Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(9): 199
https://doi.org/10.31083/j.ceog5009199

Review

Research Progress of Estrogen Receptor in Ovarian Cancer

Mengchen Zhang[1,2,†], Haohui Xu[1,2,†], Yixin Zhang[1,2], Zhanfei Li[1,2], Wenqiang Meng[1,2], Jiayi Xia[1,2], Wentao Lei[1,2], Kai Meng[1,3,*], Yan Guo[4,*]

[1]Collaborative Innovation Center for Birth Defect Research and Transformation of Shandong Province, Jining Medical University, 272067 Jining, Shandong, China
[2]College of Second Clinical Medical, Jining Medical University, 272067 Jining, Shandong, China
[3]Lin He's Academician Workstation of New Medicine and Clinical Translation, Jining Medical University, 272067 Jining, Shandong, China
[4]College of Basic Medicine, Jining Medical University, 272067 Jining, Shandong, China
*Correspondence: mengkai521888@126.com (Kai Meng); 15166798126@163.com (Yan Guo)
[†]These authors contributed equally.
Academic Editor: Felix Wong
Submitted: 18 April 2023 Revised: 2 June 2023 Accepted: 8 June 2023 Published: 24 September 2023

Abstract

Objective: This review aims to provide some theoretical guidance for the precise treatment of ovarian cancer and the development of estrogen-related drugs. **Mechanism**: Ovarian cancer is one of the leading causes of death in gynecological cancer patients, mainly affecting middle-aged and elderly women. It has the characteristics of hidden location, strong heterogeneity and lack of specific symptoms in the early stage. Numerous studies have shown that estrogen receptor (ER) plays an important role in different types of cancer, including ovarian cancer. Accordingly, the study of ER signaling pathways and related regulatory factors in ovarian cancer cells should help us understand the pathogenesis of ovarian cancer. **Findings in Brief**: The expression of estrogen receptor subtypes is related to ovarian cancer gene and leads to ovarian cancer. Estrogen receptor modulators appear to be an important factor in the prognosis of patients with ovarian cancer after hormone therapy. **Conclusions**: This review summarizes the regulatory mechanism of ER in the occurrence and development of ovarian cancer and outlines the specific role of estrogen receptor modulators (SERMs) in the treatment and prevention of ovarian cancer.

Keywords: ovarian cancer; estrogen; estrogen receptor; receptor modulators; precise treatment

1. Introduction

Ovarian cancer, one of the most common cancers in women, is evaluated as one of the leading causes of death in the world. A cancer survey report in Poland in 2019 showed that the incidence of ovarian cancer in women in the country ranked fifth, lower than breast cancer and cervical cancer, but higher than gastric cancer, colon cancer and pancreatic cancer [1]. Due to its late diagnosis, it is typically diagnosed at an advanced stage. In recent years, the overall survival rate has not significantly improved, while treatment efficacy remains unsatisfactory; it is therefore necessary to intensify the study of the occurrence and development of ovarian cancer [2,3]. New findings on estrogen have uncovered its association with ovarian cancer, highlighting the pivotal role of estrogen receptors (ER) as its primary target. These investigations propose that ER could serve as a crucial contributing factor in the development of ovarian cancer [4,5]. Drawing upon recent research advancements, this comprehensive review highlights the intricate relationship between ovarian cancer, estrogen and its receptors. It thoroughly examines the regulatory influence exerted by ERs and selective estrogen receptor modulators (SERMs) on the initiation and progression of ovarian cancer. Furthermore, this review anticipates the promising potential of SERMs in the treatment of ovarian cancer, paving the way for a broader spectrum of therapeutic avenues [6].

2. Overview of Estrogen and Ovarian Cancer

Estrogen (E), a class of steroid hormones that includes estradiol and estrone, is mainly secreted by the ovaries. It plays an important role in reproductive organs such as the ovaries, testes, uterus, and non-reproductive organs such as skeletal muscles and mammary glands [7]. ER is a protein receptor found in many tissues such as ovary that binds to estrogen. It can be divided into nuclear receptor and membrane receptor: Among them, ERα (*ESR1*) and ERβ (*ESR2*) in the nuclear receptor superfamily have complex action pathways and slow genomic response. Thus, nuclear receptors are often referred to as SLOW-ER [8]. In addition to the classical ERs, recent research has shed light on the significance of membrane receptors in estrogen-related processes. The discovery of GPER1 (GPR30), Gq-mER, and ER-X within the membrane receptor family has revealed their role in mediating rapid cellular responses upon ligand binding, without involving genomic reactions. The membrane receptors, often referred to as RAPID-ER, exhibit a shorter duration of action. As one of the earliest studied estrogen nuclear receptors, ERα plays the role of transcription factor, while ER β, as a DNA-binding protein, has a significant multi-level inhibitory effect on ERα by affecting the expression of ERα regulatory genes, which is associated with cell signal transduction and periodic proliferation or death [9–11]. ERα and ERβ, as isoforms, are

full-length proteins composed of six different domains, including the A/B region, and ligand-independent transcriptional activation region (AF-1). Region C (DNA binding region) has a double zinc finger structure, which assists this region in binding to specific DNA. Zone D (hinged zone) may serve as the connection between zone C and zone E as well as the E/F zone containing AF-2 (LBD) [12]. The seven-transmembrane membranous G-protein-coupled estrogen receptor 1 (GPER1/GPR30) belongs to the G-protein-coupled receptor (GPCR) family and is widely distributed in the ovary and various tissue cells such as granulosa cells, related to the occurrence of ovarian granulosa cell tumor (GCT) [13].

As a common cancer affecting women, ovarian cancer can be divided into different types. Based on the classification of the primary anatomical location, ovarian cancer is divided into two main types: primary ovarian cancer (POC), which originates within the ovary itself, and secondary metastatic ovarian cancer (SMOC), which is characterized by the spread of cancer cells from other tissues to the ovary. POC can be divided into epithelial, germ cell and specific sex cord interstitial sources, among which epithelial ovarian cancer accounts for the highest proportion [14]. Kajiyama *et al*. [15] found that there are roughly four primary sites of SMOC, ranked in descending order of occurrence: the gastrointestinal tract, appendix, breast and pancreas. The incidence of gastrointestinal ovarian cancer is the highest, far more than the sum of the other three, and the harm range is the most extensive [16].

ERs have different mechanisms and outcomes depending upon the types of ovarian cancer, and the same ER can have different outcomes in different types of ovarian cancer. At present, most of the clinical literature focuses on the study of ER on a few types of high-risk ovarian cancer, such as serous ovarian cancer, mucinous ovarian carcinoma. However, some types of ovarian cancer with a low incidence and a high degree of malignancy are rarely mentioned in the current literature. The reasons are as follows: such patients have a high degree of malignancy, low 5-year survival rate, low incidence, few research cases, and lack of funding and research. It is thus of great significance to study how this type of ovarian cancer plays a role in disease progression by affecting ER, and to increase the research on the lesser studied types of ovarian cancer to elucidate the pathogenesis of ovarian cancer and subsequent new drug development. In several rare cases of ovarian cancer, the literature only describes the clinical manifestations, while the relationship with ER has not been studied thoroughly or at all. Simultaneously, owing to the heterogeneity of ovarian cancer, the efficacy of drug therapy varies. Each drug exhibits distinct effects in the treatment of specific ovarian cancer subtypes. While certain drugs may play a role in one ovarian cancer subtype or in a variety of ovarian cancer subtypes, the role of currently known modulators is not fully elucidated. Exploring the detailed effects of various modulators on different types of ovarian cancer and achieving accurate treatment of drugs will be crucial for the treatment of ovarian cancer. Accordingly, we summarize the degree and source of benign and malignant ovarian cancer according to the type of ovarian cancer (Table 1, Ref. [17–32]), in an effort to supplement the content of this review.

