients with relapsed EC to resume endocrine therapy, inhibition of NPM may represent a strategy to promote ERα re-expression and ultimately restore the sensitivity of EC to hormone therapy (133). Moreover, the expression of ERα in EC has been found to negatively correlate with human phosphatidylethanolamine-binding protein 4 (hPEBP4), PKCα and antisense oligodeoxyribonucleotides against ERα, suggesting that hPEBP4, PKCα and nucleic acid therapeutics may counter the ERα and serve as potential agents against the proliferation of EC cells (134-136).

Given the widespread clinical application of endocrine therapy specific to ERα, ERα can be used as a good prognostic indicator in EC (22). Among patients with EC, those with

Table IV. ERα-associated potential drugs for EC.

First author/s, year	Drug	Mechanism	Effect on EC	(Refs.)
Xu *et al*, 2014	BTB	Inhibits the transactivation of ERα	Inhibits the development of EC	(187)
Han *et al*, 2016	TSEC	Inhibits the transcriptional activity of ERα and promotes the degradation of ERα	Inhibits the development of EC	(55)
Labrie *et al*, 2001	EM-652	Inhibits the AF-1 and AF-2 functions of ERα	Inhibits the development of EC	(188)
Miki *et al*, 2022	hnRNPK	Interacts with ERα	Inhibits the development of EC	(131)
Fadiel *et al*, 2015	Phenytoin	Interacts with the LBD of ERα and thus interferes with the binding of ERα ligands to ERα	Inhibits the development of EC	(189)
Lian *et al*, 2006	Juzen-taiho-to, Shimotsu-to	Inhibit the expression of ERα mRNA	Inhibit the development of EC	(190)
Bae-Jump *et al*, 2008	Arsenic trioxide	Downregulates ERα by phosphorylation of p42/p44	Inhibits the development of EC	(125)
Amita *et al*, 2016	Clomiphene citrate	Induces ERα protein degradation	Inhibits the development of EC	(124)
Boisen *et al*, 2015	Kaempferol	Inhibits ERα and survivin, and induces p53	Inhibits the development of EC	(122)
Faigenbaum *et al*, 2013	FTS and MPA	Inhibits the transcriptional activity of ERα	Inhibits the proliferation of EC	(130)
Guo *et al*, 2013	hPEBP4	Downregulates the expression of ERα	Inhibits the proliferation of EC	(134)
Zhang *et al*, 2016	Urolithin A	May downregulate the expression of ERα	Inhibits the proliferation of EC	(191)
Fournier *et al*, 2001	PKCα	May downregulate the expression of ERα	Inhibits the proliferation of EC	(136)
Taylor *et al*, 2002	Oligodeoxyribonucleotides	May downregulate the expression of ERα	Inhibits the proliferation of EC	(135)
Karaboğa *et al*, 2018	α-chaconine, α-solanine	Reduce the expression and activity of the ERα signaling pathway	Inhibits the proliferation of EC	(192)
Hu *et al*, 2020	Metformin	Inhibits ERα	Inhibits the proliferation of EC	(97)
Krakstad *et al*, 2012	HDAC inhibitors	Downregulate ERα and its downstream genes	Inhibits the proliferation of EC	(132)
Leong *et al*, 2001	DIM	Mediates ERα-dependent TGF-α transcriptional activation	Inhibits the proliferation of EC	(193)
Yamamoto *et al*, 2012	DY131	Inhibits ERRγ.	Inhibits the proliferation of EC	(128)
Aoyama *et al*, 2005	Bromoethane	May upregulate the expression of ERα	Promotes the proliferation of EC	(194)
Kim *et al*, 2015	NJK14013	Activates ERα-mediated transcription in EC	Promotes apoptosis and inhibits proliferation of EC	(195)
Karaca *et al*, 2021	Doxazosin, erlotinib	Inhibits the expression of ERα	Promotes the apoptosis of EC	(196)
Wang *et al*, 2013	Conjugated linoleic acid	Inhibits the ERα-mediated pathway	Promotes the apoptosis of EC	(197)
Droog *et al*, 2017; Emons *et al*, 2020	Tamoxifen	Affects the interaction of ERα with co-regulators and changes the DNA binding characteristics of ERα in EC	Supports the development of EC and is used as a treatment for EC	(116, 119)

Table IV. Continued.

First author/s, year	Drug	Mechanism	Effect on EC	(Refs.)
Shah *et al*, 2005	Methylseleninic acid	Inhibits the expression of ERα-dependent genes, such as pS2 and c-myc	Promotes tamoxifen-resistant EC resensitization to tamoxifen	(198)
Lin *et al*, 2016	NPM inhibitor	Downregulates the expression of ERα	Sensitizes to hormone therapy	(133)
Watanabe *et al*, 2008	Melatonin and paclitaxel	Inhibits the expression of ERα	Has an enhanced chemotherapy effect on EC	(129)
Boisen *et al*, 2015	ICI-182780	Binds ERα to inhibit E2 and induces ERα degradation	May protect against E2-associated EC	(122)

AF, activation function; BTB, 3-butoxy-1,8,9-trihydroxy-6H-benzofuro[3,2-c]benzopyran-6-one; DIM, 3,3'-diindolylmethane; E2, estrogen/estradiol; EC, endometrial carcinoma; ERα, estrogen receptor α; ERRγ, estrogen receptor-related receptor γ; FTS, S-farnesylthiosalicylic acid; HDAC, histone deacetylase; hnRNPK, heterogeneous nuclear ribonucleic protein K; hPEBP4, human phosphatidylethanolamine-binding protein 4; LBD, ligand-binding domain; MPA, medroxyprogesterone acetate; PKCα, protein kinase C α; TSEC, tissue-selective estrogen complex.

ERα-positive tumors have relatively good survival and the high expression of ERα is associated with an improved DFS in both type I and II EC (137,138). Through the analysis of 214 patients with endometrial adenocarcinoma, Mylonas (139) found that the loss of ERα was associated with poor survival. Furthermore, in another study ERα mRNA upregulation was shown to be an indicator of good prognosis in patients with EC (115). The expression of ERα is associated with the stage, histological grade and survival of EC (140), and ERα upregulation is considered to provide prognostic information independent of tumor grade and stage in women with EC (141). Although Mylonas did not find ERα to be an independent factor affecting survival in patients with endometrial adenocarcinoma, it was suggested that the combined analysis of ERα and ERb may be used to identify high-risk patients with endometrioid adenocarcinoma (139). The uptake of 16α-[^{18}F]fluoro-17β-estradiol (FES) is closely correlated with ERα expression, and the 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)/FES ratio is negatively correlated with ERα expression, both of which can reflect the differentiation degree of EC (142). Given the high expression of ERα in low-grade EC, it was suggested that FES positron emission tomography in combination with FDG can be used to noninvasively assess ERα distribution and function, and has potential in the prognosis of EC and determination of its treatment (142). As in EC, it has also been proposed that ERα could be used as a prognostic indicator in serous uterine carcinoma. The expression of ERα in serous uterine carcinoma is associated with advanced stage, and a prognosis that is significantly worse than that of serous uterine carcinoma without ERα expression (143).

7. Discussion

The role of ERα in EC is becoming increasingly clear. In general, ERα, as a transcriptional factor, is an oncogenic factor in EC. ERα regulates transcriptional activity with modulation by upstream co-regulatory factors, and then promotes transcription of its downstream target genes via the E2/ERα signaling pathway, thus promoting the occurrence and development of EC, with the induction of proliferation, invasion, metastasis and anti-apoptosis effects.

However, two important aspects of ERα in EC merit further investigation. One is that the progressive loss of ERα seems to be associated with the progressive malignancy of EC (89). That is, highly differentiated EC typically retains ERα expression in the early stages, while in advanced stages, poorly differentiated EC tends to lack this receptor (144). Pathirage *et al* (145) found that ERα expression was significantly elevated in grade 1 EC compared with normal tissues and higher grade EC, and observed a significant negative correlation between ERα expression and the grade of EC. Using immunohistochemistry, Hu *et al* (97) observed that the positive expression rate of ERα was higher in patients with moderately and highly differentiated EC than in those with poorly differentiated EC, and showed that ERα expression was higher in the early stage of EC development compared with the late stage of EC. Therefore, they hypothesized that ERα promotes endometrial dysplasia and the early progression of EC through interaction with E2 (97). However, they observed that ERα sensitivity to E2 changed and more ERα-negative EC cells appeared during EC progression, resulting in a lower expression of ERα in advanced EC (97).

