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The role of endoglin and its soluble form in pathogenesis of preeclampsia

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Abstract

Preeclampsia remains till today a leading cause of maternal and fetal morbidity and mortality. Pathophysiology of the disease is not yet fully elucidated, though it is evident that it revolves around placenta. Cellular ischemia in the preeclamptic placenta creates an imbalance between angiogenic and anti-angiogenic factors in maternal circulation. Endoglin, a transmembrane co-receptor of transforming growth factor β (TGF-β) demonstrating angiogenic effects, is involved in a variety of angiogenesis-dependent diseases with endothelial dysfunction, including preeclampsia. Endoglin expression is up-regulated in preeclamptic placentas, through mechanisms mainly induced by hypoxia, oxidative stress and oxysterol-mediated activation of liver X receptors. Overexpression of endoglin results in an increase of its soluble form in maternal circulation. Soluble endoglin represents the extracellular domain of membrane endoglin, cleaved by the action of metalloproteinases, predominantly matrix metalloproteinase-14. Released in circulation, soluble endoglin interferes in TGF-β1 and activin receptor-like kinase 1 signaling pathways and inhibits endothelial nitric oxide synthase activation, consequently deranging angiogenesis and promoting vasoconstriction. Due to these properties, soluble endoglin actively contributes to the impaired placentation observed in preeclampsia, as well as to the pathogenesis and manifestation of its clinical signs and symptoms, especially hypertension and proteinuria. The significant role of endoglin and soluble endoglin in pathophysiology of preeclampsia could have prognostic, diagnostic and therapeutic perspectives. Further research is essential to extensively explore the potential use of these molecules in the management of preeclampsia in clinical settings.

Keywords Endoglin · Soluble endoglin · Preeclampsia · Pathophysiology · Pathogenesis

Introduction

Preeclampsia is a multisystem pregnancy-specific disease affecting both maternal and fetal health, which belongs in the broad spectrum of hypertensive disorders of pregnancy. It is characterized by the appearance of new-onset hypertension after 20 weeks of gestation, accompanied by symptoms indicating involvement of other systems, usually new-onset proteinuria [1, 2]. Hypertensive pregnancy disorders represent common gestational complications, affecting approximately 5–10% of pregnancies globally [3, 4]. Preeclampsia is epidemiologically predominant in this category of disorders, occupying as much as 50% of hypertensive disorders' cases, while its global incidence is estimated between 2 and 4% of all pregnancies [5–7]. Worldwide, preeclampsia is steadily listed among the leading causes of maternal and

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fetal mortality and morbidity in low, medium, as well as high-income countries [8, 9].

Despite increasing and intensive research efforts, the pathophysiology of preeclampsia is not yet completely clarified. However, it is clear that etiopathogenesis of the disease revolves around placenta, since its subsequent delivery after birth remains till today the only effective known treatment. The pivotal role of placenta in preeclampsia is confirmed by the withdrawal of maternal clinical symptoms after its removal [10, 11]. The prominent theory concerning the pathophysiological base of preeclampsia supports that defective remodeling of spiral arteries leads to cellular ischemia in placenta and consequently to an imbalance between angiogenic and anti-angiogenic factors in maternal circulation [12, 13]. This imbalance in favor of anti-angiogenic agents is responsible for the generalized inflammatory response and endothelial dysfunction detected in all systems of a preeclamptic pregnant woman, which further trigger the occurrence of systemic symptoms [14, 15].

A variety of angiogenic and anti-angiogenic molecules have been studied as potential contributors to the pathogenesis of preeclampsia. Endoglin, a transmembrane glycoprotein with angiogenic effect, has been analyzed among other factors, since its expression is augmented in the preeclamptic placenta. Proteolytic cleavage of endoglin by specific types of metalloproteinases produces a soluble isoform of the protein, soluble endoglin, a molecule with anti-angiogenic effect which is increased in preeclamptic pregnancies. The objective of the present review of literature is to summarize the structural, biological and biochemical properties of endoglin and soluble endoglin and explore their role and involvement in the pathophysiology of preeclampsia, incorporating current knowledge and recent updates on the field. Furthermore, attempting to connect theory and clinical practice, it presents increasing evidence supporting the potential exploitation of endoglin and its soluble form in clinical settings, as diagnostic biomarkers or even future treatment targets that may improve the management of preeclamptic patients.

Endoglin

Structure and expression of endoglin

Endoglin was first detected and described in 1985, as a protein expressed in a B-pre-leukemic cell line [16]. Human endoglin (CD105) is a homodimeric transmembrane type I glycoprotein, consisted of 633 amino acids, with a total molecular weight of 180 kDa. The molecule is formed by a large extracellular domain, a hydrophobic transmembrane domain and a smaller intracellular tail [17]. There are two variants of the protein arising from alternative splicing, L (long) and S (short) isoform. The main structural and biochemical characteristics that differentiate the two isoforms are the length of their intracellular domain, their tissue distribution and the extent of theirphosphorylation. L-endoglin is the predominant isoform expressed mainly in endothelial cells, it contains a cytoplasmic domain of 47 residues and it is highly phosphorylated. L isoform uses ALK1 (activin receptor-like kinase 1) pathway to promote intracellular signaling, while S isoform seems to be involved in ALK5 (activin receptor-like kinase 5) pathway. Both pathways activate different intracellular signaling cascades, therefore leading in transcription of different target-genes [18].

The endoglin gene is located on 9q34 chromosomal site and it contains 14 exons. Gene mutations, especially those affecting the structure of extracellular domain of the protein, lead to the manifestation of type 1 hereditary hemorrhagic telangiectasia syndrome (Rendu-Osler-Weber syndrome) [19].

