REVIEW
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Correlation of bisphenol A action on genes interfering with estrogen signaling pathways and the development of endometriosis

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Nan Li: Conceptualization and writing of the original draft, critical revision, and final approval of the submitted version. Yu-Han Duan and Lei Chen: Conceptualization of the original draft, critical revision of the submitted version. Kun Zhang: Conceptualization of the original draft, critical revision, and final approval of the submitted version.

Competing interests
The authors declare no conflicts of interest.

Abbreviations
BPA, bisphenol A; EMs, endometriosis; CTD, comparative toxicology database; EGFR, epidermal growth factor receptor gene; RT-PCR, reverse transcription-polymerase chain reaction; ESR2, estrogen receptor-beta gene; ERK1, recombinant extracellular signal regulated kinase 1; AP1, activated protein-1; PPARγ, peroxisome proliferator-activated receptor γ; MAPK, mitogen-activated protein kinase; GPR30, G protein-coupled receptor 30; ERRγ, estrogen-related receptor γ; EGF, epidermal growth factor; Erβ, estrogen receptor-β; ER-α, estrogen receptor-α; Raf, rapidly accelerated fibraosarcoma; PI3K, phosphoInositide-3 kinase; Akt, protein kinase B; NF-KB, nuclear factor kappa beta; JAK1/2, janus kinase 1/2; STAT3, signal transduction and activators of transcription 3; PR, progesterone receptor, AhR, aryl hydrocarbon receptor; MMP, matrix metallo protein; P, progesterone; E_2, estradiol.

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Abstract
Bisphenol A(BPA), as an environmental endocrine disruptor, affects human health by interfering with hormone secretion in the body. Endometriosis (EMs) is an estrogen-dependent disease that is influenced by a variety of factors such as genetics, oxidative stress, immunity, and environment for its onset. In recent years, special attention has been paid to the influence of genetic polymorphisms on the pathogenesis of EMs. A search of the Comparative Toxicology Database revealed that BPA can act on a variety of different genes to induce disease development by regulating gene expression and that some genes play equally important roles in the development of EMs. Among them, we selected four genes (EGFR, ESR2, FOS, KRAS) in the estrogen signaling pathway, and now we review the mechanism of BPA acting on these four genes in different ways and the role of these four genes in the development of EMs, which will provide a reference for the subsequent study of the mechanism of BPA involvement in the development of EMs.

Keywords: bisphenol A; EMs; EGFR; ESR2; FOS; KRAS

Background

Previous studies have suggested that Bisphenol A (BPA) has estrogenic activity. BPA, a typical environmental endocrine disruptor, has been shown to be reproductively toxic in numerous studies. Among them, the relationship between BPA and the development of Endometriosis (EMs) has been extensively studied, but the exact mechanism has not been elucidated. Although EMs is a benign disease, it is a malignant disease characterized by invasion, migration, and recurrence, which greatly affects the physical and mental health of the affected women. Therefore, further investigation of the possible role of BPA in the development of EMs and the related mechanisms is important for the prevention, diagnosis, and treatment of EMs, and further investigation is necessary.

In recent years, studies have identified a genetic predisposition to the development of EMs, but studies attempting to identify specific genetic components have failed to explain much of the heritability of EMs, and it has been hypothesized that there may be gene-environment interactions in the development of the disease, including early exposure to environmental chemicals. Our initial search of the literature on environmental chemical exposure and EMs revealed more comprehensive evidence for an association between BPA and EMs. Further searches of the Comparative Toxicology Database (which provides collated and inferred chemical-gene and disease associations from the published literature) with BPA revealed that EMs ranked ninth in terms of BPA-disease associations. Among its 158 associated genes, we found that these top-ranked genes clustered in the estrogen signaling pathway. Finally, we targeted the top four genes (epidermal growth factor receptor gene (EGFR), estrogen receptor-beta gene (ESR2), FOS, KRAS) on the estrogen pathway to help investigators develop hypotheses about the potential mechanisms of BPA's role in EMs by reviewing the mechanisms of BPA's role with the four genes in other diseases for the next study.