3. The Mechanism of Estrogen Nuclear Receptor in Regulating the Occurrence and Development of Ovarian Cancer

Estrogen, as a fat-soluble steroid hormone, can enter the cell membrane and bind to nuclear receptors in a free diffusion state, that is, the two combine to form an E-ER polymer complex on the nuclear membrane [33]. After estrogen binds to nuclear receptors, the quaternary spatial structure of the complex will change under the induction of heat shock protein (Hsp90), and then binds to an ERα/β to form a homologous or heterologous ER dimer complex [33–35]. Estrogen-response element (ERE) is a DNA fragment containing a palindrome structure. It has confirmed that ER recruits and collects costimulatory factors such as P160. Under the synergistic effect of these costimulatory factors, the complex polymer binds to the estrogen response element, and then binds to form an E-ER-ERE complex. The complex regulates the expression of transcription products such as a long non-coding RNA (ElncRNA1) in the upstream of ovarian cancer target genes [36–39]. Studies have shown that this long non-coding RNA is induced by estrogen and promotes the occurrence of epithelial ovarian cancer (EOC) [39,40]. If the ERE element is absent, the AP-1 transcription factor can replace it, but ER cannot directly act on the AP-1 sequence, so other proteins (such as Jun/Fos coactivator) must be used as mediators [9,41]. It should be emphasized that the action pathways of ERα and ERβ are different here. The AF domain on the E-ERα complex binds to Jun/Fos, facilitating the transcription of target genes, an interaction that may contribute to the development and progression of ovarian cancer. The E-ERβ complex can inhibit the downstream transcription pathway initiated by AP-1 [42,43].

Cyclin D1 gene is a kind of proto-oncogene downstream of AP-1 sequence. Cyclin D1 promotes the proliferation of serous ovarian carcinoma (SOC) cells by regulating cyclin-dependent kinases (CDKs) to phosphorylate specific target proteins. The combination of cyclin D1 and CDKs is the rate-limiting step in regulating the cell cycle [44]. Studies have shown that ERα up-regulates the expression of *cyclin D1* gene without affecting ovarian cancer cells such as PEO14 and BG1. ERβ down-regulates the expression of *cyclin D1* in a ligand-independent manner and inhibits the development of ovarian cancer cells such as PEO14 and BG1 [12]. Nuclear *PELP1* is a proto-oncogene in the vast majority of ovarian cancer cases, and its combined expression with *cyclin D1* gene is closely related to the incidence of ovarian cancer [12,45,46]. There-

Table 1. Benign and malignant degree of different types of ovarian cancer and their source.

Type of ovarian cancer	Benign/Malignant	Primary/metastatic (source)	References
Fibroma	Benign	Primary (Ĥ specific sex cord stroma)	[17]
Mucinous tumors	Benign	Primary (ovarian germinal epithelium)	[18]
Serous cystadenoma	Benign	Primary (ovarian germinal epithelium)	[18,19]
Immature Teratoma	Benign	Primary (germ cell)	[20]
Asexual cell tumor	Malignant	Primary (germ cell)	[21]
Choriocarcinoma	Malignant	Primary (germ cell)	[22]
Clear cell carcinoma	Malignant	Primary (ovarian germinal epithelium)	[23]
Embryonal carcinoma	Malignant	Primary (germ cell)	[24]
Endodermal sinus tumor	Malignant	Primary (germ cell)	[25]
Endometrioid tumor	Malignant	Primary (ovarian germinal epithelium)	[26]
Granulosa cell tumor	Malignant	Primary (Ĥ specific cord stroma)	[27]
Mixed germ cell tumor	Malignant	Primary (germ cell)	[28]
Metastatic carcinoma of digestive tract	Malignant	Metastatic (digestive tract)	[29]
Metastatic carcinoma of breast	Malignant	Metastatic (Mammary gland)	[30]
Metastatic carcinoma of genital tract	Malignant	Metastatic (genital tract)	[31]
Serous Ovarian Carcinoma	Malignant	Primary (ovarian germinal epithelium)	[18,19]
Sex cord stromal tumor	Malignant	Primary (Ĥ specific cord stroma)	[32]
Testicular blastoma of ovary	Malignant	Primary (Ĥ specific cord stroma)	[31]

fore, immunohistochemical staining of cyclin D1 and nuclear PELP1 gene coding products can be used to predict the diagnosis of ERα overexpression and ERβ loss of expression. In addition, ecotropic viral integration site-1 (EVI1) is also associated with the occurrence of ovarian cancer. The expression of this gene is related to the invasion of ovarian cancer cells into other cells. It has been reported that EVI1 can not only regulate the occurrence of high-grade serous ovarian cancer (HGSOC) through non-genomic pathways, but also affect the expression of ERα to indirectly interfere with the proliferation of HGSOC [5,47]. For example, EVI1 can activate transcription in the upstream of ERα gene, promote the expression of ERα, and induce the occurrence of high-grade serous ovarian cancer. At the same time, it can regulate the ERK/mTOR signaling pathway by activating the target gene *PBK*, thereby affecting the proliferation and prognosis of high-grade serous ovarian cancer [5,48]. Meanwhile, Andersen *et al.* [49] found that HGSOC cells were dependent on E2 stimulation under 2d, 3D growth and forced suspension cultures, and observed that the endocrine response of fulvestrant was more intense than that treated with 4OHT in the xenotransplantation model of infected mice. The expression of ERα gene was inhibited by ERα inhibitor XCT790, and it was non-toxic to cells [50]. A small number of nuclear receptors present in the cytoplasm bind to cell membrane surface proteins (caveolin-1, HPIP, etc.) and participate in signal transduction pathways mediated by MAPK and AKT pathways [51,52]. Studies have found that the activation of p38 MAPK signaling pathway can inhibit the proliferation and invasion of ovarian cancer cells such as OVCAR3 and SKOV3, which is negatively correlated with the overall survival rate of ovarian cancer patients [53]. PI3K/AKT/mTOR axis can inhibit the expression of P-CNA protein in ovarian cancer cells, inhibit the development of ovarian cancer, and inhibit PI3K-AKT pathway, which is helpful to the prognosis and survival of patients with endometrioid ovarian carcinoma [54,55].

ERα inhibitor tamoxifen (TAM) down-regulates genes related to oxidative phosphorylation and activates the mitogen activated protein kinase (MAPK) signaling pathway. It competitively antagonizes estradiol, occupies receptors, and inhibits ERα to play a role in inhibiting the growth of ovarian cancer cells. Moreover, moderate to high doses of tamoxifen can significantly suppress the growth and proliferation of SKOV3 ovarian cancer cells by regulating vascular endothelial growth factor (VEGF) [56–58]. In line with these findings, Velden *et al.* [59] reported that 40% of ovarian cancer patients had stable CA125 titer following tamoxifen treatment, and there was no clinical progress. In addition, the nuclear receptor can initiate the transcription of some special substances related to the expression of estrogen, such as LDL, progesterone receptor B, GATA1, and STAT5 after binding with the important factor Sp1 that plays a transcriptional intermediary role [9,60–63]. Transcriptional regulators can also regulate these processes: Li *et al.* [64] found that transcriptional regulator PES1 regulates the expression of ERα or ERβ, while its ablation results in a significant down-regulation of ERα and promotes transcriptional activity in EOC. This process is limited by receptor modulators.

