

## Soluble endoglin is an accurate predictor and a pathogenic molecule in pre-eclampsia\*

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Pre-eclampsia is characterized by new-onset hypertension (>140/90 mmHg), proteinuria and oedema after 20 weeks of gestation in previously normotensive, non-proteinuric women. This disease occurs in 5% of pregnancies in the United States and Europe, and can be complicated by renal failure, pulmonary oedema and coagulopathy [1]. Although there has been marked progress toward understanding its pathogenesis, only little advances have been made in prediction and management of pre-eclampsia and it remains a leading cause of maternal and foetal morbidity and mortality worldwide [1].

This editorial is based on an article recently published by the Calcium for Pre-eclampsia Prevention Study Group on the prognostic value of circulating levels of endoglin (Eng) and other angiogenic factors in pre-eclampsia [2]. The study included 72 women who had pre-term pre-eclampsia (<37 weeks), as well as 480 randomly selected women: 120 women with pre-eclampsia at term (>37 weeks), 120 women with gestational hypertension, 120 normotensive women who delivered infants who were small for gestational age and 120 normotensive controls who delivered infants who were not small for gestational age. They reported that after the onset of clinical disease, the mean circulating soluble endoglin (s-Eng) levels in women with pre-term pre-eclampsia was > four times higher than controls. Beginning at 17 weeks through 20 weeks of gestation, in women in whom pre-term pre-eclampsia later developed, s-Eng levels were significantly higher (about two times) than

controls. Increased plasma concentrations of s-Eng was usually accompanied by an increased ratio between plasma concentrations of soluble receptor for Vascular endothelial growth factor (VEGF) fms-like tyrosine kinase 1 (s-FLT1) and the pro-angiogenic protein placental growth factor (PlGF). The risk of pre-eclampsia was greatest among women in the highest quartile of the control distributions for both biomarkers (sEng and sFlt1:PlGF ratio), but not for either biomarker alone. The authors concluded that increased circulating levels of soluble endoglin and ratios of sFlt1:PlGF presage the onset of pre-eclampsia. Elevations in s-Eng were more pronounced and therefore, potentially most useful for prediction, among women in whom pre-term pre-eclampsia developed or women in whom pre-eclampsia developed and who had a small-for-gestational-age infant. To better understand the meaning of these results, we will briefly revise what is endoglin as well as the function of endoglin in the endothelium.

### What is endoglin?

Eng, also called CD105, is a 180-kDa homodimeric transmembrane glycoprotein expressed mainly in endothelial cells, but also in many other cell types [3]. Eng is an intriguing molecule that functions as an auxiliary receptor (type III receptor) for several of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily members. Eng modulates TGF- $\beta$  signalling by interacting with TGF- $\beta$  receptors types I and II [4]. Mutations in the gene encoding Eng (*Eng*) is associated with hereditary haemorrhagic telangiectasia type 1 (HHT1), an autosomal dominant vascular disorder characterized by focal telangiectases and arteriovenous malformations. Eng is upregulated in tissues undergoing angiogenesis and *in vitro* inhibition of its expression on endothelial cells impairs cell proliferation and survival [3]. Eng-null (*Eng*<sup>-/-</sup>) mice die at mid-gestation from defective angiogenesis and severe cardiovascular abnormalities, while Eng heterozygous

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mice have normal life spans, but are predisposed to develop HHT-like vascular abnormalities [5,6]. These results suggest a role for Eng in vascular remodelling and homeostasis. Supporting this view, it has been reported that endothelial nitric oxide (NO) synthase (eNOS) expression was reduced, and that NO synthesis was impaired in these mice [7–9]. Furthermore, isolated endothelial cells from *Eng*<sup>+/-</sup> mice display reduced proliferation and migration, impaired capillary formation and reduced eNOS activity and VEGF secretion [10]. These changes were associated with decreased blood vessel formation in *in vivo* models of angiogenesis [10], indicating that Eng plays a major role in adult angiogenesis.

### The origin and effects of soluble endoglin

It has been recently published that preeclamptic placentas overexpressed sFlt and Eng mRNA as well as Eng protein. Furthermore, recombinant s-Eng and s-Flt induced a phenotype in pregnant rats similar to the clinical features of preeclampsia in humans. *In vitro* studies suggested that s-Eng inhibits TGF- $\beta$ 1 signalling and blocks TGF- $\beta$ 1-mediated nitric oxide synthase activation in endothelial cells. Furthermore, they also demonstrated that s-Eng interfered with endothelial proliferation and capillary formation [11]. While these experiments support a pathogenic role of s-Eng in pre-eclampsia, the exact mechanism of action of s-Eng is far from being elucidated. It has been suggested that s-Eng plays its anti angiogenic effects and pro-hypertensive effects in pre-eclampsia through binding to circulating molecules such as TGF- $\beta$ 1, thus preventing the binding of these molecules to the cell membrane Eng [12], and consequently the pro-angiogenic and vasodilatory effects of TGF- $\beta$ 1 in the normal endothelium. It is interesting to note that a variant form of membrane Eng with a short cytosolic domain also displays opposite angiogenic effects than full length Eng [13].