The other key aspect of ERα in EC is that it may also act as a tumor suppressor. It has been shown that ERα localized in the cytoplasm promotes cardiovascular protection in mice but does not promote the occurrence and development of EC (146). Furthermore, it has been demonstrated that the ERα-mediated signaling pathway regulates the expression of olfactomedin 4 (OLFM4), and that the expression of OLFM4 and ERα are positively correlated (147). While the increased expression of OLFM4 during the development of EC is associated with the differentiation of endometrioid adenocarcinoma, the downregulation of OLFM4 promotes the proliferation, migration and invasion of EC cells, and is associated with a reduced survival rate in patients with endometrioid adenocarcinoma (147). In addition, ERα blocks the formation of tumor blood vessels (148). The high levels of ERα in EC have

been indicated to inhibit tumor growth via the regulation of angiogenic factors such as integrin αvβ3, thereby reducing the blood supply (148,149). In addition, ERα interacts with the Sp3 protein, which inhibits VEGF expression and thus blood supply in EC (150). Moreover, Joshi *et al* (151) observed endometrial hyperplasia/carcinoma in 88.9% of $Pten^{+/-}$ $ER\alpha^{-/-}$ mice. These mice also exhibit a high incidence of carcinoma *in situ* and invasive carcinoma, suggesting that EC can develop in the absence of ERα (151).

In addition to ERα, there are some *ESR1* gene, ERα mRNA and ERα protein variants that influence the occurrence and development of EC (152-154). Wedren *et al* (152) found that *ESR1* intron variants are associated with EC risk. Furthermore, Jazaeri *et al* (153) detected ERα mRNA variants in all endometrial samples, including premenopausal and postmenopausal endometrial samples, but only observed ERα protein splicing variants in EC. ERα36, a variant of ERα protein, triggers the activation of epidermal growth factor receptor-associated extracellular signal-regulated kinases, which play a carcinogenic role in EC (154). Similarly, the ERα variant d5 exhibits a dominant positive activity on ERα-regulated promoters, which maintains the expression of E2-responsive genes in the absence of E2, resulting in EC (155). Therefore, further exploration of variants of ERα provides a feasible direction for further understanding the pathogenesis of EC.

Although ERα is the most common target of targeted therapy in breast cancer, anti-ERα therapy has shown inconsistent results in EC, with very limited therapeutic efficacy and sometimes even an increased risk of cancer (123). Since the study based on TCGA database in 2013 (156), a new molecular classification of EC has emerged, which is mainly based on overall mutational burden, *p53*, polymerase-epsilon (*POLE*), *Pten* mutations, microsatellite instability and histology, which helps to refine the prognosis of EC (156-158). It divides EC into four molecular subtypes: *POLE* ultra-mutated, microsatellite instability hyper-mutated, copy-number low and copy-number high (157,158). Due to the high cost of the genetic analysis of *POLE*, another simplified version of molecular typing is commonly used in clinical practice, which divides EC into POLE-mutant, mismatch repair deficient, no specific molecular profile (NSMP) and p53-aberrant subtypes (157). Among these, only NSMP usually comprises ERα and PR, while in the other three subtypes, hormone receptors are usually absent (157,159). In NSMP, the level of copy number alterations is low, the tumor mutation burden is moderate, and mutation mainly occurs in the PI3K/AKT/mTOR and WNT/β-catenin signaling pathways (157). Targeted therapy for ERα or hormonal therapy, alone or in combination with mTOR inhibitors, is indicated to further improve outcomes in patients with NSMP (160). By contrast, a range of treatments targeting ERα may not have much effect on the other three molecular subtypes. Clinically, in addition to targeting ERα, a number of drugs target other biological molecules: E2, including anastrozole and letrozole; PR, such as medrysone; VEGF, including bevacizumab and lenvatinib; mTOR, such as everolimus and ridaforolimus; and programmed cell death protein, for example, pembrolizumab and dostarlimab in the treatment of EC (161-165). Studies have shown that the combination of tamoxifen with anastrozole, bevacizumab, everolimus or pembrolizumab can be used to control the proliferation and metastasis of breast cancer (166-169). However, in EC, there have been few studies on the combination of anti-ERα drugs with other drugs, and it is not clear whether they affect the prognosis of EC. Furthermore, when combined with chemotherapy drugs or mTOR inhibitors, anti-ERα drugs can have serious side effects and these occur frequently (170). Therefore, it is necessary to find improved ERα-targeting drugs or combinations of drugs in future studies, so as to further improve the prognosis of patients and reduce the occurrence of side effects.

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Availability of data and materials

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Authors' contributions

MY and XJ conceived the study. YG, XN and JL collated the data. YG, XN and JL wrote the manuscript. MY and XJ revised and edited the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Urick ME and Bell DW: Clinical actionability of molecular targets in endometrial cancer. Nat Rev Cancer 19: 510-521, 2019.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
3. Zhou Y, Shen J, Xia L and Wang Y: Estrogen mediated expression of nucleophosmin 1 in human endometrial carcinoma clinical stages through estrogen receptor-alpha signaling. Cancer Cell International 14: 540, 2014.
4. Koskas M, Amant F, Mirza MR and Creutzberg CL: Cancer of the corpus uteri: 2021 update. Int J Gynecol Obstet 155: 45-60, 2021.