4. Mechanism of Regulating the Development of Ovarian Cancer beyond Nuclear Receptors

Several studies have shown that the combination of estrogen and GPER1 can activate MAP kinase pathway

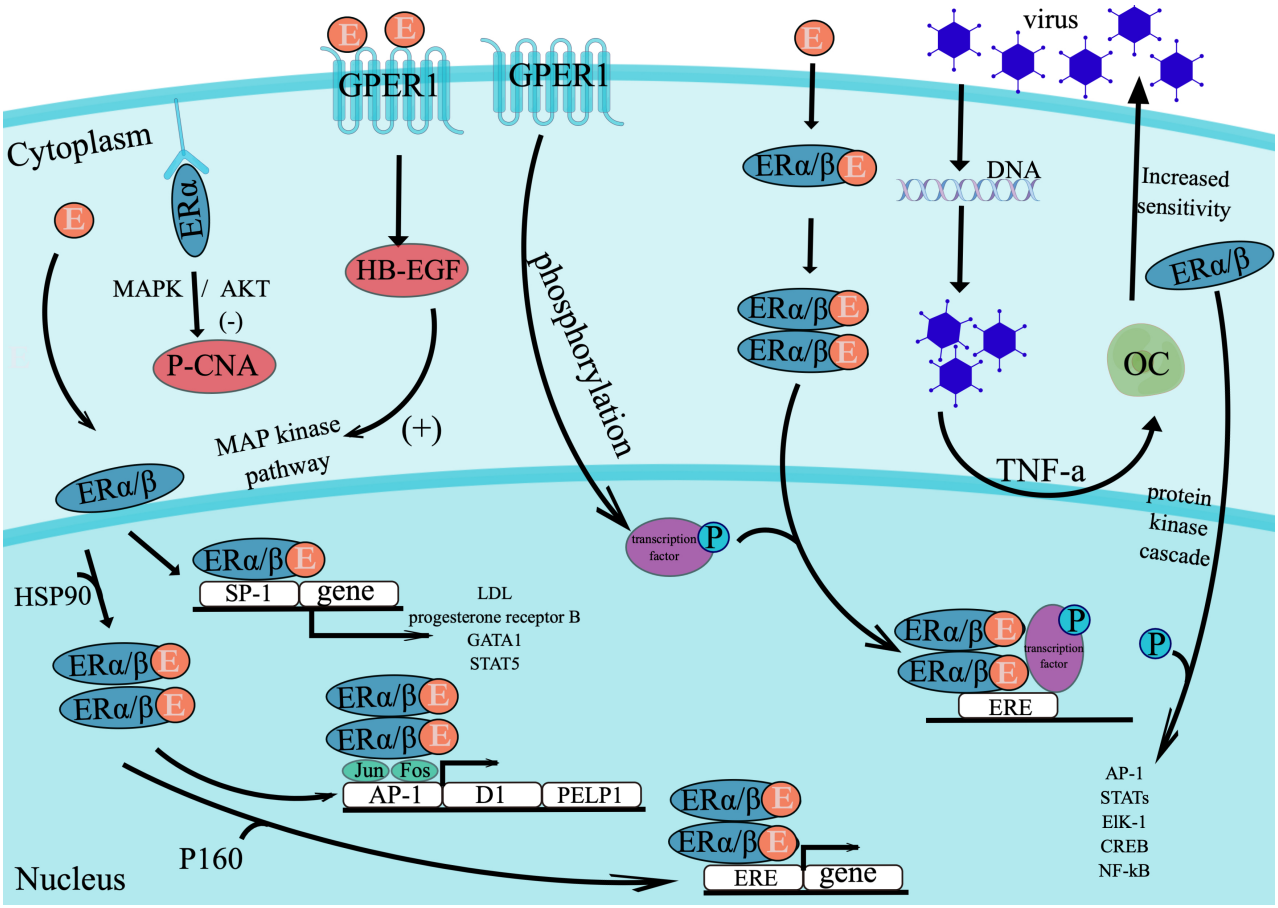

Fig. 1. This figure shows the effect of estrogen on cell gene expression by acting on nuclear receptors and membrane receptors. By Figdraw. E, estrogen; ER, estrogen receptor; OC, ovarian cancer cell; virus, oncolytic adenoviruses; P-CAN, proliferating cell nuclear antigen; HB-EGF, heparin-binding epidermal growth factor; ERE, estrogen-response element; P, phosphorylation.

by releasing heparin-binding epidermal growth factor (HB-EGF). Overexpression of mitogen-activated protein kinase kinase kinase 3 (MAP3K3) is recognized as an indicator of poor prognosis in ovarian cancer. High expression of phosphorylated p38 MAPK in EOC leads to an increased risk of death in ovarian cancer patients [65,66]. The increase of GPER1 expression is accompanied by the increase of matrix metalloproteinase-9 (MMP9) (r = 1.000, p = 0.002) [67]. The high expression of MMP9, MMP10, MMP12 and MMP25 is positively correlated with the overall survival rate of ovarian cancer [67,68]. Based on these findings, GPER1 may be involved in the invasion and metastasis of EOC, and is a potential indicator for early diagnosis and malignant degree prediction of EOC. Schüler-Toprak *et al.* [69] demonstrated that treatment with GPER1 agonist G-1 led to transcriptome responses related to growth inhibition and reduced the growth of OVCAR-3 and OAW-42 ovarian cancer cell lines.

Nuclear and membrane receptors both play an independent role and can synergistically interfere with ovarian cancer: hormones bind to a small number of nuclear receptors in the cytoplasm, which dimerize and migrate to the nucleus and bind to transcription factors phosphorylated by GPER1, and then bind to ERE and other sites through nuclear receptors to regulate transcription. ERα, ERβ and GPER1 can also initiate gene transcription by phosphorylation of transcription factors AP-1, STATs, Elk-1, CREB and nuclear factor kappa b (NF-κB) outside the nuclear membrane through protein-kinase cascade [9,70]. The classical NF-κB pathway involves the activation of the NF-κB transcription factor complex in the cytoplasm, followed by ERα binding to NF-κB, exhibiting a priming effect. The complex quickly enters the nucleus and binds to the promoter region of DNA, inducing the occurrence of ovarian cancer [71,72]. ERs have two signal pathways: nuclear initiated steroid signaling (NISS) and membrane initiated steroid signaling (MISS), both of which are signal transduction in the form of E-ER complex [45]. Studies have shown that some protein fragments of ERα and ERβ can bind to other cofactors or be phosphorylated by PKA and PKC signaling pathways to activate ER [73]. Some cytokines that do not require estrogen-mediated action alone also fall into this category: Salako *et al.* [74] found that the decrease of tumor necrosis factor-α (TNF-α) increased the sensitivity of ovarian cancer cells to oncolytic adenoviruses. The viral complex inhibited the expression of cellular inhibitor

of apoptosis-1 and -2 (cIAP1 and cIAP2) by producing cytokines such as TNF-α, which reduced the expression of X-linked inhibitor of apoptosis protein (XIAP). The knockdown of this protein gene enhanced the effect of carboplatin on ovarian cancer cells and decreased cell viability [74]. In addition, ligands on the surface of cancer cells can promote ovarian cancer metastasis after binding to the domain of the selectin in the adhesion molecule [75]. We map the mechanism by which estrogen nuclear receptors and non-nuclear receptors regulate the initiation and progression of ovarian cancer (Fig. 1) at the conclusion of this article.