The regulation of endoglin expression involves numerous biochemical mechanisms. Genetic expression of endoglin is amplified by a variety of molecules partaking in signaling pathways of TGF-β factor, such as TGF-β1, BMP-9 and ALK1 [20]. Hypoxia is a regulating factor of endoglin expression which has been extensively studied. In hypoxic conditions, hypoxia-inducible transcription factor 1a (HIF-1a) affects specific sites of the endoglin promoter, triggering the transcription of the gene and ultimately the protein synthesis of endoglin [21]. Moreover, endoglin expression is upregulated by liver X receptors (LXR) agonists. These molecules are transcription factors activated by binding to retinoid X receptors (RXR). The heterodimeric complexes formed by this conjunction regulate the genetic expression of various target-genes. The endoglin gene contains 6 response elements capable of binding LXR/RXR heterodimeric complexes, therefore triggering the expression of endoglin through this process [22]. In addition to the above, transcriptional activation of endoglin gene has been described as a response to endothelial cell injury in respective cell cultures [23].

Endoglin is predominately expressed in endothelial cells. However, the protein is also expressed in tissues undergoing active angiogenesis, as well as in non-endothelial histotypes, namely vascular smooth muscle cells, fibroblasts, hematopoietic progenitor cells, mesangial cells and syncytiotrophoblast cells [24] (Fig. 1).

Signaling pathways of endoglin

Endoglin is a co-receptor of transforming growth factor β (TGF-β). TGF-β is a cytokine regulating cell proliferation, differentiation and migration, which also plays an important role in the process of vasculogenesis and initiation of inflammatory response [25]. On the cellular surface, endoglin

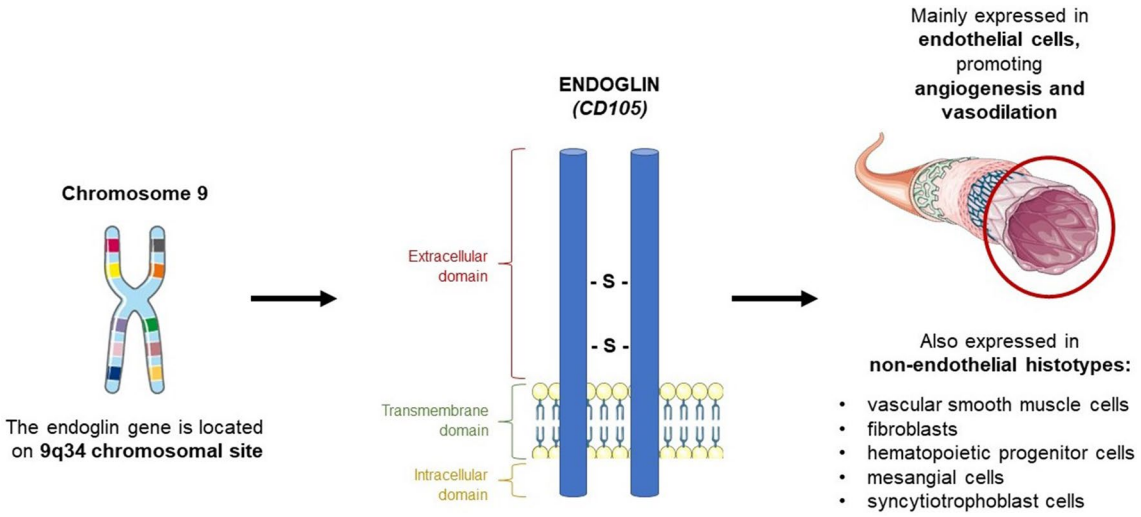

Fig. 1 Expression of membrane endoglin. The gene of endoglin is located on 9q34 chromosomal site. Expression of the gene through transcription and translation leads to the production of endoglin, a homodimeric transmembrane type I glycoprotein that consists of a large extracellular domain, a hydrophobic transmembrane domain and a smaller intracellular tail. Endoglin is mainly expressed in endothelial cells, demonstrating proangiogenic and vasodilatory properties; it is also expressed in non-endothelial cell types, including placental syncytiotrophoblast cells. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

interacts with TGF-β type I receptors, such as activin receptor-like kinase 1 (ALK1) and activin receptor-like kinase 5 (ALK5), as well as with TGF-β type II receptors [26]. Endoglin binds TGF-β1 and TGF-β3 molecules with high affinity only when they are connected as ligands to TGF-βII receptors. The formation of such a complex activates the cytoplasmic kinase function of TGF-βII receptor, which phosphorylates the TGF-βI receptor (ALK1 or ALK5), thus enabling the later to interact with intracellular signaling molecules [27, 28]. There are two antagonistic signaling pathways involving TGF-βI receptors. The first one is the ALK5 kinase pathway, which leads to phosphorylation of SMAD 2/3 factors and inhibits cellular response to TGF-β binding. The second pathway, ALK1 kinase pathway, includes phosphorylation of SMAD 1/5 factors and enhancement of cellular response triggered by TGF-β binding on the cellular surface [29, 30]. In both pathways, SMAD factors are responsible for the signal transduction to the cell nucleus, where they participate in transcriptional activity regulation and they modify the expression of multiple genes [20, 31]. It is worth mentioning that apart from TGF-β1 and TGF-β3, endoglin is also capable of binding other molecules belonging to the broad spectrum of TGF-β family, such as activin-A, BMP-7, BMP-2 and BMP-9 proteins [25] (Fig. 2).

Biological roles of endoglin

The involvement of endoglin in the process of angiogenesis is rather expected, given its close connection to TGF-β system, as well as its tissue distribution. Endoglin is overexpressed in proliferating endothelial cells which form new blood vessels [32]. In genetically modified endoglin-deficient mice, complete loss of endoglin expression is lethal during fetal life, due to defective angiogenesis affecting both the yolk sac and the embryonic vasculature [33]. Moreover, the fact that endoglin gene mutations are responsible for hereditary hemorrhagic telangiectasia syndrome, which is characterized by the presence of hemorrhage-prone telangiectasias and arteriovenous malformations in multiple organs, further accentuates the protein's role in angiogenetic procedures [19]. The lack of intervening capillaries between arteries and veins due to impaired vascularization, as well as the irregular endothelium revealed by pathological examination of the malformations both result from the alteration of endoglin expression in endothelial cells. Consequently, it can be deducted that endoglin acts as a protective agent in endothelium and any decrease or loss of its expression leads to endothelial dysfunction [34, 35]. In general, there is a variety of recent studies in literature indicative of a direct relationship between endoglin and proper function of the endothelium [32], 36, 37]; for instance it has been suggested that reduced expression of endoglin results in increased endothelial permeability and loss of endothelial barrier function, which are considered typical manifestations of endothelial dysfunction [37].

