

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 ER α . As a key nuclear transcription factor, ER α 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 ER α and the regulation of ER α in multiple dimensions

are described. In addition, the classical E2/ER α signaling pathway and the crosstalk between ER α and other EC regulators are elucidated, as well as the therapeutic targeting of ER α , which may provide a new direction for clinical applications of ER α 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-[¹⁸F]fluoro-2-deoxy-D-glucose; FES, 16 α -[¹⁸F]fluoro-17 β -estradiol; FTO, fat mass and obesity-associated protein; GJIC, gap junctional intercellular communication; GPER, G protein-coupled ER; hnRNP, 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; PKC α , protein kinase C α ; PPAR γ , 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 α , signaling pathway, regulator

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 ER α and ER β , 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, ER α was the first to be identified, has been most comprehensively researched and is the most well understood (15). ER α 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). ER α 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 ER α in 100% of 43 cases of endometrial hyperplasia, which is a precursor of EC, and 88.5% of 368 cases of EC. Although ER α is oncogenic in EC, patients with ER α -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 ER α 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 ER α and regulation of the *ESR1* gene, ER α mRNA and ER α protein are firstly introduced, respectively. Next, the classical E2/ER α signaling pathway and the role of ER α in EC, according to upstream, co-regulatory and downstream factors, are described in detail. Finally, the clinical significance of ER α in EC is discussed, focusing on ER α -targeted therapy and its role as an indicator of good prognosis of EC.

2. Structure of ER α

ER α 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-ER α 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 ER α homodimer binds to the palindromic GGTCAnnnTGACC 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 ER α (29). Moreover, the D domain has been shown to act 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 ER α (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).

ER β is similar to ER α in protein structure, and also contains A, B, C, D, E and F domains (20). However, the major difference between ER β and ER α is in AF-1. The activity of AF-1 of ER β is relatively low, while that of AF-2 is similar to that of ER α , 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 ER β is weaker than that of ER α , and they are equivalent if only AF-2 is required (32).

3. Regulation of ER α

The regulation of ER α can be divided into three different aspects: Transcription of *ESR1*, translation of ER α mRNA and post-translational modification of ER α protein (33-35). The different types of regulation of ER α 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 ER α in EC, the following sections mainly summarize the regulation of ER α in relation to EC (Table II).

Regulation of the transcription of ESR1. Compared with the translational regulation of ER α 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.