5. Saito A, Yoshida H, Nishikawa T and Yonemori K: Human epidermal growth factor receptor 2 targeted therapy in endometrial cancer: Clinical and pathological perspectives. World J Clin Oncol 12: 868-881, 2021.
6. Engelsen IB, Stefansson IM, Akslen LA and Salvesen HB: GATA3 expression in estrogen receptor alpha-negative endometrial carcinomas identifies aggressive tumors with high proliferation and poor patient survival. Am J Obstet Gynecol 199: 543.e1-e7, 2008.
7. Koshiyama M, Konishi I and Fujii S: Pathology, hormonal aspects, and molecular genetics of the two types of endometrial cancer. Cancer J France 11: 277-283, 1998.
8. Musicco C, Cormio G, Pesce V, Loizzi V, Cicinelli E, Resta L, Ranieri G and Cormio A: Mitochondrial dysfunctions in type I endometrial carcinoma: Exploring their role in oncogenesis and tumor progression. Int J Mol Sci 19: 2076, 2018.
9. Gullo G, Etrusco A, Cucinella G, Perino A, Chiantera V, Laganà AS, Tomaiuolo R, Vitagliano A, Giampaolino P, Noventa M, *et al*: Fertility-sparing approach in women affected by stage I and low-grade endometrial carcinoma: An updated overview. Int J Mol Sci 22: 11825, 2021.
10. Tan DSP, Lambros MBK, Marchio C and Reis-Filho JS: ESR1 amplification in endometrial carcinomas: Hope or hyperbole? J Pathol 216: 271-274, 2008.
11. Jongen V, Sluijmer AV and Heineman MJ: The postmenopausal ovary as an androgen-producing gland; hypothesis on the etiology of endometrial cancer. Maturitas 43: 77-85, 2002.
12. AlZaabi A, AlAmri H, ALAjmi G, Allawati M, Muhanna F, Alabri R, AlBusaidi F, AlGhafri S, Al-Mirza AA and Al Baimani K: Endometrial surveillance in tamoxifen and letrozole treated breast cancer patients. Cureus 13: e20030, 2021.
13. Travaglino A, Raffone A, Mascolo M, Guida M, Insabato L, Zannoni GF and Zullo F: TCGA molecular subgroups in endometrial undifferentiated/dedifferentiated carcinoma. Pathol Oncol Res 26: 1411-1416, 2020.
14. Barton M, Filardo EJ, Lolait SJ, Thomas P, Maggiolini M and Prossnitz ER: Twenty years of the G protein-coupled estrogen receptor GPER: Historical and personal perspectives. J Steroid Biochem Mol Biol 176: 4-15, 2018.
15. Fuentes N and Silveyra P: Estrogen receptor signaling mechanisms. In: Donev R (ed.). Intracellular Signalling Proteins. pp135-170, 2019.
16. Zhang Z, Qin P, Deng Y, Ma Z, Guo H, Guo H, Hou Y, Wang S, Zou W, Sun Y, *et al*: The novel estrogenic receptor GPR30 alleviates ischemic injury by inhibiting TLR4-mediated microglial inflammation. J Neuroinflammation 15: 206, 2018.
17. Prossnitz ER and Barton M: The G-protein-coupled estrogen receptor GPER in health and disease. Nat Rev Endocrinol 7: 715-726, 2011.
18. Tecalco-Cruz AC, Zepeda-Cervantes J and Ortega-Dominguez B: Estrogenic hormones receptors in Alzheimer's disease. Mol Biol Rep 48: 7517-7526, 2021.
19. Rahman MT, Nakayama K, Rahman M, Ishikawa M, Katagiri H, Katagiri A, Ishibashi T, Sato E, Iida K, Ishikawa N, *et al*: ESR1 gene amplification in endometrial carcinomas: A clinicopathological analysis. Anticancer Res 33: 3775-3781, 2013.
20. Lara-Castillo N: Estrogen signaling in bone. Appl Sci Basel 11: 4439, 2021.
21. Lebeau A, Grob TJ, Hoist F, Seyedi-Fazlollahi N, Moch H, Terracciano L, Turzynski A, Choschzick M, Sauter G and Simon R: Oestrogen receptor gene (ESR1) amplification is frequent in endometrial carcinoma and its precursor lesions. J Pathol 216: 151-157, 2008.
22. Guo WY, Zeng SMZ, Deora GS, Li QS and Ruan BF: Estrogen Receptor α (ERα)-targeting compounds and derivatives: Recent advances in structural modification and bioactivity. Curr Top Med Chem 19: 1318-1337, 2019.
23. Krasner C: Aromatase inhibitors in gynecologic cancers. J Steroid Biochem Mol Biol 106: 76-80, 2007.
24. Rao J, Jiang X, Wang Y and Chen B: Advances in the understanding of the structure and function of ER-alpha 36, a novel variant of human estrogen receptor-alpha. J Steroid Biochem Mol Biol 127: 231-237, 2011.
25. Arao Y and Korach KS: Transactivation Function-1-mediated partial agonist activity of selective estrogen receptor modulator requires homo-dimerization of the estrogen receptor alpha ligand binding domain. Int J Mol Sci 20: 3718, 2019.
26. Jia M, Dahlman-Wright K and Gustafsson J: Estrogen receptor alpha and beta in health and disease. Best Pract Res Clin Endocrinol Metab 29: 557-568, 2015.
27. Bouricha EM, Hakmi M, Akachar J, Zouaidia F and Ibrahimi A: In-silico identification of potential inhibitors targeting the DNA binding domain of estrogen receptor alpha for the treatment of hormone therapy-resistant breast cancer. J Biomol Struct Dyn 40: 5203-5210, 2020.
28. Arao Y and Korach KS: The physiological role of estrogen receptor functional domains. Essays Biochem 65: 867-875, 2021.
29. Tecalco-Cruz AC, Perez-Alvarado IA, Ramirez-Jarquin JO and Rocha-Zavaleta L: Nucleo-cytoplasmic transport of estrogen receptor alpha in breast cancer cells. Cell Signal 34: 121-132, 2017.
30. Skafar DF and Zhao C: The multifunctional estrogen receptor-alpha F domain. Endocrine 33: 1-8, 2008.
31. Zwart W, de Leeuw R, Rondaij M, Neefjes J, Mancini MA and Michalides R: The hinge region of the human estrogen receptor determines functional synergy between AF-1 and AF-2 in the quantitative response to estradiol and tamoxifen. J Cell Sci 123: 1253-1261, 2010.
32. Božović A, Mandušić V, Todorović L and Krajnović M: Estrogen receptor Beta: The promising biomarker and potential target in metastases. Int J Mol Sci 22: 1656, 2021.
33. Rocha W, Sanchez R, Deschenes J, Auger A, Hébert E, White JH and Mader S: Opposite effects of histone deacetylase inhibitors on glucocorticoid and estrogen signaling in human endometrial ishikawa cells. Mol Pharmacol 68: 1852-1862, 2005.
34. Chen X, Yan Q, Li S, Zhou L, Yang H, Yang Y, Liu X and Wan X: Expression of the tumor suppressor miR-206 is associated with cellular proliferative inhibition and impairs invasion in ER alpha-positive endometrioid adenocarcinoma. Cancer Lett 314: 41-53, 2012.
35. Hermon TL, Moore AB, Yu L, Kissling GE, Castora FJ and Dixon D: Estrogen receptor alpha (ER alpha) phospho-serine-118 is highly expressed in human uterine leiomyomas compared to matched myometrium. Virchows Archiv 453: 557-569, 2008.
36. Bao W, Zhang Y, Li S, Fan Q, Qiu M, Wang Y, Li Y, Ji X, Yang Y, Sang Z, *et al*: miR-107-5p promotes tumor proliferation and invasion by targeting estrogen receptor-alpha in endometrial carcinoma. Oncol Rep 41: 1575-1585, 2019.
37. Wu Y, Zeng K, Wang C, Wang S, Sun H, Liu W, Wang X, Niu J, Cong SY, Zhou X and Zhao Y: Histone acetyltransferase MOF is involved in suppression of endometrial cancer and maintenance of ERα stability. Biochem Biophys Res Commun 509: 541-548, 2019.
38. Kershah SM, Desouki MM, Koterba KL and Rowan BG: Expression of estrogen receptor coregulators in normal and malignant human endometrium. Gynecol Oncol 92: 304-313, 2004.
39. Gao M, Sun PM, Wang JL, Li XP, Zhao C and Wei LH: Different biological effect of estrogen receptor-related receptor alpha in estrogen receptor-positive and -negative endometrial carcinoma. Mol Med Rep 1: 917-924, 2008.
40. Shiozawa T, Itoh K, Horiuchi A, Konishi I, Fujii S and Nikaido T: Down-regulation of estrogen receptor by the methylation of the estrogen receptor gene in endometrial carcinoma. Anticancer Res 22: 139-143, 2002.
41. Liu B, Che Q, Qiu H, Bao W, Chen X, Lu W, Li B and Wan X: Elevated MiR-222-3p promotes proliferation and invasion of endometrial carcinoma via targeting ERα. PLoS One 9: e87563, 2014.
42. Song Q, An Q, Niu B, Lu X, Zhang N and Cao X: Role of miR-221/222 in tumor development and the underlying mechanism. J Oncol 2019: 7252013, 2019.
43. Zhang G, Hou X and Gao S: Stimulation of peroxisome proliferator-activated receptor gamma inhibits estrogen receptor alpha transcriptional activity in endometrial carcinoma cells. Oncol Rep 33: 1227-1234, 2015.
44. Uchida S, Saimi M, Li ZL, Miyaso H, Nagahori K, Kawata S, Omotehara T, Ogawa Y and Itoh M: Effects of phosphorylated estrogen receptor alpha on apoptosis in human endometrial epithelial cells. Anat Sci Int 95: 240-250, 2020.
45. Zhang P, Gao K, Jin X, Ma J, Peng J, Wumaier R, Tang Y, Zhang Y, An J, Yan Q, *et al*: Endometrial cancer-associated mutants of SPOP are defective in regulating estrogen receptor-α protein turnover. Cell Death Dis 6: e1687, 2015.
46. Sentis S, Le Romancer M, Bianchin C, Rostan MC and Corbo L: Sumoylation of the estrogen receptor alpha hinge region regulates its transcriptional activity. Mol Endocrinol 19: 2671-2684, 2005.
47. O'Doherty A, Church SW, Russell SEH, Nelson J and Hickey I: Methylation status of oestrogen receptor-alpha gene promoter sequences in human ovarian epithelial cell lines. Br J Cancer 86: 282-284, 2002.