In addition to vasculogenesis, endoglin plays a pivotal role in the regulation of vascular tone, demonstrating vasodilatory properties. It has been described that endoglin promotes nitric oxide-dependent vasodilation by regulating the expression of endothelial nitric oxide synthase (eNOS) [38].

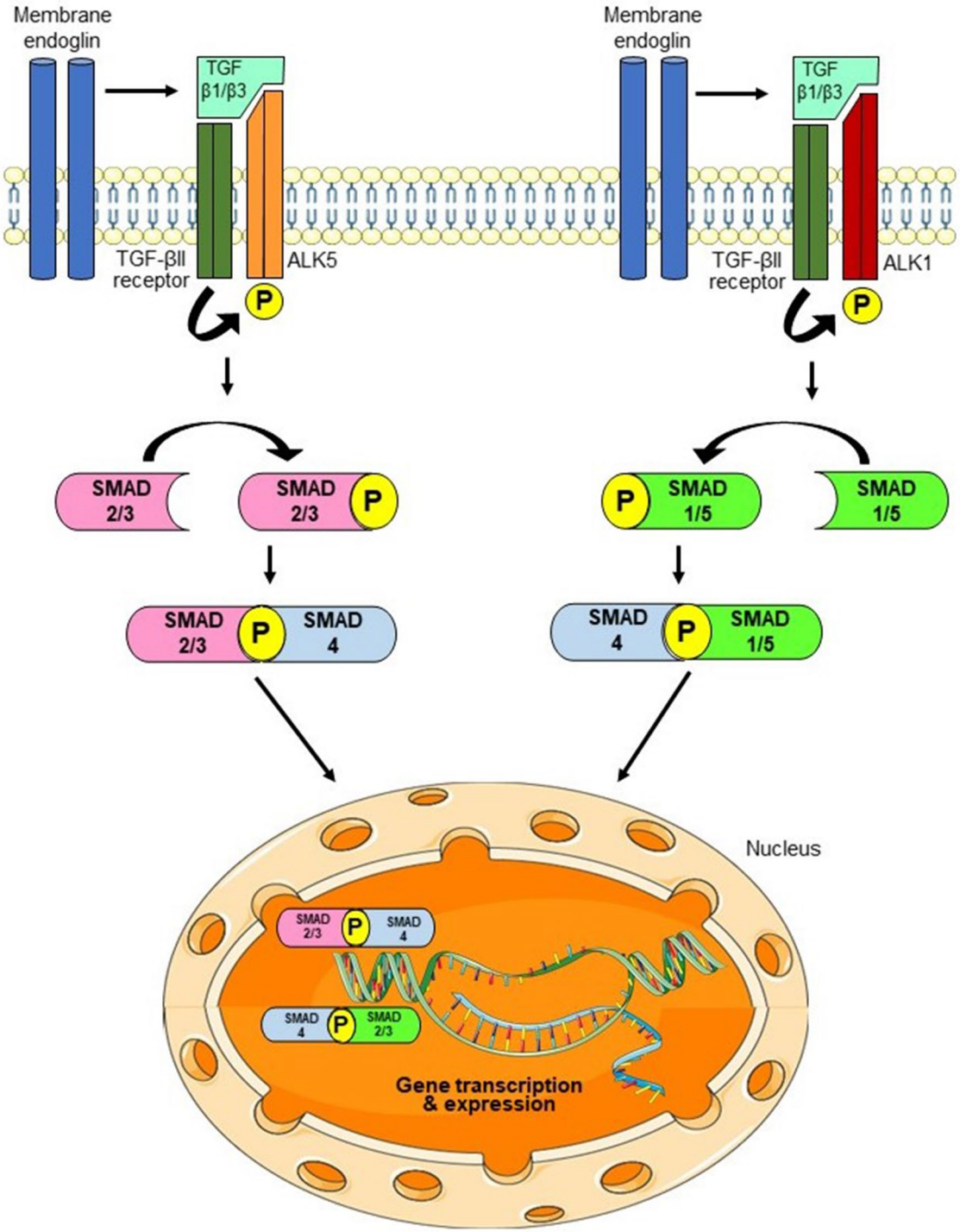

Fig. 2 Signaling pathways of membrane endoglin. Endoglin is a co-receptor of transforming growth factor β (TGF-β), thus it participates in TGF-β signaling pathway. On cellular surface, circulating TGF-β1 and TGF-β3 bind to TGF-β type II and type I receptors (such as ALK5 and ALK1). Endoglin binds TGF-β molecules with high affinity only when they are connected as ligands to TGF-βII receptors. The formation of such complexes between endoglin, TGF-β and TGF-βI and II receptors leads to phosphorylation of ALK5 or ALK1 by TGF-βII receptors. Phosphorylation of ALK5 and ALK1 activates ALK5 and ALK1 signaling pathways respectively, which both include the phosphorylation of SMAD factors and their transfer into cell nucleus. There, phosphorylated SMAD proteins affect transcriptional activity, modifying the expression of multiple genes as a response to TGF-β binding. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

Research about endoglin has been majorly focused on its expression in endothelial cells. However, recent studies examine the expression of endoglin in other cell types, as well as its influence in their biological behavior. In addition to the signaling pathway described above, endoglin is also involved in biological procedures which do not require ligand binding. It has been reported that endoglin can bind to integrins on leukocytes, especially in the presence of inflammatory stimuli, enabling their ligand-free extravasation through a process called trans-endothelial migration [39]. The regulatory role of endoglin in leukocyte trafficking through vascular endothelium further accentuates the relationship between endoglin and endothelial dysfunction. This proinflammatory effect of endoglin suggests that it actively contributes in inflammation-induced endothelial dysfunction in endothelial cells [36, 40].