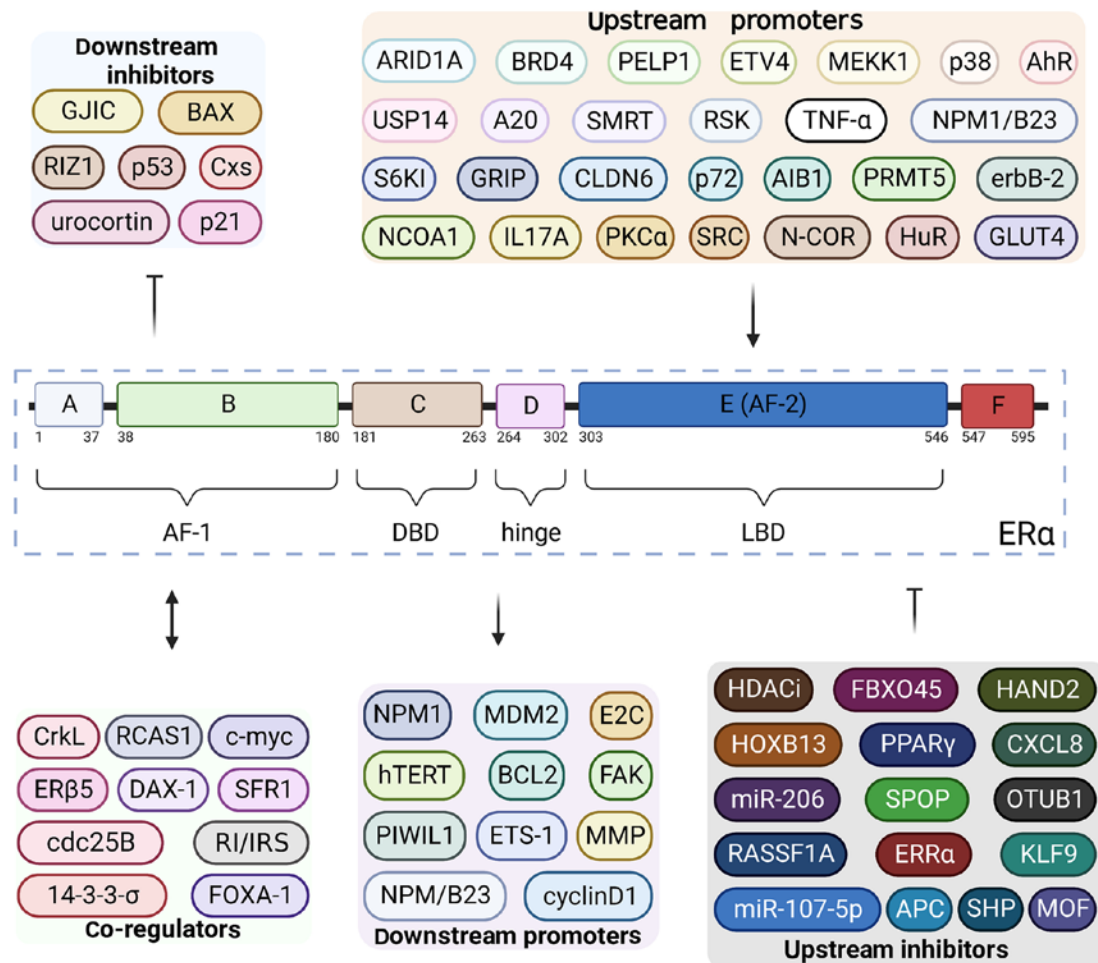


Figure 1. Structure and regulation of ERα. ERα is composed of six domains, A-F, and had upstream, downstream and co-regulators. The upstream and downstream factors include promoters and inhibitors. These regulators can affect the role of ERα in endometrial cancer. ERα, estrogen receptor α.

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 ER α in EC.

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

Table II. Continued.

First author/s, year	Regulation	Regulator	Site	Mode	Effect	(Refs.)
Stanišić <i>et al</i> , 2009		OTUB1	C/D domain	De-ubiquitination	Inhibits the transcriptional activity of ER α and the development of EC	(172)
Su <i>et al</i> , 2023		USP14	N/A	De-ubiquitination	Promotes the development of EC	(56)
Lv <i>et al</i> , 2019		A20	N/A	De-ubiquitination	Promotes the development of EC	(57)
Wu <i>et al</i> , 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; ER α , estrogen receptor α ; ERR α , estrogen receptor-related receptor α ; FBXO45, F-box protein 45; HDACi, histone deacetylase inhibitor; HNRNPG, heterogeneous nuclear ribonucleoprotein G; HTRA2- β 1, high-temperature requirement serine protease A2- β 1; miR, microRNA; MOF, males absent on the first; N/A, not applicable; N-COR, nuclear receptor corepressor; OTUB1, OUT deubiquitinase, ubiquitin aldehyde binding 1; PPAR γ , 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 ER α mRNA, indicating that these regulatory factors may be associated with EC. Conversely, it has been suggested that ER-related receptor (ERR) α may regulate ER α -mediated pathways by interfering with ER α transcription (39). Also, in EC, methylation of the CpG island of the *ESR1* gene has been found to be negatively associated with ER α expression (40). In addition, histone deacetylase (HDAC) inhibitors directly inhibit the transcription of *ESR1* promoters and thus regulate the E2/ER α signaling pathway (33).

Regulation of the translation of ER α mRNA. Studies on translational regulation have mainly focused on the regulation of ER α mRNA by microRNAs (miRNAs or miRs). Bao *et al* (36) showed that miR-107-5p directly targets ER α mRNA to downregulate the expression of ER α mRNA and protein, thereby promoting tumor proliferation and EC invasion. Similarly, other studies have shown that miR-222-3p downregulates the expression of ER α , thereby promoting the proliferation and invasion of EC and increasing raloxifene resistance (41,42). Furthermore, miR-206 has been reported to inhibit ER α -dependent proliferation, impair the invasion ability of ER α -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 (PPAR γ) expression inhibited ER α expression at the mRNA and protein levels, and impaired the ability of Ishikawa cells to migrate and invade. Therefore, activation of PPAR γ may enhance the effects of anti-E2 therapy in ER α -positive EC through ER α -mediated ER transactivation (43).