48. Li Y, Zhou Y, Mao F, Shen S, Zhao B, Xu Y, Lin Y, Zhang X, Cao X, Xu Y, *et al*: miR-452 reverses abnormal glycosylation modification of ERα and estrogen resistance in TNBC (Triple-Negative Breast Cancer) Through Targeting UGT1A1. Front Oncol 10: 1509, 2020.
49. Onate SA, Boonyaratanakornkit V, Spencer TE, Tsai SY, Tsai MJ, Edwards DP and O'Malley BW: The steroid receptor coactivator-1 contains multiple receptor interacting and activation domains that cooperatively enhance the activation function 1 (AF1) and AF2 domains of steroid receptors. J Biol Chem 273: 12101-12108, 1998.
50. Kato S, Endoh H, Masuhiro Y, Kitamoto T, Uchiyama S, Sasaki H, Masushige S, Gotoh Y, Nishida E, Kawashima H, *et al*: Activation of the estrogen-receptor through phosphorylation by mitogen-activated protein-kinase. Science 270: 1491-1494, 1995.
51. Vilgelm A, Lian ZL, Wang H, Beauparlant SL, Klein-Szanto A, and Ellenson LH and Di Cristofano A: Akt-mediated phosphorylation and activation of estrogen receptor alpha is required for endometrial neoplastic transformation in Pten(+/-) mice. Cancer Res 66: 3375-3380, 2006.
52. Kato E, Orisaka M, Kurokawa T, Chino Y, Fujita Y, Shinagawa A and Yoshida Y: Relation between outcomes and expression of estrogenreceptor-alphaphosphorylatedatSer(167)inendometrioid endometrial cancer. Cancer Sci 105: 1307-1312, 2014.
53. Lee H and Bai W: Regulation of estrogen receptor nuclear export by ligand-induced and p38-mediated receptor phosphorylation. Mol Cell Biol 22: 5835-5845, 2002.
54. Ohtake F, Fujii-Kuriyama Y and Kato S: AhR acts as an E3 ubiquitin ligase to modulate steroid receptor functions. Biochem Pharmacol 77: 474-484, 2009.
55. Han SJ, Begum K, Foulds CE, Hamilton RA, Bailey S, Malovannaya A, Chan D, Qin J and O'Malley BW: The dual estrogen receptor α inhibitory effects of the tissue-selective estrogen complex for endometrial and breast safety. Mol Pharmacol 89: 14-26, 2016.
56. Su Y, Zeng K, Liu S, Wu Y, Wang C, Wang S, Lin L, Zou R, Sun G, Luan R, *et al*: Ubiquitin-specific peptidase 14 maintains estrogen receptor α stability via its deubiquitination activity in endometrial cancer. J Biol Chem 299: 102734, 2023.
57. Lv Q, Xie L, Cheng Y, Shi Y, Shan W, Ning C, Xie B, Yang B, Luo X, He Q, *et al*: A20-mediated deubiquitination of ERα in the microenvironment of $CD163^+$ macrophages sensitizes endometrial cancer cells to estrogen. Cancer Lett 442: 137-147, 2019.
58. Xu ZX, Liu J, Gu LP, Huang B and Pan XJ: Biological effects of xenoestrogens and the functional mechanisms via genomic and nongenomic pathways. Environmental Rev 25: 306-322, 2017.
59. Stefkovich ML, Arao Y, Hamilton KJ and Korach KS: Experimental models models for evaluating non-genomic estrogen signaling. Steroids 133: 34-37, 2018.
60. Wang ZY and Yin L: Estrogen receptor alpha-36 (ER-α36): A new player in human breast cancer. Mol Cell Endocrinol 418: 193-206, 2015.
61. Manavathi B, Samanthapudi VSK and Gajulapalli VNR: Estrogen receptor coregulators and pioneer factors: The orchestrators of mammary gland cell fate and development. Front Cell Dev Biol 2: 34, 2014.
62. Che Q, Liu BY, Liao Y, Zhang HJ, Yang TT, He YY, Xia YH, Lu W, He XY, Chen Z, *et al*: Activation of a positive feedback loop involving IL-6 and aromatase promotes intratumoral 17β-estradiol biosynthesis in endometrial carcinoma microenvironment. Int J Cancer 135: 282-294, 2014.
63. Zhang ZP and Teng CT: Estrogen receptor alpha and estrogen receptor-related receptor alpha 1 compete for binding and coactivator. Mol Cell Endocrinol 172: 223-233, 2001.
64. Gao M, Sun PM, Zhao D, Wang JL, Li XP and Wei LH: Regulatory effect of 17beta-estradiol on expression of orphan nuclear receptor ERRalpha in endometrial carcinoma cell lines. Ai Zheng 25: 538-542, 2006 (In Chinese).
65. Mylonas I, Jeschke U, Shabani N, Kuhn C, Kriegel S, Kupka MS and Friese K: Normal and malignant human endometrium express immunohistochemically estrogen receptor alpha (ER-alpha), estrogen receptor beta (ER-beta) and progesterone receptor (PR). Anticancer Res 25: 1679-1686, 2005.
66. Su T, Qu JJ, Wang K, Li BL, Zhao D, Zhu YP, Ye L, Lu W and Wan XP: Cross-talk between p21-activated kinase 4 and ER alpha signaling triggers endometrial cancer cell proliferation. Oncotarget 8: 68083-68094, 2017.
67. Zhou XH, Xu ST, Song WY and Teng XD: Expression of receptor-binding cancer antigen expressed on SiSo cells in endometrial carcinoma and the correlation thereof with the expression of estrogen receptor subtypes. Zhonghua Yi Xue Za Zhi 87: 1900-1903, 2007 (In Chinese).
68. Hou X, Zhao M, Wang T and Zhang G: Upregulation of estrogen receptor mediates migration, invasion and proliferation of endometrial carcinoma cells by regulating the PI3K/AKT/mTOR pathway. Oncol Rep 31: 1175-1182, 2014.
69. Zhao L, Watanabe M, Yano T, Yanagisawa J, Nakagawa S, Oishi H, Wada-Hiraike O, Oda K, Minaguchi T, Yasugi T, *et al*: Analysis of the status of the novel estrogen receptor alpha (ERα) coactivator p72 in endometrial cancer and its cross talk with erbB-2 in the transactivation of ERα. Mol Med Rep 1: 387-390, 2008.
70. Nagarajan S, Hossan T, Alawi M, Najafova Z, Indenbirken D, Bedi U, Taipaleenmäki H, Ben-Batalla I, Scheller M, Loges S, *et al*: Bromodomain protein BRD4 is required for estrogen receptor-dependent enhancer activation and gene transcription. Cell Rep 8: 460-469, 2014.
71. Vadlamudi RK, Balasenthil S, Broaddus RR, Gustafsson JA and Kumar R: Deregulation of estrogen receptor coactivator proline-, glutamic acid-, and leucine-rich protein-1/modulator of nongenomic activity of estrogen receptor in human endometrial tumors. J Clin Endocrinol Metab 89: 6130-6138, 2004.
72. Thorne AM, Jackson TA, Willis VC and Bradford AP: Protein Kinase C α modulates estrogen-receptor-dependent transcription and proliferation in endometrial cancer cells. Obstet Gynecol Int 2013: 537479, 2013.
73. Frigo DE, Basu A, Nierth-Simpson EN, Weldon CB, Dugan CM, Elliott S, Collins-Burow BM, Salvo VA, Zhu Y, Melnik LI, *et al*: p38 mitogen-activated protein kinase stimulates estrogen-mediated transcription and proliferation through the phosphorylation and potentiation of the p160 coactivator glucocorticoid receptor-interacting protein 1. Mol Endocrinol 20: 971-983, 2006.
74. Kojima M, Sugimoto K, Kobayashi M, Ichikawa-Tomikawa N, Kashiwagi K, Watanabe T, Soeda S, Fujimori K and Chiba H: Aberrant Claudin-6-adhesion signaling promotes endometrial cancer progression via estrogen receptor α. Mol Cancer Res 19: 1208-1220, 2021.
75. Lee H, Jiang F, Wang Q, Nicosia SV, Yang J, Su B and Bai W: MEKK1 activation of human estrogen receptor alpha and stimulation of the agonistic activity of 4-hydroxytamoxifen in endometrial and ovarian cancer cells. Mol Endocrinol 14: 1882-1896, 2000.
76. Lian Z, De Luca P and Di Cristofano A: Gene expression analysis reveals a signature of estrogen receptor activation upon loss of Pten in a mouse model of endometrial cancer. J Cell Physiol 208: 255-266, 2006.
77. Velarde MC, Zeng Z, McQuown JR, Simmen FA and Simmen RCM: Kruppel-like factor 9 is a negative regulator of ligand-dependent estrogen receptor alpha signaling in Ishikawa endometrial adenocarcinoma cells. Mol Endocrinol 21: 2988-3001, 2007.
78. Cheng R, Xue X and Liu X: Expression of IL17A in endometrial carcinoma and effects of IL17A on biological behaviour in Ishikawa cells. J Int Med Res 48: 300060520950563, 2020.
79. Wang D, Wang M, Hu CE, Shuang T, Zhou Y and Yan X: Expression of the ELAV-like protein HuR in the cytoplasm is associated with endometrial carcinoma progression. Tumor Biol 35: 11939-11947, 2014.
80. Gu CJ, Xie F, Zhang B, Yang HL, Cheng J, He YY, Zhu XY, Li DJ and Li MQ: High glucose promotes epithelial-mesenchymal transition of uterus endometrial cancer cells by increasing ER/GLUT4-mediated VEGF secretion. Cell Physiol Biochem 50: 706-720, 2018.
81. Nan F, Wei S, Guan D, Zhang L, Guo Q, Cao S, Liu Y, Liu Y and Sun M: Suppressive efficiency of RASSF1A in endometrial carcinoma via inhabiting estrogen receptor alpha expression and ERK pathway activation. Int J Clin Exp Pathol 11: 577-585, 2018.
82. Tanwar PS, Zhang L, Roberts DJ and Teixeira JM: Stromal deletion of the APC tumor suppressor in mice triggers development of endometrial cancer. Cancer Res 71: 1584-1596, 2011.
83. Tong H, Ke JQ, Jiang FZ, Wang XJ, Wang FY, Li YR, Lu W and Wan XP: Tumor-associated macrophage-derived CXCL8 could induce ERα suppression via HOXB13 in endometrial cancer. Cancer Lett 376: 127-136, 2016.