The association between endoglin, vascular inflammation and endothelial dysfunction indicates that the molecule could also be involved in atherosclerosis, a chronic inflammatory disease of the arteries. Interestingly, it appears that endoglin might play a protective role in atherogenesis. The expression of endoglin in macrophages, smooth muscle cells and endothelial cells is increased in atherosclerotic compared to normal arteries. Endoglin expression is associated with smooth cell migration and proliferation, repair of the vessel wall and production of collagen it also promotes neoangiogenesis and plaque stabilization of advanced atherosclerotic lesions [41, 42].

Apart from leukocytes, endoglin seems to interfere with the behavior and function of other hematopoietic cell types. Endoglin is overexpressed in hematopoietic stem cells, thus inducing their differentiation to blood cells; it also demonstrates an important role in erythropoietic cell maturation and in the differentiation of monocytes into M1 and M2 macrophages in tissues [39].

Endoglin is always expressed in mesenchymal stem cells and is considered as one of their most important markers. The absence of endoglin expression in this cell type leads to the creation of a more differentiated mesenchymal cell phenotype, characterized by increased osteogenic gene expression. Furthermore, endoglin expression has also been described in sarcomas, malignant tumors deriving from abnormal mesenchymal cells [39, 43].

Activated fibroblasts demonstrate high activity of TGF-β signaling pathway, a fact indicating the involvement of endoglin in fibrosis. Endoglin expression has been reported in a variety of prefibrotic cell types, such as myofibroblasts, renal fibroblasts and mesangial cells, while it is under investigation whether endoglin partakes in liver, myocardial and renal fibrosis [39, 44].

The prominent role of endoglin in angiogenesis, as well as its expression in numerous epithelial cell types has raised questions about its possible involvement in carcinogenesis. In prostate cancer, loss of endoglin expression in cancerous epithelial cells has been associated with increased metastatic potential [45]. Correspondingly, in breast cancer and esophageal squamous cell carcinomas, absence of endoglin expression in tumor cells is correlated with unfavorable clinical outcomes [39]. On the contrary, endoglin overexpression enhances the invasion capacity of tumor cells in ovarian and renal cancer [39], as well as the formation of metastases in hepatocellular carcinomas [46]. Taking all the above into consideration, it is concluded that the role of endoglin expression in carcinogenesis is not fully elucidated, but rather differs between various the types of cancer. Future research on the involvement of endoglin in carcinogenesis could also explore its potential use in diagnosis and treatment of cancer [25].

Endoglin expression in preeclampsia

Endoglin in overexpressed through various mechanisms in syncytiotrophoblast and extravillous trophoblast cells of the preeclamptic placenta. Numerous studies have shown that cellular hypoxia, which is associated with up-regulated expression of both membrane and soluble endoglin, is involved in the pathophysiology of certain medical conditions, such as preeclampsia and cancer [23]. Early in pregnancy, around 10th gestational week, placentation is conducted under low oxygen pressure conditions. At this point, even in normal pregnancies, there is a temporary increase of membrane endoglin expression in the syncytiotrophoblasts of placental tissue which is restored as soon as intrauterine oxygen tension is increased and it remains stable throughout pregnancy. On the contrary, in preeclamptic placentas, membrane endoglin expression in syncytiotrophoblast cells progressively increases and remains upregulated until delivery. TGF-β3 and HIF-1α levels are also increased in the hypoxic placental tissue of preeclamptic women, compared to non-preeclamptic placentas. Since these molecules are involved in the regulation of endoglin expression, as described above, an increase in their levels is anticipated to cause a subsequent overexpression of placental membrane endoglin [47].

Furthermore, there is evidence supporting that oxidative stress, which is involved in the pathogenesis of preeclampsia, also enhances the expression of membrane endoglin in placenta. Lack of endogenous antioxidant agents in trophoblast placental tissue in preeclampsia, such as heme oxygenase, superoxide dismutase and glutathione peroxidase possibly contribute to the enhanced expression of endoglin and production of its soluble form [48].

Several studies have reported that LDL cholesterol, a molecule prone to oxidation that produces oxidated LDL particles rich in oxysterols, is increased in the serum of preeclamptic pregnant women. Oxysterols behave as natural agonists of liver X receptors (LXRs), which can modify the

expression of endoglin. Thus, the oxysterol-induced activation of LXR receptors result in an increase of endoglin expression in preeclamptic placentas [22] (Fig. 3).

Soluble endoglin

Production and biological functions of soluble endoglin

Apart from membrane endoglin, a soluble form of the molecule has also been described and found in serum, plasma and urine samples of patients with various conditions, such as preeclampsia, atherosclerosis and cancer [23]. Soluble endoglin is formed via proteolytic cleavage of membrane endoglin through the action of metalloproteinases (MMP). The main enzyme mediating endoglin shedding is metalloproteinase MT1-MMP (or matrix metalloproteinase 14, MMP-14), which hydrolyzes the glycine—leucine peptide bond at protein site 586 of endoglin close to its transmembrane domain, thus releasing its extracellular domain in circulation as the soluble isoform of endoglin. However, the contribution of other metalloproteinases in this proteolytic process cannot be ruled out [49] (Fig. 4).