5. Treatment and Prevention of Ovarian Cancer

We summarized the risk factors of ovarian cancer and the different effects of ER modulators on ovarian cancer. Our summary of the risk factors of ovarian cancer should enhance women's awareness of prevention and help protect women from ovarian cancer. Our focus on SERMs should contribute to researchers' further exploration of non-toxic and efficient anti-cancer drugs [76,77]. Risk factors of ovarian cancer include postmenopausal estrogen therapy, unmarried infertility, smoking, obesity, and age. [77]. The ovaries of unmarried infertile women will continue to ovulate, causing damage to the ovarian epithelium, which may lead to mutations in tumor suppressor genes such as *TP53* and *BRCA1/2*. Bilateral salpingectomy and delayed salpingectomy (BS/DO) have been found to reduce the risk of ovarian cancer in *BRCA1/2* mutation carriers, Meanwhile, a study investigated that loss of paired box 2 (*PAX2*) in murine oviductal epithelium (MOE) implies a precursor of high-grade serous ovarian cancer (HGSOC) with secretory cell proliferation (SCOUT), deletion of which generates a messenger RNA expression pattern [78,79]. It is closely related to the enrichment of estrogen signaling genes and the increase of estrogen receptor α expression [78]. Therefore, the removal of fallopian tubes may delay the development of cancer by affecting the expression of genes related to ER and estrogen transmission [78,79]. Tobacco can accelerate cell proliferation and invasion and inhibit cell apoptosis by promoting mesenchymal transformation at the cellular level. Obesity may promote the occurrence of ovarian cancer by producing IGF-1 and hyperinsulinemia [70,76]. Studies have shown that the incidence rate of women aged 65 years and older accounts for approximately half of the total age group, which may be due to the damage to ovarian epithelium caused by the longer ovarian ovulation time of elderly women [2]. Where possible, minimizing these conditions can serve as a more effective approach for ovarian cancer prevention.

Chan *et al*. [80] reported that MPP inhibits the growth of SKOV3 ovarian cancer cells by targeted regulation of ERα and blocking ERα-mediated phosphorylation of Ser473 (serine 473) in AKT. In addition, MPP can indirectly reduce the expression level of AKT by inhibiting Erα and increasing the expression of pro-apoptotic protein (caspase-3 and Bax) and tumor suppressor gene *p53*, thus breaking the balance of cell apoptosis. This pathway can promote the apoptosis of ovarian cancer cell A2780, inhibiting the cell cycle and proliferation of ovarian cancer cells [81]. Sun *et al*. [82] found that the AKT/mTOR/p70S6 pathway can promote the apoptosis of ovarian cancer. Curcumin, which has an inhibitory effect on this pathway, can increase the expression of pro-apoptotic protein (caspase-3 and Bax) and inhibit the expression of proliferation protein (PCNA). As an ERα inhibitor, curcumin can inhibit the malignant proliferation of ovarian cancer cells SKOV3 and A2780 [82,83]. Ki67 is a nuclear protein related to the proliferation of tumor cells such as ovarian cancer; its low expression indicates that the activity of cell proliferation is inhibited [84]. At the same time, two epigenetic regulators, DOT1L and menin, can also play a synergistic anti-proliferation role in OC cells by regulating the estrogen receptor signaling pathway, thereby improving the survival and treatment of OC patients [85]. By comparing the ovarian cancer in the combination group with the control group, it was found that the combination of cisplatin-curcumin can reduce the volume and weight of ovarian cancer in rats by more than 80%, while the expression of Ki67 protein in rats significantly decreased, which reduced the size of ovarian tumors in appearance and inhibited the resistance of ovarian cancer rats to cisplatin [86]. After treatment of SKOV3 cells with ERβ agonist DPN, the expression of phosphorylated AKT was reduced by 80%, which inhibited ovarian cancer cells [80]. At the same time, the tumor formation was also significantly reduced after the inhibitor AZD8835 inhibited AKT phosphorylation, both of which demonstrated the necessity of PI3K/AKT signaling pathway in the progression of EOC. FAK and PI3K/AKT signaling pathways can also be induced by ERβ agonist ERB-041, mediating cell cycle arrest and apoptosis, reducing the migration and invasion of ovarian cancer cells [87]. Experiments have shown that the affinity of ERβ agonist S-DPN to ER (Ki = 0.27 $\pm$ 0.05) is very close to that of cognate ligandE2 (Ki = 0.13 $\pm$ 0.02). Compared with its enantiomer R-DPN (Ki = 1.82 $\pm$ 0.21), S-DPN is an *in vitro* transcriptional activator and a bioactive form of DPN [88].

The combination of ER modulator and receptor can not only regulate ovarian cancer through PI3K/AKT signal pathway, but also through NF-κB channel for adjustment: Schüler-Toprak *et al*. [89] treated OVCAR-3 and OAW-42 cells with four ERβ agonists (ERB-041, WAY200070, 3β-Adiol, Liquiritigenin) and found that the expression of *PTCH2*, an ERβ agonist-regulated gene, was significantly down-regulated, indicating growth inhibition of ovarian cancer cell lines. Liquiritigenin and S-equol, two ERβ agonists, significantly reduce the activity of NF-κB in ovarian cancer cells such as SKOV3, which is beneficial to the apoptosis of ovarian cancer cells. Liu *et al*. [90] found that caffeic acid phenethyl ester (CAPE) can inhibit the

Table 2. Comparison of CAS numbers of different estrogen nuclear receptor modulators and the classification of regulatory effects.

Regulator	CAS number	ERα agonist	ERα inhibitor	ERβ agonist	ERβ inhibitor	Mechanism of action	References
Tamoxifen	10540-29-1		√		√	Tamoxifen blocks the mitosis of estrogen by competitively binding to ER and exerts its antiproliferative effect.	[57]
curcumin	458-37-7		√	√		Curcumin promotes the expression of apoptosis promoting protein and Circ-PLEKHM3, inhibit the expression of proliferation protein and AKT/mTOR/p70S6 pathway.	[82,83]
Bisphenol AF	1478-61-1	√			√	BPAF can exert a higher estrogenic effect than BPA through the GPER pathway.	[101]
Bisphenol C	79-97-0	√			√	Due to the enlarged halogen bond, BPC has a strong binding ability to the two ERs, and is very active for ERα, but antagonizes ERβ.	[102]
Bisphenol AP	1571-75-1	√			√	Halogen atom-based dispersion is the main driving force for the activity of ERα-agonists and ERβ-antagonists .	[103]
Bispheno B	77-40-7	√			√	Combination of BPB and GPER leads to activation of subsequent signaling pathways.	[101]
Bisphenol Z	843-55-0	√			√	Halogen atom-based dispersion is the main driving force for the activity of ERα-agonists and ERβ-antagonists .	[103]
Apigenin	520-36-5	√		√		Apigenin competitively binds to E2 and has weak selectivity for ERβ.	[104]
Liq	578-86-9			√		Liq significantly down-regulation of *PTCH2* gene expression and decrease of NF-κB activity in SKOV3 and other ovarian cancer cells.	[89]
ERB-041	524684-52-4			√		ERB-041 reduces migration and invasion of ovarian cancer cells by mediating FAK and PI3K / AKT signaling pathways to induce cell cycle arrest and apoptosis.	[87]
WAY200070	440122-66-7			√		Downregulation of *PTCH2* gene expression regulated by ERβ agonist inhibits growth of ovarian cancer cell lines.	[89]
3β-Adiol	unk			√		3β-Adiol significantly down-regulated the expression of ERβ agonist-regulated gene *PTCH2* and inhibited the growth of ovarian cancer cell lines.	[89]
OSU-ERb-12	unk			√		Increased expression of tumor suppressors FOXO1 and FOXO3a inhibits epithelial-mesenchymal transition (EMT).	[92,93]
LY500307	533884-09-2			√		LY500307 upregulates cell cycle arrest gene *CDKN1A* to promote ovarian cancer stem cell apoptosis.	[94]
Diaryl propionitrile	1428-67-7			√		Diaryl propionitrile reduced phosphorylated AKT expression by 80 %.	[80]
Cyclic Ketoximes	unk			√		Cyclic Ketoximes recruits coactivators to form active complexes with ERβ with nanomolar affinity.	[105]

