

BCL6, a key oncogene, in the placenta, pre-eclampsia and endometriosis

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BACKGROUND: The key oncogene B-cell lymphoma 6 (BCL6) drives malignant progression by promoting proliferation, overriding DNA damage checkpoints and blocking cell terminal differentiation. However, its functions in the placenta and the endometrium remain to be defined.

OBJECTIVE AND RATIONALE: Recent studies provide evidence that BCL6 may play various roles in the human placenta and the endometrium. Deregulated BCL6 might be related to the pathogenesis of pre-eclampsia (PE) as well as endometriosis. In this narrative review, we aimed to summarize the current knowledge regarding the pathophysiological role of BCL6 in these two reproductive organs, discuss related molecular mechanisms, and underline associated research perspectives.

SEARCH METHODS: We conducted a comprehensive literature search using PubMed for human, animal and cellular studies published until October 2021 in the following areas: BCL6 in the placenta, in PE and in endometriosis, in combination with its functions in proliferation, fusion, migration, invasion, differentiation, stem/progenitor cell maintenance and lineage commitment.

OUTCOMES: The data demonstrate that BCL6 is important in cell proliferation, survival, differentiation, migration and invasion of trophoblastic cells. BCL6 may have critical roles in stem/progenitor cell survival and differentiation in the placenta and the endometrium. BCL6 is aberrantly upregulated in pre-eclamptic placentas and endometriotic lesions through various mechanisms, including changes in

gene transcription and mRNA translation as well as post-transcriptional/translational modifications. Importantly, increased endometrial BCL6 is considered to be a non-invasive diagnostic marker for endometriosis and a predictor for poor outcomes of IVF. These data highlight that BCL6 is crucial for placental development and endometrium homeostasis, and its upregulation is associated with the pathogenesis of PE, endometriosis and infertility.

WIDER IMPLICATIONS: The lesson learned from studies of the key oncogene BCL6 reinforces the notion that numerous signaling pathways and regulators are shared by tumors and reproductive organs. Their alteration may promote the progression of malignancies as well as the development of gestational and reproductive disorders.

Key words: B-cell lymphoma 6 / placenta / pre-eclampsia / endometriosis / infertility / proliferation / migration / fusion and differentiation / inflammation / stem and progenitor cells

Introduction

B-cell lymphoma 6 (BCL6), a key oncogene, is a master regulator of humoral immunity and lymphoma survival (Bunting and Melnick, 2013; Cardenas et al., 2017). Interestingly, recent studies show that it has important functions in trophoblastic cells (Louwen et al., 2014; Muschol-Steinmetz et al., 2016; Jasmer et al., 2017; Ritter et al., 2020) and is upregulated in pre-eclamptic placenta (Enquobahrie et al., 2008; Sitrans et al., 2009; Winn et al., 2009; Nishizawa et al., 2011; Xiang et al., 2013; Louwen et al., 2014; Trifonova et al., 2014; Sober et al., 2015; Than et al., 2018; Guo et al., 2021a; Ren et al., 2021) as well as in endometriotic lesions (Evans-Hoeker et al., 2016; Almquist et al., 2017; Gong et al., 2017; Yoo et al., 2017; Likes et al., 2019; Nezhath et al., 2020; Sansone et al., 2021; Shen et al., 2021). These interesting observations provide evidence that this key oncogene may play physiological and pathological roles in the placenta and the endometrium.

BCL6 was identified as a locus affected by chromosomal translocations in diffuse large B-cell lymphomas (Ye et al., 1993). It plays a major role in many lymphomas independent of genetic lesions, where it drives the malignant phenotype by promoting proliferation, deactivating DNA damage checkpoints, and inhibiting cell terminal differentiation (Cardenas et al., 2017). BCL6 is a master regulator of B cell differentiation in germinal centers (GCs), being critical for the initiation and maintenance of GC reactions, and a key oncogene in B-cell lymphomagenesis (Basso and Dalla-Favera, 2010; Hatzi and Melnick, 2014). Beside B cells in GCs, BCL6 is also selectively expressed in follicular helper T cells (T_{FH}) (Nurieva et al., 2009). There is compelling evidence demonstrating that BCL6 is a lineage-defining transcription factor essential for T_{FH} differentiation (Nurieva et al., 2009) and maintenance (Alterauge et al., 2020).

BCL6 binds to canonical DNA sequences in the regulatory region of diverse target genes and recruits corepressor complexes that repress gene transcription. It consists of an N-terminal BTB/POZ domain mediating transcriptional repression, an unstructured middle region containing a second repression domain (RD2), and a series of six C₂H₂ zinc fingers at the C-terminus that bind to DNA sequences and other proteins (Hatzi and Melnick, 2014). To mediate repression, its N-terminal BTB domain recruits the corepressor proteins SMRT (silencing mediator of retinoic acid and thyroid hormone receptor), NCOR (nuclear receptor corepressor) and BCOR (BCL6 interacting corepressor) to an extended groove motif along the BTB dimer interface (Ahmad et al., 2003; Ghetu et al., 2008), whereas the central RD2 region interacts with CtBP (C-terminal binding protein), NuRD (nucleosome remodeling domain), MTA2 (metastasis-associated protein 2) and HDAC2 (histone deacetylase 2) to assist the repression of genes

(Huang et al., 2014). These interactions enable BCL6 to repress the transcription of diverse genes (Basso et al., 2010; Basso and Dalla-Favera, 2012; Hatzi and Melnick, 2014), including proliferation inhibitors such as *CDKN1A* (cyclin-dependent kinase inhibitor 1A), *CDKN1B*, *CDKN2A* and *CDKN2B*, DNA damage response regulators like *ATR* (ataxia telangiectasia and *rad3*-related protein), *CHEK1* (checkpoint kinase 1) and *TP53* (tumor protein 53) and cell differentiation suppressors including *IRF4* (interferon regulatory factor 4) and *PRDM1* (positive regulatory domain containing 1) (Hatzi and Melnick, 2014).

As BCL6 is also found in various tissues including skeletal muscle, breast and prostate (Bajalica-Lagercrantz et al., 1998; Logarajah et al., 2003), it is not surprising that numerous studies demonstrate its involvement in solid tumors. Increased BCL6 expression has been reported in breast cancer (Bos et al., 2003; Logarajah et al., 2003; Walker et al., 2015), gastric cancer (Hirata et al., 2009), ovarian cancer (Wang et al., 2015), non-small-cell lung cancer (Sun et al., 2016) and glioblastoma (Ruggieri et al., 2014; Song et al., 2018), which is associated with a range of malignant characteristics including tumor cell proliferation, survival, migration, invasion and therapy resistance (Bos et al., 2003; Hurtz et al., 2011; Walker et al., 2015; Cardenas et al., 2017; Guo et al., 2021b). These observations highlight that BCL6 is also an important oncoprotein in solid tumors, although the precise molecular mechanisms remain to be elucidated.

Intriguingly, BCL6 is richly expressed in the human placenta, and its increased expression is associated with the common disease of pregnancy, pre-eclampsia (PE) (Enquobahrie et al., 2008; Winn et al., 2009; Sitrans et al., 2009; Nishizawa et al., 2011; Xiang et al., 2013; Louwen et al., 2014; Trifonova et al., 2014; Sober et al., 2015; Than et al., 2018; Guo et al., 2021a; Ren et al., 2021). Recent studies also demonstrate that BCL6 is a diagnostic marker for endometriosis and its associated infertility (Evans-Hoeker et al., 2016; Almquist et al., 2017; Gong et al., 2017; Yoo et al., 2017; Likes et al., 2019; Nezhath et al., 2020; Sansone et al., 2021; Shen et al., 2021). These data suggest that BCL6 is an important player in normal development as well as in disease of the placenta and the endometrium. In this narrative review, we have summarized the available data and discussed the pathophysiological roles of BCL6 in these two reproductive organs.

Methods

A comprehensive search of the PubMed database was conducted for this narrative review to identify peer-reviewed publications in English until October 2021, focused on the expression and roles of BCL6 in the human placenta, and the pathogenesis of PE and endometriosis.

The search included the keywords BCL6, proliferation, migration, invasion, differentiation, fusion, inflammation and infertility, either alone or in combination with 'placenta', 'pre-eclampsia', 'endometrium', 'endometriosis' or 'in vitro fertilization'.

BCL6 in the placenta and pre-eclampsia

The human placenta

The placenta is a transient organ essential for fetal growth and development (Burton and Fowden, 2015). Being a multifunctional organ, the placenta fulfills a plethora of tasks such as providing nutrients and oxygen to the growing fetus, producing/releasing hormones into both the fetal and maternal circulation, and removing waste products (Gude et al., 2004). The placenta also serves as a defense front against pathogens and provides a protective environment through multiple mechanisms including triggering interferon type III signaling, microRNA (miRNA)-mediated autophagy and the nuclear factor- κ B pathway (Roland et al., 2016; Kreis et al., 2020). The key events of placental development depend on the differentiation of progenitor cells, called villous cytotrophoblasts (vCTBs), into the syncytiotrophoblast (STB) as well as extravillous trophoblasts (EVTs) (Turco and Moffett, 2019). The STB, formed and maintained by fusion of proliferative progenitor vCTBs, builds the key interface between maternal and fetal blood (Arora et al., 2017). Moreover, vCTBs of the anchoring villi undergo a degree of epithelial-mesenchymal transitions and differentiate into invasive interstitial EVT (iEVTs), which invade the maternal decidua and are able to remodel the uterine spiral arteries to ensure adequate placental perfusion (O'Tierney-Ginn and Lash, 2014). In addition, these iEVTs also develop and invade into other lumen structures of the uterine wall such as veins, glands, and lymph vessels (Huppertz, 2019). During the early stages of placental development, trophoblast cell lineage specification and differentiation are tightly regulated by a variety of molecular signaling pathways, including Wnt and Notch, which control trophoblast stemness/differentiation and formation of invasive trophoblast progenitors, respectively (Knofler et al., 2019).

