

How transcription factors regulate apoptosis in endometriosis (Review)

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Abstract. Endometriosis (EM) is a common chronic gynaecological disease that affects 10% of women of reproductive age globally. EM is defined as the presence of endometrial glands and stroma in extrauterine locations, and it can result in pelvic pain and infertility. Inflammation, oxidative stress and apoptosis dysregulation serve a key role in endometriotic lesions. The pathogenesis of EM remains unclear, posing major clinical challenges in its diagnosis and treatment. Apoptosis contributes to the maintenance of cellular homeostasis during the menstrual cycle by eliminating ageing cells from the functional layer of the uterine endometrium. Inhibition of apoptosis facilitates ectopic endometrial cell invasion, implantation and survival, and it promotes the occurrence and development of EM. Transcription factors are pivotal regulators of cellular processes and serve key roles in regulating apoptosis to promote EM. Therefore, identifying the mechanisms by which transcription factors regulate apoptosis in EM may help identify novel targets for the treatment of this disease. The present review summarizes the regulation of apoptosis by different transcription factors in the pathogenesis of EM, contributing to the development of promising biomarkers and therapeutic strategies.

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1. Introduction

Endometriosis (EM) is an inflammatory, fibrotic and oestrogen-dependent disease caused by ectopic endometrial glands and stroma; these ectopic tissues are located mainly in the ovaries, pelvic peritoneum and rectovaginal diaphragm, and they are rarely located in tissues such as the diaphragm, pleura and pericardium (1,2). EM is a benign disease, but it shares several similarities with cancer, including immune escape, adhesion, invasion and angiogenesis (3).

The pathogenesis of EM remains unclear; however, Sampson's hypothesis of retrograde menstruation is widely accepted (4). Although retrograde menstruation occurs in ~90% of women of reproductive age, only 10% of women of reproductive age are diagnosed with EM (5-7). This finding indicates that retrograde menstruation may be merely one of several factors contributing to the development of EM and that additional conditions are necessary for ectopic endometrial colonization and growth. Apoptosis serves a notable role in this process. During the normal menstrual cycle, the number of apoptotic cells in the functional layer of the endometrium increases late in the secretory phase and peaks during menstruation. Programmed cell death ensures that shed endometrial tissues cannot survive or proliferate in ectopic locations, thereby preventing the occurrence of EM (8,9). However, in individuals with EM, apoptosis is suppressed, characterized by elevated expression levels of the Bcl-2 antiapoptotic factor and reduced expression levels of the Bax and Fas proapoptotic factors (10,11). Consequently, the failure of retrograded endometrial tissue to initiate programmed cell death ultimately leads to the formation of ectopic lesions.

Transcription factors are key regulators of essential biological processes, including cell signal transduction and gene expression, and serve indispensable roles in apoptosis. Apoptosis, a process of programmed cell death, is divided into exogenous and endogenous apoptosis according to the mechanism of occurrence (12,13). Exogenous apoptosis is associated with Fas/death receptor (DR)4/DR5 on the cell membrane, whereas endogenous apoptosis is related to mitochondrial function and is mediated primarily by the Bcl-2 antiapoptotic

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protein and the Bcl-2 homologous antagonist killer (Bak) proapoptotic protein. Both pathways converge by facilitating the release of cytochrome *c* from mitochondria, which initiates the caspase cascade to trigger apoptosis (14,15). Transcription factors can indirectly or directly inhibit apoptosis via interference with the transcription of target genes, thereby promoting the formation and progression of EM lesions. In EM, aberrant expression of certain transcription factors inhibits apoptosis by interfering with the transcription of apoptosis-related genes, thereby promoting disease progression. For example, Meis homeobox 1 (MEIS1) expression is downregulated in both eutopic and ectopic endometria of patients with EM. Knockdown of MEIS1 suppresses apoptosis through the regulation of TNF receptor 1 and increases the proliferation of endometrial stromal cells (ESCs) (6). FOXL2 is upregulated in EM, and knockout of FOXL2 increases cleaved-caspase-3 expression and promotes apoptosis (16). These results demonstrate that transcription factors influence EM pathogenesis by regulating important apoptotic molecules, such as caspases, Bcl-2 family proteins and DRs, and suggest their potential as therapeutic targets.

The present review summarizes the functions of key transcription factors regulating apoptosis in EM, with a primary focus on TFEB, NF- κ B and FOXO1, while also discussing the roles of additional regulators in subsequent sections. These findings provide novel perspectives for EM therapy and prognosis on the basis of these transcription factors and their signalling pathways.

2. TFEB

TFEB, a member of the microphthalmia/transcription factor E family of basic helix-loop-helix leucine zipper transcription factors, is a master regulator of the autophagy-lysosomal pathway and modulates nuclear signaling (17). The repression of apoptosis by TFEB is dependent on autophagy, as TFEB upregulates autophagic flux to suppress apoptosis (18,19). Although autophagy and apoptosis are two distinct processes, they can be mutually regulated via core components, such as Bcl-2 family proteins, p53 and ATG proteins (20,21). Autophagy blocks the initiation of apoptosis, whereas the activation of apoptosis-associated cysteine asparaginase switches off the autophagic process (22). TFEB inhibits the occurrence of apoptosis through the autophagic lysosomal pathway, which is essential for the development and clinical treatment of cancer (23,24), cardiovascular disease (25,26) and renal disease (27). Furthermore, recent studies have highlighted the considerable involvement of TFEB in the pathogenesis of EM (19,28).