Relevance of EGFR to the development of EMs

Role of EGFR in EMs

EGFR is a factor that regulates angiogenesis and is a mediator of sex hormone-induced cell growth and differentiation. It plays a crucial role in the growth, differentiation, and migration of normal and tumor cells. A case-control study suggested that the genotype of EGFR rs11977660 was significantly associated with EMs (genotype and allele $P < 0.05$) and may increase the risk of EMs in Chinese [1]. Another study from Japan similarly showed that the prevalence of EMs was significantly higher in patients with EGFR amplification motifs (85%) than in those without EGFR amplification (35%) ($P < 0.0001$); moreover, EGFR RNA levels were significantly higher in samples from patients with EMs than in those without EMs according to reverse transcription-polymerase chain reaction (RT-PCR) analysis ($P = 0.037$), the findings suggest a possible association between EMs and EGFR gene amplification [2]. A study found that phosphorylated EGFR was significantly more immunoreactive in stage III/IV EMs in situ endometrium and ovarian ectopic endometrial capsule wall than in endometrium without EMs and stage I/II EMs in situ endometrium and that epidermal growth factor is required to induce hyaluronan synthase 2 and hyaluronan expression via EGFR to promote cell migration and invasion [3]. In addition, EGFR may induce matrix metalloproteinase-7 upregulation via the Recombinant Extracellular Signal Regulated Kinase 1 -activated protein-1 (ERK1-AP1) axis, thereby promoting the epithelial-mesenchymal transition of endometriotic lesions in a mouse model of ovarian EMs [4]. EGFR expression is greater in patients with EMs-derived ovarian clear cell carcinoma compared to patients with EMs alone [5], and EGFR expression may be associated with EMs malignancy. In a study using microarray data to screen and bioinformatically analyze differentially expressed genes in EMs, EGFR was ranked first in the protein interaction network analysis of 2663 differential genes screened with its 134 connectivity [6], suggesting that EGFR affects the development of EMs through different pathways of action.

Pathogenic mechanisms associated with the action of BPA and the EGFR

BPA is a ubiquitous endocrine disruptor that can affect human health. Numerous studies have shown that BPA targets the female reproductive system. Protein blotting data from one study showed that exposure of human oocyte granulosa cells to BPA for 15 min accelerated EGFR phosphorylation and caused rapid activation, which had a direct effect on human oocyte granulosa cells by promoting peroxisome proliferator-activated receptor γ (PPARγ)/EGFR/ERK1/2 pathways promoting elevated levels of steroidogenic acute regukatory protein (STAR) mRNA and progesterone [7]. Another study found that human uterine leiomyoma cells exposed to BPA had increased levels of tyrosine phosphorylation of Src and EGFR thereby activating the mitogen-activated protein kinase (MAPK) pathway and promoting cell proliferation [8]. The expression of G protein-coupled receptor 30 (GPR30) mRNA, EGFR mRNA, and their proteins were significantly increased in BPA-treated uterine smooth muscle tumor tissues compared to controls ($P < 0.05$) and indicated that the GPR30-EGFR signaling pathway plays an important role in BPA-stimulated smooth muscle tumor cell proliferation [9]. Another RT-PCR analysis showed that BPA increased EGFR mRNA expression in endometrial cancer cells and induced cell proliferation through the BPA/ estrogen-related receptor γ (ERRγ)/ epidermal growth factor (EGF)/ EGFR/ ERK signaling pathway [10]. Differential methylation sites of genes in the mammary gland of prepubertal rats after BPA exposure were identified using methyl capture sequencing, EGFR being one of the methylation sites, and it was proposed that prepubertal BPA exposure alters the signaling pathway of pro-mammary cancer action [11].

Significance of the role of BPA and EGFR genes in the pathogenesis of EMs

Various studies have shown that BPA increases EGFR protein phosphorylation levels, EGFR mRNA expression, and the degree of methylation of EGFR genes, thereby affecting downstream signaling to play a pathogenic role in various estrogen-dependent diseases. As mentioned above, EGFR likewise plays an important role in the development of EMs. There is currently no information on whether BPA can play a role in the developmental progression of EMs via EFGR, which warrants further investigation.