Pre-eclampsia

An imbalance between trophoblast proliferation and differentiation causes severe placental pathologies and pregnancy complications such as PE (Huppertz et al., 2002). PE is a gestational hypertensive disorder with a global prevalence of up to 8% (Steegers et al., 2010). It is not only a leading cause of maternal and perinatal mortality and morbidity worldwide, but also a risk factor of cardiovascular and metabolic complications for both mother and offspring later in life (MacKay et al., 2001; Rana et al., 2019). PE is defined by concurrent hypertension (blood pressure \geq 140/90 mmHg) and proteinuria or any other end-organ damage, including liver or brain, occurring after 20 weeks of gestation (Phipps et al., 2019). Clinically, PE can be classified into distinct subgroups: early-onset PE with delivery at $<34+0$ weeks of gestation; preterm PE with delivery at $<37+0$ weeks of gestation; late-onset PE with delivery at $\geq 34+0$ weeks of gestation; and term PE with delivery at $\geq 37+0$ weeks of gestation (Poon et al., 2019). Pathologically, PE is generally regarded to progress in two stages: placental dysfunction

caused by genetic, maternal and immunological factors, and the release of placental antiangiogenic factors and inflammatory mediators inducing a generalized maternal endothelial activation leading to maternal symptoms such as hypertension and proteinuria (Roberts and Hubel, 2009; Phipps et al., 2019). This may further lead to multiorgan dysfunction (Chappell et al., 2021) and maternal decompensation including eclampsia and the HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome (Flint et al., 2019). Mechanistically, PE is a multifactorial disease that encompasses several subclasses, including the subclass featured with maternal vascular malperfusion and the subclass with signs of allograft rejection (Leavey et al., 2015, 2016, 2019).

The etiology of PE is not completely understood, and defective placentation is considered to be causative for the development of PE. Diverse pathological processes have been proposed for abnormal placentation and placental ischemia, including abnormal spiral artery remodeling and immune intolerance at the maternal-fetal interface leading to the release of soluble toxic factors into the maternal circulation (Phipps et al., 2019; Rana et al., 2019). These soluble factors include high levels of circulating antiangiogenic factors, such as sFLT1 (soluble fms-like tyrosine kinase 1) and soluble endoglin and low levels of circulating proangiogenic factors, like VEGF (vascular endothelial growth factor) and PlGF (placental growth factor), causing an imbalanced angiogenic state, and contribute to maternal manifestations of PE including systemic endothelial dysfunction, inflammation, and organ failures (Romero and Chaiworapongsa, 2013; Rana et al., 2019). The pathological cellular and molecular events in the pre-eclamptic placenta are varied, such as failed transformation of proliferative vCTBs into the invasive endovascular subtype (Zhou et al. 1997), deficient aggregaphy, aberrant pyroptosis, compromised unfolded protein response, abnormal release of placental extracellular vesicles containing miRNAs and long non-coding RNAs (lncRNAs), defective fusion, increased syncytial knots and excessive STB stress (Rana et al., 2019; Redman et al., 2020; Bai et al., 2021; Nakashima et al., 2021).

BCL6 in the placenta and its involvement in pre-eclampsia

Transcriptomic profiling analyses of pre-eclamptic placentas have revealed diverse sets with hundreds of genes specific for placental dysfunction (Sober et al., 2015; Leavey et al., 2016; Brew et al., 2016; Than et al., 2018). Interestingly, BCL6 is one of the prominent genes frequently altered in pre-eclamptic placentas shown by systematic meta- and expression network analysis (Kleinrouweler et al., 2013; Tejera et al., 2013; Vaiman et al., 2013; Brew et al., 2016). In fact, BCL6 has been repeatedly reported to be upregulated in placentas of patients with early- as well as late-onset PE (Table I) (Enquobahrie et al., 2008; Winn et al., 2009; Sitrans et al., 2009; Nishizawa et al., 2011; Xiang et al., 2013; Louwen et al., 2014; Trifonova et al., 2014; Sober et al., 2015; Than et al., 2018; Guo et al., 2021a; Ren et al., 2021). Of importance, BCL6 was highly expressed in preterm pre-eclamptic placentas and its overexpression activated the expression of ARNT2 (aryl hydrocarbon receptor nuclear translocator 2) (Than et al., 2018), an interaction partner of hypoxia-inducible factor 1 α (HIF-1 α) (Maltepe et al., 2000) involved in trophoblast invasion and the pathogenesis of PE (Rosario et al., 2008; Chakraborty et al., 2016). Upregulation of these two transcription regulatory genes, BCL6 and

Table 1 BCL6 expression in human pre-eclamptic placentas.

Reference	Sample number/patient information	Method/dataset/GEO	Main results
Enquobahrie et al. (2008)	n = 18 controls (38.9 wk, 5.6% preterm delivery <37 wk and 38.9% CS, 72.2% labor). n = 18 PE (35.8 wk, 50% preterm delivery and 55.6% CS, 66.7% labor).	Microarray (Operon's Human Genome Array Ready Oligo Set™ version 2.1) and qPCR.	58 genes (56 up- and 2 downregulated) were differentially expressed in PE placentas, including upregulated BCL6, with a fold change of 1.78 ($P = 0.0154$).
Winn et al. (2009)	n = 11 preterm labor with no evidence of infection (30.2 ± 7.1 wk, range 24–36, 18% CS and 100% labor). n = 12 severe PE (30.7 ± 9.1 wk, range 24–36, 50% CS and 83% labor).	Microarray platform high-density HG-U133A and HG-U133B GeneChips (Affymetrix, Santa Clara, CA); GEO accession number: GSE14722.	55 genes were differentially expressed in PE placentas, including upregulated BCL6, with a fold change of 1.69.
Sitras et al. (2009)	n = 21 controls (277 ± 9 days, 38% CS). n = 16 severe PE (238 ± 25 days, 69% CS).	30 K Human Genome Survey Microarray v.2.0 (Applied Biosystems); GEO accession number: GSE10588.	213 genes were significantly upregulated in severe PE placentas, including BCL6, with a fold change of 2.2 ($P = 0.01$). 82 genes were downregulated. 168 genes were differentially expressed between EO- versus LO-PE placentas, suggesting differences in pathophysiology.
Nishizawa et al. (2011)	n = 8 controls (38.1 ± 0.8 wk). n = 8 FGR (37.3 ± 1.0 wk). n = 8 severe PE (34.4 ± 1.8 wk), all CS.	Microarray experiments with Affymetrix GeneChip system (Affymetrix, Santa Clara, CA, USA). GEO accession number: GSE24129.	62 genes were differentially expressed in both PE and FGR. TP53-downstream apoptosis-related genes, such as BCL6 and BAX, were found to be more highly upregulated in PE- than in FGR placentas. BCL6 was upregulated in PE placentas with a fold change of 2.02 ($P = 0.0024$).
Xiang et al. (2013)	n = 22 (5 for microarray) uncomplicated pregnancies (39.38 ± 1.19 wk), CS. n = 23 (7 for microarray) PE (35.34 ± 3.07 wk), CS.	Microarray experiments with Roche Nimblegen Gene Expression 126135 K Arrays. GEO accession number: GSE43942.	1312 genes were differentially expressed in PE placentas, including upregulated BCL6 (fold change 2.51, $P = 0.0026$; Supplementary Table S2).
Trifonova et al. (2014)	n = 11 physiological pregnancies (40 ± 2 wk, 0% premature birth). n = 10 PE (38 ± 1 wk, 50% premature birth), 6 moderate PE and 4 severe PE.	HT-12 BeadChip microarrays (Illumina, USA).	63 genes were differentially expressed in PE placentas (50 up- and 13 downregulated). BCL6 was upregulated with a fold change of 2.36 ($P = 0.0006$).
Louwen et al. (2014)	n = 7 controls (37.6 ± 0.7 wk, 4 with CS, 2 with eCS, 1 with opVD). n = 7 PE (37.1 ± 0.5 wk; 5 × CS, 1 × eCS with labor, 1 × opVD).	Self-designed TaqMan gene array, Applied Biosystems (Darmstadt, Germany); qPCR verification.	BCL6 gene was upregulated in LO-PE with a fold change of 1.47 ($P = 0.087$). Increased BCL6 may be involved in deregulated cell cycle regulation, survival, and differentiation processes of villous trophoblasts in pre-eclamptic placentas.
Sober et al. (2015)	n = 4 LO-PE with IUGR. n = 4 LO-PE without IUGR (266.1 ± 3.94 days, delivery mode VD/CS: 2/6).	Library preparation with Nextera™ Technology (Illumina) total RNA sequencing was performed on Illumina HiSeq2000.	199 and 98 genes were differentially expressed in PE without IUGR and PE with IUGR, respectively. BCL6 was in the top-gene list and upregulated in LO-PE with IUGR (\log_2 fold change 0.77, $P = 0.00081$, Supplementary Data S3).
Than et al. (2018)	n = 5 preterm control (31.0 wk, range 30.9–34.0), CS. n = 12 preterm severe PE with and without HELLP (31.2 wk, range 29.3–33.2), CS.	Whole-Human Genome Oligo Microarray G4112A (Agilent Technologies, Santa Clara, CA); GEO accession numbers GSE65866, GSE65940, and GSE66273.	BCL6 upregulation sensitized trophoblasts to ischemia and repressed differentiation (\log fold change 1.86, absolute fold change 3.64, $P = 0.00065$; Supplementary Data S1). BCL6 was highly expressed in preterm but not in term PE placentas, suggesting its potential role only in the pathology of preterm cases.

