Role of ubiquitin-proteasome system in preeclampsia (Review)

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Abstract. Preeclampsia (PE) is a multifactorial pregnancy disorder characterized by hypertension and proteinuria, primarily resulting from placental abnormalities and endothelial dysfunction. The present review explores the role of ubiquitination and deubiquitination (key post-translational modifications), in the pathogenesis of PE. Ubiquitination, catalyzed by E1, E2 and E3 enzymes, and reversed by deubiquitinating enzymes, regulates protein stability and function, thereby influencing key cellular processes in trophoblasts. Dysregulation of these pathways impairs trophoblast functions and contributes to PE development. In addition, the present review discusses emerging therapeutic strategies targeting the ubiquitin-proteasome system, including deubiquitinase-targeting chimera and proteolysis-targeting chimeras. Targeting ubiquitination and deubiquitination mechanisms presents a promising avenue for the treatment of PE. Further research into these pathways may lead to novel interventions aimed at improving maternal and fetal outcomes.

Contents

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1. Introduction

Preeclampsia (PE) is a pregnancy-specific multisystem disorder that typically arises after the 20th week of gestation. It is primarily defined by new-onset hypertension (systolic blood pressure ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg) and proteinuria (urinary protein excretion of ≥0.3 g/24 h) (1). Hypertension, a hallmark clinical feature of PE, may develop gradually or abruptly and is often accompanied by symptoms such as headaches and blurred vision (2). Proteinuria reflects renal impairment and its progression may lead to generalized edema, extending from the lower limbs to the entire body (3). PE can also result in hepatic and renal dysfunction, coagulation abnormalities and intrauterine growth restriction. Globally, the prevalence of PE ranges from 2 to 8% (4), with increased rates observed in developing countries (5). High-risk factors include nulliparity, maternal age extremes (<18 or >35 years), multiple gestations, family history of PE (6), chronic hypertension, diabetes, obesity (7), genetic predisposition, environmental influences, immune dysregulation (8) and paternal contributions, such as paternal history of PE in previous pregnancies (doubling the risk in subsequent partners), partner change leading to loss of maternal immune tolerance, inadequate maternal exposure to paternal seminal fluid (associated with shorter cohabitation duration) and genetic contributions via paternal human leukocyte antigens that disrupt maternal-fetal immune crosstalk (9). The pathogenesis of PE is multifactorial, involving abnormal placentation, immune dysfunction and endothelial injury. Inadequate trophoblast invasion results in shallow placental implantation and defective remodeling of the uterine spiral arteries, leading to reduced placental perfusion (10). This hypoperfusion induces placental hypoxia and oxidative stress, contributing to cellular damage via lipid peroxidation, DNA oxidation and protein modification (11,12). These changes culminate in widespread cellular and tissue dysfunction, a key feature of PE. Furthermore, an aberrant maternal immune response to the feto-placental unit triggers excessive production of inflammatory mediators, disrupting the immune balance required for a healthy pregnancy (13). Post-translational protein modifications (PTMs) of proteins carry out a central role in these processes by regulating protein structure, function, localization and stability. Key PTMs include, phosphorylation, acetylation and particularly ubiquitination (due to its involvement in cell signaling, gene

regulation) and cell cycle control, all of which are associated with the onset and progression of PE (14-16).

Ubiquitin-proteasome system (UPS) regulates cellular homeostasis through ubiquitination and deubiquitination (Fig. 1) (17). Ubiquitination is a PTM process that involves the attachment of ubiquitin molecules to target proteins. This process requires three main types of enzymes: Ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2) and ubiquitin ligases (E3). First, the E1 enzyme activates ubiquitin, which is then transferred to the E2 enzyme. The E3 ligase subsequently facilitates the transfer of ubiquitin to specific substrate proteins (18). Ubiquitination can occur as monoubiquitination or polyubiquitination, with different ubiquitin chain types regulating protein stability, activity and subcellular localization. These modifications are integral to diverse cellular processes, including cell cycle progression, signal transduction and gene expression (19). Conversely, deubiquitination, which is the removal of ubiquitin moieties, is mediated by deubiquitinating enzymes (DUBs), which counteract ubiquitination and fine-tune protein turnover and function. To date, >100 DUBs have been identified and are classified into ≥9 families based on conserved domains and sequence homology. These include ubiquitin-specific proteases, ubiquitin C-terminal hydrolases, Machado-Joseph disease protein domain proteases, ovarian tumor proteases, motif-interacting with ubiquitin-containing novel DUB family, JAB1/MPN/MOV34 metalloenzymes, permuted papain fold peptidases, zinc finger-containing ubiquitin peptidase 1 and monocyte chemoattractant protein-induced protein-1 (20). The balance between ubiquitination and deubiquitination is essential for cellular integrity and function.

In the context of PE, dysregulation of this balance may impair trophoblast functions such as proliferation, invasion and migration, and fusion. It may also disrupt apoptosis, provoke endothelial cell stress responses and exacerbate endoplasmic reticulum (ER) and oxidative stress in trophoblasts. Understanding the roles of ubiquitination and deubiquitination in PE pathogenesis is therefore key for identifying novel molecular targets and developing effective therapeutic interventions.

2. The role of ubiquitination in PE

Ubiquitin ligase constitutively photomorphogenic 1 (COP1). Serine/threonine kinase 40 (STK40), a Ser (serine)/threonine protein kinase, interacts with cyclin-dependent kinase inhibitor 1C (P57Kip2), a cyclin-dependent kinase inhibitor essential for trophoblast cell fusion (21,22). During this fusion process, STK40 downregulates P57Kip2 protein levels by binding to its CDK/cyclin domains, thereby promoting COP1-mediated ubiquitination. This process reduces P57Kip2 protein levels without affecting its mRNA expression (23), highlighting a post-translational regulatory mechanism key for trophoblast fusion. Both STK40-P57Kip2 interaction and COP1-mediated ubiquitination are essential for this regulatory pathway (21). In hypertensive disorders of pregnancy, such as PE, STK40 is abnormally upregulated, potentially impairing trophoblast fusion (21), by accelerating the degradation of P57Kip2. This disruption may contribute to the development of PE. Furthermore, STK40 overexpression or knockdown modulates the expression of genes associated with P57Kip2, components of the E3 ubiquitin ligase complex and trophoblast cell markers, thereby affecting overall trophoblast function. In summary, STK40, through its interaction with COP1 and regulation of P57Kip2 ubiquitination, may carry out a pivotal role in the pathogenesis of PE by disrupting trophoblast fusion and cell cycle regulation when upregulated.

Ubiquitin ligase ankyrin repeat and SOCS box containing protein 4 (ASB4). ASB4 is an E3 ubiquitin ligase that targets specific proteins for proteasomal degradation (24,25). It is involved in pregnancy and has been implicated in the development of PE (25). ASB4-knockout mice exhibit hallmark symptoms of PE, including hypertension, proteinuria and reduced offspring numbers (25,26). These abnormalities are exacerbated in mice subjected to a high-fat diet, consistent with a study that associate the ASB4 gene polymorphisms to obesity-related PE in humans (27). Mechanistically, ASB4 mediates the ubiquitination and subsequent degradation of inhibitor of DNA binding 2 (ID2), an inhibitor of DNA-binding proteins (25). This degradation relieves the suppression of basic helix-loop-helix transcription factors, which are essential for cellular differentiation (28). The function of ASB4 is thus key for trophoblast differentiation, implantation and placental development (25). Additionally, ASB4 deficiency impairs angiogenesis, with reduced vascular endothelial growth factor (VEGF) expression levels observed in the blood vessels of *Asb4*-deficient mice, although the regulatory mechanisms remain unclear (27). For instance, while reduced ID2 expression levels promote VEGF secretion in hepatocellular carcinoma, the impact of elevated ID2 levels on VEGF production in trophoblasts is not yet understood (29,30). In summary, ASB4 regulates protein turnover during pregnancy and is important for trophoblast differentiation and placental function. Its dysfunction may be a critical factor in the pathogenesis of PE.