Regulation of the post-translational modification of ER α protein. The post-translational modification of ER α includes

phosphorylation, ubiquitination, acetylation, sumoylation, methylation and glycosylation, among which phosphorylation, ubiquitination and acetylation are associated with EC development (37,44-48). Phosphorylation of ER α generally regulates the transcriptional activity of ER α 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 ER α S118 is necessary for the activity of AF-1, *in vivo* and *in vitro*. Furthermore, another study demonstrated that the phosphorylation of ER α 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 ER α S167, thereby increasing the ability of ER α 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 ER α at S167, and the levels of such phosphorylation are elevated in advanced EC. In the normal endometrium during the menstrual cycle, phosphorylation of ER α 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 ER α T311, which blocks ER α nuclear export and promotes the interaction between ER α and steroid receptor co-activator p160 (53).

Ubiquitination of ER α 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 ER α and triggers ER α 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 ER α (55). AhR has been shown

to promote the ubiquitination and degradation of ER α 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 ER α for degradation (54). By contrast, de-ubiquitination mediated by de-ubiquitinating enzymes, including ubiquitin-specific protease 14 and ubiquitin-editing enzyme A20, promotes the transcriptional activity of ER α by inhibiting its degradation, thereby leading to the development of EC (56,57). Regarding the acetylation of ER α , Wu *et al* (37) demonstrated that moesin absent on the first (MOF), also known as lysine acetyltransferase 8, mediates the acetylation of ER α , maintains the stability of ER α , and regulates the activity of ER α and its target genes. However, the study also indicated that MOF inhibits the proliferation of EC cells (37).

4. Classical E2/ER α 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 ER α , which belongs to the superfamily of nuclear receptors, only the classical E2/ER α signaling pathway is outlined here (Fig. 2).

The classical E2/ER α 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 ER α to form a homologous or heterodimer of ER α (60). In the classic approach, the third step is that the activated ER α binds to E2 response elements (EREs), which comprise two AGGTCA motifs in a palindromic structure (39). The ER α -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 ER α with EREs, and co-regulators act synergistically with ER α 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 ER α 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). ER α 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/ER α signaling pathway plays a key role in the occurrence and development of EC. For instance, ER α 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, ER α also binds EREs and co-activators with ERR α (63). However, E2 down-regulates the expression of ERR α at the mRNA and protein levels in Ishikawa cells by a mechanism involving ER α (64).

ERR α competes with ER α for the same target gene loci and co-regulators, which interferes with the E2/ER α signaling pathway and thereby potentially suppresses the development of EC (39).

5. Roles of ER α in EC

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

Upstream of ER α . Several upstream proteins of ER α participate in the occurrence and development of EC by affecting the transcriptional activity and expression of ER α (Table III). Since the proteins that mediate the post-translational modifications of ER α 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 ER α . 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 ER α , thereby inducing the transactivation of ER α in EC; this suggests that transactivation of ER α 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/ER α signaling pathway has been shown to trigger the proliferation of EC cells (66). Specifically, E2 increases the expression and activation of Pak4 in ER α -positive EC cells via the PI3K/AKT/mTOR signaling pathway, and the accumulation of Pak4 and phosphorylated Pak4 in the nucleus promotes ER α transactivation, which enhances the transcriptional activity of ER α and ER α -dependent gene expression, leading to EC cell proliferation (66). Although these upstream regulators of ER α 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 (PKC α) expression stimulates the ligand-independent activation of ER-dependent promoters to enhance the transcriptional capacity of ER α , thereby inducing endometrial proliferation (72). Furthermore, Frigo *et al* (73) showed that p38 promotes the proliferation of EC cells by stimulating ER α -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 ER α Ser518 in a ligand-independent manner to activate the transcriptional activity of ER α , thereby promoting tumor migration. In addition, mitogen-activated protein kinase kinase kinase 1 also induces the transcriptional activity of ER α 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