Continued

Table 1 Continued

Reference	Sample number/patient information	Method/dataset/GEO	Main results
Guo et al. (2021)	n = 20 from 7 controls delivered preterm (n = 7, <34 wk) or at term (n = 13, >36 wk). n = 24 PE including EO (n = 8, <34 wk), severe LO (n = 4, >36 wk) and non-severe LO (n = 12; >36 wk).	The study performed a deeply re-analyzing of publicly available datasets (Agilent-039494 SurePrint G3 Human GE v2 8x60K Microarray 039381 (Feature Number version)).	1016 genes were differentially expressed in severe EO-PE. Severe LO-PE showed a deregulation of 133 genes. The comparison between EO-PE versus LO-PE identified 226 differentially expressed genes. BCL6 was upregulated only in EO-PE with a log fold change of 1.603 ($P = 0.00026$).
Ren et al. (2021)	n = 32 from 30 controls including twins (273.90 ± 8.45 days). n = 33 PE including twins (n = 9 for EO severe PE, 216.80 ± 15.20 days; n = 15 (14) for severe LO-PE, 260.60 ± 13.87 days; n = 9 (7) for LO mild PE, 266.10 ± 10.09 days).	TruSeq RNA Kit (Illumina) followed by paired-end sequencing using Illumina HiSeq 2500.	2977 genes, which are enriched with metabolism-related pathways and transporter functions, were differentially expressed in severe EO-PE, whereas 375 genes, which are enriched with immune-related pathways, were differentially expressed in severe LO-PE. BCL6 was upregulated in both EO- and LO-PE (log2 fold change 0.85, $P = 1.51 \times 10^{-6}$; Supplementary Table S3).

BCL6, B-cell lymphoma 6; CS, cesarean section; eCS, emergency cesarean section after the onset of labor; EO-PE, early-onset pre-eclampsia; FGR, fetal growth restriction; GEO, Gene Expression Omnibus; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; IUGR, intrauterine growth restriction; LO-PE, late-onset pre-eclampsia; opVD, operative vaginal delivery; PE, pre-eclampsia; VD, vaginal delivery; wk, week.

ARNT2, led to dysregulation of most predominant PE-related genes such as *FLT1* under hypoxia (Than et al., 2018).

To investigate the significance of BCL6 in normal placental development and the pathogenesis of PE, we have analyzed gene expression of pre-eclamptic placentas compared with control samples using an array containing genes involved in several important signaling pathways (Louwen et al., 2014). The data showed that genes associated with migration and angiogenesis were mostly altered in pre-eclamptic placentas. Notably, the *BCL6* gene, among several crucial genes, was significantly increased and correlated with enhanced *FLT1* and *LEPTIN* in pre-eclamptic placenta samples (Louwen et al., 2014), hallmark genes of PE. In support of this observation, BCL6 has been shown to be a key regulator of target genes of three critical pathways in the placenta, namely FOXO (forkhead box O), ribosome and HIF1 signaling (Ren et al., 2021). Collectively, these studies underscore the notion that BCL6 is an important regulator that is deregulated in malignant cells as well as pre-eclamptic trophoblasts (Louwen et al., 2012).

While the BCL6 protein was mainly localized in the nuclei of vCTBs in term placentas (Louwen et al., 2014), it is abundantly present in nuclei as well as in the cytoplasm of vCTBs, the STB and in syncytial sprouts in first trimester placentas (Fig. 1A). BCL6 is also expressed in cell column trophoblasts (CCTs) of anchoring villi in first trimester placentas (Ritter et al., 2020). The high presence of BCL6 in the CCTs, the source for all subtypes of invasive EVT (Huppertz, 2019), suggests its roles in both proliferation and differentiation in those cells. Moreover, BCL6 is also richly present in iEVTs of the maternal decidua (Fig. 1B). Of note, the expression of BCL6 in vCTBs and the STB decreases during gestation (Fig. 1C). In addition, HTR-8/SVneo cells, a widely used first trimester trophoblast cell line (Graham et al., 1993), express much more BCL6 than other trophoblastic cell lines (Muschol-Steinmetz et al., 2016). These observations suggest that BCL6 may be

crucial in early placental development and could be associated with the pathogenesis of PE.

Potential molecular mechanisms by which BCL6 is upregulated in pre-eclampsia

The aberrant expression of BCL6 in hematopoietic malignancy is attributed to a variety of mechanisms (Cardenas et al., 2017). These include altered gene transcription (Pasqualucci et al., 2003; Saito et al., 2007; Yang and Green, 2019), deregulated epigenetics (Lai et al., 2010), activated heat shock protein 90 (HSP90) (Cerchiatti et al., 2009) and changed post-translational modifications (Yang and Green, 2019) such as phosphorylation (Niu et al., 1998; Phan et al., 2007), acetylation (Bereshchenko et al., 2002) and methylation (Lu et al., 2018). In cancer cells, the heat shock factor 1 (HSF1) was shown to bind to the BCL6 promoter and activate its gene expression upon stress (Fernando et al., 2019). In addition, deregulated miRNAs and lncRNAs were reported to induce aberrant expression of BCL6 in various cancer cells (Wei et al., 2015; Sun et al., 2016; Yan et al., 2016; Li et al., 2018; Wang et al., 2020). These data highlight that BCL6 is upregulated and stabilized in malignant cells through diverse mechanisms including transcriptional and translational regulation and post-translational modifications.

BCL6 may be pivotal in controlling a variety of challenging situations associated with PE, which are characterized by a myriad of diverse stressors such as oxidation, chronic hypoxia and inflammation. To respond to these stresses, the placenta must activate its response machinery, which could give rise to the highly expressed and stabilized BCL6, a central component of the stress response (Phan et al., 2007; Fernando et al., 2019).

Similar to malignant cells, the mechanisms by which BCL6 is upregulated in pre-eclamptic placentas might also be multilateral (Fig. 2). First, HSP90 is a major regulator stabilizing and activating BCL6 (Cardenas

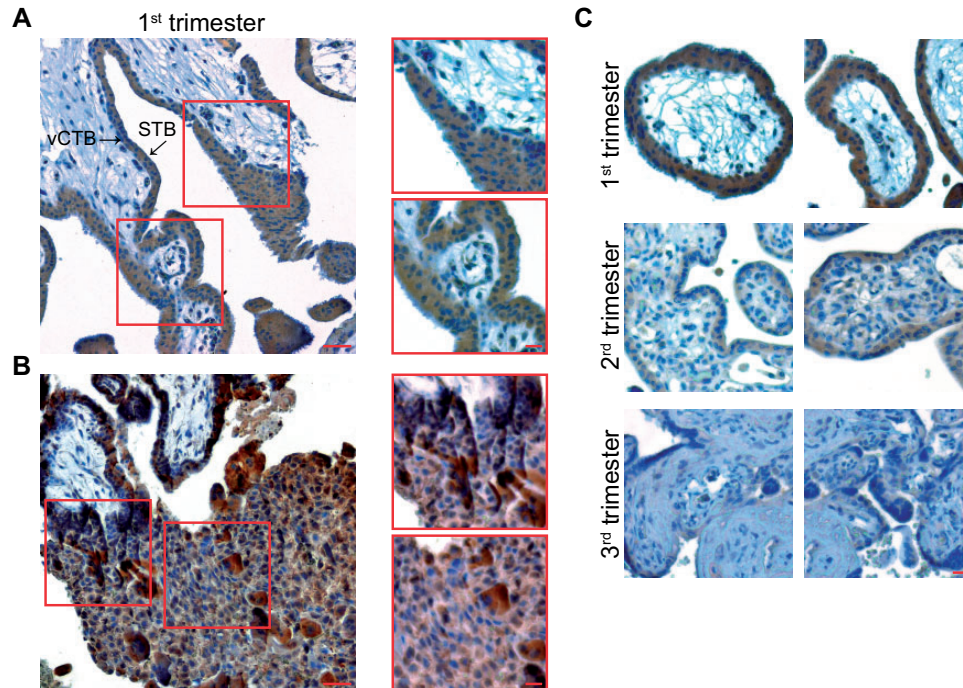


Figure 1. BCL6 is expressed in various trophoblast types of first trimester placentas and its expression declines during gestation. (A) First trimester placental tissue sections were immunohistochemically stained for BCL6 and DNA. Left: a representative image is shown. Scale: 50 μ m. Right: enlarged villi. Scale: 20 μ m. STB, syncytiotrophoblast; vCTB, villous cytotrophoblast. (B) Representative EVTs positively stained with BCL6 antibody in the decidua of first trimester placenta (left, scale: 50 μ m) and enlarged regions with positive EVTs (right, scale: 20 μ m). EVT, extravillous trophoblast. (C) Representative images are shown for first (upper panel), second (middle panel) and third trimester placental tissues (lower panel) stained for BCL6 and DNA. Scale: 50 μ m.

et al., 2017), and studies have indicated a link between PE and deregulated HSP90 (Padmini *et al.*, 2012; Ren *et al.*, 2021), which could affect the stability and activity of BCL6 in pre-eclamptic placentas. It will also be of interest to study if PE-related proinflammatory cytokines, such as tumor necrosis factor- α (TNF α) and IL8, which increase and activate the HSP members (Jee *et al.*, 2021), could be responsible for the stabilized BCL6 in pre-eclamptic placentas. Second, maternal circulating IL6 was shown to be increased in PE (Lau *et al.*, 2013), which could contribute to the high expression of BCL6, as reported in T_{FH} cells (Nurieva *et al.*, 2009). Third, BCL6 may also be stabilized by post-translational modifications, such as phosphorylation by the mitogen-activated protein kinase (MAPK) and acetylation by the cyclic AMP response element binding protein, which have been reported to be deregulated in pre-eclamptic placentas (Qi *et al.*, 2021; Sadeghi *et al.*, 2021). Fourth, three CpG islands on Chromosome 3 were reported to be differentially methylated in trophoblasts from pre-eclamptic placentas (Than *et al.*, 2018), suggestive of a potential methylation alteration in the BCL6 promoter. Fifth, HSF1 activated BCL6 gene expression in GC B cells as well as in cancer cells under stress (Fernando *et al.*, 2019), and it will be of importance to examine whether HSF1 is increased in stressed trophoblasts and involved in BCL6 gene activation in pre-eclamptic placentas. Sixth, the expression of aberrant miRNAs and lncRNAs has been observed in pregnancy complications including PE (Yang and Meng, 2019; Ali *et al.*, 2020), and deregulated miRNAs may

result in enhanced expression of BCL6 in pre-eclamptic placentas. The detailed mechanisms by which BCL6 is highly expressed and stabilized in pre-eclamptic placentas remain to be elucidated.