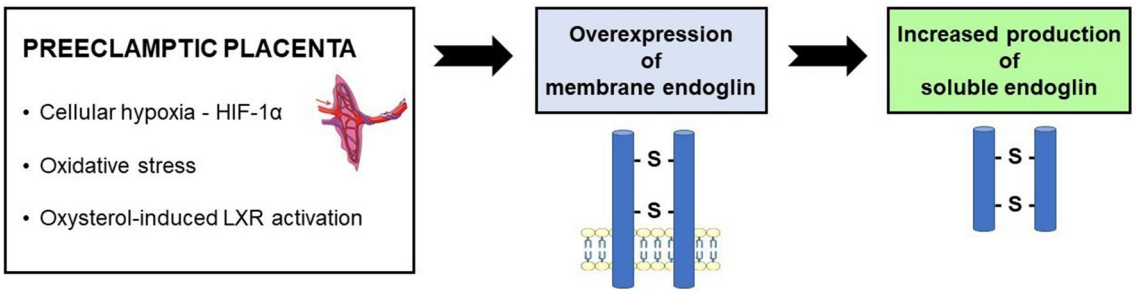

Fig. 3 Expression of membrane endoglin in preeclampsia. Membrane endoglin is overexpressed in syncytiotrophoblast cells of the preeclamptic placenta. This enhanced expression is attributed to a variety of mechanisms, including the oxidative stress and cellular hypoxia observed in the ischemic placental tissue, as well as increased HIF-1α levels and oxysterol-induced activation of Liver X receptors. The upregulation of membrane endoglin in preeclampsia consequently results in an increase of soluble endoglin concentration in maternal circulation, since the soluble form of the protein is produced via proteolytic cleavage of membrane endoglin. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

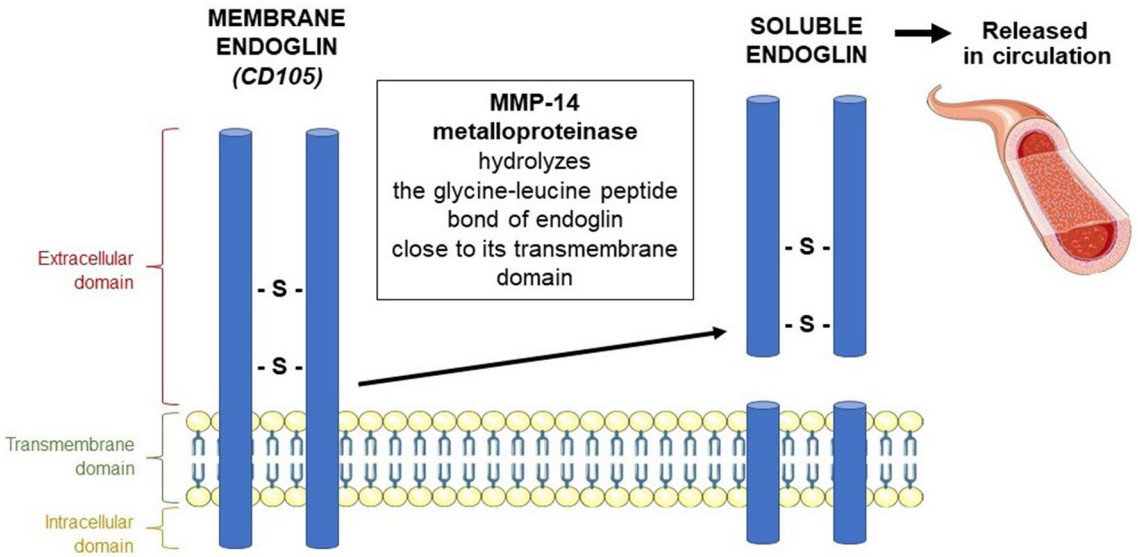

Fig. 4 Production of soluble endoglin. Soluble endoglin is formed by the proteolytic cleavage of membrane endoglin through the action of metalloproteinases (MMP). Matrix metalloproteinase 14 (MMP-14), the predominant enzyme mediating endoglin shedding, hydrolyzes the glycine—leucine peptide bond at protein site 586 of endoglin close to its transmembrane domain. As a result, the long extracellular domain of membrane endoglin is released into circulation as the soluble isoform of endoglin. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

After its release in circulation, soluble endoglin is able to bind to several molecules, such as TGF-β1, BMP-9 and BMP-10. The formation of soluble endoglin—TGF-β1 complexes reduces the bioavailability of TGF-β1 factor in circulation. Therefore, there are fewer TGF-β1 molecules available to interact with TGF-βI and βII receptors and consequently with membrane endoglin. As a result, the balance of TGF-β1 pathway is disrupted and the eNOS enzyme activation is inhibited, leading to decreased nitric oxide production, vasoconstriction and finally to deranged angiogenesis [50] (Fig. 5).

The anti-angiogenic effect of soluble endoglin have been widely studied. It has been reported that soluble endoglin inhibits VEGF-induced angiogenesis in chicken chorioallantoic membrane, as well as in in-vitro formation of new capillary vessels. Moreover, the anti-angiogenic effect of soluble endoglin has been confirmed through its capability to suppress the growth of tumorous masses in mice, which were created by subcutaneous injection of cancerous cells extracted from intestinal adenocarcinoma [23].

The angiogenic properties of membrane endoglin derived from its ability to activate the ALK1 signaling pathway, where main ligands are BMP-9 and BMP-10 factors. Specifically, the extracellular domain of membrane endoglin can bind with high affinity to these molecules. Taking into consideration that soluble endoglin is actually composed of the extracellular domain of the membrane isoform, it is speculated that the anti-angiogenic effect of soluble endoglin can be partially attributed to its ability to bind to BMP-9 and BMP-10 factors, thus reducing their amounts which are available to interact with membrane endoglin and therefore activate ALK1 pathway [48]. However, a recent study revealed that the interaction between soluble endoglin and BMP-9 is more complicated, supporting that soluble endoglin does not solely act as an inhibitory ligand trap for BMP-9. On the contrary, sEng-BMP9 complexes, formulated by the incubation of purified monomeric sEng molecules with BMP-9 molecules, can demonstrate signaling ability in the presence of membrane endoglin, as circulating soluble endoglin might preferentially enhance BMP-9 signaling via cell-surface endoglin at the endothelium [51].