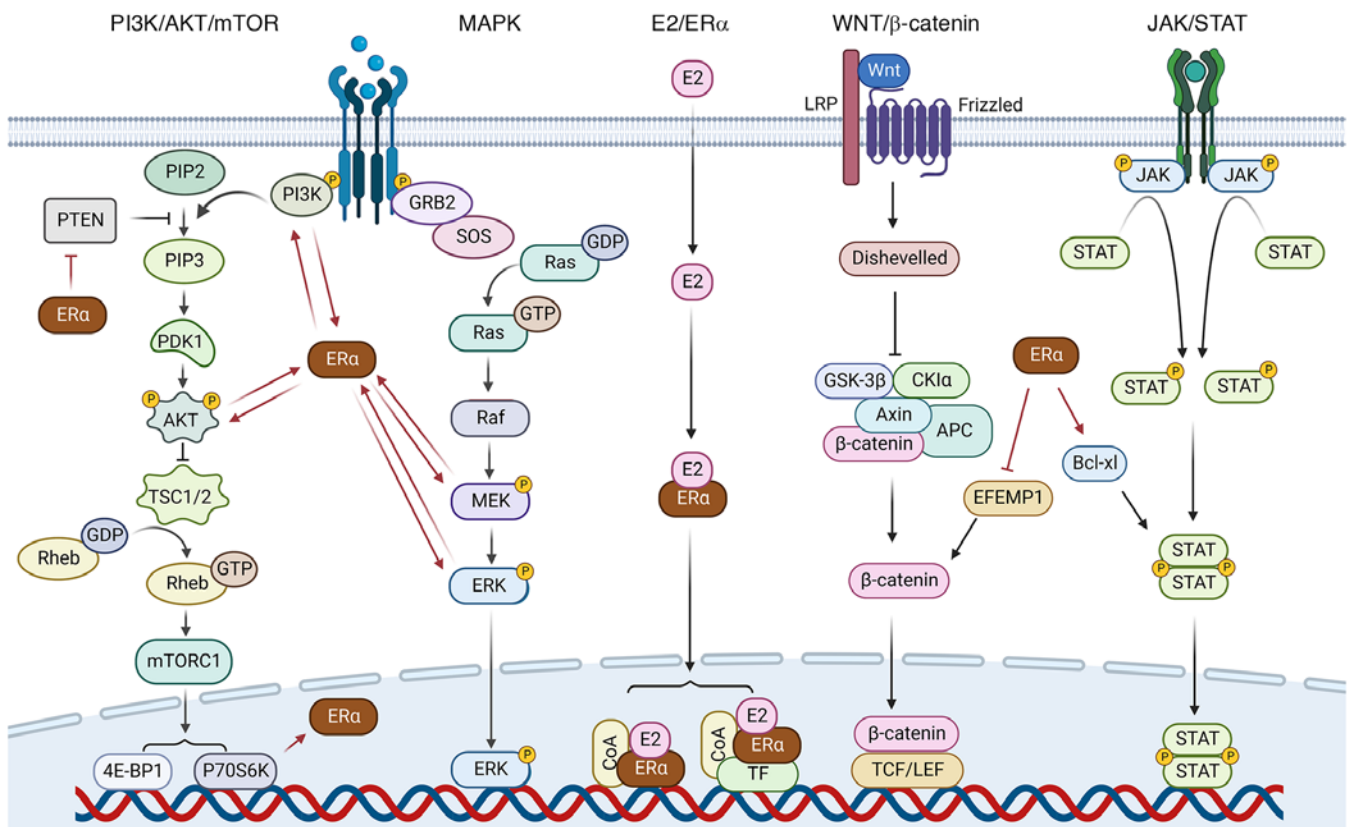


Figure 2. Signaling pathways associated with ER α . ER α is mainly involved in the E2/ER α signaling pathway, which includes classical and non-classical approaches. In addition, ER α regulates the PI3K/AKT/mTOR, MAPK, WNT/ β -catenin and JAK/STAT signaling pathways. ER α , estrogen receptor α ; E2, estrogen/estradiol.

negative upstream regulators that inhibit the transcription of ER α and thus inhibit EC development. For example, the activation of Pten and subsequent inhibition of AKT have an inhibitory effect on several ER α -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 ER α in endometrial epithelial cells, and suggested that it acts at a node of the ER α genomic pathway to negatively regulate the proliferation of EC.

Another means by which upstream regulators regulate ER α is by affecting the expression of ER α . For example, Cheng *et al* (78) found that interleukin 17A induced the proliferation and metastasis of EC cells by promoting the expression of ER α . Likewise, human antigen R has been reported to increase the expression of ER α 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 ER α , leading to accelerated epithelial-mesenchymal transition (EMT) in EC (80). Conversely, the inhibition of ER α expression delays the development of EC. For example, the downregulation of ER α 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 ER α 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 ER α 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 ER α expression (83). Specifically, CXCL8 secreted by tumor-associated macrophages was shown to downregulate the expression of ER α in EC cells via homeobox 13, which was associated with the invasive ability of the cells (83).

