RESEARCH HIGHLIGHT

A suppressor role for soluble endoglin in cancer

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Elevated levels of a circulating form of the transforming growth factor- β (TGF- β) coreceptor endoglin correlate with poor clinical outcome in different types of cancer. Soluble endoglin (Sol-Eng) is primarily produced by cleavage of cell-surface endoglin by the transmembrane metalloprotease MMP14 that releases most of its extracellular domain. Sol-Eng has been found to contribute to different cardiovascular pathologies, including preeclampsia, a severe hypertensive syndrome of pregnancy. While the anti-angiogenic and pro-hypertensive functions of Sol-Eng appear well established, its role in cancer has not been fully investigated. Recently, we reported that Sol-Eng strongly inhibits signaling through the hepatocyte growth factor (HGF) tyrosine kinase receptor Met in mouse skin spindle carcinoma cells. Sol-Eng also blocked basal and HGF-mediated stimulation of carcinoma cell proliferation, migration and invasion. Taken together, the above results and the anti-angiogenic function exerted by Sol-Eng suggest a suppressor role for Sol-Eng in cancer. This conclusion is discussed in the paradoxical context of Sol-Eng as a marker of poor prognosis and as a potential contributor to the decreased risk of preeclamptic mothers to develop breast cancer later in life.

Keywords: soluble endoglin; TGF- β ; Met; cancer; preeclampsia

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Endoglin (CD105) is a 180-kDa homodimeric transmembrane glycoprotein that behaves as an auxiliary receptor for the transforming growth factor- β (TGF- β) family of cytokines. It binds TGF- β 1, TGF- β 3, activin-A, and bone morphogenetic proteins (BMPs) BMP2, BMP9 and BMP10^[1], and plays a crucial role in hematopoiesis, cardiovascular development, vascular remodeling and angiogenesis^[2, 3]. Accordingly, *Endoglin*-deficient mice (*Eng*^{-/-}) die at midgestation as a result of cardiovascular abnormalities^[4, 5]. The *Endoglin* gene is mutated in hereditary haemorrhagic telangiectasia type I (HHT1), a vascular disorder historically known as the Osler-Weber-Rendu syndrome. HHT patients display arteriovenous malformations that result in cutaneous

telangiectasias and nose and gastrointestinal bleeds, more dangerous and threatening when occur in large vessels of the liver, brain and lungs^[6, 7].

Endoglin plays an important role in cancer at two different levels: i) in endothelial cells as a regulator of tumor angiogenesis; and ii) in tumor cells as a modulator of malignancy^[1, 8]. Expression of endoglin is high in peritumoral and intratumoral blood vessels of different types of cancer and has proved to be a useful target for tumor imaging and antiangiogenic therapy. Indeed, humanized anti-endoglin antibodies are currently being explored to destroy the tumor vasculature and halt tumor cell growth^[9, 10].

Table 1. Ligands binding to Sol-Eng

Ligand	Procedure/Reference	Comments
TGF- β 1	Interference with binding of radiolabeled TGF- β 1 to T β RII ³²	No direct binding was assessed
	SPR ³⁴	Sol-Eng directly binds TGF- β 1 with low affinity
BMP9	SPR ³³⁻³⁵	Sol-Eng directly binds BMP9 with high affinity
BMP10	SPR ³³	Sol-Eng directly binds BMP10 with high affinity
β 1 integrin	Interference with endoglin-mediated adhesion to β 1 integrin of leukocytes ²⁴	No direct binding was assessed
Met	Coimmunoprecipitation ⁴⁷	No direct binding was assessed

T β RII, TGF- β type II receptor; SPR, surface plasmon resonance

Endoglin expression has also been detected in cancer cells, where it modulates tumor cell proliferation, invasion and metastasis. Thus, endoglin behaves not only as a tumor suppressor in esophageal, prostate and breast carcinomas^[11-13], but also as a promoter of malignancy in melanoma and Ewing sarcoma^[14]. Moreover, endoglin appears to contribute to chemotherapy resistance in ovarian and pancreatic cancer^[15, 16]. In a pioneer work, we demonstrated a dual role for endoglin during multistage mouse skin carcinogenesis *in vivo*^[17, 18]. The skin of endoglin haploinsufficient mice (*Eng*^{+/-}) was subjected to a single topical dose of 7,12-dimethylbenz(*a*)anthracene (DMBA) followed by twice a week treatment with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). This protocol induces the outgrowth of benign papillomas after several weeks of initiation with DMBA, from which a small proportion progress to malignant squamous cell carcinomas. *Eng*^{+/-} mice developed a lesser number of tumors than wild-type mice, but progression to carcinomas in these endoglin haploinsufficient mice was vastly accelerated and a substantial proportion of tumors were classified as highly aggressive undifferentiated spindle cell carcinomas. The tumor phenotype of *Eng*^{+/-} mice was quite similar to that of transgenic mice with targeted expression of TGF- β 1 in the epidermis^[19], a result that provided the proof-of-concept for the double and contradictory role of TGF- β 1 in cancer as a suppressor at early stages of carcinogenesis and a stimulator of malignancy at later stages^[20, 21].