Functions of BCL6 in trophoblasts of the placenta

BCL6 promotes proliferation and survival of trophoblasts

Rapidly and dynamically regulated proliferation of placental cells, including trophoblasts, mesenchymal stem/stromal cells and endothelial cells, is mandatory for proper placental development. Beginning at implantation, trophoblast lineages derived from extraembryonic tissue expand rapidly to form placental villi during the first weeks of gestation (Hemberger *et al.*, 2020; Aplin and Jones, 2021). During the 40 weeks of gestation, these villi undergo dynamic morphological changes and develop into highly vascularized structures (Burton *et al.*, 2009). By term, extensive branching morphogenesis of the villi results in a total epithelial surface area of $\sim 12\text{--}14\text{ m}^2$ to meet the increasing demands of the growing fetus (Knofler *et al.*, 2019). Dynamic and rapid development of the placenta is highly co-ordinated by spatiotemporal regulation of trophoblast proliferation through a great number of signaling pathways and various regulators.

BCL6 is highly expressed in vCTBs (Fig. 1) and CCTs in the first trimester (Ritter *et al.*, 2020), and its expression is significantly lower in

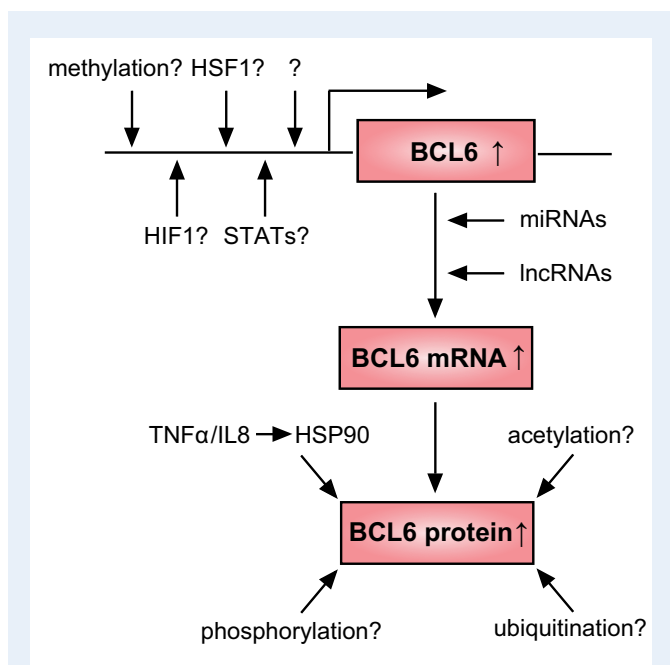


Figure 2. Proposed working model by which BCL6 is upregulated in pre-eclamptic placentas.

Upregulation and activation of BCL6 in pre-eclamptic placentas may be caused at transcriptional, translational and post-translation level. HIF1, hypoxia-inducible factor 1; HSF1, heat shock factor 1; HSP90, heat shock protein 90; IL8, interleukin 8; lncRNA, long non-coding RNA; miRNA, microRNA; STAT, signal transducer and activator of transcription; TNF α , tumor necrosis factor alpha.

second trimester placentas (Prater et al., 2021), suggestive of its importance in trophoblast expansion and differentiation in early placental development. Indeed, inhibition of BCL6 significantly reduced proliferation and resulted in apoptosis in trophoblastic cell lines, in particular under stress situation (Muschol-Steinmetz et al., 2016). The genes *CDKN1A* and *TP53*, coding for the important cell cycle regulators p21 and p53, respectively, are controlled by BCL6 in normal GC B cells (Basso et al., 2010). However, the expression of *CDKN1A* was hardly changed, whereas *TP53* was significantly decreased in trophoblastic cells depleted of BCL6 (Muschol-Steinmetz et al., 2016), indicating that BCL6 may differentially affect gene expression depending on the cellular context. Interestingly, BCL6 upregulation was associated with overexpression of cyclin D1, p53 and HIF-1 α in breast cancer tissue (Bos et al., 2003), which might be responsible for enhanced proliferation, invasion and stress response. By targeting distinct genes and pathways, BCL6 functions as a proliferation promoter and survival guardian in various tissues including the placenta. Enhancing BCL6 might be one of the molecular mechanisms that allow cytotrophoblasts to proliferate under low oxygen conditions in early pregnancy, which are normally stressful for cells in other tissues.

BCL6 blocks differentiation and fusion processes of vCTBs

The multinucleated STB has a limited lifespan and must be regularly replenished with fresh cytoplasm and nuclei by controlled differentiation and fusion of its underlying vCTBs (Aplin and Jones, 2021;

Jaremek et al., 2021). Importantly, vCTBs are a heterogeneous cell population showing different cellular features with different functions (Aplin and Jones, 2021). Based on single-cell RNA sequencing of human placental samples from the first and second trimester, at least three subpopulations of vCTBs were reported: one population expressed cell cycle genes belonging to the cycling fraction, the second showed high differentiation genes related to cellular fusion such as syncytin 1 and 2, and the third population was proposed to be a G0 'reserve' cell population, possibly progenitor/stem cells (Liu et al., 2018). These observations suggest that vCTB development and progression are highly orchestrated, ensuring a functional STB throughout gestation. Integration of multiple signaling pathways and transcription factors has been implicated in the process of vCTB differentiation, including repression of Wnt and activin/transforming growth factor-beta (TGF β) signaling as well as activation of cAMP/protein kinase A (PKA) and MAPK pathways (Jaremek et al., 2021). vCTB differentiation also involves the activity of numerous transcription factors and epigenetic regulators, including PPAR γ (peroxisome proliferator-activated receptor γ), DLX3 (distal-less homeobox 3), GCM1 (glial cell missing-1), TFAP2A (transcription factor AP-2), OVOL1 (OVO homolog-like 1), p21 (Lu et al., 2017; Kreis et al., 2021) and many others (Knofler et al., 2019). BCL6 might be one of these many factors involved in vCTB differentiation and fusion, based on its functions in other cell types and tissues (Reljic et al., 2000; Logarajah et al., 2003). In fact, BCL6 has been found to be one of the key transcription factors for regulating vCTB differentiation toward the STB (Liu et al., 2018).

Interestingly, suppression of BCL6 using siRNA promoted the fusion rate of BeWo cells, a widely used fusogenic trophoblastic cell line (Zachariades et al., 2011), as well as primary vCTBs by enhancing the levels of fusion-related genes *ERVW-1* (endogenous retrovirus group W member 1, syncytin 1), *HERV-FRD* (endogenous retrovirus group FRD member 1, syncytin 2) and *CGB3* (chorionic gonadotrophin beta 3, β -hCG). The amount of secreted β -hCG from cells depleted of BCL6 was increased about 1.5-fold relative to control cells. In contrast, BeWo cells stably overexpressing BCL6, mimicking the situation observed in PE, displayed decreased fusion capacity. Importantly, reduction of BCL6 significantly facilitated the fusion capability of BeWo cells under hypoxia (Jasmer et al., 2017). As knockdown of BCL6 enhanced the expression of the fusion-related genes, such as *ERVW-1*, *HERV-FRD* and *CGB3*, in trophoblastic cell lines as well as in primary vCTBs (Jasmer et al., 2017), it is tempting to suggest that BCL6 could directly target these genes. These data indicate BCL6 as a negative regulator for differentiation and fusion of vCTBs into the STB, and increased BCL6 in pre-eclamptic placenta may impair proper differentiation and successful fusion, contributing to the pathogenesis of PE.

Interestingly, connective tissue growth factor was reported to regulate the fusion of osteoclast precursors by inhibiting BCL6 (Choi et al., 2020). BCL6 was also shown to block differentiation and fusion of osteoclasts in mouse (Miyamoto 2011). Moreover, enhanced BCL6 inhibited lymphocyte terminal differentiation in lymphomagenesis (Reljic et al., 2000). In addition, increased BCL6 in breast tissues impeded differentiation of epithelial cells and supported the progressive development of cancer (Logarajah et al., 2003). These data strongly suggest that BCL6 plays an important role in controlling differentiation in various tissues by targeting the respective genes.

*BCL6 facilitates migration and invasion of EVT*s

The finely tuned regulation by a multitude of regulators and pathways is fundamental for proper migration and invasion of EVTs. Multiple pathways, such as FAK/Rho (focal adhesion kinase/Rho), PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase B), TGF β and Wnt signaling, have been reported to regulate migration and invasion of EVTs (Pollheimer and Knofler, 2005; Knofler and Pollheimer, 2012; Knofler et al., 2019). In particular, Wnt signaling is critical for regulating EVT function (Sonderegger et al., 2010). Alterations in the Wnt pathway were reported to contribute to the pathogenesis of PE by affecting migration and invasion of trophoblasts (Wang et al., 2018; Chen et al., 2021). Intriguingly, Wnt signaling is targeted by BCL6 in GC B cells (Basso et al., 2010). BCL6 was also reported to be associated with migration and invasion of breast cancer cells (Yu et al., 2015), glioblastoma cells (Song et al., 2018) and ovarian cancer cells (Wang et al., 2015). It is thus reasonable to hypothesize that BCL6 might play similar roles in trophoblast migration and invasion.