Ubiquitin ligase neural precursor cell expressed developmentally down-regulated protein 4 (NEDD4). NEDD4, an E3 ubiquitin ligase, contributes to the pathogenesis of PE by mediating K48-linked ubiquitination, leading to proteasomal degradation of its substrates (31). Thrombospondin 1 (THBS1), which is downregulated in PE placental tissues and inversely correlates with blood pressure levels (32), inhibits the interaction between NEDD4 and TGF-β-activated kinase 1 (TAK1) (33). Loss of THBS1 enhances NEDD4-mediated ubiquitination and degradation of TAK1, thereby impairing trophoblast fusion and function (32). Moreover, THBS1 deficiency induces necroptosis in trophoblast cells, a form of programmed cell death accompanied by the release of damage-associated molecular patterns, which can activate inflammatory responses and disrupt cellular homeostasis (34). Notably, this necroptosis can be reversed by specific necroptosis inhibitors such as Necrostatin-1 and GSK'872, while the pan-caspase inhibitor Z-VAD-FMK is ineffective in this context (4). Furthermore, *THBS1* silencing inhibits trophoblast cell proliferation, migration and invasion, while promoting cell cycle arrest and apoptosis (4). In summary, THBS1 carries out a protective role in maintaining trophoblast cell function by preventing NEDD4-mediated TAK1 ubiquitination and degradation. In PE, downregulation of THBS1

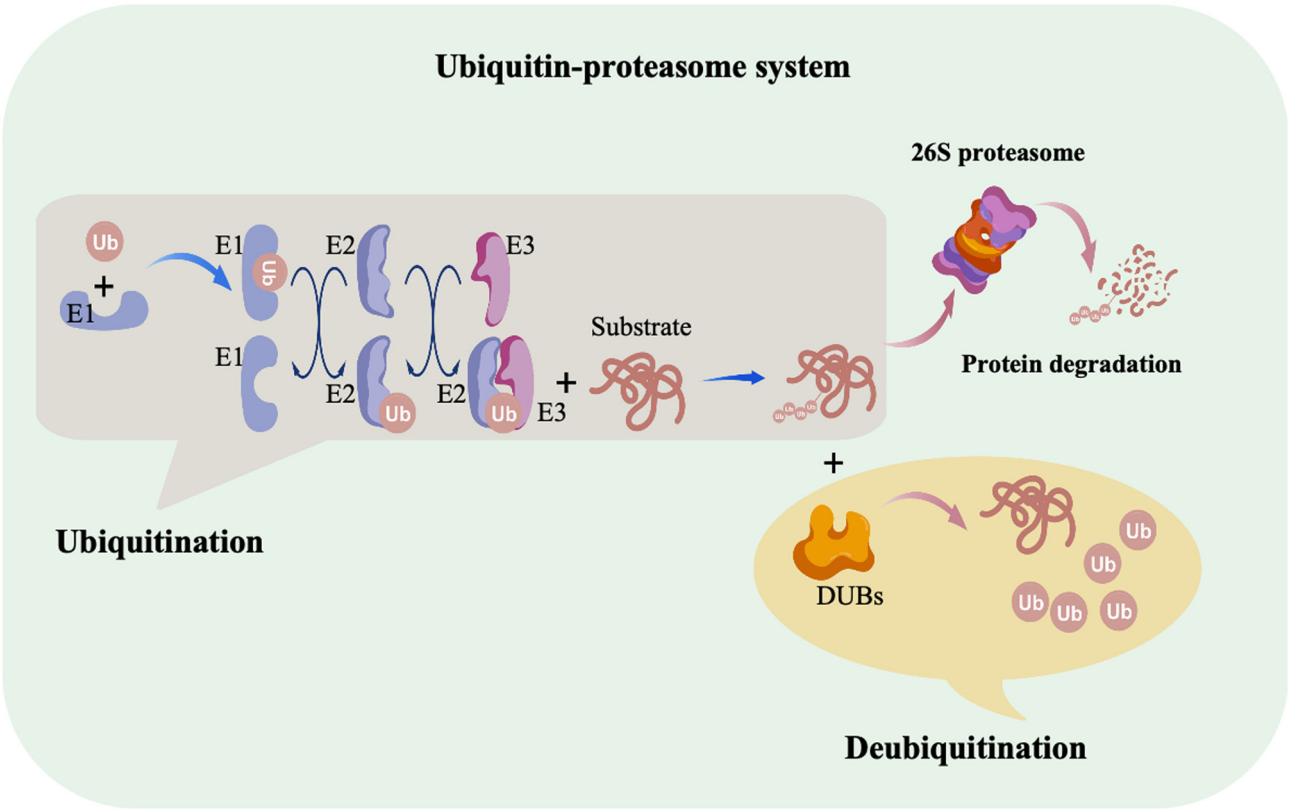

Figure 1. Principles of ubiquitination and deubiquitinating enzymes in the ubiquitin-proteasome system. During the ubiquitination process, Ub is conjugated to the substrate through the actions of E1, E2 and E3 enzymes. During the deubiquitination process, DUBs remove ubiquitin from the substrate. The substrate labeled with ubiquitin is then recognized and degraded by the 26S proteasome, resulting in protein degradation products. Ub, ubiquitin; DUBs, deubiquitinating enzymes.

activates this ubiquitination pathway, triggering necroptosis and inflammatory responses that contribute to disease progression. These findings underscore the critical role of THBS1 in trophoblast regulation and suggest potential therapeutic targets for PE prevention and treatment.

Ubiquitin ligase neural precursor cell expressed developmentally downregulated gene 4-like (NEDD4L). NEDD4L, a ubiquitin ligase of the NEDD4 family, mediates the addition of ubiquitin to target proteins, such as epithelial sodium channel (ENaC), promoting their degradation or altering their function (35). ENaC is a key transporter that regulates sodium reabsorption in the distal convoluted tubule and collecting duct of the kidney (36). NEDD4L regulates ENaC activity through the ubiquitination pathway. In patients with PE, although NEDD4L expression does not change considerably, ENaC levels in urinary extracellular vesicles are notably upregulated, which may contribute to sodium retention and hypertension symptoms in patients with PE (37). These findings suggest that regulatory mechanisms other than NEDD4L may influence the expression and activity of ENaC in PE. Overall, these findings offer valuable insights into the pathophysiology of PE and highlight novel therapeutic targets to regulate sodium reabsorption and blood pressure in patients with PE.