Correlation of ESR2 with the development of EMs

The role of ESR2 in EMs

The activity of estrogen on target cells may be mediated through the estrogen receptor. the ESR2 gene encodes Estrogen Receptor- β (Erβ), the primary estrogen receptor in patients with EMs. Previous studies have shown that ESR2 interacts with the inflammatory vesicle complex and cytoplasmic apoptotic mechanisms to enhance proliferation and adhesion activity of EMs tissue and prevent tumor necrosis factor α-induced cell death [12]. Several studies have demonstrated that ESR2 gene polymorphisms increase the risk of developing EMs. A study using the high-resolution melting technique to analyze blood samples from 200 patients with EMs for genetic polymorphisms found a significant association between single nucleotide polymorphisms in the ESR2 (rs17179740) gene and the incidence of EMs [13]. Ryo Maekawa et al, using RT-PCR in ovarian EMs analyzed ESR2 expression levels in cases of ovarian EMs, and the results suggested that the level of ESR2 gene expression in ectopic endometrial tissues, on the other hand, was significantly higher than in normal endometrium [14].In their study, Qing Xue et al. found that ESR2 mRNA was significantly elevated in ectopic endometrial mesenchymal cells (approximately 34-fold; $P = 0.015$), whereas in situ endometrial mesenchymal cells were low or even not expressed. Next, they determined the methylation status of the ESR2 promoter region by bisulfite genome sequencing and found that most of the endometrial mesenchymal cells with low ESR2 mRNA levels were severely methylated, whereas most of the endometrial

ectopic mesenchymal cells with high ESR2 mRNA levels were unmethylated and the percent methylation of the ESR2 promoter region was significantly negatively correlated with ESR2 mRNA expression. significantly negatively correlated with ESR2 promoter region methylation, therefore, they suggested that ESR2 methylation status may be a potentially useful adjunct to morphological criteria for the diagnosis of EMs [15].

Pathogenic mechanisms associated with the action of BPA and ESR2

Assessment of ERβ expression in ventral prostate epithelial cells cultured in vitro using immunocytochemical analysis revealed that BPA treatment upregulated ERβ expression and increased ERβ expression with increasing doses of BPA compared to controls [16]. In another study, feeding BPA (50 and 500 μg/kg/day) to pregnant mice increased ESR2 expression in the developing prostate mesenchymal cells of male fetal mice and increased methylation of ESR2 promoter CpG islands with increasing BPA dose [17]. In addition, BPA exposure significantly increased the expression of ESR2 mRNA in the mouse spermatocyte GC-2 cell line, and this increase was time-dependent [18]. In mouse mammary tissue, in utero BPA exposure increased ESR2 protein and mRNA expression levels 3-fold compared to controls ($p < 0.04$) [19]. In a mouse model of autoimmune myocarditis, BPA exposure in drinking water increased ERβ expression in the spleen of mice in plastic cages after 24 hours and significantly increased ERβ phosphorylation levels [20]. A study evaluating BPA-induced uterotoxicity in adolescent rats showed that ERβ expression was significantly upregulated by approximately 1.4-fold compared to control rats [21].

Significance of the role of BPA and ESR2 genes in the pathogenesis of EMs

In different tissues (including the uterus), BPA can increase ESR2 protein phosphorylation levels, ESR2 mRNA expression, and the degree of methylation of the ESR2 gene to affect disease development, but the exact mechanism is not clear. Exploring the changes in ESR2 gene expression mediated by BPA in other diseases and the related mechanisms, is a reference for further research on the effect of BPA on the occurrence of EMs.