Indeed, as in malignant cells (Bos et al., 2003; Cardenas et al., 2017), BCL6 is crucial in the migration and invasion of trophoblastic cells (Ritter et al., 2020). Knockdown of BCL6 reduced the motility of trophoblastic cells by affecting numerous genes of regulatory proteins in the actin cytoskeleton, including PAK1 (p21 activated kinase 1) and ACTG1 (gamma actin 1), in ECM (extracellular matrix) remodeling such as MMP2 (matrix metalloproteinase 2) and CAV1 (caveolin 1), as well as in the MAPK and PI3K pathway like RPS6KA (ribosomal protein S6 kinase alpha-1) and DUSP16 (dual-specificity protein phosphatase 16) (Ritter et al., 2020). Suppression of BCL6 also decreased the cellular signals of p-FAK, p-Akt and p-Erk1/2, which are important for cell migration and invasion (Ritter et al., 2020). These data imply that BCL6, like in cancer cells, acts as a key player in the migration and invasion of trophoblasts through the regulation of diverse cellular activities, which could be of vital importance in early placental development.

Potential impact of BCL6 on trophoblast stem/progenitor cells

Key events of placental development include the spatially and temporally balanced regulation of stem cell/progenitor maintenance and self-renewal, and their timely differentiation into other cell types (Knofler et al., 2019). The molecular mechanisms that control trophoblastic stem cell/progenitor quiescence, self-renewal, lineage commitment and differentiation into all trophoblast types during early placental development remain to be fully elucidated.

BCL6 has been demonstrated to be involved in the maintenance and differentiation of stem/progenitor cells in various tissues and cell types (Hurtz et al., 2011; Pietras et al., 2014; Tiberi et al., 2014; Bonnefont et al., 2019; Fabre et al., 2020; Solanki et al., 2020; Kawabata et al., 2021; Li et al., 2021). Recently, it has been revealed that the motifs of the two transcription factors, BCL6 and CBX3 (chromobox protein homolog 3), are significantly overrepresented in early placental villous tissues (Prater et al., 2021). Notably, CBX3 is a BCL6 target gene (Polo et al., 2007), indicating a regulatory role of BCL6 over CBX3, strengthening BCL6's significance in the early placental development. In support of this notion, BCL6 is richly present in vCTBs in first trimester placenta (Ritter et al., 2020) (Fig. 1), and some of vCTBs have been proposed as G0 progenitors/stem cells (Liu et al., 2018; Aplin and Jones, 2021). BCL6 is also highly expressed in CCTs of anchoring villi (Ritter et al., 2020). The proximal CCTs undergo a multistep differentiation process and further differentiate into

non-proliferating distal CCTs, ready to invade the maternal decidua (Silini et al., 2020). The high presence of BCL6 in vCTBs and CCTs of first trimester placenta suggests its potential roles in stem/progenitor cell maintenance/survival and differentiation (Fig. 3), which require further investigations.

Taken together, BCL6 may play multiple cellular roles in trophoblasts including proliferation, survival, migration, invasion, differentiation and fusion. While increased BCL6 in pre-eclamptic placenta may promote proliferation and survival of vCTBs (Muscholsteinmetz et al., 2016), and facilitate migration and invasion of EVTs (Ritter et al., 2020), it could impair differentiation and fusion of vCTBs into the STB (Jasmer et al., 2017) and compromise EVT differentiation into further subtypes, such as endoarterial EVTs. This imbalanced proliferation and differentiation might be associated with the progression of PE (Fig. 4).

BCL6 in endometriosis and its related infertility

The uterine endometrium

Deregulated BCL6 is not only linked to PE but also to endometriosis, a common disorder of the uterine endometrium. The uterine endometrium, the inner uterine cell layer, is composed of two layers, the functionalis and the basalis, the latter being responsible for regeneration of the former during the proliferative phase (Cooke et al., 2013). Depending on the phases of the menstrual cycle, the endometrium undergoes cyclical regeneration, differentiation and shedding in response to the steroid hormones estrogen and progesterone under the control of the hypothalamic-pituitary-ovarian axis (Jabbour et al., 2006; Hawkins and Matzuk, 2008; Garry et al., 2009). While estrogen induces mitosis of endometrial cells including luminal and glandular epithelial cells, stromal fibroblasts and vascular components throughout the proliferative phase, progesterone causes secretory transformation of epithelial cells and differentiation of stromal fibroblasts after ovulation. In addition to the regulation by the steroid hormones, these dynamic processes of the endometrium are supported by cytokines/chemokines, such as IL6, IL10 and monocyte chemoattractant protein 1, produced by endometrial stromal cells (Large and DeMayo, 2012; Vallve-Juanico et al., 2019).

The extraordinarily high regenerative capacity of the endometrium indicates the presence of stem cell-like endometrial cell populations capable of self-renewal and differentiation. Indeed, numerous studies have demonstrated the presence of a stem cell population in the basalis of the endometrium, which is responsible for the formation of endometrial stromal fibroblasts (Schwab and Gargett, 2007; Masuda et al., 2012; Yin et al., 2019). Additionally, several putative endometrial stem cell-like populations have been identified, including side population cells, endometrial mesenchymal stem cells (eMSCs), and bone marrow mesenchymal stem cells (BM-MSCs) (Yilmaz and Bulun 2019). The side population may represent endometrial stem cells offering migration and angiogenesis abilities (Masuda et al., 2010), whereas eMSCs are self-renewing, multipotent and clonogenic mesenchymal stem cells giving rise to mesodermal lineages *in vitro* (Gargett et al., 2016). Additionally, BM-MSCs may improve endometrial regeneration through secreting paracrine factors to stimulate resident endometrial

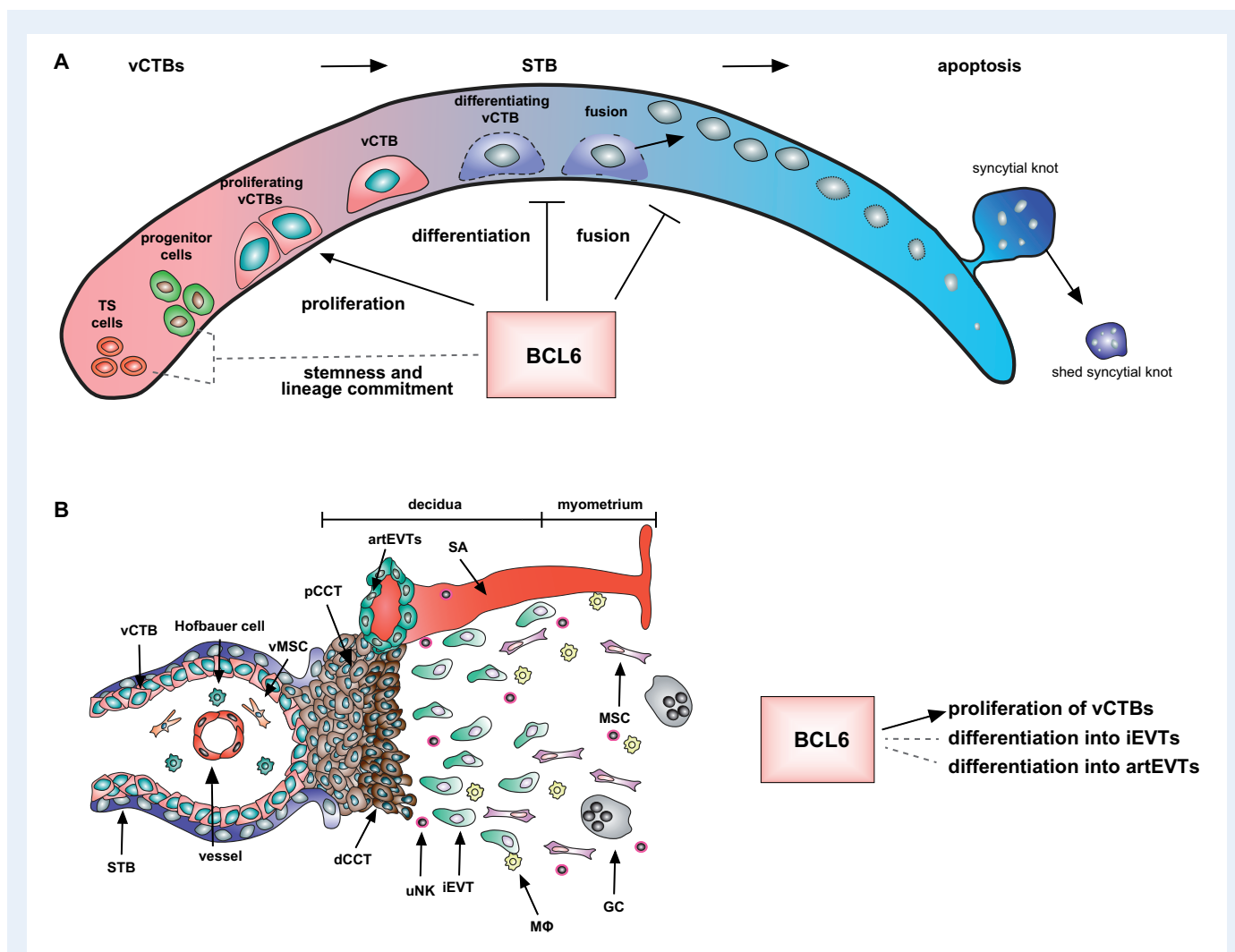


Figure 3. BCL6 may affect stemness and differentiation of trophoblast stem/progenitor cells. (A) Potential functions of BCL6 in vCTBs. BCL6 may promote vCTB proliferation, inhibit differentiation and fusion of vCTBs into the STB, and possibly affect stemness and lineage commitment of trophoblast stem/progenitor cells. (B) Potential functions of BCL6 in trophoblasts within the cell column. BCL6 may facilitate proliferation of vCTBs, and affect differentiation of vCTBs into iEVTs and artEVTs. artEVT, endoarterial EVT; dCCT, distant cell column trophoblast; EVT, extravillous trophoblast; GC, giant cell; iEVT, interstitial EVT; MΦ, macrophage; pCCT, proximal cell column trophoblast; SA, spiral artery; STB, syncytiotrophoblast; vCTB, villous cytotrophoblast; vMSC, villous mesenchymal stromal cell; uNK, uterine natural killer.

stem cells (Yilmaz and Bulun, 2019). The co-ordinated regulation of these self-renewal and differentiation populations is essential for dynamic endometrial tissue regeneration and homeostasis.