Chen *et al* (19) reported that the expression levels of TFEB and the LC3 autophagy-related protein were elevated in patients with EM compared with normal controls; in addition, western blot analysis revealed elevated expression of these proteins in the ectopic endometrium compared with the eutopic endometrium. TFEB upregulation enhanced cell viability, promoted Bcl-2 expression, inhibited Bax expression and inhibited caspase-3 cleavage. Notably, the suppression of apoptosis by TFEB was diminished in the presence of chloroquine (CQ), an autophagy inhibitor, suggesting that TFEB may contribute to EM development by stimulating autophagy

and increasing autophagic flux to inhibit apoptosis. Similar findings have been reported by Zheng *et al* (18), who demonstrated that TFEB overexpression in rat nucleus pulposus cells upregulated downstream genes, such as LC3, Beclin1 and P62, along with other autophagy-related mRNAs, thereby increasing autophagic flux activity. TFEB also attenuated the effects of tert-butyl hydroperoxide-induced DNA damage and the levels of cleaved caspase-3 and cyclin-dependent kinase inhibitor 2A, whereas CQ diminished the protective effects of TFEB, suggesting that TFEB inhibited apoptosis by increasing autophagic flux activity. Consequently, we hypothesize that the inhibition of apoptosis in patients with EM may be due to the upregulation of TFEB expression, which activates autophagy and ultimately contributes to invasion, proliferation and growth of ectopic EM lesions.

The activation of TFEB is regulated primarily by classical pathways, such as the PI3K/AKT and MEK/ERK pathways. These pathways activate mTOR, a key negative regulator of autophagy, which induces the phosphorylation of TFEB, thereby preventing the nuclear translocation of TFEB to initiate autophagy and eventual degradation in the cytoplasm (17,29). Studies have revealed that high mTOR and AKT expression in patients with EM prevents the onset of autophagy (30–32). Because these findings contradict the aforementioned upregulation of TFEB and autophagic flux in patients with EM, we hypothesize that TFEB expression may be induced in patients with EM via other non-classical pathways.

Zhang *et al* (33) demonstrated that increased reactive oxygen species (ROS) levels activated TFEB through a non-mTOR-dependent pathway. In this mechanism, ROS stimulated the activation of transient receptor potential mucopolipin 1 (TRPML1) on lysosomes, leading to Ca^{2+} -dependent dephosphorylation of TFEB. TFEB was activated upon dephosphorylation, translocated to the nucleus and promoted the transcription of target genes, including autophagy-related protein (ATG)5, Beclin1, LC3b and sequestosome 1/P62, subsequently inducing autophagy-lysosome biogenesis (27,34). A study on ovarian EM has revealed that mitochondria exhibited greater functionality, greater energy production and increased ROS levels in patients with ovarian EM compared with controls (35). The pathogenesis of EM is associated with inflammation, which can cause ROS accumulation (36). We hypothesize that increased ROS levels activate TRPML1 to release Ca^{2+} , which causes dephosphorylation of TFEB, thereby activating autophagy and suppressing apoptosis, ultimately facilitating the invasion and proliferation of ectopic lesions in EM.

TFEB nuclear translocation increases the expression levels of downstream genes such as LC3 and P62. The P62 protein, an autophagy substrate, interacts with the LC3 protein on autophagosomes and is specifically degraded by lysosomes, ultimately triggering the activation of autophagy (19,37,38). This is an explanation of why increased LC3 protein levels and decreased P62 protein levels have been reported in patients with EM (39). P62 is involved in the apoptosis pathway in the caspase-8 cascade. Reduced P62 levels lead to elevated Bcl-2 expression and decreased levels of cleaved caspase-3, cleaved caspase-9 and Bax, thereby inhibiting apoptosis (40,41). Additionally, P62 binds to familial adenomatous polyposis-1 (Fap-1), a tyrosine phosphatase and negative regulator of Fas.

This interaction facilitates the degradation of P62, promoting Fas phosphorylation and apoptosis (42). Therefore, in patients with EM, TFEB nuclear translocation is promoted to activate the LC3 and P62 genes, which stimulate autophagy, leading to increased LC3 protein levels and P62 protein degradation. Degradation of the P62 protein leads to the upregulation of Bcl-2 expression and the downregulation of proteins such as cleaved-caspase-3, cleaved-caspase-9 and Bax, which weakens the inhibitory effect of P62 on Fap-1 and promotes Fas phosphorylation, thereby inhibiting endometrial cell apoptosis and promoting cell proliferation, invasion and EM lesion development and progression (19,39).

TFEB overexpression upregulates Beclin1 expression, which inhibits the activation of the Bax-/Bak-initiated caspase cascade at the mitochondrial level, thereby suppressing the induction of endogenous apoptosis (43). ATG5 directly interacts with the C-terminal death structural domain of Fas-associated death domain protein (FADD), inhibiting the ability of FADD to promote procaspase-8 cleavage, initiate the caspase cascade and prevent the activation of exogenous apoptosis (44). In conclusion, therapeutic strategies targeting TFEB may help prevent apoptosis in patients with EM by upregulating Beclin1 to inhibit Bax-/Bak-mediated endogenous apoptosis and enhancing ATG5 to suppress FADD-mediated exogenous apoptosis.

Zhan *et al* (45) reported that TFEB overexpression regulated the Bcl-2 promoter to upregulate Bcl-2 expression, thereby inhibiting apoptosis. This finding suggests that EM directly upregulates Bcl-2 expression by promoting TFEB expression, which reduces the incidence of apoptosis in EM, improves the survival of ectopic endometrial tissue and promotes the progression of EM lesions (45,46).