Structurally, the extracellular (EC) region of endoglin is composed of an orphan domain and a zona pellucida (ZP) domain^[2]. It is highly glycosylated, containing five potential N-linked sites within the orphan domain, and a putative O-glycan motif in the ZP domain proximal to the transmembrane region (Figure 1). An Arg-Gly-Asp (RGD) peptide within the ZP domain of human endoglin constitutes a prototypic member of a family of motifs involved in integrin-based interactions between the extracellular matrix

and certain cell surface proteins^[22, 23]. It has been demonstrated that membrane-bound endoglin interacts with integrin α 5 β 1 via its RGD motif^[24, 25]. The RGD motif is present in endoglin from primates, while functionally related RGD-like motifs are found in endoglin from other animals, stressing the physiological importance and conservation of this motif^[22, 24]. It has been reported^[26, 27] that the membrane-bound matrix metalloprotease-14 (MMP-14), also known as MT1-MMP, cleaves the EC region of endoglin at a juxtamembrane site, releasing a circulating form termed soluble endoglin (Sol-Eng).

The body fluids (plasma, serum and urine) from patients with preeclampsia, hypercholesterolemia, atherosclerosis and cancer contain high levels of Sol-Eng^[1, 8, 28, 29]. Furthermore, Sol-Eng is a marker of cardiovascular damage in patients suffering of hypertension and diabetes^[30]. Preeclampsia is a systemic syndrome affecting 3-5% of pregnancies characterized by hypertension and proteinuria, which results in significant morbidity and mortality to both mothers and fetuses^[28]. Interestingly, preeclamptic placentas express MMP14 that apparently mediates the release of Sol-Eng^[31]. It has been reported that Sol-Eng plays an antagonistic role with respect to membrane endoglin as an anti-angiogenic and pro-hypertensive molecule by interacting with cytokines of the TGF- β family^[26, 27, 32]. Sol-Eng impairs endothelial cell proliferation, capillary formation and blood vessel sprouting^[26, 32, 33], and increases blood pressure and vascular permeability^[27, 32]. In addition, Sol-Eng may inhibit the anti-atherogenic effects induced by TGF- β ^[29], and alter vascular homeostasis by scavenging TGF- β 1, thus preventing its binding to endothelial cell surface receptors^[32]. However, this issue remains controversial as there are reports demonstrating that Sol-Eng binds with high affinity BMP9 and BMP10, but not TGF- β 1 and TGF- β 3^[33-35] (Table 1).

Elevated levels of Sol-Eng are found in breast, colorectal and prostate cancer patients associated with tumor progression and metastasis^[36-40]. In addition, high levels of Sol-Eng are detected in the plasma of patients with lung cancer^[41], and correlate with proliferation and angiogenesis in myeloid malignancies^[42-44]. In a mouse skin chemical carcinogenesis model, we found that endoglin is shed from both endothelial and tumor cells, and that release of Sol-Eng into the tumor stroma and the blood stream is associated with advanced stages of tumor progression^[45]. Therefore, it can be postulated that Sol-Eng interacts with different proteins in the extracellular matrix as well as on the surface of stromal and tumor cells. An interesting cross-talk between the tumor and the stroma, using an *in vitro* cellular system, has been reported^[46]. This model involves the cleavage of membrane endoglin and the subsequent release of Sol-Eng from MCF-7 breast cancer cells by soluble MMP14 originated from bone

Figure 1. Structure of soluble endoglin and its function in cancer related cells. Left, schematic representation of the release of Sol-Eng after proteolytic cleavage of membrane-bound endoglin. Endoglin contains an orphan domain and a zona pellucida (ZP) domain within the extracellular region. Potential, N-glycosylations in the orphan domain and O-glycosylation in the ZP domain are indicated by purple dots. The purple pentagon in the ZP domain represents the RGD tripeptide sequence involved in the binding of endoglin to integrins. The known and unknown effects of Sol-Eng on tumor and stromal cells are indicated on the right. The tumor stroma contains endothelial cells, pericytes, fibroblasts, neutrophils, macrophages, mast cells and dendritic cells, among others. Whereas several studies have reported effects of Sol-Eng on the behavior of tumor and endothelial cells, it remains to be investigated the action of Sol-Eng on the rest of stromal cells. For additional details see the text. CAF, cancer-associated fibroblasts.

marrow-derived stromal cells. Production of soluble MMP14 is likely triggered by the action of TGF- β 1, which is secreted by MCF-7 tumor cells, initiating a cycle of heterotypic interactions tumor-stroma that results in increased malignancy of breast cancer cells [46]. This study also points out that a direct interaction between membrane-bound MMP14 and endoglin on the cell surface is not a strict requirement for endoglin shedding [26]. However, the effect of Sol-Eng on the behavior of tumor and stromal cells was not investigated in this study.

