Endoglin-mediated angiogenic responses are regulated by its cytosolic domain

Nuñez-Gomez E1; Ollauri-Ibañez C1; Pérez-Roque L1; Bernabeu C2; Rodríguez-Barbero A1; Pericacho M1; Lopez-Novoa JM1

1Renal and Cardiovascular Physiology Unit, Physiology and Pharmacology Department, University of Salamanca; Biomedical Research Institute of Salamanca (IBSAL); Iñigo Alvarez de Toledo Renal Foundation, Madrid; 2Centro de Investigaciones Biológicas, Spanish Research Council (CSIC), Madrid, Spain

Objectives: Underlying the pathogenesis of HHT, an impaired angiogenesis has been postulated, leading to HHT vascular defects. Endoglin proper functions are key for an accurate angiogenesis. There are two physiological membrane-bound Endoglin isoforms, full length Endoglin (L-Eng) and S-Endoglin (S-Eng) lacking most part of the intracellular domain. Endoglin isoforms have been proposed to have different effects in angiogenesis. Here, we have assessed a role for Endoglin cytosolic domain in the modulation of angiogenesis, and specific endothelial processes affected.

Methods and Results: We used mice that ubiquitously overexpress either L-Eng (*L-Eng+*), or S-Eng (*S-Eng+*). *S-Eng+* mice presented a delayed and impaired reperfusion after hindlimb ischemia compared with *L-Eng+* and WT mice. Moreover, subcutaneous Matrigel-implants were less invaded by vascular endothelial cells when engrafted in *S-Eng+* mice, compared with *L-Eng+* and WT mice. We also assessed in vitro cell invasion of Matrigel-covered transwells and capillary-like structures formation in Matrigel using endothelial cells overexpressing L-Eng or S-Eng. We observed that S-Eng+ cells show a reduced motility compared with L-Eng+ or WT cells. On the other hand, we found an enhanced sprouting initiation in aortic rings from *S-Eng+* mice, although this did not lead to more mature capillaries.

Conclusions: S-Endoglin, lacking most part of the cytosolic domain, results in an impaired angiogenic response in vivo, whereas L-Endoglin overexpression has no effect on angiogenic rate, compared with WT animals. S-Endoglin effect is caused, at least in part, by a reduction of cell motility and invasion of the extracellular matrix, so we can hypothesize a role of Endoglin cytosolic domain in angiogenesis modulation.

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