Co-regulators of ER α . ER α 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, ER α and ER β 5 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 ER α expression was positively correlated with c-myc expression, suggesting that c-myc expression may contribute to the development of EC through ER α . With regard to specific effects, ER α 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 ER α .

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

Table III. Continued.

First author/s, year	ER α	Regulator	Result	Effect on EC	(Refs.)
Collins <i>et al</i> , 2020	Co-regulator	ER β 5	Forms a heterodimer with ER α	Promotes development	(88)
Wincewicz <i>et al</i> , 2011		STAT3 and BCL-xL	Interacts with STAT3 and BCL-xL	Promotes development	(112)
Feng <i>et al</i> , 2013		SFR1	Interacts with ER α	Promotes development	(181)
Wu <i>et al</i> , 2003		Cdc25	Interacts with ER α	Promotes development	(182)
Bircan <i>et al</i> , 2005		c-myc	Interacts with ER α	Promotes development	(89)
Padmanabhan <i>et al</i> , 2011		CrkL	Interacts with ER α	Promotes proliferation	(183)
Saito <i>et al</i> , 2005		DAX-1	Interacts with ER α	Inhibits proliferation	(87)
Wang <i>et al</i> , 2014		FOXA1	Interacts with ER α	Inhibits proliferation	(91)
Zhou <i>et al</i> , 2008		RCAS1	Interacts with ER α	Promotes metastasis	(84)
Tian <i>et al</i> , 2019		Insulin/insulin receptor signaling pathway	Crosstalk with ER α	Promotes development	(85)
Zhang <i>et al</i> , 2019		EGFR/ERK signaling pathway	Crosstalk with ER α	Promotes development and resistance to chemotherapy	(86)
Nakayama <i>et al</i> , 2005		14-3-3 σ	Synergistic effect with ER α	Promotes proliferation and inhibits apoptosis	(90)
Chen <i>et al</i> , 2020	Downstream	PIWIL1	Upregulates PIWIL1	Promotes proliferation	(92)
Zhang <i>et al</i> , 2012		BCL2	Upregulates BCL2	Promotes proliferation	(95)
Chao <i>et al</i> , 2013		NPM	Upregulates NPM	Promotes proliferation	(96)
Hu <i>et al</i> , 2020		Cyclin D1	Upregulates cyclin D1	Promotes proliferation	(97)
Zhang <i>et al</i> , 2012		BAX	Downregulates BAX	Promotes proliferation	(95)
Hu <i>et al</i> , 2020		p21	Downregulates p21	Promotes proliferation	(97)
Saito <i>et al</i> , 2004		GJIC	Downregulates GJIC	Promotes proliferation	(98)
Mizumoto <i>et al</i> , 2002		MMP-1, -7, -9	Upregulates MMP-1, -7, -9	Promotes invasion and metastasis	(102)
Mizumoto <i>et al</i> , 2002		ETS-1	Upregulates ETS-1	Promotes invasion and metastasis	(102)
Flamini <i>et al</i> , 2011		FAK	Upregulates FAK	Promotes invasion and metastasis	(93)
Liu <i>et al</i> , 2020		E2C	Upregulates E2C	Promotes invasion and metastasis	(103)
Yang <i>et al</i> , 2016		EFEMP1	Downregulates EFEMP1	Promotes invasion and metastasis	(106)
Owens <i>et al</i> , 2017		RIZ1	Downregulates RIZ1	Promotes invasion and metastasis	(108)
Yang <i>et al</i> , 2017		Urocortin	Downregulates urocortin	Promotes invasion and metastasis	(107)
Abe <i>et al</i> , 2011		AKT	AKT nuclear localization	Inhibits apoptosis	(111)
Sayed <i>et al</i> , 2007		p53	Downregulates p53	Inhibits apoptosis	(94)
Sulkowska <i>et al</i> , 2015		Cx43	Downregulates Cx43	Influences apoptosis	(113)
Sulkowska <i>et al</i> , 2015		Cx26	Downregulates Cx26	Influences apoptosis	(113)
Abe <i>et al</i> , 2021		miR-29b	Downregulates miR-29b	Induces drug resistance	(114)
Abe <i>et al</i> , 2021		BAG3	Upregulates BAG3	Induces drug resistance	(114)
Abe <i>et al</i> , 2021		Mcl-1	Upregulates Mcl-1	Induces drug resistance	(114)

Table III. Continued.