ER, estrogen receptor; √, the regulator has a promoting effect; unk, unknow.

progression of ovarian cancer cells by NF-κB pathway, inhibiting the survival, metastasis and immune escape of cancer stem cells. Morin can also inhibit the expression of NF-κB and IL6/8 induced by TNF-α and reduce the tumor volume of ovarian cancer in nude mice [91]. These studies show that inhibition of the NF-κB pathway has a positive effect on inhibiting ovarian cancer progression. In breast cancer cell lines, ERβ agonists (OSU-ERb-12 and LY500307) can promote the expression of tumor suppressor FOXO1 and FOXO3a [92]. OSU-ERb-12 also reduces the occurrence of ovarian cancer stem cells (OCSCs) by inhibiting epithelial-to-mesenchymal transition (EMT) [93]. At the genetic level, LY500307 (Erteberel) significantly reduced the invasiveness of OCSCs and up-regulated the cell cycle arrest gene *CDKN1A* to promote OCSCs apoptosis [94]. Studies have shown that decreased expression of apoptosis and cell cycle arrest gene *CDKN1A* in epithelioid SKOV3 and HEY ovarian cancer cells can lead to cell proliferation [95]. Overexpression of FOXO1 is associated with a low survival rate of EOC, and miRNA-96 negatively regulates FOXO3a in the miRNA-96/FOXO3a axis. A decrease in miRNA-96 levels reduces ovarian cancer cell invasion by targeting FOXO3a and increasing its levels [96,97]. Studies evaluated that the high incidence of tumor suppressor gene *p53* mutation and high expression of ERβ2 and FOXM1 are markers of HGSOC, and ERβ2-mutant p53-FOXM1 axis promotes proliferation of HGSOC cell lines, inhibits apoptosis, and increases carboplatin resistance. This axis may thus be used as a new therapeutic target for HGSOC with a therapeutic potential for HGSOC [98]. In addition, curcumin can also promote the expression of a tumor suppressor (Circ-PLEKHM3), which increases the expression of suppressor of morphogenesis in genitalia 1 (SMG1) after down-regulating the expression of miR-320a, which is beneficial to the apoptosis of cancer cells and reduces the degree of aggregation [82,99,100]. Curcumin has a dual inhibitory effect on tumor growth and development [82,99,100] (Table 2, Ref. [57,80,82,83,87,89,92–94,101–105]).

6. Summary and Outlook

This review provides an overview of ovarian cancer, estrogen and its receptors, highlighting the mechanisms underlying ovarian cancer development, the involvement of estrogen receptors, and the significance of ER modulators. Current evidence suggests that ER signaling is associated with the development of ovarian cancer. However, the underlying mechanism of how ER and related signals regulate the growth of ovarian cancer needs to be further elucidated; further prospective research is warranted. Goals of such research should be to clarify the pathway of ER activity, find suitable and convenient therapeutic targets, and to choose efficient ERα inhibitors, ERβ agonists or alternative modes of ovarian cancer treatment.

Author Contributions

YG and KM contributed to the study conception and design. KM, MZ and HX performed the research. MZ, HX, ZL and WM wrote the manuscript. YG and KM revised the manuscript critically for important intellectual content. ZL, WM, HX, YZ, JX and WL contributed to the acquisition, analysis, or interpretation of data for the work. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was supported by grants from Research Fund for Lin He's Academician Workstation of New Medicine and Clinical Translation in Jining Medical University (JYHL2021MS13), Teachers Research Support Fund in Jining Medical University (JYFC2019KJ001) and College Students' Innovation Training Program of Jining Medical University (cx2021038).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Didkowska J, Wojciechowska U, Michalek IM, Caetano Dos Santos FL. Cancer incidence and mortality in Poland in 2019. Scientific Reports. 2022; 12: 10875.

[2] Tew WP. Ovarian cancer in the older woman. Journal of Geriatric Oncology. 2016; 7: 354–361.

[3] Forstner R. Early detection of ovarian cancer. European Radiology. 2020; 30: 5370–5373.

[4] Langdon SP. Estrogen Receptor Signaling in Cancer. Cancers. 2020; 12: 2744.

[5] Wang Z, Li Y, Wang N, Li P, Kong B, Liu Z. EVI1 overexpression promotes ovarian cancer progression by regulating estrogen signaling. Molecular and Cellular Endocrinology. 2021; 534: 111367.

[6] Goldstein S. SERMs: past and present. Maturitas. 2019; 124: 125–125.

[7] Ikeda K, Horie-Inoue K, Inoue S. Functions of estrogen and estrogen receptor signaling on skeletal muscle. The Journal of Steroid Biochemistry and Molecular Biology. 2019; 191: 105375.

[8] Wojnarowski K, Cholewińska P, Palić D, Bednarska M, Jarosz M, Wiśniewska I. Estrogen Receptors Mediated Negative Effects of Estrogens and Xenoestrogens in Teleost Fishes-Review. International Journal of Molecular Sciences. 2022; 23: 2605.

[9] Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Advances in Protein Chemistry and Structural Biology. 2019; 116: 135–170.