In conclusion, the accumulation of ROS in patients with EM may induce the dephosphorylation and nuclear translocation of TFEB by promoting Ca^{2+} release from lysosomes, which in turn promotes the expression of downstream target genes, inhibits endometrial cell apoptosis and promotes the progression of EM lesions. The specific mechanism is presented in Fig. 1.

3. NF- κ B

NF- κ B is a transcription factor complex composed of homodimers and heterodimers of five members of the Rel family, RelA/P65, RelB, c-Rel, P50/P105 and P52/P100. Among these, the P50/P65 heterodimer, which remains inactive by binding to the I κ B NF- κ B inhibitory protein, is one of the most common combinations (47). As a key transcription factor, NF- κ B regulates the expression of numerous target genes and is involved in regulating a wide range of biological processes, including apoptosis, which is associated with various diseases, such as breast cancer (48), cervical cancer (49), ovarian cancer (50) and EM (51).

NF- κ B is activated through three distinct pathways; however, in EM, it is activated primarily via the classical and alternative pathways (52,53). The classical activation pathway is initiated by TNF- α and IL-1 β , which mediate the activation of the IKK complex. The IKK complex consists of the IKK α and IKK β catalytic subunits and the regulatory subunit NF- κ B essential modulator (NEMO/IKK γ). IKK

activation leads to the phosphorylation and degradation of the I κ B protein by proteolytic enzymes, thus activating NF- κ B. Activated NF- κ B translocates to the nucleus, where it binds to the DNA-binding element of NF- κ B and induces the transcription of target genes. This process increases the expression levels of antiapoptotic genes, including X-linked inhibitor of apoptosis protein, Bcl-2 and Bcl-xl, eventually inhibiting apoptosis (51,54-57). The alternative pathway is activated by NF- κ B-inducing kinase, which is mediated by CD40 and other receptors. Activation of the alternative pathway leads to the sequential activation of IKK α , which then phosphorylates the P100 protein in the P100-Rel B dimer. The phosphorylated (P-)P100 protein is partially hydrolysed and processed to form the transcriptionally active P52-Rel B dimer. The P52-Rel B dimer then translocates to the nucleus (58,59), where it binds to the promoters of the Bcl-xl and Pim-2 antiapoptotic genes, promoting the expression of Bcl-xl and Pim-2 (60,61), which ultimately inhibits apoptosis.

The levels of latent transforming growth factor β binding protein 2 (LTBP2) have been revealed to be increased in the serum and endometrial tissue of patients with EM (62). Notably, Wang *et al* (62) reported that LTBP2 expression was increased in ectopic endometrium compared with eutopic endometrium. Overexpression of LTBP2 inhibited apoptosis and promoted the proliferation of ESCs in patients with EM. NF- κ B was activated by overexpressed LTBP2 in the EM, facilitating the invasion and proliferation of ESCs. Pang *et al* (63) reported that LTBP2 knockdown reduced the expression levels of TNF- α , P65, P50 and other key molecules. TNF- α levels are elevated in the peritoneal fluid of patients with EM, and TNF- α activates the NF- κ B pathway (64). Therefore, LTBP2 may initiate the classical activation pathway of NF- κ B by upregulating TNF- α expression. Furthermore, Delaney *et al* (65) reported that Krüppel-like factor (KLF)10 expression was selectively diminished in ectopic EM compared with eutopic uterine endometrium, and that reduced KLF10 expression markedly upregulated CD40 and its CD154 ligand. Wang *et al* (66) demonstrated that decreased KLF10 expression reversed the inhibition of p-IKBA and p-NF- κ B by PDZ and LIM domain 2, which promoted cell proliferation, migration and inflammation. In conclusion, low KLF10 expression may contribute to the pathogenesis of EM by inducing the activation of CD40 and initiating the alternative activation pathway of NF- κ B, which promotes cell invasion and proliferation, ultimately leading to the development of EM lesions.

There is evidence suggesting that the activation of NF- κ B may directly or indirectly inhibit P53 (67). In the lesion area of patients with EM, P53 expression is reduced, whereas Bcl-2 expression is increased (11). P53 causes apoptosis by transcriptionally activating the expression of proapoptotic genes, including P53 upregulated modulator of apoptosis, Bax and Noxa (a BH3-only proapoptosis protein that neutralizes Mcl-1 to promote mitochondrial apoptosis). Additionally, P53 interacts with several antiapoptotic proteins, such as Bcl-2, Bcl-xl and myeloid cell leukemia-1 (MCL-1), which in turn counteracts their inhibitory effects and indirectly induces apoptosis (68). P53 also promotes the expression of KILLER/DR5 (a death receptor that binds TRAIL to activate extrinsic apoptosis), Fas and the Fas ligand (FasL) on the cell