Relevance of proto-oncogene (FOS) to the development of EMs

The role of FOS in EMs

FOS encodes the c-fos protein, a member of the AP-1 protein family, which plays a key role in the control of cell death. FOS is a proto-oncogene involved in cell proliferation and differentiation in normal tissues following extracellular stress stimulation. Its dysregulation is associated with oncogenic transformation and tumor progression. FOS is considered to be a key gene in the early response to estrogen, and estrogen can induce rapid and significant FOS gene expression. Earlier studies found that FOS may enhance estrogenic activity to induce endometrial proliferation by inducing transcription of genes that control cell division. In several studies, FOS genes were found to be significantly differentially expressed in EMs. A recent study using NanoString technology to detect differential genes in ectopic and situ endometria in EMs found that FOS was the most overexpressed gene in EMs [22]. It was suggested that matrix metalloproteinase-9 expression regulated by the FOS gene is involved in the 17β-estradiol-promoted invasion of human endometrial stromal cells [23]. In one study, analysis of gene expression changes in ectopic endometrium in a baboon EMS model of disease progression revealed that FOS was a single gene differentially regulated between control and 6–7 month disease models and that its involvement in the EGF signaling pathway and ERK/MAPK signaling pathway was significantly regulated [24].

Pathogenic mechanisms associated with the action of BPA and FOS

In a study on the interaction between BPA and FOS genes, low concentrations of BPA bound to membrane GPR30 and activated the EGFR-MAPK pathway, thereby activating FOS genes and triggering spermatocyte apoptosis [25]. In another study, using mouse spermatogonia GC-1 cells as an experimental model, it was found that BPA induced GC-1 cell proliferation by activating GPR30, EFGR-ERK, and Estrogen Receptor-α (ER-α) to induce FOS gene expression [26]. A siRNA analysis in an experimental model of human breast cancer cell lines suggested that BPA may induce transcriptional regulation of c-fos through GPR30 expression and regulate c-fos expression through an AP1-mediated pathway [27]. In SKBR3 human breast cancer cells, BPA regulates c-fos expression through the GPER/EGFR/ERK transduction pathway and promotes the proliferation and migration of breast cancer cells [28].

Significance of the role of BPA and FOS genes in the pathogenesis of EMs

As above, the FOS gene is a downstream gene of the estrogen pathway, and BPA as an environmental estrogen-like substance mediates the interaction of BPA with the FOS gene mostly through the estrogen receptor (GPR30, ER-α). However, the specific regulatory mechanism varies in different diseases. Referring to the role of BPA on FOS genes in other diseases will help us to further understand its possible effects and related mechanisms in estrogen-dependent diseases such as EMs.

Relevance of oncogenes (KRAS) to the development of EMs

The role of KRAS in EMs

K-Ras is one of the most common mutated oncogenes in human cancers and can activate multiple Ras effector pathways, such as the rapidly accelerated fibraosarcoma (Raf)/ERK/MAPK kinase cascade and PhosphoInositide-3 Kinase (PI3K)/protein kinase B (Akt)-mediated cascade, and promote cell proliferation, differentiation, and survival. Early studies have shown that some cancer driver genes are frequently mutated in ovarian EMs and ovarian cancer associated with EMs. In contrast, somatic mutations in oncogenes such as KRAS may be important driving events in the process of normal endometrium causing EMs as well as in the malignant transformation of EMs. The genetic characteristics of ovarian EMs and ovarian endometrioid carcinoma samples were evaluated using next-generation sequencing technology, and the KRAS gene was found to be included among the characteristic mutated genes in EMs [29]. Ectopic endometrium showed significantly increased KRAS staining compared to in situ endometria, and KRAS knockdown inhibited endometrial stromal cell invasion and migration [30]. A study assessed cell proliferation in the presence of KRAS LCS6 variant alleles using BrdU labeling and showed that KRAS LCS6 variants increased BrdU labeling by 71% in endometrial stromal cells, indicating that endometrial cells proliferated at a higher rate in women carrying the variant allele than in women with the non-variant allele [31]. In a mouse model, heterozygous endometrial grafts containing KRAS variants exhibited increased proliferation and reduced progesterone receptor levels [31]. Quantitative real-time RT-PCR analysis showed that KRAS 4A mRNA expression levels were 2.7-fold higher in EMs than in non-EMs in situ samples [32].