84. Zhou XH, Teng XD, Song WY and Wu YJ: Expression of receptor-binding cancer antigen expressed on SiSo cells and estrogen receptor subtypes in the normal, hyperplastic, and carcinomatous endometrium. Int J Gynecol Cancer 18: 152-158, 2008.
85. Tian W, Teng F, Gao J, Gao C, Liu G, Zhang Y, Yu S, Zhang W, Wang Y and Xue F: Estrogen and insulin synergistically promote endometrial cancer progression via crosstalk between their receptor signaling pathways. Cancer Biol Med 16: 55-70, 2019.
86. Zhang F, Peng L, Huang Y, Lin X, Zhou L and Chen J: Chronic BDE-47 exposure aggravates malignant phenotypes and chemoresistance by activating ERK through ERα and GPR30 in endometrial carcinoma. Front Oncol 9: 1079, 2019.
87. Saito S, Ito K, Suzuki T, Utsunomiya H, Akahira J, Sugihashi Y, Niikura H, Okamura K, Yaegashi N and Sasano H: Orphan nuclear receptor DAX-1 in human endometrium and its disorders. Cancer Sci 96: 645-652, 2005.
88. Collins F, Itani N, Esnal-Zufiaurre A, Gibson DA, Fitzgerald C and Saunders PTK: The ERβ 5 splice variant increases oestrogen responsiveness of ERαpos Ishikawa cells. Endocr Relat Cancer 27: 55-66, 2020.
89. Bircan S, Ensari A, Ozturk S, Erdogan N, Dundar I and Ortac F: Immunohistochemical analysis of c-myc, c-jun and estrogen receptor in normal, hyperplastic and neoplastic endometrium. Pathol Oncol Res 11: 32-39, 2005.
90. Nakayama H, Sano T, Motegi A, Oyama T and Nakajima T: Increasing 14-3-3 sigma expression with declining estrogen receptor alpha and estrogen-responsive finger protein expression defines malignant progression of endometrial carcinoma. Pathol Int 55: 707-715, 2005.
91. Wang J, Bao W, Qiu M, Liao Y, Che Q, Yang T, He X, Qiu H and Wan X: Forkhead-box A1 suppresses the progression of endometrial cancer via crosstalk with estrogen receptor α. Oncol Rep 31: 1225-1234, 2014.
92. Chen Z, Yang HJ, Lin Q, Zhu MJ, Yu YY, He XY and Wan XP: Estrogen-ERα signaling and DNA hypomethylation co-regulate expression of stem cell protein PIWIL1 in ER alpha-positive endometrial cancer cells. Cell Commun Signal 18: 84, 2020.
93. Flamini MI, Sanchez AM, Genazzani AR and Simoncini T: Estrogen regulates endometrial cell cytoskeletal remodeling and motility via focal adhesion kinase. Fertility Sterility 95: 722-726, 2011.
94. Sayeed A, Konduri SD, Liu W, Bansal S, Li F and Das GM: Estrogen receptor alpha inhibits p53-mediated transcriptional repression: Implications for the regulation of apoptosis. Cancer Res 67: 7746-7755, 2007.
95. Zhang R, He Y, Zhang X, Xing B, Sheng Y, Lu H and Wei Z: Estrogen receptor-regulated microRNAs contribute to the BCL2/BAX imbalance in endometrial adenocarcinoma and precancerous lesions. Cancer Lett 314: 155-165, 2012.
96. Chao A, Lin CY, Tsai CL, Hsueh S, Lin YY, Lin CT, Chou HH, Wang TH, Lai CH and Wang HS: Estrogen stimulates the proliferation of human endometrial cancer cells by stabilizing nucleophosmin/B23 (NPM/B23). J Mol Med (Berl) 91: 249-259, 2013.
97. Hu G, Zhang J, Zhou X, Liu J, Wang Q and Zhang B: Roles of estrogen receptor α and β in the regulation of proliferation in endometrial carcinoma. Pathol Res Pract 216: 153149, 2020.
98. Saito T, Tanaka R, Wataba K, Kudo R and Yamasaki H: Overexpression of estrogen receptor-α gene suppresses gap junctional intercellular communication in endometrial carcinoma cells. Oncogene 23: 1109-1116, 2004.
99. Zhu Y, Shen J, Gao L and Feng Y: Estrogen promotes fat mass and obesity-associated protein nuclear localization and enhances endometrial cancer cell proliferation via the mTOR signaling pathway. Oncol Rep 35: 2391-2397, 2016.
100. Chen R, Zhang M, Liu W, Chen H, Cai T, Xiong H, Sheng X, Liu S, Peng J, Wang F, *et al*: Estrogen affects the negative feedback loop of PTENP1-miR200c to inhibit PTEN expression in the development of endometrioid endometrial carcinoma. Cell Death Dis 10: 4, 2018.
101. Scully MM, Palacios-Helgeson LK, Wah LS and Jackson TA: Rapid estrogen signaling negatively regulates PTEN activity through phosphorylation in endometrial cancer cells. Horm Cancer 5: 218-231, 2014.
102. Mizumoto H, Saito T, Ashihara K, Nishimura M, Tanaka R and Kudo R: Acceleration of invasive activity via matrix metalloproteinases by transfection of the estrogen receptor-α gene in endometrial carcinoma cells. Int J Cancer 100: 401-406, 2002.
103. Liu Y, Zhao R, Chi S, Zhang W, Xiao C, Zhou X, Zhao Y and Wang H: UBE2C is upregulated by estrogen and promotes epithelial-mesenchymal transition via p53 in endometrial cancer. Mol Cancer Res 18: 204-215, 2020.
104. Zhang Z, Zhou D, Lai Y, Liu Y, Tao X, Wang Q, Zhao G, Gu H, Liao H, Zhu Y, *et al*: Estrogen induces endometrial cancer cell proliferation and invasion by regulating the fat mass and obesity-associated gene via PI3K/AKT and MAPK signaling pathways. Cancer Lett 319: 89-97, 2012.
105. Wik E, Raeder MB, Krakstad C, Trovik J, Birkeland E, Hoivik EA, Mjos S, Werner HM, Mannelqvist M, Stefansson IM, *et al*: Lack of estrogen receptor-alpha is associated with epithelial-mesenchymal transition and PI3K alterations in endometrial carcinoma. Clin Cancer Res 19: 1094-1105, 2013.
106. Yang T, Zhang H, Qiu H, Li B, Wang J, Du G, Ren C and Wan X: EFEMP1 is repressed by estrogen and inhibits the epithelial-mesenchymal transition via Wnt/β-catenin signaling in endometrial carcinoma. Oncotarget 7: 25712-25725, 2016.
107. Yang T, Ren C, Jiang A, Yu Z, Li G, Wang G and Zhang Q: RIZ1 is regulated by estrogen and suppresses tumor progression in endometrial cancer. Biochem Biophys Res Commun 489: 96-102, 2017.
108. Owens GL, Lawrence KM, Jackson TR, Crosbie EJ, Sayan BS, Kitchener HC and Townsend PA: Urocortin suppresses endometrial cancer cell migration via CRFR2 and its system components are differentially modulated by estrogen. Cancer Med 6: 408-415, 2017.
109. Mita AC, Mita MM, Nawrocki ST and Giles FJ: Survivin: Key regulator of mitosis and apoptosis and novel target for cancer therapeutics. Clin Cancer Res 14: 5000-5005, 2008.
110. Chuwa AH, Sone K, Oda K, Tanikawa M, Kukita A, Kojima M, Oki S, Fukuda T, Takeuchi M, Miyasaka A, *et al*: Kaempferol, a natural dietary flavonoid, suppresses 17β-estradiol-induced survivin expression and causes apoptotic cell death in endometrial cancer. Oncol Lett 16: 6195-6201, 2018.
111. Abe N, Watanabe J, Tsunoda S, Kuramoto H and Okayasu I: Significance of nuclear p-Akt in endometrial carcinogenesis rapid translocation of p-Akt into the nucleus by estrogen, possibly resulting in inhibition of apoptosis. Int J Gynecological Cancer 21: 194-202, 2011.
112. Wincewicz A, Baltaziak M, Kanczuga-Koda L, Koda M, Sulkowska U, Famulski W and Sulkowski S: STAT3 and apoptosis regulators: Bak and Bcl-xL in endometrioid adenocarcinomas of different estrogen receptor-alpha immunoprofile. Gynecol Endocrinol 27: 536-540, 2011.
113. Sulkowska U, Wincewicz A, Kanczuga-Koda L, Koda M and Sulkowski S: Eventual proapoptotic or anti-apoptotic impact of aberrantly expressed Cx43 and Cx26 can depend on ER-alpha overexpression in human endometrioid adenocarcinoma. Gynecol Endocrinol 31: 604-608, 2015.
114. Abe S, Iwasaki M, Habata S, Mariya T, Tamate M, Matsuura M, Satohisa S and Saito T: ERα increases endometrial cancer cell resistance to cisplatin via upregulation of BAG3. Oncol Lett 21: 20, 2021.
115. Zhang JW and Peng ZL: Association between the expression of estrogen receptor subunit in endometrial carcinoma and the prognostic factors of endometrial carcinoma. Sichuan Da Xue Xue Bao Yi Xue Ban 35: 843-845, 2004 (In Chinese).
116. Droog M, Nevedomskaya E, Dackus GM, Fles R, Kim Y, Hollema H, Mourits MJ, Nederlof PM, van Boven HH, Linn SC, *et al*: Estrogen receptor alpha wields treatment-specific enhancers between morphologically similar endometrial tumors. Proc Natl Acad Sci USA 114: E1316-E1325, 2017.
117. Sakamoto T, Eguchi H, Omoto Y, Ayabe T, Mori H and Hayashi S: Estrogen receptor-mediated effects of tamoxifen on human endometrial cancer cells. Mol Cell Endocrinol 192: 93-104, 2002.
118. Shah YM and Rowan BG: The Src kinase pathway promotes tamoxifen agonist action in Ishikawa endometrial cells through phosphorylation-dependent stabilization of estrogen receptor (alpha) promoter interaction and elevated steroid receptor coactivator 1 activity. Mol Endocrinol 19: 732-748, 2005.
119. Emons G, Mustea A and Tempfer C: Tamoxifen and endometrial cancer: A Janus-Headed Drug. Cancers 12: 2535, 2020.
120. Nikolic I, Andjelkovic M, Zaric M, Zelen I, Canovic P, Milosavljevic Z and Mitrovic M: Induction of mitochondrial apoptotic pathway by raloxifene and estrogen in human endometrial stromal ThESC cell line. Arch Med Sci 13: 293-301, 2017.