Ubiquitin ligase ubiquitin protein ligase E3A (UBE3A). A molecular regulatory axis involving microRNA (miR)-218-5p, UBE3A and special AT-rich sequence binding-protein 1 (SATB1) has been identified in the context of PE pathogenesis (38). UBE3A, an E3 ubiquitin ligase, mediates their ubiquitination of target proteins, marking them for proteasomal degradation (39). Among its substrates, UBE3A specifically targets the SATB1 protein, a key regulator of trophoblast cell function. Reduced SATB1 expression levels are associated with impaired trophoblast migration and invasion and have been implicated in the development of PE (40,41). miR-218-5p negatively regulates UBE3A expression levels, thereby attenuating UBE3A-mediated ubiquitination and degradation of SATB1 (38). This inhibition helps maintain SATB1 protein stability, promoting trophoblast cell infiltration and mitigating ER and oxidative stress. In animal models of PE, administration of miR-218-5p agomir was revealed to alleviate pathological features, enhance trophoblast invasion and reduce ER and oxidative stress (38). These findings suggest that miR-218-5p may have therapeutic potential in PE by stabilizing SATB1 through the suppression of UBE3A. Moreover, the expression levels of miR-218-5p, UBE3A and SATB1 could serve as predictive or prognostic biomarkers for PE. In summary, the miR-218-5p/UBE3A/SATB1 axis carries out a key role in maintaining trophoblast cell function, and its modulation offers a promising molecular target for PE prevention and treatment.

Ubiquitin ligase casitas B-lineage lymphoma (Cbl). Cbl-mediated ubiquitination of Met disrupts hepatocyte growth factor (HGF) signaling in early-onset PE (E-PE) (42), which is defined as PE diagnosed before 34 weeks of gestation (43).

HGF regulates trophoblast migration/invasion via Met receptor activation-activating the MEK/Erk, PI3K and STAT3 pathways (44), which are essential for placental nutrient exchange. These processes are essential for the role of the placenta in mediating nutrient exchange between the mother and fetus. In mice, the absence of HGF or Met results in embryonic lethality and placental dysfunction, highlighting the importance of the HGF/Met pathway (45,46). Furthermore, in E-PE, the suppression of this signaling pathway associates with enhanced internalization and subsequent ubiquitination of the Met receptor. Normally, the Met receptor undergoes CAV-1-mediated internalization and Cbl-mediated ubiquitination after activation to maintain signaling homeostasis (47). However, under hypoxic stress in E-PE, CAV-1 binding to Met increases, leading to more frequent Met internalization. Meanwhile, Cbl expression levels are reduced, impairing the ubiquitination and degradation of Met (47). This leads to Met accumulation in trophoblast cells, forming aggregates that disrupt HGF/Met signaling, ultimately diminishing the invasiveness of trophoblast cells (47). Consequently, this disruption is closely associated with PE development, affecting placental formation and function, which can compromise fetal blood and nutrient supply. The hypoxic environment and disrupted Met signaling may create a cycle that worsens trophoblast cell dysfunction and contributes to PE pathogenesis. The effect of hypoxia on the internalization of membrane receptors, as observed in receptors such as glutamate receptor 1 (48) and the transferrin receptor (49), may similarly apply to preeclamptic placentas.

These findings suggest that dysregulated ubiquitin-mediated degradation, particularly involving the Met receptor, is central to the pathogenesis of E-PE. In conclusion, aberrant Met receptor internalization and ubiquitination, along with suppression of the HGF/Met signaling pathway, likely carry out a key role in the early stages of PE. Understanding this mechanism provides valuable insight into the molecular basis of PE and highlights potential therapeutic targets for its prevention and treatment.

Ubiquitin ligase tripartite motif containing 72 (TRIM72). Cytotrophoblast-derived mesenchymal stem cells (CVMSCs) have emerged as a promising therapeutic approach for PE due to their robust self-renewal capacity and low immunogenicity (50). Recent studies highlight the role of CVMSC-derived exosomes in modulating trophoblast behavior through the ubiquitination pathway (50-52), particularly by regulating p53 protein levels. As a tumor suppressor, p53 governs key cellular processes, including proliferation, apoptosis and genomic stability (53). Li *et al* (52) demonstrated that CVMSC-derived exosomes upregulate the expression of TRIM72, an E3 ubiquitin ligase that directly interacts with p53, promoting its ubiquitination and subsequent proteasomal degradation. This downregulation of p53 reduces trophoblast apoptosis while enhancing their proliferation and migration, which are essential functions for proper placental development and function. The ubiquitination cascade involves the sequential action of ubiquitin-activating, -conjugating and -ligating enzymes, with E3 ligases such as TRIM72 conferring substrate specificity. The upregulation of TRIM72 and the consequent suppression of p53 and its downstream signaling highlight a key mechanism by which CVMSC-derived exosomes support trophoblast viability and function (52). By attenuating p53-mediated apoptosis, these exosomes may help restore placental function and mitigate PE progression. Therefore, CVMSC-derived exosomes regulate trophoblast apoptosis, proliferation and migration via TRIM72-mediated p53 ubiquitination, offering a novel therapeutic strategy for PE.

Ubiquitin ligase ring finger protein 123 (RNF123). PE, a hypertensive disorder of pregnancy, is characterized by impaired trophoblast cell invasiveness, often associated with the upregulation of Cyclin G2 (CCNG2) (54). Elevated CCNG2 expression in the placentas of patients with PE associates with diminished trophoblast migration, invasion and endothelial-like network formation, key processes for normal placental development (54). CCNG2 inhibits the JNK-dependent Wnt/PCP signaling pathway by promoting the ubiquitination and proteasomal degradation of the Dvl2 protein, thereby reducing the expression of downstream epithelial-mesenchymal transition (EMT) markers and MMPs (54-57). While CCNG2 does not alter Dvl2 mRNA levels, it decreases Dvl2 protein stability via the ubiquitin-proteasome pathway (54,57). Recent studies have identified RNF123, an E3 ubiquitin ligase, as a downstream effector of CCNG2 (54). RNF123 interacts with Dvl2, facilitating its ubiquitination and degradation, thereby impairing trophoblast cell function. By enhancing RNF123 expression and its interaction with Dvl2, CCNG2 suppresses the Wnt/PCP-JNK signaling cascade, ultimately limiting trophoblast migration, invasion and network formation (54). These findings provide mechanistic insights into the pathogenesis of PE and highlight potential molecular targets for therapeutic intervention.

Ubiquitin ligase β-transducin repeat-containing protein (β-TrCP). Severe PE is also associated with reduced trophoblast invasiveness and increased expression of β-TrCP, a component of the Skp1-cullin1-F-box E3 ubiquitin ligase complex. β-TrCP mediates the ubiquitination and degradation of several key regulatory proteins (58). β-TrCP inhibits the expression of Snail, a zinc finger transcription factor that promotes EMT by repressing E-cadherin (59). Overexpression of β-TrCP suppresses trophoblast migration and invasion, whereas its knockdown enhances these functions (60). β-TrCP also regulates VEGFR2 protein levels, a key factor in angiogenesis, through the ubiquitin-proteasome pathway (60). Research reveals that silencing β-TrCP prolongs the half-life of Snail protein and the inhibition of trophoblast migration and invasion by β-TrCP can be partially reversed with the proteasome inhibitor MG132 (59-61).

Notably, PE placental tissues exhibit considerably reduced expression of miR-135a-5p, which negatively associates with β-TrCP levels (62). Functional studies demonstrate that miR-135a-5p enhances trophoblast migration and invasion *in vitro* (62) and directly targets β-TrCP in trophoblast cells (62). Overexpression of β-TrCP counteracts the promotive effects of miR-135a-5p on trophoblast invasion and migration (62). At the molecular level, miR-135a-5p increases N-cadherin, vimentin and β-catenin expression while suppressing E-cadherin levels, effects that are attenuated by β-TrCP overexpression (62). These findings suggest that β-TrCP contributes to PE pathogenesis by regulating Snail through the ubiquitin-proteasome

pathway, thereby impairing EMT and trophoblast invasiveness. As such, β-TrCP represents a promising molecular target for the prevention and treatment of PE.