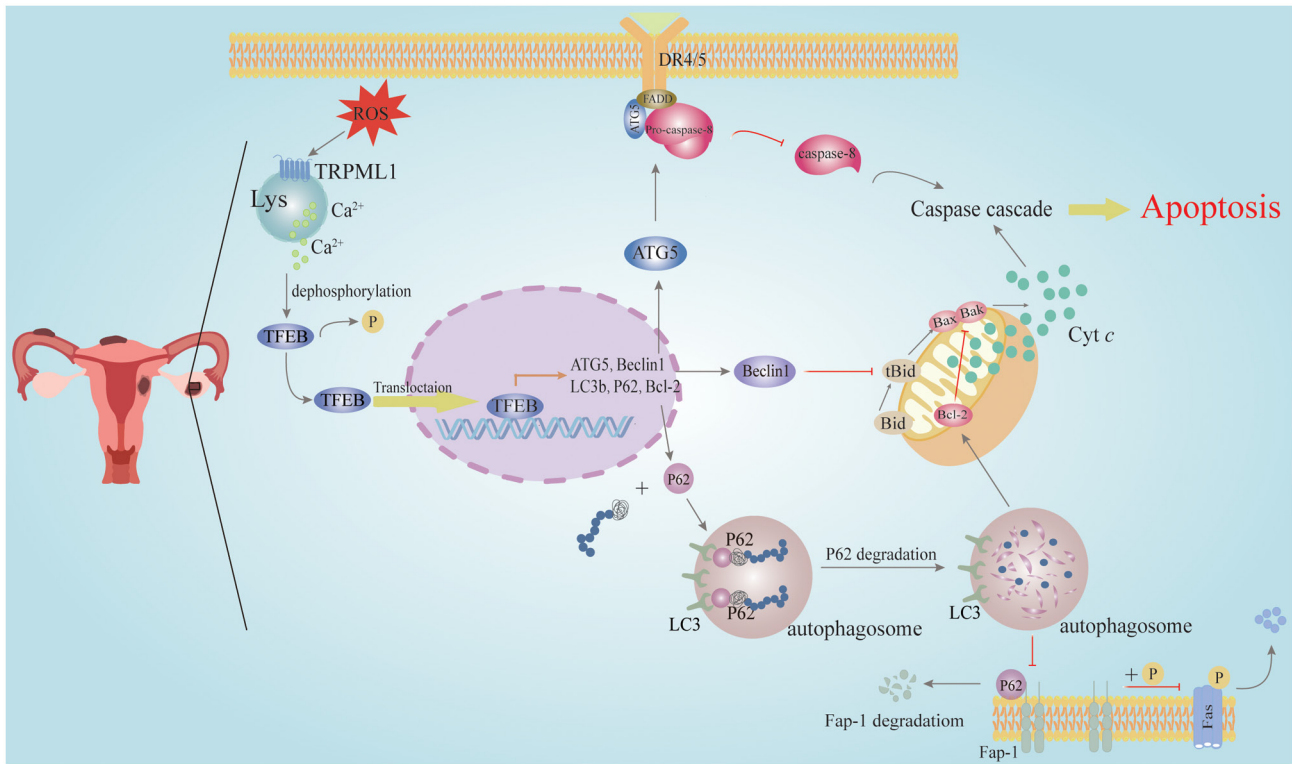


Figure 1. Accumulation of ROS in the lesion area of patients with endometriosis triggers Ca^{2+} release through the activation of TRPML1 on lysosomes. This Ca^{2+} release promotes the dephosphorylation and nuclear translocation of TFEB, facilitating the transcription of certain target genes, such as ATG5, Beclin1, LC3b, P62 and Bcl-2. Upregulated ATG5 directly interacts with and inhibits FADD, which suppresses procaspase-8 cleavage, ultimately inhibiting the caspase cascade and apoptosis. Similarly, upregulated Beclin1 inhibits the tBid-mediated activation of Bax/Bak on mitochondria, preventing Cyt c efflux and endogenous apoptosis. LC3 binds to the P62 protein and promotes P62 degradation. The degradation of P62 prevents the phosphorylation and degradation of Fap-1. Thus, P62 degradation directly inhibits endogenous apoptosis and indirectly suppresses apoptosis via its regulation of Fap-1. ROS, reactive oxygen species; TRPML1, transient receptor potential mucolipin 1; Lys, lysosome; TFEB, transcription factor EB; P, phosphorylated; ATG5, autophagy related 5; FADD, Fas-associated death domain protein; DR4/5, death receptor 4/5; Fap-1, familial adenomatous polyposis-1; Cyt c, cytochrome c; tBid, truncated BH3 interacting-domain death agonist; Bak, Bcl-2 homologous antagonist killer.

membrane (69,70), which activates caspase-8, thus triggering the caspase cascade and ultimately promoting apoptosis.

Accordingly, we hypothesize that in patients with EM, NF- κ B activation may inhibit P53 function, thereby reducing apoptosis and promoting the invasion and colonization of ectopic endometrial cells. The specific mechanism is presented in Fig. 2.

4. FOXO1

The FOXO1 transcription factor contains the following four functional domains: A nuclear localization signal domain, a nuclear export signal, a transactivation domain and a forkhead (FKH) domain (71,72). The FKH domain has a conserved and specific 100-residue DNA-binding domain (73), which is the primary domain for its regulatory effect. FOXO1 is involved in the regulation of cell cycle progression, oxidative stress, metabolism, apoptosis and other cellular processes (71). FOXO1 has been implicated in the initiation and progression of several diseases, including diabetes (74), polycystic ovary syndrome (75) and breast cancer (76), as well as in the regulation of EM development (77). As a multifunctional transcription factor, FOXO1 has recently emerged as a key player in EM pathogenesis (77-79) and may represent a novel therapeutic target for EM.