First author/s, year	ER α	Regulator	Result	Effect on EC	(Refs.)
Ali <i>et al</i> , 2000		Angiogenic factor	Downregulates angiogenic factor	Inhibits cancer blood vessel formation	(148)
Suga <i>et al</i> , 2007		MDM2	Downregulates p21	Promotes development	(184)
Duan <i>et al</i> , 2014		OLFM4	Downregulates OLFM4	Inhibits development	(147)
Boggess <i>et al</i> , 2006		hTERT	Promotes hTERT gene transcription and telomerase activation	Promotes malignant transformation	(185)
Chen <i>et al</i> , 2018		miR-200c	Upregulates miR-200c	Promotes proliferation and inhibits apoptosis	(100)
Chen <i>et al</i> , 2018		Pten	Downregulates Pten	Promotes proliferation and inhibits apoptosis	(100)
Zhou <i>et al</i> , 2014		NPM1	Upregulates NPM1	Promotes proliferation, inhibits differentiation and inhibits apoptosis	(3)
Hou <i>et al</i> , 2014		p58 α	Activates the PI3K/AKT/mTOR signaling pathway	Promotes proliferation, migration and invasion	(68)
Zhu <i>et al</i> , 2016; Zhang <i>et al</i> , 2012		PI3K/AKT/mTOR signaling pathway	Nuclear localization and nuclear accumulation of FTO	Promotes proliferation, invasion and metastasis	(99, 104)
Jing <i>et al</i> , 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; ER α , 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; PKC α , 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 ER α and 14-3-3 σ , 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 ER α may be involved in the development and metastasis of EC. Crosstalk between ER α 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/ER α 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 ER α 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 ER α in EC cells. Additionally, ER α 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 ER α . In addition to the upstream and co-regulators of ER α , downstream proteins or target genes are also involved in the promotion of EC development by ER α . These mainly contribute to three aspects: Proliferation, metastasis and invasion, and anti-apoptosis (Table III) (92-94).

Proliferation. ER α 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, ER α 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, ER α 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 ER α -mediated signaling rather than via ER β , 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/ER α 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, ER α 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, ER α 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 ER α by E2 stimulated cell growth and inhibited GJIC by inhibiting the expression of Cxs, leading to the proliferation of EC cells.

ER α 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 ER α overexpression promotes the phosphorylation of p85 α , 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 ER α 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/ER α 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 ER α 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 ER α 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 ER α 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 ER α 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/ER α also stimulates the invasion of EC cells through the PI3K/AKT/mTOR and MAPK signaling pathways (104). However, Wik *et al* (105) found that ER α -negative tumors are also associated with EMT, which is linked to the PI3K/AKT/mTOR signaling pathway. In addition to the aforementioned substrates, ER α 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/ER α signaling pathway downregulated EFEMP1 expression in EC cells by the direct binding of ER α 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 ER α reduces the expression of urocortin, a protein that inhibits EC cell migration; therefore, the E2/ER α 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 ER α antagonist ICI182780 reversed this effect, suggesting that a potential mechanism by which RIZ1 promotes EC involves the E2/ER α signaling pathway (107).

Anti-apoptosis. There have been only a few studies on ER α in terms of anti-apoptosis and drug resistance. It has been shown that by directly binding to p53, ER α 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 ER α and survivin in EC cells, which reduced the apoptosis of these cells. In addition, during the G1 phase of EC, the E2/ER α 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 ER α may enhance the interaction between

STAT3 and the apoptosis regulator BCL-extra large, which is crucial for the development of endometrioid adenocarcinoma (112). Furthermore, ER α 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 ER α 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 ER α overexpression improves the survival of EC cells in the presence of cisplatin, suggesting that ER α may enhance the resistance of EC cells to anticancer drugs via the overexpression of BAG3 (114).