An issue not fully elucidated by Karumanchis studies is how s-Eng is produced in pre-eclampsia. Apparently, s-Eng does not derive from alternative splicing of the *Eng* gene in the placenta. Instead, a proteolytic processing of the membrane bound Eng leading to s-Eng is proposed. A partial peptide sequence of purified circulating s-Eng suggests that it is an N-terminal cleavage product of full-length Eng [11]. Given that betaglycan, another TGF- $\beta$  type III receptor, with partial sequence identity to endoglin, can be shed by membrane-type metalloprotease-1 (interstitial collagenase) present in trophoblasts [14], it can be speculated a similar processing for the circulating s-Eng.

### Clinical consequences of these findings

From a clinical point of view, there are several evidences reporting an increased NO synthesis during pregnancy, whereas endothelial dysfunction has been reported in women with pre-eclampsia. Thus, it can be

deduced that pre-eclampsia is a disease with a major endothelial dysfunction component, and that endothelial dysfunction plays a role in pre-eclampsia-associated hypertension and other manifestations such as renal disease [15]. In this sense, *Eng*<sup>+/-</sup> mice show an impaired endothelial-dependent vasodilatation associated to the decreased NO production [7] that was compensated by increased COX-2 expression and PGE-2 production [8]. Also, TGF- $\beta$ 1 has NO-mediated vasodilator effects '*ex vivo*', and these effects are lower in the *Eng*<sup>+/-</sup> mice [16]. Thus, Eng seems to have also a role in regulating endothelial cell function, and this function seems to be altered by Eng deficiency or by the presence of s-Eng, as seems to be the case during pre-eclampsia.

### Conclusion

Plasma levels of s-Eng seem to be promising as an accurate marker to presage pre-eclampsia appearance, thus allowing early diagnosis and preventive therapy. More prospective studies are necessary to confirm the effective diagnostic value of this biomarker. In addition, further mechanistic studies on the role of s-Eng in vascular biology should contribute to a better understanding on the pathogenic mechanisms responsible for pre-eclampsia which in turn will favour the development of therapeutic strategies to this disease that seems practically untreatable so far.

*Conflict of interest statement.* None declared.

### References

- Sibai BM, Caritis S, Hauth J. What we have learned about preeclampsia. *Semin Perinatol* 2003; 27: 239–246
- Levine RJ, Maynard SE, Qian C *et al.* Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004; 350: 672–683
- Fonsatti E, Maio M. Highlights on endoglin (CD105): from basic findings towards clinical applications in human cancer. *J Transl Med* 2004; 2: 18 (<http://www.translational-medicine.com/content/2/1/18>)
- Guerrero-Esteo M, Sanchez-Elsner T, Letamendia A, Bernabeu C. Extracellular and cytoplasmic domains of endoglin interact with the transforming growth factor-beta receptors I and II. *J Biol Chem* 2002; 277: 29197–29209
- Bourdeau A, Dumont DJ, Letarte M. A murine model of hereditary hemorrhagic telangiectasia. *J Clin Invest* 1999; 104: 1343–1351
- Torsney E, Charlton R, Diamond AG *et al.* Mouse model for hereditary hemorrhagic telangiectasia has a generalized vascular abnormality. *Circulation* 2003; 107: 1653–1657
- Jerkic M, Rivas-Elena JV, Prieto M *et al.* Endoglin regulates nitric oxide-dependent vasodilatation. *FASEB J* 2004; 18: 609–611
- Jerkic M, Rivas-Elena JV, Santibanez JF *et al.* Endoglin regulates cyclooxygenase-2 expression and activity. *Circ Res* 2006; 99: 248–526
- Toporsian M, Gros R, Kabir MG *et al.* Role for endoglin in coupling eNOS activity and regulating vascular tone revealed in hereditary hemorrhagic telangiectasia. *Circ Res* 2005; 96: 684–692
- Jerkic M, Rodriguez-Barbero A, Prieto M *et al.* Reduced angiogenic responses in adult endoglin heterozygous mice. *Cardiovasc Res* 2006; 69: 845–854

11. Venkatesha S, Toporsian M, Lam C *et al.* Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006; 12: 642–649
12. Luft FC. Soluble endoglin (sEng) joins the soluble fms-like tyrosine kinase (sFlt) receptor as a pre-eclampsia molecule. *Nephrol Dial Transplant* 2006; 21: 3052–3054
13. Perez-Gomez E, Eleno N, Lopez-Novoa JM *et al.* Characterization of murine S-endoglin isoform and its effects on tumor development. *Oncogene* 2005; 24: 4450–4461
14. Kaufmann P, Castellucci M. Extravillous trophoblast in the human placenta. A review. *Trophoblast Res* 1997; 10: 21–65
15. Davison JM, Homuth V, Jeyabalan A *et al.* New aspects in the pathophysiology of preeclampsia. *J Am Soc Nephrol* 2004; 15: 2440–2448
16. Santibanez JF, Letamendia A, Perez-Barriocanal F *et al.* Endoglin increases eNOS expression by modulating smad2 protein levels and smad2-dependent TGF- $\beta$  signaling. *J Cell Physiol* 2007; 210: 456–468

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