FOXO1 is located mainly in the nucleus, where its transcriptional activity is regulated by various posttranscriptional modifications, including phosphorylation, dephosphorylation, acetylation and deacetylation. The nuclear/cytoplasmic shuttling of FOXO1, which mediates transcriptional activation or inhibition, is influenced by these posttranscriptional modifications (80-82). Upon phosphorylation, FOXO1 binds to the 14-3-3 chaperone protein, forming a complex that translocates out of the nucleus, preventing it from acting on target genes to induce apoptosis (83). By contrast, unphosphorylated FOXO1 accumulates in the nucleus, where it must be acetylated to exert proapoptosis effects, including upregulating the expression of proapoptosis genes such as Fas, Bcl-2 interacting mediator of cell death (Bim) and TNF-related apoptosis-inducing ligand (TRAIL) (84,85). Wang *et al* (77) reported that NIMA-related kinase 2 (NEK2) phosphorylated FOXO1 at the serine 184 site, decreasing FOXO1 stability and promoting the proliferation, migration and invasion of ectopic endometrial cells, thus facilitating the progression of EM (77). Su *et al* (86) and Yin *et al* (87) reported that the levels of p-AKT were increased but that nuclear FOXO1 expression was reduced in EM tissues compared with ESCs from healthy controls. In patients with EM, AKT activation via the PI3K/AKT and IL8/PTEN/AKT pathways leads to FOXO1 phosphorylation (88,89). P-FOXO1 translocates out

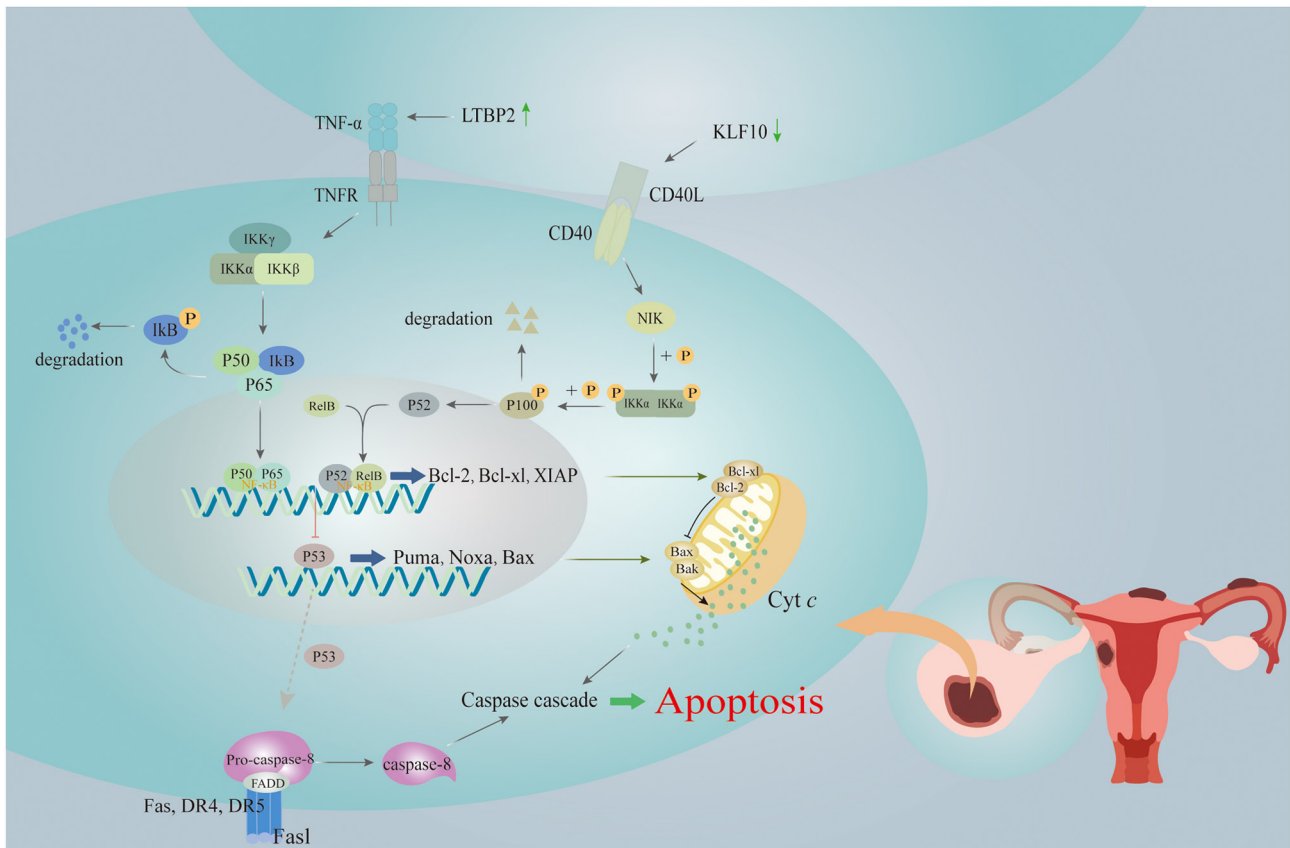


Figure 2. NF- κ B is activated in patients with EM via classical and alternative pathways. The classical pathway involves the activation of TNF- α by LTBP2 upregulation in the serum of patients with EM and ectopic endometrial tissue. TNF- α mediates the activation of the IKK complex to promote the phosphorylation and proteolytic degradation of I κ B, ultimately leading to the activation of NF- κ B and its translocation to the nucleus. The alternative pathway is initiated by low KLF10 expression in the ectopic endometria of patients with EM, which activates CD40. CD40 mediates NIK activation and the sequential activation of IKK α . Activated IKK α induces phosphorylation and partial hydrolysis of the P100 protein in the P100-Rel B dimer to form the transcriptionally active P52-Rel B dimer, which then migrates towards the nucleus. Once in the nucleus, NF- κ B promotes the expression of target genes, such as XIAP, Bcl-2 and Bcl-xL, which inhibit the activation of Bax/Bak and suppresses Cyt *c* release, thereby preventing apoptosis. Furthermore, NF- κ B nuclear translocation inhibits the function of the P53 tumour suppressor protein. This suppression reduces the expression of proapoptotic genes, such as Puma, Noxa and Bax, which are involved in Bax/Bak-mediated Cyt *c* release and apoptosis. P53 also directly promotes the expression of DR4/5, Fas and its ligand (FasL) on cell membranes, initiating exogenous apoptosis. By inhibiting P53 activity, NF- κ B indirectly contributes to the suppression of both endogenous and exogenous apoptosis pathways. EM, endometriosis; LTBP2, latent transforming growth factor β binding protein 2; TNFR, TNF receptor; P, phosphorylated; KLF10, Krüppel-like factor 10; NIK, NF- κ B-inducing kinase; XIAP, X-linked inhibitor of apoptosis; Cyt *c*, cytochrome *c*; Puma, P53 upregulated modulator of apoptosis; Noxa, a BH3-only proapoptosis protein; FADD, Fas-associated death domain protein; FasL, Fas ligand; Bak, Bcl-2 homologous antagonist killer; DR4/5, death receptor 4/5.

