Profibrotic role of endoglin is dependent on its intracellular domain

Pericacho M1; Muñoz-Felix JM1; Nuñez-Gomez E1; Perez-Roque L1; Arevalo M2; Oujo B1; Martinez-Salgado C1; Bernabeu C3; 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; 2Department of Anatomy and Histology, University of Salamanca; 3Centro de Investigaciones Biologicas, Spanish Research Council (CSIC), Madrid

Introduction and aims: Endoglin, a 180 kDa membrane glycoprotein, is a TGF-beta co-receptor which is overexpressed in several models of chronic kidney disease but its specific function in renal fibrosis remains still undefined. Two membrane isoforms generated by alternative splicing have been described, full length Endoglin (L-Eng, the most abundant isoform) and S-Eng (short) that differ from L-Eng in the absence of the cytoplasmic tail. We have recently demonstrated that L-Eng overexpression enhances fibrosis in the unilateral ureteral obstruction (UUO) model of kidney fibrosis. The aim of the present study was to assess the effect of S-Eng overexpression in renal tubulo-interstitial fibrosis induced by unilateral ureteral obstruction (UUO).

Methods: For this purpose, a transgenic mouse which ubiquitously overexpresses human S-Eng (S-ENG+) was generated. UUO was performed in S-ENG+ mice and their wild type littermates. Kidney Fibrosis was determined by morphometric techniques and by the expression of fibrosis-related molecules (collagen I, fibronectin) by western blot.

Results: Obstructed kidneys from S-ENG+ mice showed reduced tubulo-interstitial fibrotic area and lower amounts of collagen I and fibronectin than obstructed kidneys from WT mice. Moreover, western blot analysis showed that levels of p-Smad1 and p-Smad3 were higher in obstructed kidneys, being these increase significantly lower in obstructed kidneys from S-ENG+ than in those from WT animals.

Conclusions: The overexpression of S-Eng reduces kidney fibrosis. These results are exactly the opposite of those obtained in L-Eng mice. Therefore, we conclude that the intracellular domain of endoglin plays a major role in regulating its fibrotic effects.

11th International HHT Scientific Conference
June 11-14, 2015
Captiva, Florida USA