Pathogenic mechanisms associated with the action of BPA and oncogenes (KRAS)

A study applying multidimensional heteronuclear NMR spectroscopy and chemical shift perturbation analysis to characterize the interaction between BPA and KRAS found that BPA can bind to KRAS at different sites, and interfere with SOS-mediated nucleotide exchange in KRAS, inhibit KRAS activation, and thus mediate cell growth or apoptosis [33]. Another study found that BPA induces KRAS metastable activation by selectively binding to guanosine triphosphatase (GTPases) on KRAS, thereby activating the Ras signaling cascade [34]. A study on DNA methylation in the mammary glands of adult rats exposed to BPA early after birth showed that early exposure to BPA resulted in increased methylation of various genes, including KRAS, altering oncogenic signaling pathways and increasing the risk of breast cancer [35].

Significance of the role of BPA and KRAS genes in the pathogenesis of EMs

In conclusion, in previous studies, BPA can selectively activate the KRAS gene, which induces a series of Ras cascades ultimately regulating cellular responses and mediating cell growth and apoptosis, and has an important role in the progression of tumorigenesis. However, the relationship between BPA, KRAS, and EMs has not been investigated and deserves further exploration.

Summary and Outlook

BPA is a widely used environmental chemical, and both human and animal experimental evidence suggests that BPA may be an environmental factor contributing to the development of endometriosis. However, linking BPA and gene interactions with endometriosis has not been systematically investigated. In summary, BPA can contribute to the development of disease by altering the degree of gene phosphorylation or methylation, altering gene mRNA and protein expression, or mutagenically activating genes, thereby affecting downstream signaling (figure 1).

It has been shown that GPR30 mediates estrogenic effects by stimulating the activation of G proteins upregulating adenylate cyclase and mitogenic kinase activities [36]. Cellular experiments confirmed that BPA as an agonist or antagonist can interfere with estrogen signaling through this membrane receptor [37], and it is speculated that BPA may contribute to the development of EMS through this pathway; in addition, BPA can also cause a decrease in the expression level of estrogen receptor alpha, resulting in morphological changes in the vagina of female pups, promoting their uterine epithelial proliferation BPA not only interferes with ovarian luteinizing cell function, inhibits progesterone production, and promotes cytokine secretion by endometrial immune cells [38], but also activates macrophages through the ERK/Nuclear Factor Kappa Beta (NF-KB) and Janus kinase 1/2 (JAK1/2)-signal transduction and activators of transcription 3 (STAT3) signaling pathways, promoting the secretion of inflammatory cytokines [39], leading to EMS. suggest that exposure to BPA may increase the risk of endometriosis and that oxidative stress may play a key role in this association [40]. By mining the database and reviewing the literature, we describe the ways in which BPA exposure alters the expression of EGFR, ESR2, FOS, KRAS genes and accounts for related pathways in endometriosis samples, which will shed light on the environment-gene relationship with the disease from a novel perspective and provide a reference for continued research on the etiology of endometriosis.

In view of the hidden and long-term toxic effects of BPA, research on the effects of BPA on human health should be conducted in a long-term and comprehensive manner, and studies on the association between BPA and EMs should also be conducted in a targeted manner based on long-term epidemiological data from a large number of population studies. Longitudinal studies of blood/urine BPA levels in larger cohorts of mothers and infants, with repeated measurements at reproductive developmental and functionally sensitive points (maternal during pregnancy, neonatal and maternal during delivery, lactating infants and maternal, and especially female infants at important developmental points and maternal blood/urine BPA levels until late menopause), and long-term follow-up of the emergence of estrogen-dependent diseases such as EMs that may be associated with blood/urine BPA levels. In addition, basic research on the pathogenesis of estrogen-dependent diseases such as EMs should be strengthened, and new technologies such as gene methylation, histone modification, and exosome detection should be used to screen for biomarkers that are highly correlated with receptor signaling pathways, oxidative stress, and immune inflammatory response pathways in various samples of EMs patients to determine the timing and intensity of exposure and identify early-induced molecular imprinting.