Ubiquitin ligase F-box and WD repeat domain containing 2 (FBW2). Glial cells missing homolog 1 (GCM1) is essential for placental development as it activates the expression of genes necessary for appropriate placental development by autoregulating its promoter activity (63). Hypoxic conditions lead to GCM1 degradation and downregulation of its target genes, which are implicated in PE pathogenesis (64,65). Chiang *et al* (66) demonstrated that under hypoxic conditions, the protein levels of GCM1 decrease due to ubiquitin-mediated proteasomal degradation. In this process, hypoxia inhibits the PI3K-Akt signaling pathway, activating GSK-3β (66), which then phosphorylates GCM1 at Ser322. This phosphorylation facilitates F-box protein FBW2, promoting the ubiquitination and subsequent proteasomal degradation of GCM1 (66). Notably, the phosphorylation of GCM1 at Ser322 and Ser326 is key for FBW2 recognition and is a prerequisite for GCM1 ubiquitination and protein degradation (66). Moreover, the use of the GSK-3β inhibitor LiCl can prevent hypoxia-induced degradation of GCM1, indicating a key role for GSK-3β in regulating the stability of GCM1 (66). Given the association of PE with hypertension, proteinuria and edema, hypoxia-induced GCM1 degradation may lead to placental insufficiency, contributing to PC. These findings offer valuable insights into potential PE interventions targeting GCM1 stability under hypoxic conditions.

Other factors influencing ubiquitination

Long non-coding (Lnc)-double homeobox A pseudogene 8 (DUXAP8). DUXAP8 is a long non-coding RNA that carries out a key role in regulating trophoblast function by modulating the ubiquitination of poly(rC) binding protein 2 (PCBP2). DUXAP8 specifically binds to PCBP2 and inhibits its K48-linked ubiquitination, thereby preventing its degradation via the ubiquitin-proteasome pathway (36). While DUXAP8 overexpression increases PCBP2 protein stability without altering its mRNA levels, its downregulation enhances PCBP2 degradation. This regulatory mechanism impacts the activation of the AKT/mTOR signaling pathway, influencing trophoblast cell proliferation, migration and invasion (67,68). Mechanistically, DUXAP8 overexpression activates the AKT/mTOR pathway, inhibits autophagy (evidenced by decreased LC3-II and increased p62 levels), impairs ER quality control and induces ER stress and protein aggregation (68). In PE models, DUXAP8 overexpression is associated with a PE-like phenotype, characterized by reduced expression of FAM134B and LC3-II and increased protein aggregation (68). These findings underscore the role of DUXAP8 in regulating autophagy and ER-selective autophagy in trophoblast cells, offering new perspectives on PE pathogenesis and potential molecular targets for its prevention and treatment.

FUNDC1. FUNDC1 is a mitochondrial autophagy receptor that initiates mitophagy under hypoxic conditions, serving as a protective cellular mechanism (69). Chen *et al* (70) demonstrated that hypoxia reduces FUNDC1 ubiquitination in trophoblast cells, implicating this modulation in PE pathogenesis. Using the proteasome inhibitor MG132 and the activator MF-094, they revealed that decreased FUNDC1 ubiquitination promotes mitophagy, whereas increased ubiquitination suppresses it. Reduced ubiquitination also influences mitochondrial membrane potential, a key apoptotic signal (70). Under hypoxia, elevated FUNDC1 levels suppress mitophagy, decrease intracellular reactive oxygen species (ROS) and malondialdehyde, and increase antioxidant markers glutathione and superoxide dismutase, indicating reduced oxidative damage (70). In models of PE, enhanced FUNDC1 ubiquitination mitigates oxidative stress-induced damage (70). These findings suggest that targeting FUNDC1 ubiquitination could be a novel approach to modulate mitophagy and oxidative stress in trophoblasts, offering potential strategies for early PE diagnosis and treatment.

Storkhead box 1 (STOX1). Regulation of the STOX1 protein depends largely on Akt-mediated phosphorylation, which influences its nucleocytoplasmic shuttling and ubiquitin-dependent degradation. STOX1 contains regulatory motifs similar to those in the FOX gene family, affecting its nucleocytoplasmic transport (71,72). Two putative Akt phosphorylation sites at Ser647 and Ser944 have been identified (70,71). Treatment with the ubiquitin-proteasome inhibitor MG132 increases cytoplasmic STOX1 levels, confirming ubiquitin-mediated degradation (73). Mutation analyses reveal that the S647A mutant and wild-type STOX1 localize primarily to the nucleus, while the phosphomimetic S647E mutation prevents nuclear entry and accelerates degradation (73). STOX1 directly binds to the promoter of catenin α 3 (CTNNA3), enhancing α-T-catenin expression levels, with the Y153H mutation strengthening this interaction and increasing mRNA expression levels (73). Matrigel invasion assays reveal that downregulation of STOX1 or α-T-catenin markedly enhances trophoblast invasion, while their overexpression inhibits it (73). Silencing STOX1 or CTNNA3 in trophoblast cells induces a shift toward a non-proliferative cell type (73). *In vitro*, trophoblasts with the STOX1 HH genotype exhibit reduced proliferation and increased CTNNA3 expression levels upon STOX1 upregulation (73). These findings indicate that Akt-mediated phosphorylation controls nucleocytoplasmic transport and ubiquitin-dependent degradation of STOX1, thereby regulating CTNNA3 transcription. Variations in the STOX1 genotype associate with trophoblast invasive and proliferative capacities, suggesting that STOX1 carries out a key role in the pathogenesis PE. Since PE is characterized by impaired trophoblast invasion leading to placental insufficiency and maternal complications, STOX1 regulation may be a considerable factor in disease development.

In summary, ubiquitination is a key PTM in PE, a pregnancy disorder marked by reduced trophoblast invasiveness. It regulates protein homeostasis, cellular signaling and membrane dynamics through enzymes such as STK40, ASB4, NEDD4, NEDD4L, UBE3A, Cb1, TRIM72, RNF123, β-TrCP and FBW2, which modulate trophoblast function via ubiquitination and degradation of key proteins (Fig. 2 and Table I). These ubiquitin ligases represent promising candidates for elucidating the pathogenesis of PE.