In recent years, enormous progress has been made in the generation and application of self-organizing 3D organoids. 3D organoids of normal and decidualized human endometrium have been established and these organoids were able to differentiate upon treatment with reproductive hormones (Turco et al., 2017). Functionally, human endometrial organoids were successfully used to study ciliogenesis of multi-ciliated endometrial cells (Haider et al., 2019). Recently, a 3D model of the human decidua, consisting of hormone-responsive endometrial stromal fibroblasts and endometrial epithelial cells, was reported (Cheung et al., 2021). These technical developments are of importance in elucidating the pathogenesis of endometrium-related diseases such as endometriosis.

Endometriosis and its related infertility

Endometriosis is an estrogen-dependent inflammatory disorder of the uterine endometrium (Bulun et al., 2019). About 5–10% of women of reproductive age are affected and up to 50% of these women are infertile (Bulun, 2009; de Ziegler et al., 2010; Taylor et al., 2021). The etiology of endometriosis remains to be defined. Among several hypotheses, ‘retrograde menstruation’ (Sampson, 1927a,b) is believed to be the primary mechanism of lesion formation (Smolarz et al., 2021). Important features of endometriosis are the high production of estrogen and deregulated expression of its receptors in endometriotic regions (Chantalat et al., 2020), and progesterone resistance (Patel et al., 2017). Endometriosis is characterized by endometrial-like tissue outside its normal location lining the uterus (Giudice, 2010). Depending on its location, endometriosis can be classified as peritoneal

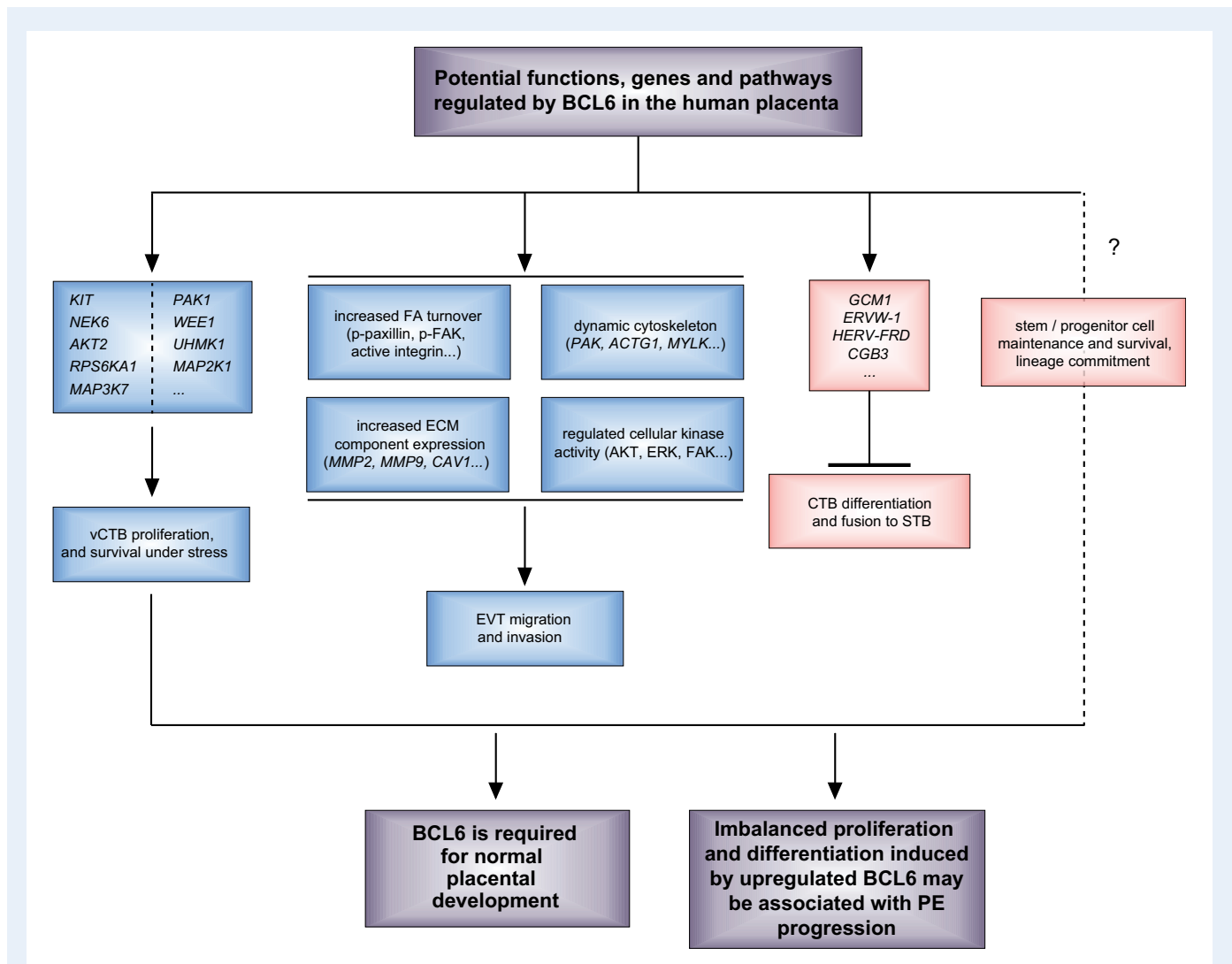


Figure 4. Potential functions of BCL6 in the human placenta. BCL6 promotes proliferation and survival of vCTBs, facilitates migration and invasion of EVT, and inhibits differentiation and fusion of vCTBs into the STB. BCL6 may also affect trophoblast stem/progenitor cell survival and differentiation. Upregulated BCL6 may cause imbalanced proliferation and differentiation, contributing to the pathogenesis of PE. *ACTG*, actin gamma; *AKT2*, AKT serine/threonine kinase 2; *CAV1*, caveolin 1; *CGB3*, chorionic gonadotropin subunit beta 3; *ECM*, extracellular matrix; *ERVW-1*, endogenous retrovirus group W member 1, syncytin 1; *FAK*, focal adhesion kinase; *GCM1*, glial cells missing transcription factor 1; *HERV-FRD*, human endogenous retrovirus group FRD, syncytin 2; *KIT*, receptor tyrosine kinase; *MAP2K1*, mitogen-activated protein kinase kinase 1; *MAP3K7*, mitogen-activated protein kinase kinase kinase 7; *MAPK*, mitogen-activated protein kinase 1; *MMP*, matrix metalloproteinase; *MYLK*, myosin light chain kinase; *NEK6*, NIMA-related kinase 6; *PAK1*, p21-activated kinase 1; *RPS6KA1*, ribosomal protein S6 kinase A1; *UHMK1*, U2 small nuclear RNA auxiliary factor 2 homology motif kinase 1; *WEE1*, G2 checkpoint kinase.

endometriotic implants, rectovaginal nodules and ovarian endometriomas (Bulun *et al.*, 2019; Kuan *et al.*, 2021). The symptoms of endometriosis are dysmenorrhea, dyspareunia, non-cyclic chronic pelvic pain and infertility (Bulun, 2009; Bulun *et al.*, 2019). Its treatment includes pharmacological and surgical therapy (Brichant *et al.*, 2021; Taylor *et al.*, 2021).

Endometriosis is associated with infertility owing to numerous factors such as distorted anatomy, local inflammatory effects on oocyte quality and an inhospitable endometrial environment for embryo implantation (Vallve-Juanico *et al.*, 2019). It is likely that $\leq 50\%$ of infertile women (Meuleman *et al.*, 2009) and $\leq 70\%$ of women with endometriosis will

not have a live birth (Bullelli *et al.*, 2010). Moreover, a larger study, based on fertilized sibling oocytes transferred into women with and without endometriosis, demonstrated reduced implantation, clinical pregnancy, ongoing pregnancy and live birth rates in women with endometriosis (Prapas *et al.*, 2012). These findings highlight that endometriosis is associated with infertility and failure of IVF.

Despite the high incidence of endometriosis, its cellular and molecular mechanisms are poorly understood. The growth of endometriotic tissue outside the uterine cavity requires degradation of the ECM, peritoneal invasion and the growth of ectopic endometrial stromal and glandular cells (Santanam *et al.*, 2002; Van Langendonck *et al.*, 2002).

The biological alterations in endometriotic lesions include increased proliferation, enhanced inflammation, decreased apoptosis, a deregulated immune response and progesterone resistance (Young and Lessey, 2010). It is generally regarded that genetic, epigenetic, environmental, autoimmune and allergic factors are among the etiological factors (Smolarz et al., 2021). Specifically, the endometrium of patients with endometriosis exhibited aberrant global DNA-methylation profiles and altered gene expression (Houshdaran et al., 2016). The deregulated immune response and inflammatory regulation, systemically and locally, were reported to play central roles in its etiology and pathophysiology (Valve-Juanico et al., 2019; Giacomini et al., 2021). In fact, the endometriotic stromal cells, including stromal fibroblasts and immune cells, expressed and secreted large amounts of immune molecules such as IL1 β , IL6 and TNF α (Tseng et al., 1996; Hornung et al., 2001). High estrogen production is of paramount importance in the pathogenesis of endometriosis, as it promotes endometriotic cell survival, inflammation and lesion progression (Bulun, 2009; Yilmaz and Bulun, 2019). Moreover, the underlying pathologic mechanisms include defectively programmed endometrial mesenchymal progenitor/stem cells (Bulun et al., 2019). Studies also highlight the involvement of the MAPK and the WNT/ β -catenin signaling pathway in the pathogenesis of endometriosis through multiple mechanisms, including proliferation, apoptosis, migration and angiogenesis (Giacomini et al., 2021).