[10] Thomas C, Gustafsson JÅ. The different roles of ER subtypes in

cancer biology and therapy. Nature Reviews. Cancer. 2011; 11: 597–608.
[11] Bossard C, Busson M, Vindrieux D, Gaudin F, Machelon V, Brigitte M, *et al*. Potential role of estrogen receptor beta as a tumor suppressor of epithelial ovarian cancer. PLoS ONE. 2012; 7: e44787.
[12] Kyriakidis I, Papaioannidou P. Estrogen receptor beta and ovarian cancer: a key to pathogenesis and response to therapy. Archives of Gynecology and Obstetrics. 2016; 293: 1161–1168.
[13] Heublein S, Mayr D, Friese K, Jarrin-Franco MC, Lenhard M, Mayerhofer A, *et al*. The G-protein-coupled estrogen receptor (GPER/GPR30) in ovarian granulosa cell tumors. International Journal of Molecular Sciences. 2014; 15: 15161–15172.
[14] Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian cancers: pathogenesis and prevention strategies. Nature Reviews. Cancer. 2017; 17: 65–74.
[15] Kajiyama H, Suzuki S, Utsumi F, Nishino K, Niimi K, Mizuno M, *et al*. Epidemiological overview of metastatic ovarian carcinoma: long-term experience of TOTSG database. Nagoya Journal of Medical Science. 2019; 81: 193–198.
[16] Syed M. Krukenberg tumour. Postgraduate Medical Journal. 2022; 98: e42.
[17] Sudour-Bonnange H, Rocourt N, Aubry E, Lervat C, Kerdraon O. A Sex Cord-stromal Tumor, Specifically a Fibroma, Arising From the Uterine Corpus: A Case Report. International Journal of Gynecological Pathology: Official Journal of the International Society of Gynecological Pathologists. 2016; 35: 33–37.
[18] Ricci F, Affatato R, Carrassa L, Damia G. Recent Insights into Mucinous Ovarian Carcinoma. International Journal of Molecular Sciences. 2018; 19: 1569.
[19] Dey P, Nakayama K, Razia S, Ishikawa M, Ishibashi T, Yamashita H, *et al*. Development of Low-Grade Serous Ovarian Carcinoma from Benign Ovarian Serous Cystadenoma Cells. Cancers. 2022; 14: 1506.
[20] El Helali A, Kwok GST, Tse KY. Adjuvant and post-surgical treatment in non-epithelial ovarian cancer. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2022; 78: 74–85.
[21] Dietl J, Horny HP, Kaiserling E. Frequent overexpression of p53 in dysgerminoma of the ovary. Gynecologic and Obstetric Investigation. 1994; 37: 141–142.
[22] Mizukawa M, Sato H, Nishikawa S, Kashimura A, Nishina H, Sakairi T. Spontaneous ovarian choriocarcinoma in a young ICR mouse. Journal of Toxicologic Pathology. 2021; 34: 123–125.
[23] Iida Y, Okamoto A, Hollis RL, Gourley C, Herrington CS. Clear cell carcinoma of the ovary: a clinical and molecular perspective. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2021; 31: 605–616.
[24] Banco B, Ferrari R, Stefanello D, Groppetti D, Pecile A, Faverzani S, *et al*. Ovarian Embryonal Carcinoma in a Dog. Journal of Comparative Pathology. 2017; 157: 291–295.
[25] Perry MF, Jackson AL, Herzog TJ, Billingsley CC. Early diagnosis and treatment challenges of endodermal sinus tumors: A case report. Case Reports in Women's Health. 2020; 27: e00198.
[26] Gómora MJ, Morales-Vásquez F, Pedernera E, Perez-Montiel D, López-Basave H, Villa AR, *et al*. Sexual steroid hormone receptors profiles of ovarian carcinoma in Mexican women. Endocrine Connections. 2018; 7: 1006–1012.
[27] Ye Y, Lv C, Xu S, Chen Y, Qian R, Wang P, *et al*. Juvenile Granulosa Cell Tumors of the Ovary. American Journal of Clinical Pathology. 2020; 154: 635–644.
[28] Zhang H, Liu F, Wei J, Xue D, Xie Z, Xu C. Mixed Germ Cell Tumor of the Endometrium: A Case Report and Literature Review. Open Medicine (Warsaw, Poland). 2020; 15: 65–70.
[29] Liu F, Gao Z, Shen D, Zhao H, Wang C, Ye Y, *et al*. Significance of SATB2 expression in colon cancer and its differential diagnosis in digestive tract adenocarcinoma and ovarian primary and metastatic carcinoma. Pathology, Research and Practice. 2019; 215: 152430.
[30] Tian W, Zhou Y, Wu M, Yao Y, Deng Y. Ovarian metastasis from breast cancer: a comprehensive review. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2019; 21: 819–827.
[31] Mercier AM, Zorn KK, Quick CM, Huffman LB. Recurrent gynandroblastoma of the ovary with germline *DICER1* mutation: A case report and review of the literature. Gynecologic Oncology Reports. 2021; 37: 100806.
[32] Martín de la Fuente L, Malander S, Hartman L, Jönsson JM, Ebbesson A, Nilbert M, *et al*. Claudin-4 Expression is Associated With Survival in Ovarian Cancer But Not With Chemotherapy Response. International Journal of Gynecological Pathology: Official Journal of the International Society of Gynecological Pathologists. 2018; 37: 101–109.
[33] Song D, He H, Indukuri R, Huang Z, Stepanauskaite L, Sinha I, *et al*. ERα and ERβ Homodimers in the Same Cellular Context Regulate Distinct Transcriptomes and Functions. Frontiers in Endocrinology. 2022; 13: 930227.
[34] Backe SJ, Sager RA, Regan BR, Sit J, Major LA, Bratslavsky G, *et al*. A specialized Hsp90 co-chaperone network regulates steroid hormone receptor response to ligand. Cell Reports. 2022; 40: 111039.
[35] Le Dily F, Beato M. Signaling by Steroid Hormones in the 3D Nuclear Space. International Journal of Molecular Sciences. 2018; 19: 306.
[36] Li X, Li M, Bai X. Upregulation of TLR2 expression is induced by estrogen via an estrogen-response element (ERE). Archives of Biochemistry and Biophysics. 2014; 549: 26–31.
[37] Walker P, Germond JE, Brown-Luedi M, Givel F, Wahli W. Sequence homologies in the region preceding the transcription initiation site of the liver estrogen-responsive vitellogenin and apo-VLDLII genes. Nucleic Acids Research. 1984; 12: 8611–8626.
[38] Chen D, Huang SM, Stallcup MR. Synergistic, p160 coactivator-dependent enhancement of estrogen receptor function by CARM1 and p300. The Journal of Biological Chemistry. 2000; 275: 40810–40816.
[39] Qiu JJ, Zhang XD, Tang XY, Zheng TT, Zhang Y, Hua KQ. ElncRNA1, a long non-coding RNA that is transcriptionally induced by oestrogen, promotes epithelial ovarian cancer cell proliferation. International Journal of Oncology. 2017; 51: 507–514.
[40] Rehman N, Khan S, Manzoor S, Abubakar M, Sami R, Alharthy SA, *et al*. Estrogen Induces c-myc Transcription by Binding to Upstream ERE Element in Promoter. Applied Sciences. 2022; 12: 6853.
[41] Bhosale PB, Kim HH, Abusaliya A, Vetrivel P, Ha SE, Park MY, *et al*. Structural and Functional Properties of Activator Protein-1 in Cancer and Inflammation. Evidence-based Complementary and Alternative Medicine: ECAM. 2022; 2022: 9797929.
[42] Kushner PJ, Agard DA, Greene GL, Scanlan TS, Shiau AK, Uht RM, *et al*. Estrogen receptor pathways to AP-1. The Journal of Steroid Biochemistry and Molecular Biology. 2000; 74: 311–317.
[43] Paech K, Webb P, Kuiper GG, Nilsson S, Gustafsson J, Kushner PJ, *et al*. Differential ligand activation of estrogen receptors ER-alpha and ERbeta at AP1 sites. Science (New York, N.Y.). 1997; 277: 1508–1510.
[44] Abdelrahman AE, Fathy A, Elsebai EA, Nawar N, Etman WM. Prognostic impact of Apaf-1, Cyclin D1, and AQP-5 in serous ovarian carcinoma treated with the first-line chemotherapy. Annals of Diagnostic Pathology. 2018; 35: 27–37.
[45] Bardin A, Hoffmann P, Boulle N, Katsaros D, Vignon F, Pujol