Identifying their substrates could enable targeted regulation using Proteolysis-Targeting Chimeras (PROTACs), an innovative drug development strategy. PROTACs consist of three components: A ligand that binds the target protein, a linker

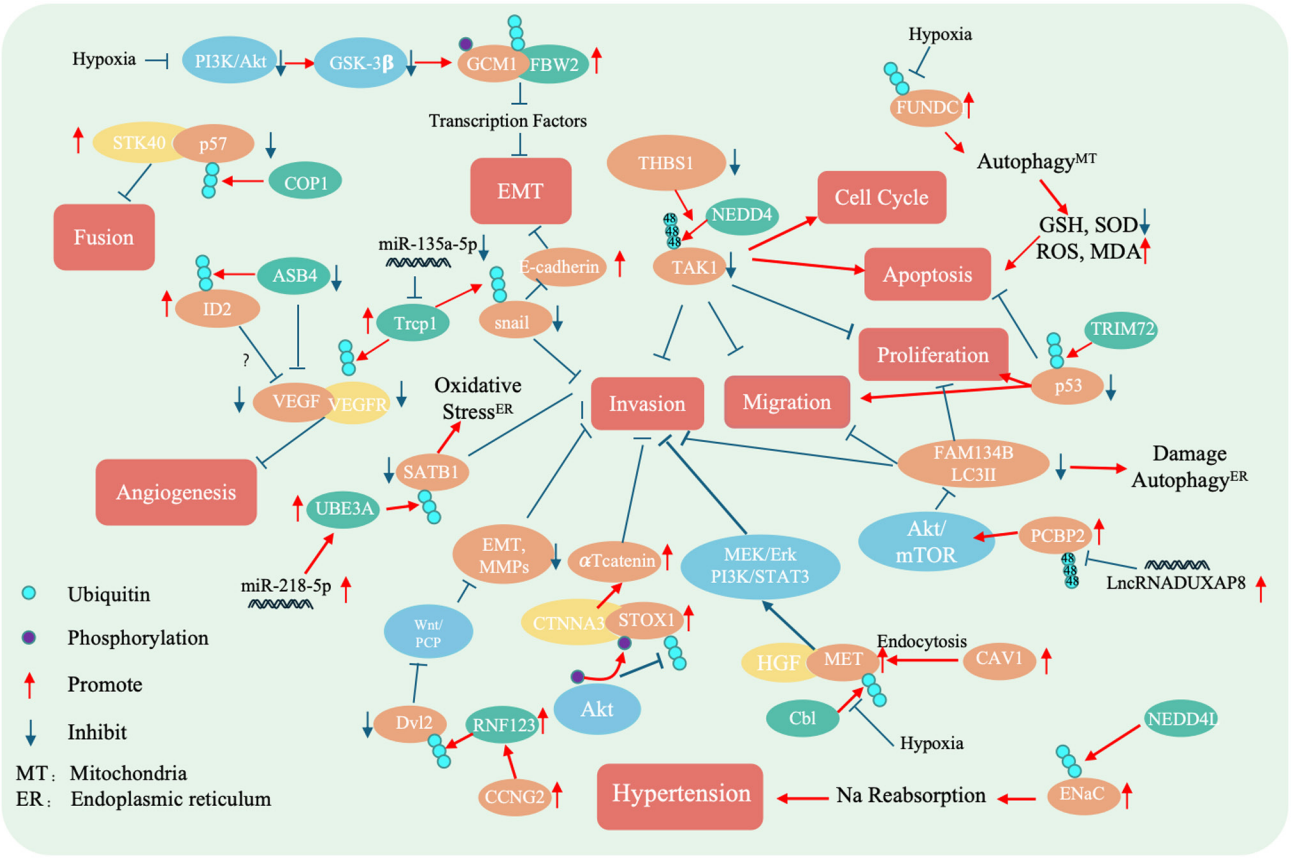

Figure 2. Mechanistic diagram of ubiquitinating enzymes in preeclampsia. COP1 promotes the degradation of p57, thereby impairing trophoblast fusion. The ASB4 targets ID2 for degradation, inhibiting angiogenesis. Silencing THBS1 enhances the NEDD4-mediated ubiquitination and degradation of TAK1, which suppresses trophoblast fusion, proliferation, migration and invasion, while increasing the cell cycle arrest and apoptosis. NEDD4L adds ubiquitin to ENaC, promoting its degradation or altering its function. miRNA-218-5p upregulates the UBE3A expression, which facilitates the degradation of SATB1, thereby inhibiting trophoblast migration, invasion and ER/oxidative stress. Cbl promotes MET degradation, reducing trophoblast invasion. TRIM72 facilitates p53 degradation, suppressing apoptosis and enhancing proliferation and migration. The upregulation of RNF by CCNG2 promotes Dvl12 degradation, suppressing EMT markers and MMP expression via the Wnt/PCP pathway, thereby reducing cell invasion. β-TrCP1 degrades Snail and VEGFRs, blocking EMT and angiogenesis. FBW2 degrades GCM1, disrupting the EMT processes. The downregulation of LncRNA-DUXAP8 enhances PCBP2 ubiquitination and degradation, which activates the Akt/mTOR signaling pathway. This activation decreases FAM134B, a known inhibitor of cell proliferation, invasion, migration and ER stress. Hypoxia reduces FUNDC1 ubiquitination, which promotes trophoblast autophagy. Akt phosphorylates STOX1, influencing its ubiquitination and stability, and modulating trophoblast invasion and proliferation. miRNA, microRNA; ER, endoplasmic reticulum; GCM1, glial cells missing transcription factor 1; FBW2, F-box and wd repeat domain containing 2; STK40, serine/threonine kinase 40; COP1, constitutively photomorphogenic 1; ASB4, ankyrin repeat and SOCS box containing 4; ID2, inhibitor of DNA binding 2; Trcp1, transient receptor potential cation channel subfamily C member 1; SATB1, special AT-rich sequence binding-protein 1; UBE3A, ubiquitin-protein ligase E3A; THSB1, thrombospondin 1; NEDD4, neural precursor cell expressed developmentally downregulated 4; TAK1, TGF-β-activated kinase 1; FUNDC1, FUN14 domain-containing protein 1; GSH, glutathione; SOD, superoxide dismutase; ROS, reactive oxygen species; MDA, malondialdehyde; TRIM72, tripartite motif containing 72; FAM124B, family with sequence similarity 124 member B; LC2II, microtubule-associated protein 1 light chain 3-II; MEK, mitogen-activated protein kinase kinase; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition factor; Cbl, casitas B-lineage lymphoma; RNF123, ring finger protein 123; Dvl2, dishevelled segment polarity protein 2; PCP, planar cell polarity; CCNG2, cyclin G2; ENaC, epithelial sodium channel; CAV1, caveolin 1; PCBP2, poly (rC)-binding protein 2; MT, mitochondria.

and a ligand recruiting an E3 ubiquitin ligase. By bringing the target protein into proximity with the E3 ligase, PROTACs facilitate ubiquitination and subsequent proteasomal degradation, enabling precise protein control (74). Conventional small molecules typically inhibit protein function by binding active sites, which is ineffective against undruggable targets lacking accessible pockets (75). PROTAC technology overcomes this limitation by inducing degradation independent of active-site binding, thus expanding the druggable proteome (76). In complex diseases such as PE, characterized by dysregulated protein networks (77), PROTACs offer a promising approach for precise therapeutic intervention (78). By selectively targeting aberrant proteins involved in ubiquitination, PROTACs could provide more effective treatments (78). This novel strategy not only addresses current challenges in PE drug development but also holds considerable potential for advancing targeted therapies, offering new hope for improved management of this complex condition.

3. The role of deubiquitination in PE

Ubiquitin-specific protease (USP)22: Regulating protein stability. USP22 is a regulator of trophoblast function. The interaction between USP22 and a disintegrin and metalloproteinase 9 (ADAM9) carries out a key role in modulating trophoblast cell function during the pathogenesis of PE (79). ADAM9, a metalloproteinase involved in various physiological processes, is regulated by the deubiquitinating activity of USP22, which removes ubiquitin moieties from ADAM9, thereby enhancing its stability and maintaining its activity (79,80). Experimental data

Table I. List of ubiquitinating enzymes, their substrates and functions associated with PE.