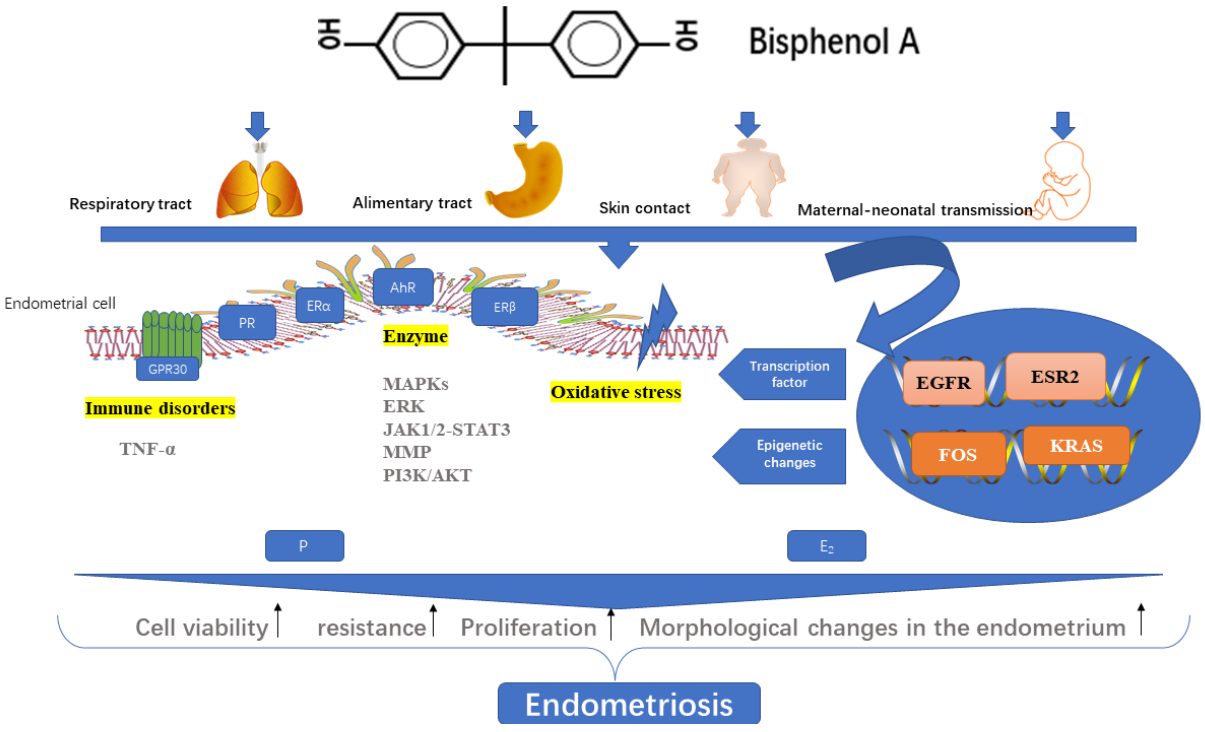

Figure 1 Schematic diagram of the potential effects of BPA on EMs. BPA, bisphenol A; EMs, endometriosis; EGFR, epidermal growth factor receptor gene; ESR2, estrogen receptor-beta gene; ERK, recombinant extracellular signal regulated kinase; MAPK, mitogen-activated protein kinase; GPR30, G protein-coupled receptor 30; ERβ, estrogen receptor-β; ERα, estrogen receptor-α; PI3K, phosphoInositide-3 kinase; Akt, protein kinase B; JAK1/2, janus kinase 1/2; STAT3, signal transduction and activators of transcription 3; PR, progesterone receptor, AhR, aryl hydrocarbon receptor; MMP, matrix metallo protein; P, progesterone; E_2, estradiol.

Only with a large amount of relevant data and ready to conduct historical control and cohort studies to find the manifestations of EMs and other diseases and the corresponding rapid response detection indicators in a timely and accurate manner can we provide strong evidence for the retrospective investigation of this study; provide help for the early diagnosis and prevention of EMs; and ultimately provide a scientific basis for the government to set relevant standards.

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