Molecular mechanisms of soluble endoglin release from placenta in preeclampsia

Circulating soluble endoglin levels are increased in pregnant women with preeclampsia, since the molecule derives from the membrane isoform of the protein, which is overexpressed in preeclamptic placentas. Soluble endoglin concentration in maternal serum begins to rise about 8–10 weeks before the onset of clinical manifestations of preeclampsia. Interestingly, the correlation between the severity of clinical presentation and the protein's levels is stronger for soluble endoglin compared to sFlt-1, another well-studied soluble factor

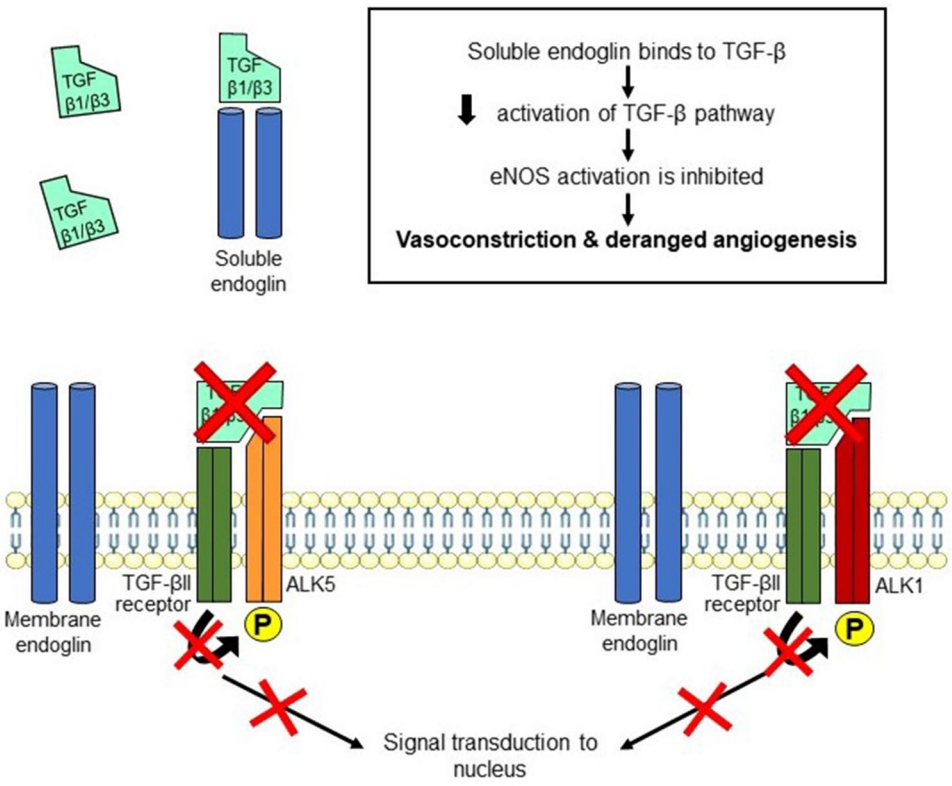

Fig. 5 Mechanism of action of soluble endoglin. Circulating soluble endoglin is able to bind to a variety of molecules, especially TGF-β. By forming complexes with TGF-β, soluble reduces the bioavailability of TGF-β factor in circulation, leading to a reduce in the amount of TGF-β molecules available to interact with TGF-βI and βII receptors and consequently with membrane endoglin. Therefore, soluble endoglin acts by inhibiting TGF-β1 pathway and eNOS enzyme activation and it demonstrates opposite effects, compared to membrane endoglin, since it finally promotes vasoconstriction and disrupts angiogenetic procedures. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

whose concentration rises in preeclamptic pregnancies [48]. The exact molecular mechanisms involved in the excessive release of soluble endoglin from placenta in preeclampsia are not yet fully clarified. MMP-14 metalloproteinase, the predominant enzyme mediating soluble endoglin's shedding from membrane-bound endoglin, is highly expressed in the syncytiotrophoblasts of preeclamptic placentas through a hypoxia-induced mechanism. Consequently, it promotes, by proteolysis, the release of soluble endoglin in circulation [23, 48]. The presence and activity of other metalloproteinases in placental tissue, such as MMP-16, MMP-24 and MMP-25, has also been described; though none of them is overexpressed in preeclampsia. Moreover, there is evidence that MMP-15 and MMP-17 metalloproteinases are overexpressed in preeclampsia, but they do not appear to be associated with the proteolytic cleavage and release of soluble endoglin [47].

Studies performed on pregnant rats with placental ischemia, produced by reduced uterine perfusion pressure, reported an increase in levels of hypoxia-inducible transcription factor HIF-1a with a simultaneous increase of soluble endoglin concentration. Hence, it can be deduced that hypoxia triggers a rise not only in the expression of membrane endoglin, but also in the placental release of soluble endoglin in circulation [52].

In preeclampsia, the placenta is developed under oxidative stress conditions. Reactive oxygen species (ROS), a product of oxidative stress, initiate an inflammatory response which may contribute to the process of soluble endoglin release. In addition, other biomolecules whose production is disturbed due to oxidative stress are probably involved in the release of soluble endoglin from the preeclamptic placenta [23]. Heme oxygenase 1 (HO-1) is an enzyme which inhibits, through its action, the proteolytic release of soluble endoglin. In preeclampsia, decreased levels of HO-1, as a result of oxidative stress, are associated with increased release of soluble endoglin [53]. Another mechanism of soluble endoglin release in preeclampsia combines the effect of hypoxia and oxidative stress with an increase of oxysterols observed in preeclamptic patients. It has been suggested that oxysterols, which activate liver X receptors (LXR), can upregulate the expression of MMP-14 metalloproteinase, leading to augmented production and release of soluble endoglin [54]. In a similar manner, leukemia inhibitory factor receptor (LIFR), a protein detected in syncytiotrophoblasts and cytotrophoblasts of the placenta which is increased in preeclamptic pregnancies, appears to enhance both the expression of MMP-14 metalloproteinase and the shedding of soluble endoglin [55–57].

Recently, an increase in growth arrest and DNA damage 45 (Gadd45) protein has been reported in preeclamptic pregnancies. As a reaction to cellular stress, this protein activates another stress-induced response molecule, p38 protein, which is also overexpressed in preeclampsia. When activated, p38 protein induces the release of soluble endoglin. Specifically, there is a positive correlation between the increase of p38 protein levels and the rise of soluble endoglin concentration in plasma [58].