6. Clinical application

ER α is used as a therapeutic target for EC, and several drugs targeting ER α are currently being applied for the treatment of EC. In addition, ER α 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-ER α agents in EC. Tamoxifen affects the interaction of ER α with co-regulatory factors and alters the DNA binding characteristics of ER α in EC tissue (116). Tamoxifen contributes to the proliferation and carcinogenesis of EC via the promotion of ER α 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 ER α 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 ER α 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 ER α 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 ER α 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 ER α induced by E2 (121). Boisen *et al* (122) found that ICI-182780 binds to ER α to inhibit E2, and also competently binds to the LBD of ER α and induces ER α degradation through the ubiquitin-proteasome system. However, in primary EC, splicing variants and point mutations present in the LBD are associated with hormone-independent ER α activity, which can produce ligand-independent or anti-E2 therapy resistance (123). Similar to ICI-182780, clomiphene citrate has been shown to reduce the ER α protein level via induction of ubiquitin-proteasome system without affecting the ER α mRNA level in Ishikawa cells (124). Arsenic trioxide, however, inhibits both ER α 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

ER α -mediated oncogenic signaling pathways to induce the death of EC cells, not only via the inhibition of ER α 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 ER α 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 ER α at the protein and mRNA levels, resulting in a reduction in the expression of the ER α -target genes keratin-19 and WNT-1 (126). Compared with anti-ER α treatment alone, the dual targeting of ER α and ERR α 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 ERR γ agonist, inhibits the growth of ER α -positive EC cells but promotes the growth of ER α -negative EC cells (128). In addition, melatonin has been shown to enhance the anti-EC effect of chemotherapy, particularly paclitaxel, by the inhibition of ER α 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 ER α -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 ER α 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 ER α , 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 ER α 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 ER α in GC, and a loss of GPER in patients with ER α -positive GC is associated with a poor prognosis. Additionally, using bioinformatics they found that HDAC inhibitors may be promising drugs for the treatment of ER α -positive EC with GPER deletion (132). Although E2 activates NPM via ER α , increased NPM expression inhibits ER α (133). Since strategies to promote ER α re-expression may allow patients with relapsed EC to resume endocrine therapy, inhibition of NPM may represent a strategy to promote ER α re-expression and ultimately restore the sensitivity of EC to hormone therapy (133). Moreover, the expression of ER α in EC has been found to negatively correlate with human phosphatidylethanolamine-binding protein 4 (hPEBP4), PKC α and antisense oligodeoxynucleotides against ER α , suggesting that hPEBP4, PKC α and nucleic acid therapeutics may counter the ER α and serve as potential agents against the proliferation of EC cells (134-136).

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

Table IV. ER α -associated potential drugs for EC.