First author/s, year	Ubiquitinating enzymes	Substrates	Associated proteins	Functions	Expression in PE	(Refs.)
Zhang *et al*, 2024	COP1	P57Kip2	STK40	Promotes ubiquitination and degradation of p57Kip2, affecting trophoblast cell fusion	Up	(18)
Li *et al*, 2024; Ferguson *et al*, 2007	ASB4	ID2	VEGF	Mediates ID2 ubiquitination and proteasomal degradation, and affects trophoblast cell differentiation	Down	(21,24)
Ling *et al*, 2014; Lasorella *et al*, 2005	NEDD4	TAK1	THBS1	Promotes TAK1 ubiquitination and degradation, and affects trophoblast proliferation, migration, invasion, cell cycle and apoptosis	-	(28,29)
Murao *et al*, 2021; Manning and Kumar, 2018; Busst *et al*, 2013	NEDD4L	ENaC	-	Mediates ENaC ubiquitination and degradation, and affects sodium retention	No change	(34-36)
Leung *et al;* 2023; Wang *et al*, 2019; Rao *et al*, 2018	UBE3A	SATB1	miR-218-5p,	Promotes SATB1 ubiquitination and degradation, and affects trophoblast cell invasion, migration and endoplasmic reticulum/oxidative stress	Down	(37,39,40)
Uehara *et al*, 1995	Cb1	MET	CAV1, HGF, MEK/ERK, PI3K/STAT3	Promotes MET ubiquitination and degradation, and affects trophoblast invasion	Down	(45)
Uder *et al*, 2018	TRIM72	p53	-	Promotes p53 ubiquitination and degradation, and affects trophoblast apoptosis, proliferation and migration	Up	(50)
Li *et al*, 2021	RNF123	Dvl2	CCNG2, Wnt/ PCP, EMT, MMPs	Promotes Dvl2 ubiquitination and degradation, and affects trophoblast invasion	UP	(52)
van Amerongen and Nuss, 2009; Lerner and Ohlsson, 2015; Orian *et al*, 2000	β-TrCP	Snail	E-cadherin, VEGFR, miR-135-5p	Promotes Snail ubiquitination and degradation, and affects trophoblast invasion, EMT and angiogenesis	UP	(56-58)
Yu *et al*, 2002	FBW2	GCM1	PI3K/Ak, GSK-3β	Promotes GCM1 ubiquitination and degradation, and affects trophoblast EMT	-	(64)

PE, preeclamsia; miR, microRNA; COP1, constitutively photomorphogenic 1; ASB4, ankyrin repeat and SOCS box containing 4, NEDD4, neural precursor cell expressed developmentally downregulated 4; NEDD4L, neural precursor cell expressed developmentally downregulated 4 like; UBE3A, ubiquitin-protein ligase E3A; ID2, inhibitor of DNA binding 2; TAK1, TGF-β-activated kinase 1; ENaC, epithelial sodium channel; SATB1, special AT-rich sequence binding-protein 1; STK40, serine/threonine kinase 40; THSB1, thrombospondin 1; Cbl, casitas B-lineage lymphoma; MET, mesenchymal-epithelial transition factor; TRIM72, tripartite motif containing 72; RNF123, ring finger protein 123; Dvl2, dishevelled segment polarity protein 2; β-Trcp1, transient receptor potential cation channel subfamily C member 1; FB2, F-box protein 2; Snail, snail family transcription factor; GCM1, glial cells missing transcription factor 1; EMT, epithelial-mesenchymal transition.

reveal that USP22 overexpression notably stabilizes ADAM9 in trophoblast cells. This stabilization was confirmed through co-immunoprecipitation assays, demonstrating a direct interaction between USP22 and ADAM9 (79). However, the increased stability of ADAM9 exerts detrimental effects on trophoblast function. USP22 overexpression suppresses trophoblast proliferation, migration and invasion while promoting apoptosis (79). Moreover, USP22 inhibits EMT, a key process required for trophoblast invasiveness (79). Silencing ADAM9 reverses these effects, indicating that USP22 modulates trophoblast behavior primarily through ADAM9 stabilization (79). Additionally, the USP22-ADAM9 interaction influences the Wnt/β-catenin signaling pathway, which governs cellular proliferation, migration and EMT (79). Elevated levels of USP22 and ADAM9 in placental tissues from patients with PE further support their involvement in the development of PE.

In summary, USP22 contributes to PE pathogenesis by stabilizing ADAM9 through deubiquitination, thereby inhibiting trophoblast proliferation, migration, invasion and EMT. This regulation is partly mediated via the Wnt/β-catenin signaling pathway. Understanding the USP22-ADAM9 axis offers novel insights into the molecular mechanisms underlying PE and highlights potential therapeutic targets for its prevention and treatment.

COP9 signalosome (CSN): Modulating protein stability. In the context of PE, the CSN complex, particularly its CSN1 and CSN5 subunits, carry out a key role in regulating protein stability (81). The CSN complex modulates the UPS by removing Nedd8 from Cullin-RING ubiquitin ligases, a process primarily mediated by the deubiquitinating activity of the Jab1/CSN5 subunit (82,83). In PE placentas, the expression of CSN1 and CSN5 is markedly upregulated and predominantly localized in vascular endothelial cells, syncytiotrophoblasts, stromal cells and Hofbauer cells (84). CSN1 contributes to the regulation of transcription factor stability and influences lipid metabolism and insulin-mediated gluconeogenesis. Meanwhile, Jab1/CSN5 is directly involved in protein degradation through its DUB activity (85-89). The elevated levels of CSN1 and CSN5 observed in PE placentas are associated with key pathological changes characteristic of the disorder (84). Notably, the accumulation of hypoxia-inducible factors (HIFs), HIF-1α and HIF-2α in PE placentas may result from impaired proteasome activity. Jab1/CSN5 interacts with HIF-1α and promotes its stabilization, offering a potential explanation for this phenomenon (84). This aberrant stabilization may impair normal trophoblast function and contribute to defective placental development. These findings provide new insights into the molecular mechanisms of PE and may contribute to the development of new therapeutic strategies. Additionally, understanding the regulatory role of the CSN complex may offer potential targets for the treatment of PE, helping to improve placental function and prevent the onset of the disease.

USP14: Linking inflammation and hormone regulation. Upregulation of USP14 is associated with the exacerbation of inflammatory responses in PE. USP14 promotes the activation of the NF-κB signaling pathway through its deubiquitinating activity, leading to the increased production of proinflammatory cytokines such as TNF-α, IL-6 and IL-1β (89). This inflammatory effect has been reported in trophoblast cell models exposed to hypoxia/reoxygenation, mimicking PE conditions. Increased USP14 expression in these models associates with NF-κB activation and higher levels of inflammatory cytokines. Notably, treatment with the USP14 inhibitor IU1 inhibits the hypoxia/reoxygenation-induced activation of NF-κB and MAPK, effectively reducing proinflammatory cytokine production (89). These findings suggest that USP14 carries out a key role in driving inflammation in PE, and its inhibition may represent a promising therapeutic strategy to mitigate inflammatory responses in trophoblast cells, potentially improving outcomes in PE.

In addition to its role in inflammation, USP14 also participates in hormone regulation by modulating aromatase expression in placental trophoblast cells. This regulation involves the transcription factor HAND1, whose stability is controlled by the regulator of G protein signaling 2 (RGS2). RGS2 promotes the ubiquitin-mediated degradation of HAND1, whereas USP14 counteracts this process by removing ubiquitin moieties, thereby stabilizing HAND1 (90). Stabilized HAND1 enhances repression of the aromatase gene, ultimately reducing aromatase expression. This dual functionality of USP14 (in both promoting inflammation and regulating hormone synthesis) highlights its central role in the pathogenesis of PE.