In a recent article, we explored whether Sol-Eng affects the malignant properties of highly aggressive skin spindle carcinoma cells [47]. We found that Sol-Eng inhibits carcinoma cell proliferation, as well as basal and TGF- β 1-stimulated mitogen-activated protein kinase (MAPK) signaling activity. A marked inhibitory effect of Sol-Eng on *in vitro* carcinoma cell growth was observed. By contrast, only a mild inhibition was seen *in vivo*, when measuring the growth of tumors induced by transplantation of carcinoma cells in athymic nude mice, suggesting that undefined effects of Sol-Eng on stromal cells may counteract the growth inhibition directly imposed upon tumor cells (Figure 1). At variance with these results, a strong inhibitory

effect of the EC domain of endoglin fused to an immunoglobulin Fc domain on the growth of colon adenocarcinoma cells subcutaneously implanted in mice was found [33]. A characteristic of skin spindle carcinomas shared by other types of advanced tumors, including basal breast carcinomas, is the secretion of high levels of hepatocyte growth factor (HGF) and hyperactivation of Met, its tyrosine kinase receptor. Of note, Sol-Eng strongly inhibited both basal and HGF-induced Met activation and downstream MAPK signaling activity as well as basal and HGF-stimulated carcinoma cell migration and invasion [47]. The mechanism for this action is unclear and may involve the binding of Sol-Eng to Met on the cell surface, preventing its HGF-mediated activation and dimerization, but promoting its internalization and degradation independently of HGF. Interestingly, full-length membrane endoglin also binds Met, as shown by coimmunoprecipitation experiments, but it is unable to influence Met stability and signaling activity [47]. Recent studies indicate that the binding of Sol-Eng to Met is not direct (our unpublished results) and might be mediated by some of the proteins that associate with Met in a multiprotein complex at the plasma membrane, such as plexins, the hyaluronan receptor CD44 or integrins [48]. In this regard, membrane endoglin in endothelial cells interacts

with $\alpha 5\beta 1$ integrin via its RGD motif contained within the ZP domain^[24, 25]. Moreover, endoglin-mediated cell adhesion is involved in endothelial transmigration of leukocytes and is abolished by Sol-Eng^[24], suggesting that Sol-Eng competes with membrane endoglin for binding to $\beta 1$ integrins. It will be of interest to determine whether Sol-Eng binds to the integrin partners of Met. A number of proteins able to interact with membrane-bound endoglin has been described^[1, 2]. A summary of some of the ligands reported to bind Sol-Eng *in vitro* is presented in Table 1, while the identification of ligands interacting with Sol-Eng *in vivo* should be a priority objective for those researchers interested in understanding the function of Sol-Eng in cancer and other pathologies.

Altogether, the anti-angiogenic and anti-oncogenic effects of Sol-Eng described above suggest a suppressor role for this circulating form of endoglin in carcinogenesis. This conclusion appears paradoxical taking into account the direct correlation between elevated levels of circulating endoglin and poor prognosis in different types of human cancer^[1, 8]. Because the increased production of Sol-Eng in the tumor microenvironment appears to be a late event in malignant progression^[45], an explanation for this apparent discrepancy is that, at this late stage, Sol-Eng present in the microenvironment cannot counteract the full malignant potential displayed by advanced tumors. By contrast, Sol-Eng should have a protective role for tumor formation at early stages of cancer development, as inferred from its tumor suppressor function. Indeed, epidemiological evidence indicates that preeclamptic pregnancy is associated with a lower risk for both the mother and offspring to develop breast cancer later in life^[49, 50]. Noteworthy, the levels of Sol-Eng are reportedly to be elevated not only at preeclampsia, but also many years after preeclamptic pregnancies^[49]. It should be mentioned, however, that some reports failed to find out a correlation between cancer incidence and preeclampsia^[49, 50]. Notwithstanding, serum from pregnant rats with placental ischemia (regarded as the primary initiating factor of preeclampsia) and preeclamptic-like symptoms, as well as purified Sol-Eng inhibit the proliferation of breast cancer cells *in vitro*^[50], supporting the tumor suppressor role of Sol-Eng. These results are in agreement with our own data in skin carcinoma cells^[47]. Based on these findings, it has been postulated that reduction of mammary progenitor cells and attenuation of TGF- β signaling mediated by persistently elevated levels of circulating factors, such as Sol-Eng, underlines the protective effect of preeclampsia on breast cancer^[50]. Nevertheless, the precise molecular and cellular mechanisms of this correlation remain to be elucidated.

In summary, the results from a number of laboratories,

including ours, suggest a suppressor role for Sol-Eng in tumor progression. Accordingly, Sol-Eng can be proposed as a potential new tool for therapeutic intervention in cancer. Since cancer involves a continuous cycle of deregulated tissue injury and repair, resembling in many aspects chronic fibrosis and wound healing responses^[51], the potential involvement of Sol-Eng in these processes remains to be investigated. In this sense, MMP14, the primary metalloprotease responsible for the release of Sol-Eng, appears to play an important role in pulmonary fibrosis^[52] and in mediating the crosstalk between epidermis and dermis during skin repair^[53].

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