of the nucleus, inhibiting its regulation of target genes and repressing apoptosis (81,90). EM is an oestrogen-dependent disease and studies have revealed that oestrogen binding to the oestrogen receptor induces AKT activation and phosphorylation of FOXO1, thereby suppressing the proapoptotic effects of FOXO1 (91,92). The activation of NEK2 and AKT in EM increases FOXO1 phosphorylation, which prevents FOXO1 nuclear accumulation and its proapoptotic effects; this creates a permissive environment for ectopic endometrial cell survival, invasion and colonization, which facilitates EM pathogenesis (77,93).

FOXO1 is regulated by acetylation of cAMP response element-binding protein (CREB)/P300, a transcriptional coactivator, and deacetylation of sirtuin (SIRT) (94,95). In a recent study on myocarditis, researchers reported that CREB/P300 bound to FOXO1 and triggered FOXO1 acetylation, which activated the transcriptional activity of FOXO1 on Bim (84). Upregulation of Bim induces cytochrome *c* release from mitochondria, contributing to apoptosome formation, caspase-3 activation and the initiation of the caspase cascade, thereby

inducing apoptosis (84). Acetylated FOXO1 also promotes the transcription of the TRAIL and Fas downstream target genes, which encode transmembrane proteins that recruit FADD by binding to DR4/DR5 or FasL; the recruitment of FADD activates caspase-8, which initiates the caspase cascade and induces apoptosis (85,96). While no considerable difference in CREB expression has been reported between normal endometrial cells and ESCs (97), the expression levels of the SIRT1 and FOXO1 genes markedly differ. In ESCs, SIRT1 and Bcl-xL expression is upregulated, whereas FOXO1 and Bax expression is downregulated (98). SIRT1, which is highly expressed in the nucleus, deacetylates FOXO1, preventing its activation of downstream proapoptotic genes such as Bim. Eventually, deacetylated FOXO1 suppresses apoptosis and promotes the pathogenesis of EM (98).

Therefore, the deacetylation and phosphorylation of FOXO1 in patients with EM may inhibit the regulatory effects of FOXO1 on downstream target genes, which in turn inhibits apoptosis and ultimately promotes the development of EM lesions. The specific mechanism is presented in Fig. 3.