121. Wu Y, Niwa K, Onogi K, Tang L, Mori H and Tamaya T: Effects of selective estrogen receptor modulators and genistein on the expression of ER alpha/beta and COX-1/2 in ovarectomized mouse uteri. Eur J Gynaecol Oncol 28: 89-94, 2007.
122. Boisen MM, Andersen CL, Sreekumar S, Stern AM and Oesterreich S: Treating gynecologic malignancies with selective estrogen receptor downregulators (SERDs): Promise and challenges. Mol Cell Endocrinol 418: 322-333, 2015.
123. Holst F, Hoivik EA, Gibson WJ, Taylor-Weiner A, Schumacher SE, Asmann YW, Grossmann P, Trovik J, Necela BM, Thompson EA, *et al*: Recurrent hormone-binding domain truncated ESR1 amplifications in primary endometrial cancers suggest their implication in hormone independent growth. Sci Rep 6: 25521, 2016.
124. Amita M, Takahashi T, Igarashi H and Nagase S: Clomiphene citrate down-regulates estrogen receptor-alpha through the ubiquitin-proteasome pathway in a human endometrial cancer cell line. Mol Cell Endocrinol 428: 142-147, 2016.
125. Bae-Jump VL, Zhou C, Boggess JF and Gehrig PA: Arsenic trioxide (As2O3) inhibits expression of estrogen receptor-alpha through regulation of the mitogen-activated protein kinase (MAPK) pathway in endometrial cancer cells. Reproductive Sci 15: 1011-1017, 2008.
126. Collins G, Mesiano S and DiFeo A: Effects of metformin on cellular proliferation and steroid hormone receptors in patient-derived, low-grade endometrial cancer cell lines. Reprod Sci 26: 609-618, 2019.
127. Mao X, Dong B, Gao M, Ruan G, Huang M, Braicu EI, Sehouli J and Sun P: Dual targeting of estrogen receptor alpha and estrogen-related receptor alpha: A novel endocrine therapy for endometrial cancer. Onco Targets Ther 12: 6757-6767, 2019.
128. Yamamoto T, Mori T, Sawada M, Kuroboshi H, Tatsumi H, Yoshioka T, Matsushima H, Iwasaku K and Kitawaki J: Estrogen-related receptor-γ regulates estrogen receptor-α responsiveness in uterine endometrial cancer. Int J Gynecol Cancer 22: 1509-1516, 2012.
129. Watanabe M, Kobayashi Y, Takahashi N, Kiguchi K and Ishizuka B: Expression of melatonin receptor (MT1) and interaction between melatonin and estrogen in endometrial cancer cell line. J Obstet Gynaecol Res 34: 567-573, 2008.
130. Faigenbaum R, Haklai R, Ben-Baruch G and Kloog Y: Growth of poorly differentiated endometrial carcinoma is inhibited by combined action of medroxyprogesterone acetate and the Ras inhibitor Salirasib. Oncotarget 4: 316-328, 2013.
131. Miki Y, Iwabuchi E, Takagi K, Suzuki T, Sasano H, Yaegashi N and Ito K: Co-expression of nuclear heterogeneous nuclear ribonucleic protein K and estrogen receptor α in endometrial cancer. Pathol Res Pract 231: 153795-153795, 2022.
132. Krakstad C, Trovik J, Wik E, Engelsen IB, Werner HM, Birkeland E, Raeder MB, Øyan AM, Stefansson IM, Kalland KH, *et al*: Loss of GPER identifies new targets for therapy among a subgroup of ERα-positive endometrial cancer patients with poor outcome. Br J Cancer 106: 1682-1688, 2012.
133. Lin CY, Chao A, Wang TH, Lee LY, Yang LY, Tsai CL, Wang HS and Lai CH: Nucleophosmin/B23 is a negative regulator of estrogen receptor α expression via AP2γ in endometrial cancer cells. Oncotarget 7: 60038-60052, 2016.
134. Guo T, Li B and Gu C: Expression of hPEBP4 negatively correlates with estrogen and progesterone receptors in endometrial carcinoma. J Buon 18: 465-470, 2013.
135. Taylor AH, Al-Azzawi F, Pringle JH and Bell SC: Inhibition of endometrial carcinoma cell growth using antisense estrogen receptor oligodeoxyribonucleotides. Anticancer Res 22: 3993-4003, 2002.
136. Fournier DB, Chisamore M, Lurain JR, Rademaker AW, Jordan VC and Tonetti DA: Protein kinase C α expression is inversely related to ER status in endometrial carcinoma: Possible role in AP-1-mediated proliferation of ER-negative endometrial cancer. Gynecol Oncol 81: 366-372, 2001.
137. Jongen V, Briet J, de Jong R, Ten Hoor K, Boezen M, van der Zee A, Nijman H and Hollema H: Expression of estrogen receptor-alpha and -beta and progesterone receptor-A and -B in a large cohort of patients with endometrioid endometrial cancer. Gynecol Oncol 112: 537-542, 2009.
138. Ren S, Wu J, Yin W, Liao Q, Gong S, Xuan B and Mu X: Researches on the correlation between estrogen and progesterone receptors expression and disease-free survival of endometrial cancer. Cancer Manag Res 12: 12635-12647, 2020.
139. Mylonas I: Prognostic significance and clinical importance of estrogen receptor alpha and beta in human endometrioid adenocarcinomas. Oncol Rep 24: 385-393, 2010.
140. Shabani N, Kuhn C, Kunze S, Schulze S, Mayr D, Dian D, Gingelmaier A, Schindlbeck C, Willgeroth F, Sommer H, *et al*: Prognostic significance of oestrogen receptor alpha (ERalpha) and beta (ERbeta), progesterone receptor A (PR-A) and B (PR-B) in endometrial carcinomas. Eur J Cancer 43: 2434-2444, 2007.
141. Creasman WT: Prognostic significance of hormone receptors in endometrial cancer. Cancer 71: 1467-1470, 1993.
142. Tsujikawa T, Yoshida Y, Kiyono Y, Kurokawa T, Kudo T, Fujibayashi Y, Kotsuji F and Okazawa H: Functional oestrogen receptor α imaging in endometrial carcinoma using 16α-[^{18}F]fluoro-17β-oestradiol PET. Eur J Nucl Med Mol Imaging 38: 37-45, 2011.
143. Sho T, Hachisuga T, Nguyen TT, Urabe R, Kurita T, Kagami S, Kawagoe T, Matsuura Y and Shimajiri S: Expression of estrogen receptor-α as a prognostic factor in patients with uterine serous carcinoma. Int J Gynecol Cancer 24: 102-106, 2014.
144. Kreizman-Shefer H, Pricop J, Goldman S, Elmalah I and Shalev E: Distribution of estrogen and progesterone receptors isoforms in endometrial cancer. Diagnostic Pathology 9: 77, 2014.
145. Pathirage N, Di Nezza LA, Salmonsen LA, Jobling T, Simpson ER and Clyne CD: Expression of aromatase, estrogen receptors, and their coactivators in patients with endometrial cancer. Fertility Sterility 86: 469-472, 2006.
146. Chambliss KL, Wu Q, Oltmann S, Konaniah ES, Umetani M, Korach KS, Thomas GD, Mineo C, Yuhanna IS, Kim SH, *et al*: Non-nuclear estrogen receptor alpha signaling promotes cardiovascular protection but not uterine or breast cancer growth in mice. J Clin Invest 120: 2319-2330, 2010.
147. Duan C, Liu X, Liang S, Yang Z, Xia M, Wang L, Chen S and Yu L: Oestrogen receptor-mediated expression of Olfactomedin 4 regulates the progression of endometrial adenocarcinoma. J Cell Mol Med 18: 863-874, 2014.
148. Ali SH, O'Donnell AL, Balu D, Pohl MB, Seyler MJ, Mohamed S, Mousa S and Dandona P: Estrogen receptor-alpha in the inhibition of cancer growth and angiogenesis. Cancer Res 60: 7094-7098, 2000.
149. Ali SH, O'Donnell AL, Mohamed S, Mousa S and Dandona P: Overexpression of estrogen receptor-α in the endometrial carcinoma cell line Ishikawa: Inhibition of growth and angiogenic factors. Gynecol Oncol 95: 637-645, 2004.
150. Stoner M, Wang F, Wormke M, Nguyen T, Samudio I, Vyhlidal C, Marme D, Finkenzeller G and Safe S: Inhibition of vascular endothelial growth factor expression in HEC1A endometrial cancer cells through interactions of estrogen receptor alpha and Sp3 proteins. J Biol Chem 275: 22769-22779, 2000.
151. Joshi A, Wang H, Jiang G, Douglas W, Chan JS, Korach KS and Ellenson LH: Endometrial tumorigenesis in Pten(+/-) mice is independent of coexistence of estrogen and estrogen receptor α. Am J Pathol 180: 2536-2547, 2012.
152. Wedren S, Lovmar L, Humphreys K, Magnusson C, Melhus H, Syvänen AC, Kindmark A, Landegren U, Fermér ML, Stiger F, *et al*: Estrogen receptor alpha gene polymorphism and endometrial cancer risk-a case-control study. BMC Cancer 8: 322, 2008.
153. Jazaeri O, Shupnik MA, Jazaeri AA and Rice LW: Expression of estrogen receptor alpha mRNA and protein variants in human endometrial carcinoma. Gynecol Oncol 74: 38-47, 1999.
154. Tu BB, Lin SL, Yan LY, Wang ZY, Sun QY and Qiao J: ER-α36, a novel variant of estrogen receptor α, is involved in EGFR-related carcinogenesis in endometrial cancer. Am J Obstet Gynecol 205: 227.e1-e6, 2011.
155. Bryant W, Snowhite AE, Rice LW and Shupnik MA: The estrogen receptor (ER)alpha variant Delta5 exhibits dominant positive activity on ER-regulated promoters in endometrial carcinoma cells. Endocrinology 146: 751-759, 2005.
156. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, *et al*: Integrated genomic characterization of endometrial carcinoma. Nature 497: 67-73, 2013.
157. McAlpine J, Leon-Castillo A and Bosse T: The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol 244: 538-549, 2018.
158. Travaglino A, Raffone A, Gencarelli A, Saracinelli S, Riccardi C, Mollo A, Zullo F and Insabato L: Clinico-pathological features associated with mismatch repair de fi ciency in endometrial undifferentiated/dedifferentiated carcinoma: A systematic review and meta-analysis. Gynecol Oncol 160: 579-585, 2021.

159. Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Nijman HW, Putter H, Bosse T, *et al*: Improved risk assessment by integrating molecular and clinicopathological factors in Early-stage endometrial cancer-combined analysis of the PORTEC cohorts. Clin Cancer Res 22: 4215-4224, 2016.
160. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, Leary A, Edmondson RJ, Powell ME, Crosbie EJ, *et al*: Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 28: 836-844, 2015.
161. Gao C, Wang Y, Tian W, Zhu Y and Xue F: The therapeutic significance of aromatase inhibitors in endometrial carcinoma. Gynecol Oncol 134: 190-195, 2014.
162. Chen H, Liang M and Min J: Efficacy and safety of Bevacizumab-combined chemotherapy for advanced and recurrent endometrial cancer: A systematic review and Meta-analysis. Balkan Med J 38: 7-12, 2021.
163. Stringer EM and Fleming GF: Hormone therapy plus mTOR inhibitors in the treatment of endometrial carcinoma. Eur Endocrinol 9: 18-21, 2013.
164. De Jaeghere A, Tuyaerts S, van Nuffel AMT, Lippens L, Hendrix A, Vuylsteke P, Henry S, Trinh XB, Van Dam PA, Aspeslagh S, *et al*: Pembrolizumab, SBRT, and immunomodulation for recurrent and/or refractory cervical or endometrial carcinoma. Ann Oncol 32 (Suppl 7): S1449-S1450, 2021.
165. Tsoref D, Welch S, Lau S, Biagi J, Tonkin K, Martin LA, Ellard S, Ghatage P, Elit L, Mackay HJ, *et al*: Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Gynecol Oncol 135: 184-189, 2014.
166. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Debled M, Spaëth D, *et al*: Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone Receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol 30: 2718-2724, 2012.
167. Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU, Ashley SE, Francis S, Boeddinghaus I and Walsh G; IMPACT Trialists Group: Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 23: 5108-5116, 2005.
168. Roviello G, Francini E, Perrella A, Laera L, Mazzei MA, Guerrini S, Roviello F, Marrelli D and Petrioli R: Five years of stable disease with maintenance therapy using bevacizumab and tamoxifen in a patient with metastatic breast cancer. Cancer Biol Ther 16: 493-497, 2015.
169. Barberio MT, Thomas S, Chien AJ, Rugo HS, Melisko ME, Angelidakis AN, Pawlowska N, Deal T and Munster PN: Phase II trial with tamoxifen in combination with vorinostat and pembrolizumab in estrogen receptor (+) hormone therapy resistant metastatic breast cancer patients (NCT02395627). J Clin Oncol: 34 (Suppl 15), 2016.
170. van Weelden WJ, Massuger LFAG; ENITEC; Pijnenborg JMA and Romano A: Anti-estrogen Treatment in Endometrial Cancer: A Systematic Review. Front Oncol 9: 359, 2019.
171. Hirschfeld M, Ouyang YQ, Jaeger M, Erbes T, Orlowska-Volk M, Zur Hausen A and Stickeler E: HNRNP G and HTRA2-BETA1 regulate estrogen receptor alpha expression with potential impact on endometrial cancer. BMC Cancer 15: 86, 2015.
172. Stanišić V, Malovannaya A, Qin J, Lonard DM and O'Malley BW: OTU Domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) deubiquitinates estrogen receptor (ER) alpha and affects ERalpha transcriptional activity. J Biol Chem 284: 16135-16145, 2009.
173. Mei S, Ge S, Wang J, Li H, Jing X, Liang K, Zhang X, Xue C, Zhang C and Zhang T: PRMT5 promotes progression of endometrioid adenocarcinoma via ERα and cell cycle signaling pathways. J Pathol Clin Res 7: 154-164, 2021.
174. Tong Z, Liu Y, Yu X, Martinez JD and Xu J: The transcriptional co-activator NCOA6 promotes estrogen-induced GREB1 transcription by recruiting ERα and enhancing enhancer-promoter interactions. J Biol Chem 294: 19667-19682, 2019.
175. Gori I, Pellegrini C, Staedler D, Russell R, Jan C and Canny GO: Tumor necrosis factor-α activates estrogen signaling pathways in endometrial epithelial cells via estrogen receptor α. Mol Cell Endocrinol 345: 27-37, 2011.
176. Hu H, Chen Z, Ji L, Wang Y, Yang M, Lai R, Zhong Y, Zhang X and Wang L: ARID1A-dependent permissive chromatin accessibility licenses estrogen-receptor signaling to regulate circadian rhythms genes in endometrial cancer. Cancer Lett 492: 162-173, 2020.
177. Rodriguez AC, Vahrenkamp JM, Berrett KC, Clark KA, Guillen KP, Scherer SD, Yang CH, Welm BE, Janát-Amsbury MM, Graves BJ and Gertz J: ETV4 is necessary for estrogen signaling and growth in endometrial cancer cells. Cancer Res 80: 1234-1245, 2020.
178. Ring KL, Yates MS, Schmandt R, Onstad M, Zhang Q, Celestino J, Kwan SY and Lu KH: Endometrial cancers with activating KRas mutations have activated estrogen signaling and paradoxical response to MEK inhibition. Int J Gynecol Cancer 27: 854-862, 2017.