Furthermore, many factors have been investigated as potential biomarkers for the diagnosis of endometriosis, such as IL6, IL8, hepatocyte growth factor, fibroblast growth factor, epidermal growth factor, VEGF- and platelet-derived growth factor (Smolarz et al., 2021). These growth factors and cytokines promote proliferation, invasion and angiogenesis. Notably, among these factors, IL6 is the most characteristic of endometriosis, with a sensitivity of 63% and a specificity of 69% (Nisenblat et al., 2016). IL6 impacts various vital cellular activities, including proliferation and migration by mediating the phosphorylation and activation of signal transducer and activator of transcription 3 (STAT3) (Yuan et al., 1994; Heinrich et al., 2003). Indeed, increased phosphorylated STAT3 was observed in endometriotic lesions (Kim et al., 2015). Interestingly, BCL6 is upregulated by STAT3 (Arguni et al., 2006; Walker et al., 2013), suggesting a likelihood that BCL6 could be highly expressed in endometriotic lesions.

Increased BCL6 in endometriosis and its related infertility

BCL6 is upregulated at both mRNA and protein levels in the endometrium of women with endometriosis and is considered to be a potential diagnostic marker for endometriosis (Table II) (Evans-Hoeker et al., 2016; Almquist et al., 2017; Gong et al., 2017; Yoo et al., 2017; Likes et al., 2019; Nezhath et al., 2020; Sansone et al., 2021; Shen et al., 2021). The first work came from Evans-Hoeker and colleagues reporting that BCL6 was expressed in endometrial cells during the secretory phase of the menstrual cycle and was overexpressed in eutopic endometrium from women with endometriosis (Evans-Hoeker et al., 2016). The authors reported that aberrant BCL6 expression had a high sensitivity and specificity for the diagnosis of all stages of endometriosis, indicative of BCL6 as a biomarker for endometriosis. In support of this finding, another large cohort study showed a high positive predictive value of BCL6 expression for the diagnosis of endometriosis (Nezhath et al., 2020). In combination with Sirtuin I (SIRT1), a histone

deacetylase and gene silencer, BCL6 was shown to be increased in endometrial cells of women with endometriosis (Yoo et al., 2017). In addition, BCL6 was upregulated together with ERK1/ERK2 in endometriotic tissues from rats with experimentally induced endometriosis (Nahari and Razi, 2018).

Endometriosis is associated with infertility and IVF failure (Prapas et al., 2012). Intriguingly, the prevalence of elevated endometrial BCL6 in women with unexplained infertility (UI) has been reported to be 75.3% (Almquist et al., 2017) and 80% (Evans-Hoeker et al., 2016). A prospective study in patients with UI following IVF showed a live birth rate of 11.5% versus 58% in patients with and without elevated BCL6, respectively (Almquist et al., 2017). It was also reported that the mRNA and protein levels of endometrial BCL6, along with IL21 and CXCR5 (chemokine receptor type 5), were significantly increased in women with repeated implantation failure (Gong et al., 2017). In support of these observations, Likes et al. (2019) reported that women with suspected endometriosis and aberrant endometrial BCL6 expression had worse reproductive outcomes following embryo transfer, including a high miscarriage rate, poor implantation rate, and low live birth rate and clinical pregnancy rate. Increased endometrial BCL6 is thus considered to be a negative predictor for patients with endometriosis undergoing IVF (Nezhath et al., 2020). Although more investigations are required, these findings demonstrate an association of upregulated BCL6 with endometriosis, its related infertility and IVF failure.

At the molecular level, BCL6 and SIRT1 have been shown to co-localize in the nuclei of endometriotic cells, interact with each other and bind to and repress the promoter of *GLI1* (Yoo et al., 2017), a critical mediator of progesterone action in the Indian Hedgehog pathway (Wei et al., 2010). Similarly, the BCL6/BCOR/SIRT1 complex was observed to affect the growth of human medulloblastoma cells by suppressing *GLI1* and *GLI2* of the Sonic Hedgehog pathway (Tiberi et al., 2014). These data indicate that BCL6 is an important regulator of the Hedgehog pathway, which renders upregulated BCL6 as a prime candidate driving the progesterone resistance that is crucial in the pathophysiology of endometriosis (Yoo et al., 2017). In addition, among the immune cells, T_{FH} and GC B cells, controlled by BCL6 (Hatzi and Melnick, 2014; Alterauge et al., 2020), were present in the endometrium (Shen et al., 2021), suggesting the importance of these cells through GC reactions. Among these observations, the association of increased endometrial BCL6 with progesterone resistance (Yoo et al., 2017) is of particular importance. Progesterone is the key hormone for adequate decidualization, proper implantation and successful pregnancy, as it is crucial for preparing the endometrium for implantation by blocking the proliferative effect of estrogen and by inducing genes permitting embryo attachment, as well as for regulating trophoblast invasion and migration by controlling MMP activity (Halasz and Szekeres-Bartho, 2013; Nagy et al., 2021). Abnormal endometrial BCL6-associated progesterone resistance and its other cellular activities, including deregulated proliferation, invasion and immune modulation, may be responsible for a defective endometrium, deficient endometrial receptivity, poor reproductive outcomes, and failed IVF. These data also suggest a potential involvement of BCL6 in endometrial-blastocyst cross talk during implantation.

As in trophoblasts (Fig. 2), BCL6 may be overexpressed and stabilized in endometriotic tissues by diverse causes, including altered epigenetic regulation, increased IL6/STAT3, other cytokines, stress factors, miRNAs, lncRNAs and miscellaneous protein post-translational

Table II BCL6 expression in human endometriosis.

Reference	Sample number/patient information	Methods	Main results
Evans-Hoeker <i>et al.</i> (2016)	n = 20 fertile controls. n = 29 endometriosis at laparoscopy. n = 28 fertile controls. n = 119 women with UI. Exclusion criteria were age ≥ 40 , pelvic infection/inflammation, PCOS, or fibroid tumors.	BCL6 expression by qPCR (Gene Expression Assays; Applied Biosystems (Foster City, CA)—assay HS00153368); IHC and HSCORE with BCL6 antibody clone LN22 (Leica Biosystems).	BCL6 was significantly higher in the secretory phase of patients with endometriosis versus controls ($P < 0.0001$). Both BCL6 mRNA and protein were increased in endometrial epithelium of women with endometriosis. 93.8% of BCL6 positive patients had endometriosis. A cutoff of 1.4 in HSCORE provided a likelihood ratio of 15.4 and 0.04 for positive and negative results, respectively.
Almquist <i>et al.</i> (2017)	Women with UI for > 1 year. n = 69: n = 20 pregnant, age 36.3 ± 3.2 n = 49 non-pregnant, age 34.5 ± 3.9 . Groups based on BCL6 expression: n = 17 normal expression (age 35.6 ± 3.1 ; n = 11 pregnant/n = 6 non-pregnant); n = 52 high expression (age 34.8 ± 3.9 ; n = 9 pregnant/n = 43 non-pregnant).	Prospective cohort study, IHC and HSCORE with BCL6 antibody clone LN22 (Leica Biosystems).	Clinical pregnancy rate and live birth rate per transfer were compared between women with positive or negative BCL6 staining. A high BCL6 expression was defined by a histologic score (> 1.4) and strongly associated with poor reproductive outcomes in IVF cycles in women with UI BCL6 expression, median (range) was 0.9 (0–4) in the pregnant group and 2.1 (0.5–4.0) in the non-pregnant group ($P = 0.01$). Staining for BCL6 was predominantly localized in the nucleus. 75.3% of patients with UI-tested positive for BCL6.
Gong <i>et al.</i> (2017)	n = 30 controls (age 32.77 ± 4.7). n = 30 RIF (age 33.23 ± 5.06).	qPCR and IHC with rabbit BCL6 antibody (1:100; cat no. bs2734R, BIOSS, Beijing, China).	The mRNA and protein level of BCL6 in the endometrium during the mid-luteal phase was significantly increased in the RIF group.
Yoo <i>et al.</i> (2017)	Age 18–45. For control: 21 samples from proliferative (n = 5) and secretory phase (n = 16) for WB and 23 samples from the proliferative (n = 6) and secretory (n = 17) phase for IHC. For endometriosis: 54 samples from proliferative (n = 16) and secretory (n = 38) phase for WB and 57 samples for IHC.	Results were based on the WB band intensity (BCL6 antibody 561520; BD Pharmingen, San Jose, CA) and correlation coefficient = 0.5659, $P < 0.0001$, between BCL6 and SIRT1 expression.	BCL6, KRAS and SIRT1 were co-ordinately over-expressed in eutopic endometrium of women with endometriosis and likely participated in the pathogenesis of endometriosis BCL6 and SIRT1 were co-localized in the nuclei of endometrial cells, bound to and suppressed the promoter of <i>GLII</i> , suggesting its role in progesterone action.
Likes <i>et al.</i> (2019)	Age 27–42, n = 85 cycles. Three groups: medical suppression (n = 10), laparoscopy (n = 20), controls (n = 54).	Prospective cohort study. At least 1 year of UI, underwent endometrial biopsy, and IHC for BCL6 (clone LN22, Leica Biosystems), prior to embryo transfer during an ART cycle. Subjects had elevated BCL6 (HSCORE ≥ 1.4).	Patients with positive endometrial BCL6, defined as an HSCORE > 1.4 , were associated with poor IVF outcomes and recurrent miscarriage. Increased endometrial BCL6 was associated with worse reproductive outcomes after embryo transfer, compared with women with endometriosis and treated with medical or laparoscopy.
Nezhat <i>et al.</i> (2020)	Age 29–47. n = 72 endometriosis. n = 3 with other pathologies. Inclusion criteria: women of reproductive age undergoing IVF with a diagnosis of UI or recurrent pregnancy loss,	Retrospective cohort study. Patients with endometrial BCL6 over-expression underwent laparoscopic surgery for treatment of suspected endometriosis.	The positive predictive value of BCL6 testing for endometriosis was 96%. This could help to identify a patient population that may require surgical treatment before embryo transfer.