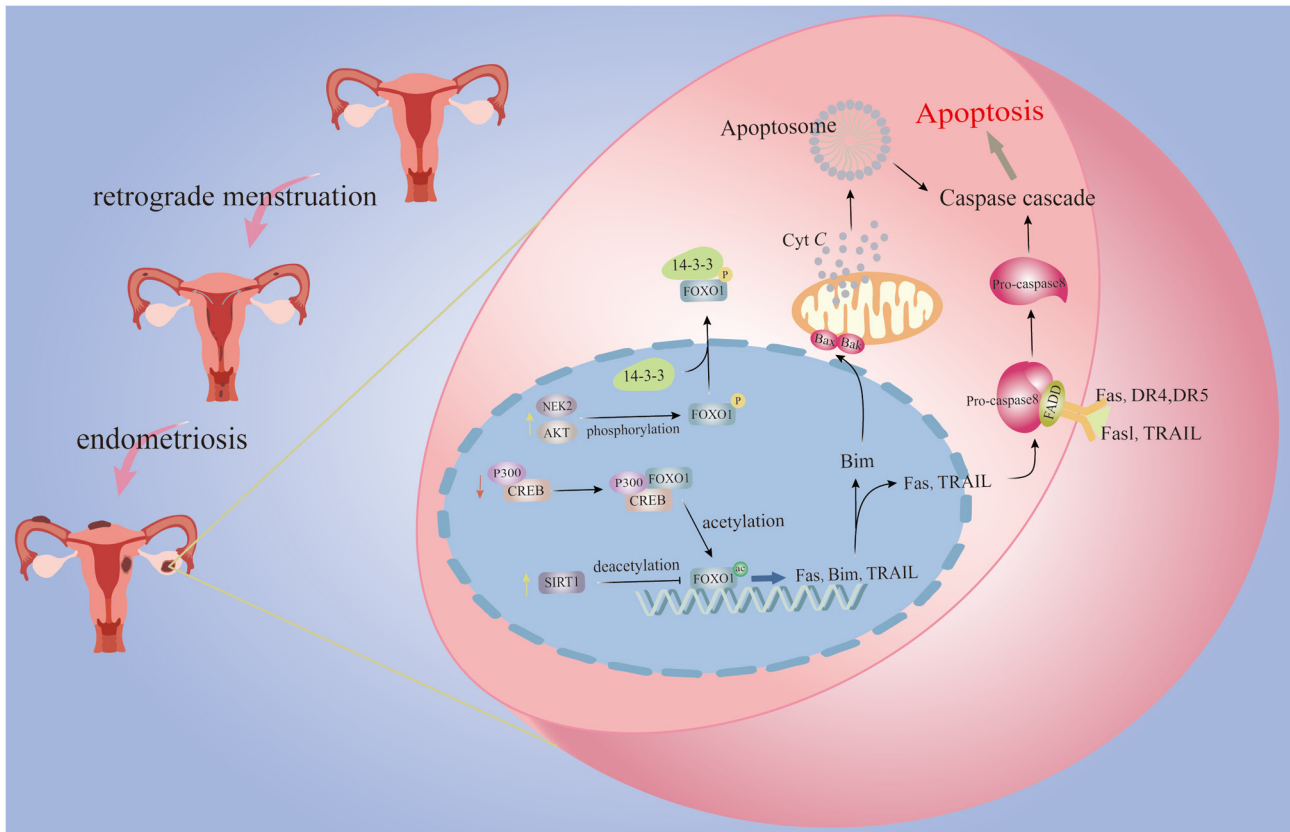


Figure 3. CREB/P300 is expressed at low levels in EM, but CREB/P300 binds to FOXO1 to promote its acetylation and activate the regulatory effects of FOXO1 on its target genes, such as Fas, Bim and TRAIL. Bim triggers Bax/Bak activation, leading to Cyt *c* release and the initiation of endogenous apoptosis. Additionally, increased expression of Fas and TRAIL enhances caspase-8 production, activating the caspase cascade and inducing exogenous apoptosis. Conversely, patients with EM exhibit high expression levels of SIRT1, which facilitates FOXO1 deacetylation and inhibits FOXO1 activation, thus preventing the initiation of apoptosis. Furthermore, increased expression levels of NEK2 and AKT in patients with EM promote FOXO1 phosphorylation. Phosphorylated FOXO1 binds to the 14-3-3 protein and translocates out of the nucleus, which inhibits the regulatory effect of FOXO1 on target genes in the nucleus and inhibits apoptosis. EM, endometriosis; CREB, cAMP response element-binding protein; Bim, Bcl-2 interacting mediator of cell death; TRAIL, TNF-related apoptosis-inducing ligand; Cyt *c*, cytochrome *c*; SIRT1, sirtuin 1; NEK, NIMA-related kinase; DR4/5, death receptor 4/5; FADD, Fas-associated death domain protein; Fasl, Fas ligand; Bak, Bcl-2 homologous antagonist killer; P, phosphorylated; ac, acetylated.

5. KLF6

KLF6, a member of the Krüppel-like family of zinc finger transcription factors, serves important roles in cell proliferation, apoptosis, invasion and angiogenesis (99). Shi *et al* (100) reported that KLF6 expression was reduced in ectopic ESCs compared with eutopic ESCs of patients with EM, and that KLF6 overexpression inhibited ectopic ESC proliferation, migration and angiogenesis by inhibiting catenin β 1. Additionally, KLF6 promotes apoptosis by upregulating Bax and downregulating Bcl-2 expression through the activating transcription factor (ATF)4/ATF3-CHOP signalling axis (101). Meng *et al* (102) reported that endoplasmic reticulum stress upregulated the expression levels of ATF4 and CHOP in patients with EM, which promoted apoptosis and inhibited ESC proliferation. Thus, ectopic ESCs in patients with EM may inhibit the ATF4/ATF3/CHOP axis and reduce Bcl-2 expression by downregulating KLF6 expression, leading to the inhibition of apoptosis and increasing the likelihood of ectopic ESC invasion, proliferation and the formation of ectopic lesions. While these findings suggest a potential mechanism underlying EM pathogenesis, to the best of our knowledge, no direct evidence has yet been reported linking this pathway to EM development.

6. Interferon regulatory factor 6 (IRF6)

IRF6 is a novel member of the IRF family of transcription factors that is involved in processes such as the regulation of cell proliferation and differentiation (103,104). IRF6 is a key player in the regulation of craniofacial development, epidermal morphogenesis and tumorigenesis (105,106); however, to the best of our knowledge, the role of IRF6 in the pathogenesis of EM remains unclear. Li *et al* (104) reported that bone marrow stromal antigen (BST)2 was upregulated in EM and that the IRF6 transcription factor interacted with the promoter of BST2 to drive its expression. BST2 activated the NF- κ B pathway to upregulate the expression of the antiapoptotic gene Bcl-2 and downregulate the expression of the proapoptotic gene Bax. Furthermore, He *et al* (107) suggested IRF6 is downregulated in EM, and BST2 overexpression increases the migratory ability of ESCs. In another study, comprehensive analyses revealed that IRF6 expression was downregulated in EM (108). An associated study in renal clear cell carcinoma (RCCC) suggested that IRF6 was hypoexpressed in RCCC, where its inhibitory effect on downstream kinesin family member (KIF)20A was reduced. KIF20A overexpression by IRF6 enhances cell viability, proliferation, migration and

resistance to apoptosis (106). However, further research is needed to clarify the role of IRF6 in the pathogenesis of EM.