P, *et al*. Involvement of estrogen receptor beta in ovarian carcinogenesis. Cancer Research. 2004; 64: 5861–5869.
[46] Thasni KA, Rakesh S, Rojini G, Ratheeshkumar T, Srinivas G, Priya S. Estrogen-dependent cell signaling and apoptosis in BRCA1-blocked BG1 ovarian cancer cells in response to plumbagin and other chemotherapeutic agents. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2008; 19: 696–705.
[47] Palomero L, Bodnar L, Mateo F, Herranz-Ors C, Espín R, García-Varelo M, *et al*. EVI1 as a Prognostic and Predictive Biomarker of Clear Cell Renal Cell Carcinoma. Cancers. 2020; 12: 300.
[48] Shan Z, Li Y, Yu S, Wu J, Zhang C, Ma Y, *et al*. CTCF regulates the FoxO signaling pathway to affect the progression of prostate cancer. Journal of Cellular and Molecular Medicine. 2019; 23: 3130–3139.
[49] Andersen CL, Sikora MJ, Boisen MM, Ma T, Christie A, Tseng G, *et al*. Active Estrogen Receptor-alpha Signaling in Ovarian Cancer Models and Clinical Specimens. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2017; 23: 3802–3812.
[50] Kokabu T, Mori T, Matsushima H, Yoriki K, Kataoka H, Tarumi Y, *et al*. Antitumor effect of XCT790, an ERRα inverse agonist, on ERα-negative endometrial cancer cells. Cellular Oncology (Dordrecht). 2019; 42: 223–235.
[51] Chambliss KL, Yuhanna IS, Mineo C, Liu P, German Z, Sherman TS, *et al*. Estrogen receptor alpha and endothelial nitric oxide synthase are organized into a functional signaling module in caveolae. Circulation Research. 2000; 87: E44–E52.
[52] Boonyaratanakornkit V. Scaffolding proteins mediating membrane-initiated extra-nuclear actions of estrogen receptor. Steroids. 2011; 76: 877–884.
[53] Yu H, Zou D, Ni N, Zhang S, Zhang Q, Yang L. Overexpression of NCAPG in ovarian cancer is associated with ovarian cancer proliferation and apoptosis via p38 MAPK signaling pathway. Journal of Ovarian Research. 2022; 15: 98.
[54] Li M, Zhang W, Wang Y, Huang K, Sun T, Qiu Z, *et al*. DDTC Suppresses Ovarian Cancer Development via the PI3K/AKT/mTOR Signaling Pathway. Disease Markers. 2022; 2022: 1941077.
[55] Hollis RL, Stanley B, Thomson JP, Churchman M, Croy I, Rye T, *et al*. Integrated molecular characterisation of endometrioid ovarian carcinoma identifies opportunities for stratification. NPJ Precision Oncology. 2021; 5: 47.
[56] Zhang Z, Park JW, Ahn IS, Diamante G, Sivakumar N, Arneson D, *et al*. Estrogen receptor alpha in the brain mediates tamoxifen-induced changes in physiology in mice. ELife. 2021; 10: e63333.
[57] Mabuchi S, Ohmichi M, Kimura A, Ikebuchi Y, Hisamoto K, Arimoto-Ishida E, *et al*. Tamoxifen inhibits cell proliferation via mitogen-activated protein kinase cascades in human ovarian cancer cell lines in a manner not dependent on the expression of estrogen receptor or the sensitivity to cisplatin. Endocrinology. 2004; 145: 1302–1313.
[58] Wen L, Hong D, Yanyin W, Mingyue Z, Baohua L. Effect of tamoxifen, methoxyprogesterone acetate and combined treatment on cellular proliferation and apoptosis in SKOV3/DDP cells via the regulation of vascular endothelial growth factor. Archives of Gynecology and Obstetrics. 2013; 287: 997–1004.
[59] Van Der Velden J, Gitsch G, Wain GV, Friedlander ML, Hacker NF. Tamoxifen in patients with advanced epithelial ovarian cancer. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 1995; 5: 301–305.
[60] Suske G, Bruford E, Philipsen S. Mammalian SP/KLF transcription factors: bring in the family. Genomics. 2005; 85: 551–556.
[61] Li C, Briggs MR, Ahlborn TE, Kraemer FB, Liu J. Requirement of Sp1 and estrogen receptor alpha interaction in 17beta-estradiol-mediated transcriptional activation of the low density lipoprotein receptor gene expression. Endocrinology. 2001; 142: 1546–1553.
[62] O'Lone R, Frith MC, Karlsson EK, Hansen U. Genomic targets of nuclear estrogen receptors. Molecular Endocrinology (Baltimore, Md.). 2004; 18: 1859–1875.
[63] Björnström L, Sjöberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Molecular Endocrinology (Baltimore, Md.). 2005; 19: 833–842.
[64] Li J, Zhuang Q, Lan X, Zeng G, Jiang X, Huang Z. PES1 differentially regulates the expression of ERα and ERβ in ovarian cancer. IUBMB Life. 2013; 65: 1017–1025.
[65] Jia W, Dong Y, Tao L, Pang L, Ren Y, Liang W, *et al*. MAP3K3 overexpression is associated with poor survival in ovarian carcinoma. Human Pathology. 2016; 50: 162–169.
[66] Hipp S, Berg D, Ergin B, Schuster T, Hapfelmeier A, Walch A, *et al*. Interaction of Snail and p38 mitogen-activated protein kinase results in shorter overall survival of ovarian cancer patients. Virchows Archiv: an International Journal of Pathology. 2010; 457: 705–713.
[67] Liu HD, Yan Y, Cao XF, Tan PZ, Wen HX, Lv CM, *et al*. The expression of a novel estrogen receptor, GPR30, in epithelial ovarian carcinoma and its correlation with MMP-9. Sheng Li Xue Bao. 2010; 62: 524–528. (In Chinese)
[68] Zeng L, Qian J, Zhu F, Wu F, Zhao H, Zhu H. The prognostic values of matrix metalloproteinases in ovarian cancer. The Journal of International Medical Research. 2020; 48: 300060519825983.
[69] Schüler-Toprak S, Skrzypczak M, Ignatov T, Ignatov A, Ortmann O, Treeck O. G protein-coupled estrogen receptor 1 (GPER-1) and agonist G-1 inhibit growth of ovarian cancer cells by activation of anti-tumoral transcriptome responses: impact of GPER-1 mRNA on survival. Journal of Cancer Research and Clinical Oncology. 2020; 146: 3175–3188.
[70] Wilkenfeld SR, Lin C, Frigo DE. Communication between genomic and non-genomic signaling events coordinate steroid hormone actions. Steroids. 2018; 133: 2–7.
[71] Harrington BS, Annunziata CM. NF-κB Signaling in Ovarian Cancer. Cancers. 2019; 11: 1182.
[72] Paul A, Edwards J, Pepper C, Mackay S. Inhibitory-κB Kinase (IKK) α and Nuclear Factor-κB (NFκB)-Inducing Kinase (NIK) as Anti-Cancer Drug Targets. Cells. 2018; 7: 176.
[73] Vrtačnik P, Ostanek B, Mencej-Bedrač S, Marc J. The many faces of estrogen signaling. Biochemia Medica. 2014; 24: 329–342.
[74] Salako MA, Kulbe H, Ingemarsdotter CK, Pirlo KJ, Williams SL, Lockley M, *et al*. Inhibition of the inflammatory cytokine TNF-α increases adenovirus activity in ovarian cancer via modulation of cIAP1/2 expression. Molecular Therapy: the Journal of the American Society of Gene Therapy. 2011; 19: 490–499.
[75] Hassan AA, Artemenko M, Tang MKS, Wong AST. Selectins: An Important Family of Glycan-Binding Cell Adhesion Molecules in Ovarian Cancer. Cancers. 2020; 12: 2238.
[76] Minlikeeva AN, Cannioto R, Jensen A, Kjaer SK, Jordan SJ, Diergaarde B, *et al*. Joint exposure to smoking, excessive weight, and physical inactivity and survival of ovarian cancer patients, evidence from the Ovarian Cancer Association Consortium. Cancer Causes & Control: CCC. 2019; 30: 537–547.
[77] Lee AW, Ness RB, Roman LD, Terry KL, Schildkraut JM, Chang-Claude J, *et al*. Association Between Menopausal Estrogen-Only Therapy and Ovarian Carcinoma Risk. Obstetrics and Gynecology. 2016; 127: 828–836.
[78] Nebgen DR, Hurteau J, Holman LL, Bradford A, Munsell

MF, Soletsky BR, *et al*. Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: A pilot study in women with BRCA1/2 mutations. Gynecologic Oncology. 2018; 150:79–84.