In placental tissues of patients with PE, the expression of RGS2 and aromatase is reduced, while HAND1 expression is increased (90,91). These findings suggest that dysregulation of the RGS2-HAND1 pathway may impair aromatase expression and consequently disrupt estrogen synthesis, a process essential for pregnancy maintenance. Clinical analyses reveal a positive correlation between RGS2 and aromatase expression in both normal and PE placental tissues, underscoring the importance of the RGS2-aromatase axis in estrogen regulation and its potential utility as a biomarker for PE and associated obstetric conditions. In addition, the human-specific lncRNA UCA1 has been identified as a key regulator in the pathogenesis of PE through its interaction with profilin 1 (PFN1) in placental tissues and maternal serum. RNA pulldown, mass spectrometry and RNA immunoprecipitation assays have confirmed a direct interaction between UCA1 and PFN1. Functioning as a molecular scaffold, UCA1 recruits the DUB USP14 to form a UCA1-USP14-PFN1 complex (92). This complex modulates the ubiquitination and stability of PFN1 (92). Protein half-life assays demonstrate that UCA1 overexpression extends the half-life of PFN1 by reducing its ubiquitination and preventing proteasomal degradation. Conversely, treatment with the USP14 inhibitor b-AP15 increases PFN1 ubiquitination and promotes its degradation, confirming the role of USP14 in stabilizing PFN1 (92). Importantly, in the context of PE, UCA1-mediated stabilization of PFN1 activates the RhoA/ROCK signaling pathway, resulting in excessive production of ROS in vascular endothelial cells. This oxidative stress contributes to endothelial injury, a hallmark of PE, and is associated with maternal vascular dysfunction and hypertension (92).

In summary, USP14 carries out a multifaceted role in the pathogenesis of PE through three key mechanisms: First, promoting inflammatory responses via NF-κB signaling; second, modulating aromatase expression and estrogen synthesis by regulating the RGS2-HAND1 axis; and third, stabilizing PFN1 to activate the RhoA/ROCK pathway and induce oxidative stress in vascular endothelial cells. These

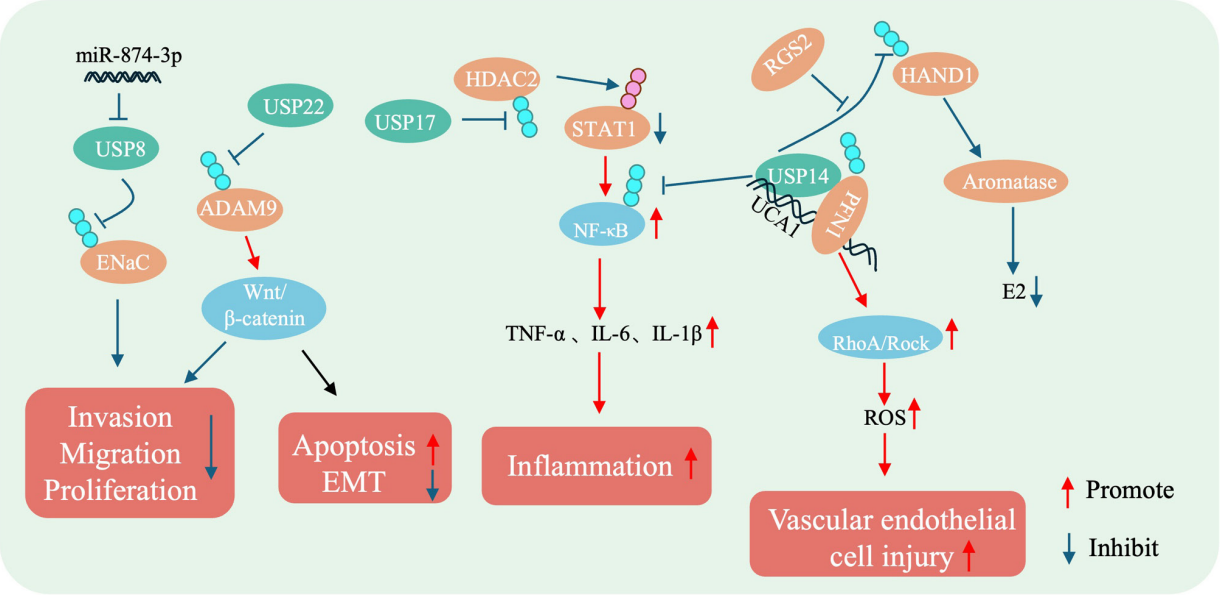

Figure 3. Mechanistic diagram of DUBs in preeclampsia. USP22 stabilizes ADAM9, inhibiting cell proliferation, migration, invasion and EMT through the Wnt/β-catenin signaling pathway. USP14 stabilizes NF-κB and HAND1, promoting proinflammatory factors and affecting estrogen synthesis. USP14 also stabilizes PFN1, contributing to vascular endothelial injury via the Rho/ROCK-signaling pathway. USP8 stabilizes ENaC, inhibiting cell invasion, migration and proliferation. USP17 stabilizes HDAC2, activating STAT1 and enhancing the secretion of proinflammatory factors. USP, ubiquitin-specific protease; ENaC, epithelial sodium channel; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; HAND1, heart and neural crest derivatives expressed 1; PFN1, penetration 1; RGS2, regulator of G-protein signaling 2.

findings highlight USP14 as a central mediator in PE and a potential therapeutic target for its prevention and treatment.

USP8: Restoring trophoblast function. USP8 has been identified as a key regulator of trophoblast cell function in the context of PE. It enhances the stability and membrane localization of ENaC by removing their ubiquitin tags, thereby preventing proteasomal degradation. This stabilization promotes trophoblast proliferation, migration and invasion, which are key processes for normal placental development (93). In PE placentas, USP8 expression is considerably reduced, correlating with impaired trophoblast function. The downregulation of USP8 disrupts ENaC stability and surface expression, contributing to the functional defects observed in trophoblast cells during PE (93). Additionally, microRNA miR-874-3p negatively regulates USP8 by binding to its 3' untranslated region, further suppressing its expression. This inhibition reduces ENaC levels on the trophoblast membrane and exacerbates dysfunction (93). However, overexpression of USP8 can counteract the effects of miR-874-3p, restoring ENaC expression and rescuing trophoblast proliferation, migration and invasion (93). These findings highlight the key role of the USP8/ENaC axis and its regulation by miR-874-3p in PE pathogenesis. USP8 represents a promising therapeutic target, with potential interventions aimed at enhancing its activity or expression to restore normal trophoblast function and improve placental development. Targeting this pathway may offer innovative strategies for the prevention and treatment of PE.

USP17: Modulating inflammatory pathways. USP17, a DUB, has emerged as a potential regulator in the pathogenesis of PE due to its markedly reduced expression in the placental tissues of patients with PE (16). USP17 maintains protein homeostasis by removing ubiquitin tags, thereby stabilizing key regulatory proteins. One such target is histone deacetylase 2 (HDAC2), whose stability is enhanced by USP17-mediated deubiquitination. This stabilization promotes trophoblast proliferation, migration and invasion, which are processes essential for normal placental development (16,94). HDAC2 also interacts with STAT1, and through deacetylation, enhances STAT1 activity (16). Activated STAT1, in turn, suppresses the NF-κB-signaling pathway, a key mediator of inflammatory responses that is associated with the development of PE (16). Thus, USP17 may influence PE progression through the HDAC2/STAT1/NF-κB signaling axis, associating protein stability to inflammatory regulation. These findings underscore the therapeutic potential of USP17 in modulating inflammation and improving trophoblast function in PE.