179. Fukuda T, Shirane A, Wada-Hiraike O, Oda K, Tanikawa M, Sakuabashi A, Hirano M, Fu H, Morita Y, Miyamoto Y, *et al*: HAND2-mediated proteolysis negatively regulates the function of estrogen receptor α. Mol Med Rep 12: 5538-5544, 2015.
180. Klinge CM, Jernigan SC and Risinger KE: The agonist activity of tamoxifen is inhibited by the short heterodimer partner orphan nuclear receptor in human endometrial cancer cells. Endocrinology 143: 853-867, 2002.
181. Feng Y, Singleton D, Guo C, Gardner A, Pakala S, Kumar R, Jensen E, Zhang J and Khan S: DNA homologous recombination factor SFR1 physically and functionally interacts with estrogen receptor alpha. PLoS One 8: e68075, 2013.
182. Wu WG, Slomovitz BM, Celestino J, Chung L, Thornton A and Lu KH: Coordinate expression of Cdc25B and ER-α is frequent in low-grade endometrioid endometrial carcinoma but uncommon in high-grade endometrioid and nonendometrioid carcinomas. Cancer Res 63: 6195-6199, 2003.
183. Padmanabhan RA, Nirmala L, Murali M and Laloraya M: CrkL is a co-activator of estrogen receptor alpha that enhances tumorigenic potential in cancer. Mol Endocrinol 25: 1499-1512, 2011.
184. Suga S, Kato K, Ohgami T, Yamayoshi A, Adachi S, Asanoma K, Yamaguchi S, Arima T, Kinoshita K and Wake N: An inhibitory effect on cell proliferation by blockage of the MAPK/estrogen receptor/MDM2 signal pathway in gynecologic cancer. Gynecol Oncol 105: 341-350, 2007.
185. Boggess JF, Zhou C, Bae-Jump VL, Gehrig PA and Whang YE: Estrogen-receptor-dependent regulation of telomerase activity in human endometrial cancer cell lines. Gynecol Oncol 103: 417-424, 2006.
186. Jing X, Peng J, Dou Y, Sun J, Ma C, Wang Q, Zhang L, Luo X, Kong B, Zhang Y, *et al*: Macrophage ERα promoted invasion of endometrial cancer cell by mTOR/KIF5B-mediated epithelial to mesenchymal transition. Immunol Cell Biol 97: 563-576, 2019.
187. Xu D, Lin TH, Yeh CR, Cheng MA, Chen LM, Chang C and Yeh S: The wedelolactone derivative inhibits estrogen receptor-mediated breast, endometrial, and ovarian cancer cells growth. Biomed Res Int 2014: 713263, 2014.
188. Labrie F, Labrie C, Bélanger A, Simard J, Giguère V, Tremblay A and Tremblay G: EM-652 (SCH57068), a pure SERM having complete antiestrogenic activity in the mammary gland and endometrium. J Steroid Biochem Mol Biol 79: 213-225, 2001.
189. Fadiel A, Song J, Tivon D, Hamza A, Cardozo T and Naftolin F: Phenytoin is an estrogen receptor α-selective modulator that interacts with helix 12. Reprod Sci 22: 146-155, 2015.
190. Lian Z, Niwa K, Onogi K, Mori H, Harrigan RC and Tamaya T: Anti-tumor effects of herbal medicines on endometrial carcinomas via estrogen receptor-α-related mechanism. Oncol Rep 15: 1133-1136, 2006.
191. Zhang W, Chen JH, Aguilera-Barrantes I, Shiau CW, Sheng X, Wang LS, Stoner GD and Huang YW: Urolithin A suppresses the proliferation of endometrial cancer cells by mediating estrogen receptor-α-dependent gene expression. Mol Nutr Food Res 60: 2387-2395, 2016.
192. Karaboğa Arslan AK and Yerer MB: α-Chaconine and α-Solanine Inhibit RL95-2 Endometrium Cancer Cell Proliferation by Reducing Expression of Akt (Ser473) and ERα (Ser167). Nutrients 10: 672, 2018.
193. Leong H, Firestone GL and Bjeldanes LF: Cytostatic effects of 3,3'-diindolylmethane in human endometrial cancer cells result from an estrogen receptor-mediated increase in transforming growth factor-alpha expression. Carcinogenesis 22: 1809-1817, 2001.
194. Aoyama H, Couse JF, Hewitt SC, Haseman JK, He H, Zheng X, Majstoravich S, Korach KS and Dixon D: Upregulation of estrogen receptor expression in the uterus of ovariectomized B6C3F1 mice and Ishikawa cells treated with bromoethane. Toxicol Appl Pharmacol 209: 226-235, 2005.

195. Kim HI, Kim T, Kim JE, Lee J, Heo J, Lee NR, Kim NJ and Inn KS: NJK14013, a novel synthetic estrogen receptor-α agonist, exhibits estrogen receptor-independent, tumor cell-specific cytotoxicity. Int J Oncol 47: 280-286, 2015.
196. Karaca B, Bakır E, Yerer MB, Cumaoğlu A, Hamurcu Z and Eken A: Doxazosin and erlotinib have anticancer effects in the endometrial cancer cell and important roles in ERα and Wnt/β-catenin signaling pathways. J Bioch Mol Toxicol 35: e22905, 2021.
197. Wang J, Liu X, Zhang X, Liu J, Ye S, Xiao S, Chen H and Wang H: Induction of apoptosis by c9, t11-CLA in human endometrial cancer RL 95-2 cells via ERα-mediated pathway. Chem Phys Lipids 175-176: 27-32, 2013.
198. Shah YM, Al-Dhaheri M, Dong Y, Ip C, Jones FE and Rowan BG: Selenium disrupts estrogen receptor (alpha) signaling and potentiates tamoxifen antagonism in endometrial cancer cells and tamoxifen-resistant breast cancer cells. Mol Cancer Ther 4: 1239-1249, 2005.