7. Hypoxia-inducible factor-1 α (HIF-1 α)

HIF-1 α is a subunit of the heterodimeric HIF-1 transcription factor, which responds to low intracellular oxygen concentrations and is associated with cell proliferation, differentiation and apoptosis (109,110). The activation of HIF-1 α is regulated by multiple mechanisms, including the PI3K/AKT/mTOR signalling pathway and the Ras/Raf/MAPK signalling pathway, as well as epigenetic modifications (111,112). AKT, MAPK and mTOR are activated in the hypoxic microenvironment created by ectopic endometrial cells, leading to the upregulation of HIF-1 α (113). Liu *et al* (114) demonstrated that HIF-1 α was highly expressed in patients with EM. Furthermore, HIF-1 α overexpression increased the expression levels of Beclin1 and LC3, thereby activating autophagy and promoting the invasion and migration of ESCs. In a flap survival study, Lin *et al* (115) reported that autophagic activation mediated by HIF-1 α stimulation upregulated Bcl-2 expression and downregulated Bax expression, thereby inhibiting apoptosis and improving the survival rate of flaps. These findings suggest that upregulation of HIF-1 α serves a key role in activating autophagy to suppress apoptosis, thereby promoting ectopic endometrial cell survival, proliferation and migration. Additionally, HIF-1 α contributes to EM-related angiogenesis and influences the disease prognosis.

8. STAT3

STAT3 is a transcription factor and a member of the STAT family that serves a key role in cell proliferation, apoptosis, metastasis and angiogenesis (116). Normally inactive in the cytoplasm, STAT3 is activated by cytokines such as IL-6, IL10 and IFN. Upon activation, STAT3 is phosphorylated by Janus kinase (JAK) and translocates to the nucleus as a dimer, where it upregulates the expression levels of antiapoptotic genes, including Bcl-2, Bcl-xl and MCL-1, thereby inhibiting apoptosis (117,118). STAT3 is hyperactivated in EM through IL-6 and other factors, and STAT3 is phosphorylated via the JAK/STAT3 pathway. p-STAT3 not only directly affects target genes to suppress apoptosis but also promotes angiogenesis and inhibits apoptosis in EM by upregulating HIF-1 α expression (119-121). STAT3 serves a key role in the inflammatory activation of EM and is associated with apoptosis, angiogenesis and fibrosis, suggesting that it is a potential therapeutic target for EM (121,122).

9. Discussion

EM is a prevalent gynaecological disorder with two clinically notable characteristics, namely, a steadily increasing global incidence and high recurrence rates following treatment (123,124). The disease pathogenesis is fundamentally driven by resistance to apoptosis in ectopic endometrial cells. Clinically, EM not only causes debilitating symptoms, including chronic pelvic pain and infertility, but also confers a substantially increased risk of ovarian malignancies. These severe health consequences underscore the need to develop mechanism-based therapeutic

interventions (124-126). Accumulating evidence indicates that apoptosis dysregulation is a fundamental pathogenic mechanism in the progression of EM (8,127,128). Mechanistically, transcription factors orchestrate an apoptosis-resistant phenotype in ectopic endometrial cells through coordinated modulation of the PI3K/AKT and NF- κ B signalling cascades. This molecular reprogramming is manifested by concomitant upregulation of antiapoptotic effectors (Bcl-2 and Bcl-xl) and suppression of proapoptotic mediators (Bax and Fas). The resulting imbalance in apoptosis-related factors allows refluxed endometrial cells to evade programmed cell death, thereby increasing their survival capability and facilitating their invasive proliferation and establishment of ectopic lesions. Furthermore, transcription factors further aggravate the pathological process of EM by regulating inflammatory factors (such as IL-6 and TNF- α), angiogenic factors (such as vascular endothelial growth factor) (129) and fibrotic pathways (such as the TGF- β /Smad pathway) (130,131), creating a cycle of apoptosis-inflammation-fibrosis. Notably, the expression levels of each transcription factor differ in EM cells from different sites, suggesting that these site-specific transcription factors hold dual clinical significance, such as site-specific diagnostic potential and prognostic stratification value (132-134).

The present review elucidated the key role of transcription factor-mediated apoptosis inhibition in EM pathogenesis through distinct molecular pathways. Systematic analysis identified aberrant expression patterns of several key transcription factors. The prosurvival factors TFEB, NF- κ B, HIF-1 α and STAT3 are highly expressed in EM, whereas the expression levels of the proapoptotic factors FOXO1 and KLF6 are reduced in EM. Notably, although IRF6 expression in EM has not been clarified, its role in the regulation of apoptosis should not be ignored. The present review focused on the mechanism by which TFEB, NF- κ B and FOXO1 modulate apoptosis in EM. TFEB directly inhibits apoptosis by promoting Bcl-2 expression and indirectly inhibits apoptosis by triggering autophagy. NF- κ B inhibits apoptosis directly or indirectly by activating downstream target genes. Furthermore, FOXO1 inhibits the activation of downstream proapoptotic genes, which in turn indirectly inhibits apoptosis. These mechanisms collectively contribute to the formation of EM lesions.

Currently, due to a lack of understanding of the pathogenesis of EM, treatment of EM is still based on symptomatic therapy. The various transcription factors and their signalling pathways discussed in the present review are not only implicated in the regulation of ectopic endometrial cell apoptosis but also influence several processes, such as invasion, migration, angiogenesis and fibrosis. These findings provide a rationale for the development of novel therapeutic regimens targeting transcription factors. For example, autophagy inhibition strategies targeting TFEB or specific antagonists of NF- κ B could be potential therapeutic options. However, the antiapoptotic effects of the transcription factors KLF6 and IRF6 remain unclear, suggesting the need for more in-depth studies of the spatiotemporal specificity of transcription factor regulatory networks.

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Authors' contributions

ZO wrote the original draft. JD, LZ, ZO and FS contributed to the review and editing of the manuscript. JD and LZ prepared the figures. FS contributed to the supervision and funding acquisition. All authors have read and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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