[79] Colina JA, Varughese P, Karthikeyan S, Salvi A, Modi DA, Burdette JE. Reduced PAX2 expression in murine fallopian tube cells enhances estrogen receptor signaling. Carcinogenesis. 2020; 41: 646–655.

[80] Chan KKL, Leung THY, Chan DW, Wei N, Lau GTY, Liu SS, *et al*. Targeting estrogen receptor subtypes (ERα and ERβ) with selective ER modulators in ovarian cancer. The Journal of Endocrinology. 2014; 221: 325–336.

[81] Ruibin J, Bo J, Danying W, Chihong Z, Jianguo F, Linhui G. Therapy Effects of Wogonin on Ovarian Cancer Cells. BioMed Research International. 2017; 2017: 9381513.

[82] Sun S, Fang H. Curcumin inhibits ovarian cancer progression by regulating circ-PLEKHM3/miR-320a/SMG1 axis. Journal of Ovarian Research. 2021; 14: 158.

[83] Liu LD, Pang YX, Zhao XR, Li R, Jin CJ, Xue J, *et al*. Curcumin induces apoptotic cell death and protective autophagy by inhibiting AKT/mTOR/p70S6K pathway in human ovarian cancer cells. Archives of Gynecology and Obstetrics. 2019; 299: 1627–1639.

[84] Liu P, Sun YL, Du J, Hou XS, Meng H. CD105/Ki67 coexpression correlates with tumor progression and poor prognosis in epithelial ovarian cancer. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2012; 22: 586–592.

[85] Alexandrova E, Lamberti J, Memoli D, Quercia C, Melone V, Rizzo F, *et al*. Combinatorial targeting of menin and the histone methyltransferase DOT1L as a novel therapeutic strategy for treatment of chemotherapy-resistant ovarian cancer. Cancer Cell International. 2022; 22: 336.

[86] Sandhiutami NMD, Arozal W, Louisa M, Rahmat D, Wuyung PE. Curcumin Nanoparticle Enhances the Anticancer Effect of Cisplatin by Inhibiting PI3K/AKT and JAK/STAT3 Pathway in Rat Ovarian Carcinoma Induced by DMBA. Frontiers in Pharmacology. 2021; 11: 603235.

[87] Chan KKL, Siu MKY, Jiang YX, Wang JJ, Leung THY, Ngan HYS. Estrogen receptor modulators genistein, daidzein and ERB-041 inhibit cell migration, invasion, proliferation and sphere formation via modulation of FAK and PI3K/AKT signaling in ovarian cancer. Cancer Cell International. 2018; 18: 65.

[88] Weiser MJ, Wu TJ, Handa RJ. Estrogen receptor-beta agonist diarylpropionitrile: biological activities of R- and S-enantiomers on behavior and hormonal response to stress. Endocrinology. 2009; 150: 1817–1825.

[89] Schüler-Toprak S, Moehle C, Skrzypczak M, Ortmann O, Treeck O. Effect of estrogen receptor β agonists on proliferation and gene expression of ovarian cancer cells. BMC Cancer. 2017; 17: 319.

[90] Liu GL, Han NZ, Liu SS. Caffeic acid phenethyl ester inhibits the progression of ovarian cancer by regulating NF-κB signaling. Biomedicine & Pharmacotherapy. 2018; 99: 825–831.

[91] Xu M, Zhang Y. Morin Inhibits Ovarian Cancer Growth through the Inhibition of NF-κB Signaling Pathway. Anti-cancer Agents in Medicinal Chemistry. 2019; 19: 2243–2250.

[92] Datta J, Willingham N, Manouchehri JM, Schnell P, Sheth M, David JJ, *et al*. Activity of Estrogen Receptor β Agonists in Therapy-Resistant Estrogen Receptor-Positive Breast Cancer. Frontiers in Oncology. 2022; 12: 857590.

[93] Banerjee A, Cai S, Xie G, Li N, Bai X, Lavudi K, *et al*. A Novel Estrogen Receptor β Agonist Diminishes Ovarian Cancer Stem Cells via Suppressing the Epithelial-to-Mesenchymal Transition. Cancers. 2022; 14: 2311.

[94] He Y, Alejo S, Venkata PP, Johnson JD, Loeffel I, Pratap UP, *et al*. Therapeutic Targeting of Ovarian Cancer Stem Cells Using Estrogen Receptor Beta Agonist. International Journal of Molecular Sciences. 2022; 23: 7159.

[95] Zheng B, Liu F, Zeng L, Geng L, Ouyang X, Wang K, *et al*. Overexpression of Pyruvate Kinase Type M2 (PKM2) Promotes Ovarian Cancer Cell Growth and Survival Via Regulation of Cell Cycle Progression Related with Upregulated CCND1 and Downregulated CDKN1A Expression. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2018; 24: 3103–3112.

[96] Liu L, Yi J, Yuan J, Yao T, Lin Z, Ning Y, *et al*. FOXO1 overexpression is correlated with poor prognosis in epithelial ovarian cancer. Cancer Biomarkers: Section a of Disease Markers. 2020; 28: 1–8.

[97] Yang N, Zhang Q, Bi XJ. MiRNA-96 accelerates the malignant progression of ovarian cancer via targeting FOXO3a. European Review for Medical and Pharmacological Sciences. 2020; 24: 65–73.

[98] Oturkar CC, Gandhi N, Rao P, Eng KH, Miller A, Singh PK, *et al*. Estrogen Receptor-Beta2 (ERβ2)-Mutant p53-FOXM1 Axis: A Novel Driver of Proliferation, Chemoresistance, and Disease Progression in High Grade Serous Ovarian Cancer (HGSOC). Cancers. 2022; 14: 1120.

[99] Zhang L, Zhou Q, Qiu Q, Hou L, Wu M, Li J, *et al*. Circ-PLEKHM3 acts as a tumor suppressor through regulation of the miR-9/BRCA1/DNAJB6/KLF4/AKT1 axis in ovarian cancer. Molecular Cancer. 2019; 18: 144.

[100] Zeng S, Liu S, Feng J, Gao J, Xue F. MicroRNA-32 promotes ovarian cancer cell proliferation and motility by targeting SMG1. Oncology Letters. 2020; 20: 733–741.

[101] Cao LY, Ren XM, Li CH, Zhang J, Qin WP, Yang Y, *et al*. Bisphenol AF and Bisphenol B Exert Higher Estrogenic Effects than Bisphenol A via G Protein-Coupled Estrogen Receptor Pathway. Environmental Science & Technology. 2017; 51: 11423–11430.

[102] Liu X, Suyama K, Nose T, Shimohigashi M, Shimohigashi Y. Bisphenol-C is the strongest bifunctional ERα-agonist and ERβ-antagonist due to magnified halogen bonding. PLoS ONE. 2021; 16: e0246583.

[103] Liu X, Matsuyama Y, Shimohigashi M, Shimohigashi Y. ERα-agonist and ERβ-antagonist bifunctional next-generation bisphenols with no halogens: BPAP, BPB, and BPZ. Toxicology Letters. 2021; 345: 24–33.

[104] Yao L, Fan Z, Han S, Sun N, Che H. Apigenin acts as a partial agonist action at estrogen receptors *in vivo*. European Journal of Pharmacology. 2021; 906: 174175.

[105] Granchi C, Lapillo M, Spena CR, Rizzolio F, Tuccinardi T, Martin TA, et al. Cyclic Ketoximes as Estrogen Receptor β Selective Agonists. ChemMedChem. 2016; 11: 1752–1761.