First author/s, year	Drug	Mechanism	Effect on EC	(Refs.)
Xu <i>et al</i> , 2014	BTB	Inhibits the transactivation of ER α	Inhibits the development of EC	(187)
Han <i>et al</i> , 2016	TSEC	Inhibits the transcriptional activity of ER α and promotes the degradation of ER α	Inhibits the development of EC	(55)
Labrie <i>et al</i> , 2001	EM-652	Inhibits the AF-1 and AF-2 functions of ER α	Inhibits the development of EC	(188)
Miki <i>et al</i> , 2022	hnRNPK	Interacts with ER α	Inhibits the development of EC	(131)
Fadiel <i>et al</i> , 2015	Phenytoin	Interacts with the LBD of ER α and thus interferes with the binding of ER α ligands to ER α	Inhibits the development of EC	(189)
Lian <i>et al</i> , 2006	Juzen-taiho-to, Shimotsu-to	Inhibit the expression of ER α mRNA	Inhibit the development of EC	(190)
Bae-Jump <i>et al</i> , 2008	Arsenic trioxide	Downregulates ER α by phosphorylation of p42/p44	Inhibits the development of EC	(125)
Amita <i>et al</i> , 2016	Clomiphene citrate	Induces ER α protein degradation	Inhibits the development of EC	(124)
Boisen <i>et al</i> , 2015	Kaempferol	Inhibits ER α and survivin, and induces p53	Inhibits the development of EC	(122)
Faigenbaum <i>et al</i> , 2013	FTS and MPA	Inhibits the transcriptional activity of ER α	Inhibits the proliferation of EC	(130)
Guo <i>et al</i> , 2013	hPEBP4	Downregulates the expression of ER α	Inhibits the proliferation of EC	(134)
Zhang <i>et al</i> , 2016	Urolithin A	May downregulate the expression of ER α	Inhibits the proliferation of EC	(191)
Fournier <i>et al</i> , 2001	PKC α	May downregulate the expression of ER α	Inhibits the proliferation of EC	(136)
Taylor <i>et al</i> , 2002	Oligodeoxyribonucleotides	May downregulate the expression of ER α	Inhibits the proliferation of EC	(135)
Karaboğ̃a <i>et al</i> , 2018	α -chaconine, α -solanine	Reduce the expression and activity of the ER α signaling pathway	Inhibits the proliferation of EC	(192)
Hu <i>et al</i> , 2020	Metformin	Inhibits ER α	Inhibits the proliferation of EC	(97)
Krakstad <i>et al</i> , 2012	HDAC inhibitors	Downregulate ER α and its downstream genes	Inhibits the proliferation of EC	(132)
Leong <i>et al</i> , 2001	DIM	Mediates ER α -dependent TGF- α transcriptional activation	Inhibits the proliferation of EC	(193)
Yamamoto <i>et al</i> , 2012	DY131	Inhibits ERR γ .	Inhibits the proliferation of EC	(128)
Aoyama <i>et al</i> , 2005	Bromoethane	May upregulate the expression of ER α	Promotes the proliferation of EC	(194)
Kim <i>et al</i> , 2015	NJK14013	Activates ER α -mediated transcription in EC	Promotes apoptosis and inhibits proliferation of EC	(195)
Karaca <i>et al</i> , 2021	Doxazosin, erlotinib	Inhibits the expression of ER α	Promotes the apoptosis of EC	(196)
Wang <i>et al</i> , 2013	Conjugated linoleic acid	Inhibits the ER α -mediated pathway	Promotes the apoptosis of EC	(197)
Droog <i>et al</i> , 2017; Emons <i>et al</i> , 2020	Tamoxifen	Affects the interaction of ER α with co-regulators and changes the DNA binding characteristics of ER α 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 <i>et al</i> , 2005	Methylseleninic acid	Inhibits the expression of ER α -dependent genes, such as pS2 and c-myc	Promotes tamoxifen-resistant EC resensitization to tamoxifen	(198)
Lin <i>et al</i> , 2016	NPM inhibitor	Downregulates the expression of ER α	Sensitizes to hormone therapy	(133)
Watanabe <i>et al</i> , 2008	Melatonin and paclitaxel	Inhibits the expression of ER α	Has an enhanced chemotherapy effect on EC	(129)
Boisen <i>et al</i> , 2015	ICI-182780	Binds ER α to inhibit E2 and induces ER α 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; ER α , estrogen receptor α ; ERR γ , 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; PKC α , protein kinase C α ; TSEC, tissue-selective estrogen complex.

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

7. Discussion

The role of ER α in EC is becoming increasingly clear. In general, ER α , as a transcriptional factor, is an oncogenic factor in EC. ER α regulates transcriptional activity with modulation by upstream co-regulatory factors, and then promotes transcription of its downstream target genes via the E2/ER α

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

The other key aspect of ER α in EC is that it may also act as a tumor suppressor. It has been shown that ER α 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 ER α -mediated signaling pathway regulates the expression of olfactomedin 4 (OLFM4), and that the expression of OLFM4 and ER α 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, ER α blocks the formation of tumor blood vessels (148). The high levels of ER α in EC have

been indicated to inhibit tumor growth via the regulation of angiogenic factors such as integrin $\alpha\beta3$, thereby reducing the blood supply (148,149). In addition, ER α 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 α ^{-/-} mice. These mice also exhibit a high incidence of carcinoma *in situ* and invasive carcinoma, suggesting that EC can develop in the absence of ER α (151).

In addition to ER α , there are some *ESR1* gene, ER α mRNA and ER α 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 ER α mRNA variants in all endometrial samples, including premenopausal and postmenopausal endometrial samples, but only observed ER α protein splicing variants in EC. ER α 36, a variant of ER α protein, triggers the activation of epidermal growth factor receptor-associated extracellular signal-regulated kinases, which play a carcinogenic role in EC (154). Similarly, the ER α variant d5 exhibits a dominant positive activity on ER α -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 ER α provides a feasible direction for further understanding the pathogenesis of EC.

Although ER α is the most common target of targeted therapy in breast cancer, anti-ER α 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 ER α 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 ER α 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 ER α may not have much effect on the other three molecular subtypes. Clinically, in addition to targeting ER α , 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-ER α 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-ER α drugs can have serious side effects and these occur frequently (170). Therefore, it is necessary to find improved ER α -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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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

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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