Apart from hypoxia and oxidative stress, other mechanisms have also been analyzed as possible contributors to the release of soluble endoglin from preeclamptic placenta. In particular, there is evidence of a connection between increase of soluble endoglin levels and detection of agonistic autoantibodies against angiotensin type I receptor (AT1-AA). These autoantibodies, identified in the serum of women with preeclampsia, are assumed to promote the expression of endothelin 1, which induces the release of soluble endoglin [59].

Summarizing the above, it can be deducted that the production and release of soluble endoglin from placenta in preeclampsia does not result from the activation of a single biochemical pathway. On the contrary, there are various distinct mechanisms which promote the cleavage of the extracellular domain from membrane endoglin, releasing soluble endoglin in circulation to exert its anti-angiogenic effects (Fig. 6).

The role of soluble endoglin in pathogenesis and manifestations of preeclampsia

As previously discussed, endoglin is overexpressed in syncytiotrophoblast and extravillous trophoblast cells. Abnormal endoglin expression has been associated with impaired differentiation of trophoblastic tissue, through negative regulation of TGF-β1 and TGF-β3 pathways. Furthermore, it has been demonstrated that endoglin overexpression reduces endothelial cell migration and invasion in mice [47]. Apart from membrane endoglin, the soluble isoform of the protein is also involved in the inadequate placentation observed in preeclampsia. In a model of pregnant mice, soluble endoglin was associated with pseudovasculogenesis, a process during which placental cytotrophoblasts convert to an endothelial phenotype, thus promoting remodeling of the spiral arteries that occurs in the preeclamptic placenta [60]. Indeed, soluble endoglin decreases the invasive ability of trophoblastic cells by regulating the expression of MMP-2 and MMP-9 metalloproteinases, enzymes which are necessary for successful trophoblast invasion [47].

Soluble endoglin demonstrates anti-angiogenic and prohypertensive properties due to its ability to bind to circulating TGF-β molecules. When interacting with membrane endoglin, TGF-β factor promotes vasodilation mediated by overexpression of endothelial nitric oxide synthase (eNOS). However, circulating soluble endoglin binds a significant proportion of TGF-β molecules, decreasing their amount available to interact with membrane endoglin and therefore

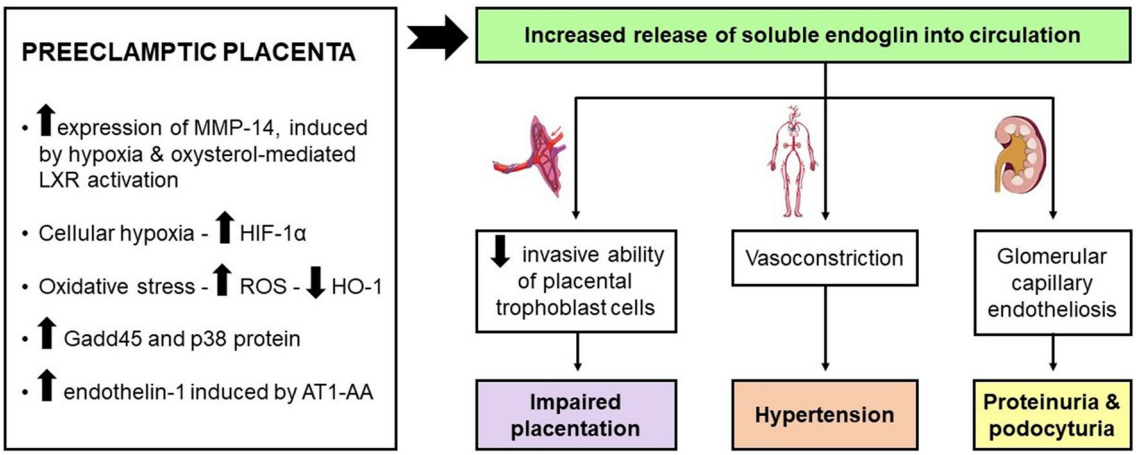

Fig. 6 Release of soluble endoglin from placenta and its role in pathogenesis of preeclampsia. In preeclamptic pregnancies, soluble endoglin is excessively released from the placenta by the action of MMP-14 metalloproteinase. The main factors that stimulate the release of soluble endoglin in preeclampsia are placental cellular hypoxia, oxidative stress and oxysterol-mediated Liver X receptor activation, which all upregulate the expression of MMP-14 in syncytiotrophoblasts. Moreover, increased levels of Gadd45 protein, p38 protein and endothelin-1 that are reported in preeclampsia can induce the proteolytic release of soluble endoglin from placenta. Soluble endoglin plays an active role in the pathogenesis of preeclampsia. Regarding placentation, it contributes to the remodeling of spiral arteries by reducing the invasive ability of placental trophoblast cells. It also demonstrates pro-hypertensive properties due to its vasoconstrictor effect and it is further involved in the renal impairment observed in preeclampsia by promoting glomerular capillary endotheliosis and eventually proteinuria. The figure was created in Microsoft Office Power Point with the use of medical art images by smart.servier.com

to display their vasodilating effects on endothelium. Through this mechanism, soluble endoglin eventually promotes vasoconstriction [47, 50, 61]. Other studies estimate that soluble endoglin on its own is unable to inhibit TGF-β signaling pathway, mostly due to its low-affinity binding to TGF-β. They alternatively suggest that soluble endoglin can bind with higher affinity to BMP-9, inducing the secretion of endothelin 1, a powerful vasoconstrictor, from endothelial cells, leading consequently to the development of hypertension [47, 48]. According to all the above evidence, it is concluded that soluble endoglin is a key factor to the pathogenesis of preeclampsia-associated hypertension.