DUBs are integral to the pathogenesis of PE, a pregnancy disorder characterized by impaired trophoblast function. USP22 stabilizes ADAM9, influencing trophoblast behavior via the Wnt/β-catenin signaling pathway. The COP9 signalosome modulates protein stability through the UPS, potentially affecting trophoblast activity. USP14 promotes NF-κB-mediated inflammation, regulates the RGS2-HAND1-aromatase axis affecting estrogen synthesis and stabilizes PFN1 to preserve vascular integrity. USP8 stabilizes ENaC, enhancing trophoblast function and is negatively regulated by miR-874-3p. Lastly, USP17 stabilizes HDAC2, thereby influencing STAT1 and suppressing NF-κB activation, the key to controlling inflammation in PE (Fig. 3 and Table II). Despite these promising targets, developing therapies that modulate protein regulation remains challenging. Currently, >85% of proteins are considered 'undruggable', as traditional small-molecule drugs often fail to bind and modulate them

Table II. List of deubiquitinating enzymes, their substrates and functions associated with PE.

First author/s, year	Deubiquitinating enzymes	Substrates	Associated proteins	Functions	Expression in PE	(Refs.)
van Dijk *et al*, 2010	USP22	ADAM9	Wnt/β-catenin	Affects trophoblast cell invasion, migration, proliferation, apoptosis and EMT	Up	(71)
Wei and Deng, 2003	COP9	HIF-1α	-	Affects trophoblast functions	Up	(81)
Dentin *et al*, 2007; Kato and Yoneda-Kato, 2009; Zhao *et al*, 2021; Tang *et al*, 2023	USP14	NF-κB, HAND1, PFN1	TNF-α, IL-6, IL-1β, RGS2, aromatase, RhoA/Rock, ROS	Affects inflammatory responses, vascular endothelial cell injury and E2 secretion	Up	(87-90)
Perschbacher *et al*, 2020	USP8	ENaC	-	Affects trophoblast proliferation, migration and invasion	Down	(91)
Wu *et al*, 2022; Zhang *et al*, 2023	USP17	HDAC2	STAT1, NF-κB	Affects trophoblast proliferation, migration, invasion and inflammatory responses	Down	(92,93)

PE, preeclamsia; USP, ubiquitin-specific protease; COP, constitutively photomorphogenic; ADAM, A disintegrin and metalloproteinase; HIF-1α, hypoxia-inducible factor 1α subunit; HAND1, heart and neural crest derivatives expressed 1; PFN ENaC, epithelial sodium channel; HDAC2, histone deacetylase 2; RGS2, regulator of G-protein signaling 2; ROS, reactive oxygen species.

effectively (95). Targeted protein degradation technologies offer a potential solution, yet diseases such as PE, driven by dysregulated ubiquitination, require even more precise strategies. DUBs carry out key roles in the pathogenesis of PE by regulating trophoblast function, inflammatory responses and hormone signaling pathways. Dysregulation of specific DUBs can lead to trophoblast dysfunction, compromised placental development and the onset of clinical manifestations associated with PE. Traditional drug development strategies often lack the specificity required to modulate DUB activity effectively. Broad-spectrum inhibitors may induce off-target effects, disrupting essential molecular pathways and complicating therapeutic outcomes. In this context, deubiquitinase-targeting chimeras (DUBTACs) represent a novel and promising therapeutic approach for PE. DUBTACs are heterobifunctional molecules designed to recruit DUBs to specific target proteins. Each molecule comprises a ligand that binds to the target protein, a chemical linker and a DUB-recruiting moiety. By facilitating this proximity, DUBTACs promote the removal of polyubiquitin chains from the target protein, thereby preventing its proteasomal degradation and enhancing its stability and function (96). Therefore, DUBTAC technology represents a promising avenue for developing targeted therapies to address the complex molecular mechanisms underlying PE, offering a new avenue for effective disease management.

4. Summary and future perspectives

The present review highlights the key roles of E3 ubiquitin ligases and DUBs in the pathogenesis of PE, emphasizing their regulatory functions in trophoblast behavior, inflammatory responses, protein stability and hormonal signaling. Ubiquitination, mediated by E3 ligases such as STK40 (21), ASB4 (27) and NEDD4 (4), influences key processes including trophoblast fusion, differentiation, invasion and migration, which are essential functions for proper placental development and are implicated in the onset of PE (47). Conversely, deubiquitination, carried out by DUBs such as USP22 (79), the COP9 signalosome (84) and USP14 (89), also carry out a pivotal role by maintaining protein homeostasis and modulating inflammation (89) and vascular integrity (84). As research into ubiquitination and deubiquitination mechanisms in PE advances, future directions are increasingly centered on translational applications. Emerging therapeutic technologies, including siRNA (97), PROTAC, DUBTAC (98) and therapeutic antibodies (99), offer promising strategies for targeting dysregulated E3 ligases and DUBs. siRNA technology enables selective silencing of mRNA transcripts encoding specific E3 ligases or DUBs, allowing for precise modulation of pathogenic pathways in PE (100). Compared with conventional small-molecule drugs, siRNA therapy offers higher specificity and reduced off-target effects. PROTAC technology represents an innovative approach for targeting previously 'undruggable' proteins by co-opting E3 ligases to tag disease-related proteins for proteasomal degradation (76). Tailoring PROTACs to target proteins implicated in PE could enable highly specific regulation of their abundance and activity (101). As a revolutionary approach, DUBTACs function by recruiting DUBs to specific target proteins, stabilizing them through the removal of polyubiquitin chains and preventing their degradation. Given

the central roles of DUBs in trophoblast function, immune regulation and hormone signaling (79), DUBTACs present a promising avenue for therapeutic intervention in PE (102). By specifically binding to E3 ligases or DUBs, therapeutic antibodies can block their interactions with other proteins, offering an alternative strategy for targeted PE therapy.

Future research should also focus on elucidating the intricate interactions between E3 ubiquitin ligases, DUBs and other signaling pathways involved in the pathogenesis of PE. A more comprehensive understanding of these complex regulatory networks is essential for the development of effective and multifaceted therapeutic strategies. In addition, exploring the role of epigenetic modifications in regulating the expression and activity of E3 ligases and DUBs may uncover novel mechanisms underlying PE and identify new therapeutic targets. Furthermore, preclinical and clinical studies are required to assess the safety, efficacy and translational potential of these emerging therapeutic approaches. Large-scale clinical trials will be key for determining optimal dosing regimens, treatment durations and potential adverse effects. Parallel efforts should also aim to identify and validate predictive biomarkers to assess patient responses to these interventions, thereby advancing the application of personalized medicine in PE management.

In conclusion, leveraging these innovative therapeutic strategies offers potential to improve clinical outcomes for both mothers and infants affected by PE. Continued research into the molecular underpinnings of PE, combined with the development and clinical validation of targeted therapies, will be pivotal in addressing the challenges posed by this complex and multifactorial pregnancy disorder.

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Authors' contributions

CZP collected literature and drafted the manuscript. XXS helped to draft and modify the manuscript. HX conceived the topic of the present review and revised the manuscript. KHB offered guidance and critically reviewed this manuscript. All authors read and approved the final version of the manuscript. Data authentication is 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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