Continued

Table II Continued

Reference	Sample number/patient information	Methods	Main results
Sansone et al. (2021)	endometrial biopsy with ReceptivaDx™. Age 18–42. n = 10 control. n = 10, stages I/II endometriosis. n = 10, stages III/IV endometriosis. Patients were of reproductive age, had regular menstrual cycles, without (PCOS) or hormonal birth control.	BCL6 and SIRT1 levels were measured in serum, plasma, urine and cervical mucus using ELISA.	Women with other pathologies (n = 3) also had endometrial BCL6 overexpression. No differences in BCL6 levels were found between patients with endometriosis and controls. No differences in BCL6 levels were found between Stages I/II and III/IV. Levels of SIRT1 in sera were significantly elevated in women with Stages III/IV compared with controls and Stages I/II.
Shen et al. (2021)	Age ≤40. n = 6. Blood and/or endometrial samples from the mid-luteal phase of the menstrual cycle.	Flow cytometry for endometrial B-cell subsets analysis.	1–5% of endometrial immune cells were B cells. FAS ⁺ IgD ⁺ BCL6 ⁺ GC B cells were present in the endometrium, indicating their roles in the human endometrial environment. T _{FH} -like cells did not have a higher expression of BCL6.

BCL6, B-cell lymphoma 6; GC, germinal center; *GLI1*, glioma-associated oncogene homolog 1; HSCORE, a method for quantifying the staining intensity and the percentage of stained cells in IHC; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; qPCR, quantitative PCR; RIF, repeated implantation failure; SIRT1, Sirtuin 1; T_{FH}, T follicular helper cells; UI, unexplained infertility; WB, western blot analysis.

modifications. Increased BCL6 may regulate multiple signaling pathways including FAK, MAPK/ERK, PI3K/AKT, WNT and Hedgehog pathways in endometriotic cells, as occurs in lymphoma cells (Basso et al., 2010). This might affect vital cellular activities such as cell proliferation, survival, differentiation, migration, invasion, immune response and inflammation regulation (Basso et al., 2010; Louwen et al., 2014; Muschol-Steinmetz et al., 2016; Jasmer et al., 2017; Ritter et al., 2020), impact various functionalities of endometriotic cells, including glandular epithelial cells, stromal fibroblasts, stromal GC B and T_{FH} cells and stem/progenitor cells, and contribute to the pathophysiology of endometriosis and its related infertility (Fig. 5).

Conclusion and perspectives

We have summarized the current data from bench to clinic showing BCL6's potential function in the placenta and its critical involvement in PE and endometriosis. BCL6 is significantly increased in pre-eclamptic placentas as well as in endometriotic lesions. Upregulated BCL6 regulates a variety of cellular activities, including proliferation, migration and invasion, and may also influence stem/progenitor cell differentiation in pre-eclamptic placentas as well as in endometriotic lesions. Increased endometrial BCL6 is considered to be a diagnostic marker for endometriosis and a predictor for poor IVF outcomes. Proper regulation of BCL6 may be crucial to orchestrate endometrial decidualization, implantation and placentation for a successful pregnancy.

Although some work has been done, the detailed molecular mechanisms by which BCL6 exerts multiple functions in the placenta as well as in the endometrium have not been completely elucidated. It is paramount to explore whether increased BCL6 is one of the causes for the initiation of PE and endometriosis owing to epigenetic modifications, or a pathological consequence of the disease-related high-stress

conditions such as chronic hypoxia, inflammation and oxidation. Further investigations are warranted to examine whether BCL6 is able to co-determine the fate of various stem/progenitor cells in the placenta and the endometrium.

Recent progress in the establishment of human trophoblast stem cells (Okae et al., 2018), placental organoids (Haider et al., 2018; Turco et al., 2018) and endometrial organoids (Turco et al., 2017; Cheung et al., 2021; Song and Fazleabas, 2021) has provided novel tools to study the molecular regulatory network of placentation, the endometrial cycle and the pathophysiology of gestational and reproductive diseases like PE and endometriosis. These new models, in combination with specific small molecule inhibitors targeting BCL6 or gene editing, will allow us to explore the individual roles of BCL6 in stemness and differentiation of trophoblastic and endometrial stem/progenitor cells. New omics technologies (Cao et al., 2017; Habib et al., 2017) will be of great help to delineate the gene landscapes controlled by BCL6 in diverse trophoblastic and endometrial cell types. Being equipped with these novel tools and techniques, we are just at the beginning of a journey to unveil the multifaceted roles of BCL6 in placental development, endometrial homeostasis, and the pathogenesis of PE and endometriosis.

Data availability

The data underlying this article are available in the article.

Authors' roles

FL and JY conceived the review concept. JY performed the literature search. FL, CS and JY analyzed and discussed the data. JY wrote the manuscript. NNK greatly modified the manuscript, summarized the

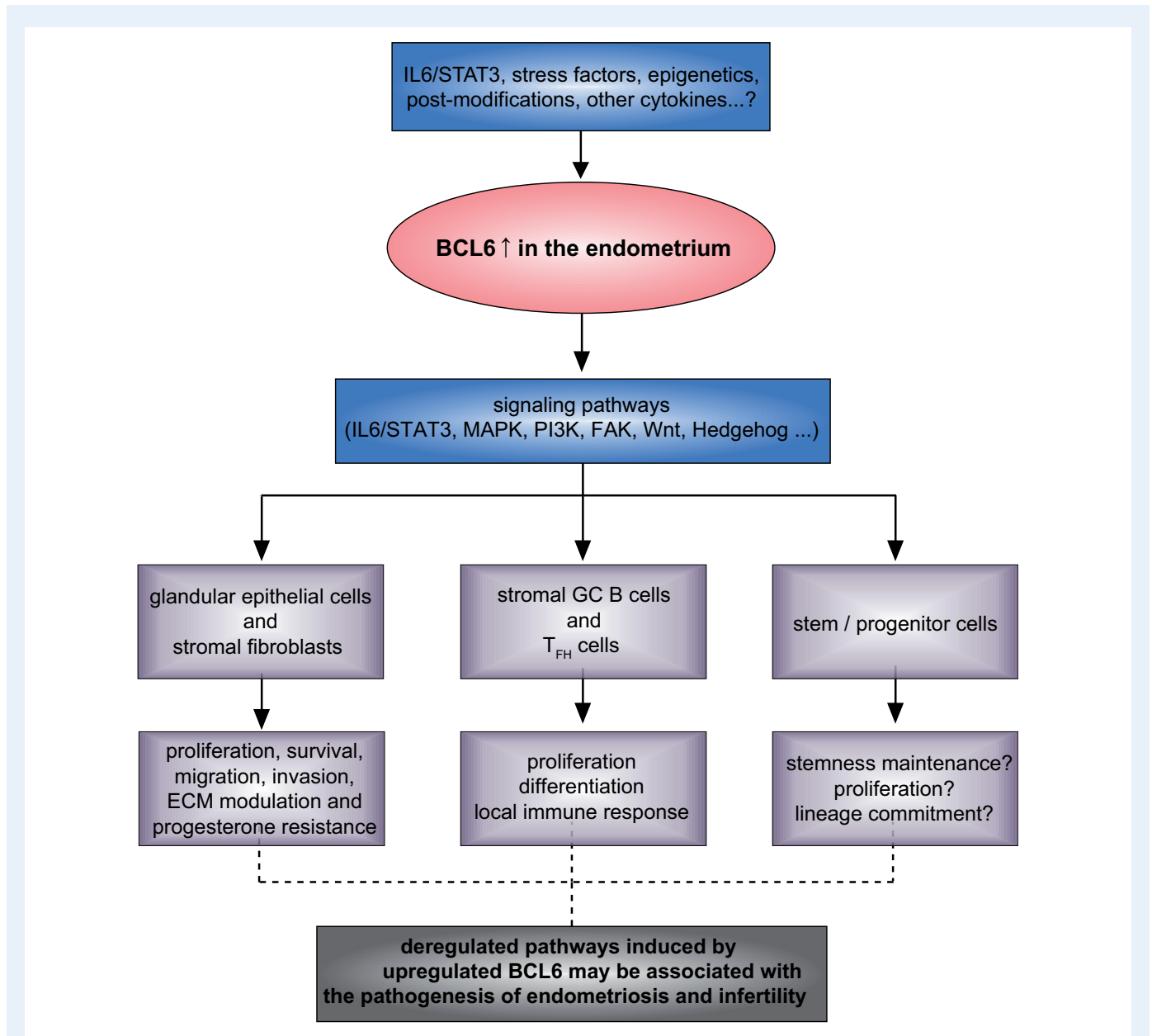


Figure 5. Increased BCL6 in endometriosis. Schematic illustration shows that various factors may upregulate and stabilize BCL6, which may impact vital cellular activities in diverse cell types of endometrial tissues through multiple signaling pathways, affecting the pathogenesis of endometriosis and its related infertility. ECM, extracellular matrix; FAK, focal adhesion kinase; GC, germinal center; IL6, interleukin 6; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; T_{FH} cells, T follicular helper cells.

expression data of BCL6 in pre-eclampsia (Table I) and in endometriosis (Table II), and contributed to Fig. 1. AR drew Figs 2–5 and performed a critical reading of the manuscript. AF contributed to Fig. 1. NNK, AR and AF were intensively involved in BCL6 studies included in this article. All authors improved the manuscript and approved the submission.

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Conflict of interest

The authors declare no conflicts of interest.

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