The renal impairment observed in preeclampsia is considered a result of injuries in renal glomerular endothelial cells. Proteinuria, a diagnostic hallmark alongside hypertension in preeclamptic pregnancies, is a consequence of glomerular capillary endotheliosis, which is mainly characterized by endothelial cell swelling. Structural alterations in glomerular capillary endotheliosis are partially attributed to the action of soluble endoglin, which is released in increased amounts from the ischemic placenta. Soluble endoglin blocks TGF-β signaling pathway, causing loss of glomerular endothelial cell fenestrae, cell swelling and eventually proteinuria [47, 62]. Additionally, it has been suggested that elevated soluble endoglin concentration is associated with increased presence of podocytes in urine of preeclamptic women. Podocytes are considered to have a crucial role in the loss of filtration capacity of kidneys, while their detection in urine samples is a poor prognostic factor for the progression of preeclampsia. As stated above, soluble endoglin is able to interact with leukocyte integrins, preventing their binding to endothelial cells. It has been proposed that through a similar mechanism, soluble endoglin interferes in the binding of podocytes to the glomerular basal membrane, inducing their detachment from it and resulting in their increased detection in urine [47, 63, 64] (Fig. 6).

Diagnostic and therapeutic perspectives of endoglin and soluble endoglin in preeclampsia

Research on the use of biomarkers as diagnostic tools of preeclampsia is recently gaining interest, focusing mainly on maternal circulation molecules indicative of placental dysfunction. The imbalance between angiogenic and anti-angiogenic factors in preeclampsia has been used as a source of potential biomarkers, in the search for a molecule easily detected in maternal blood, whose levels rise before the manifestation of symptoms or complications of the disease. Such a molecule could enable early identification of women being in risk for developing preeclampsia or early diagnosis of preeclamptic pregnancies before the onset of clinical signs and symptoms. Soluble endoglin has been studied in this context, since its concentration can be easily measured in serum or plasma samples and its levels increase weeks

before clinical manifestations of preeclampsia. A plethora of studies [65–69], including meta-analyses [70–72], have examined the diagnostic value of soluble endoglin as a biomarker of preeclampsia, in an effort to explore its potential use as a diagnostic method of the disease, with promising results. They suggest that soluble endoglin could have a considerable role in prediction and diagnosis of preeclampsia throughout pregnancy, mostly as an auxiliary method. Nevertheless, further research is essential to reach definitive conclusions and safely support the introduction and use of soluble endoglin as a prognostic and diagnostic tool for preeclampsia in clinical settings.

The measurement of soluble endoglin concentration in serum or plasma is not commonly used in clinical settings, since it is not yet been established as a diagnostic or prognostic biomarker that can be routinely evaluated in everyday clinical practice to guide the management of patients with preeclampsia or other cardiovascular and metabolic diseases where soluble endoglin levels are known to be increased. Although there is increasing evidence from recent studies implicating its potential role in the diagnosis of various diseases, including preeclampsia, as discussed in the last section of the present review, measurement of soluble endoglin levels is currently applied mostly in experimental settings. In the vast majority of studies that procced to measure soluble endoglin as part of their methodological design, the concentration of the molecule is determined by the use of enzyme-linked immunosorbent assay (ELISA) kits, as this is considered to be the most reliable method of soluble endoglin quantification in biological fluids, suitable to detect various amounts of the biomarker in human blood [73]. Due to the limited application of soluble endoglin measurement, a reference range of serum/plasma soluble endoglin concentration has not been officially established; most studies directly compare the levels of the molecule between the study groups to detect statistically significant differences. Moreover, the various ELISA kits used by different studies usually have different cut-off values for the detection of soluble endoglin in blood, making it even harder to set specific concentration ranges that can be considered normal. In an attempt to address this issue, a Japanese research group that has already established reference levels of other preeclampsia biomarkers in previous studies, such as serum sFlt1, PlGF, and sFlt1:PlGF ratio, tried to construct a reference curve representing the 90% confidence interval for serum soluble endoglin levels throughout the second half of pregnancy. According to the study results, from 20 to 27 weeks, a level of soluble endoglin of > 8 ng/mL should be considered abnormal; from 28 to 30 weeks, > 10 ng/mL is abnormal; from 31 to 33 weeks, > 15 ng/mL is abnormal; from 34 to 35 weeks, > 20 ng/mL is abnormal; from 36 to 37 weeks, > 25 ng/mL is abnormal; and at 38 weeks, > 30 ng/mL is abnormal [74]. Although these values could be used by studies measuring soluble endoglin, they represent the results of a single attempt to set reference ranges for this biomarker. In case soluble endoglin measurement is officially implemented in clinical practice as a diagnostic biomarker, prospective studies should be carefully designed to determine and establish widely accepted reference ranges for soluble endoglin.

Endoglin, as well as its soluble isoform, have not been used till today as treatment targets for preeclampsia, since there is limited research on this field. However, endoglin-based anti-angiogenic biological therapies are currently under development for angiogenesis-dependent diseases [75]. The endoglin neutralizing antibody TRC105 has been clinically tested as therapeutic agents in a variety of malignant tumors, revealing new perspectives in the management and treatment of cancer [39, 76, 77]. This evidence may implicate a potential therapeutic impact for endoglin in preeclampsia, which would further expand and improve our treatment strategies in the future.

Conclusions

Endoglin is a membrane glycoprotein expressed mainly in proliferating endothelial cells, which plays a prominent role in angiogenetic procedures. Endoglin is overexpressed through a variety of mechanisms in syncytiotrophoblast cells of preeclamptic placentas, leading to a subsequent increase of its soluble form. Soluble endoglin is produced by MMP14 metalloproteinase-mediated proteolytic cleavage of membrane endoglin and is profusely released into circulation of preeclamptic patients through the activation of various biochemical pathways. Contrary to membrane endoglin, soluble endoglin presents anti-angiogenic and vasoconstrictive properties and contributes to impaired placentation, as well as the development of clinical manifestations of preeclampsia, especially hypertension, proteinuria and podocyturia. Both endoglin and soluble endoglin are highly involved in the pathogenetic mechanisms of preeclampsia, thus representing factors with potential diagnostic, prognostic and therapeutic value. Further research is required to extensively explore the role of these molecules in the management of preeclampsia in clinical settings.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval Not applicable. The present article does not involve intervention on a population of humans and/or animals directly, it is a review of literature that gathers information from published articles.

Consent to participate Not applicable. The present article does not involve intervention on a population of humans and/or animals directly, it is a review of literature that gathers information from published articles.

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