Renal and Cardiovascular Pathophysiology Unit
Department of Physiology and Pharmacology. University of Salamanca. Spain.

[1] Renal and Cardiovascular Pathophysiology Unit, Reina Sofía Institute of Nephrological Research , University of Salamanca, Spain.

[2] Institute of Biomedical Research of Salamanca (IBSAL).

[3] Health Science Institute of Castilla y León (IECSCYL), Research Unit, University Hospital of Salamanca, Salamanca, Spain.

ALK1 HETEROZYGOUS DISRUPTION IMPAIRS TGF-β/SMAD SIGNALING AND INCREASES RENAL FIBROSIS FOLLOWING URETERAL OBSTRUCTION

José M. Muñoz-Félix[1,2], José M. López-Novoa[1,2], Carlos Martínez-Salgado[1,2,3]

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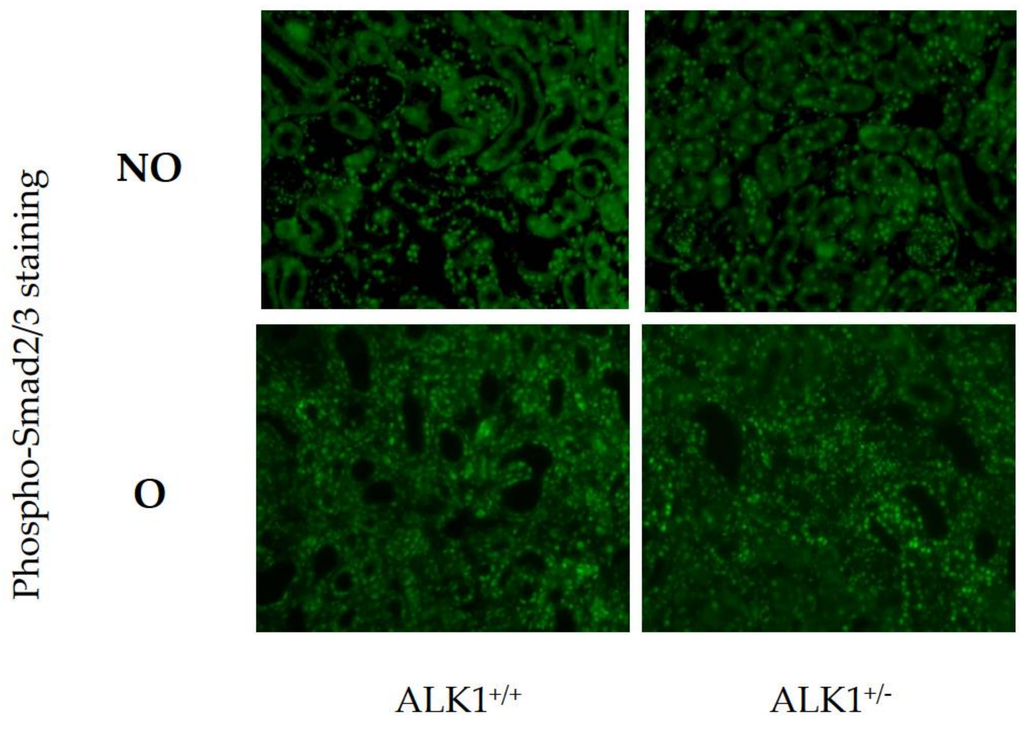
BACKGROUND AND AIMS

Tubulointerstitial fibrosis, one of the common end points of chronic renal insufficiency, is characterized by an excessive accumulation of extracellular matrix (ECM) in the renal interstitium, myofibroblast activation, cell infiltration, tubular apoptosis and proliferation. Transforming growth factor-beta 1 (TGF-β1) is considered a fundamental profibrotic cytokine. ALK1 (activin receptor-like kinase I) is a type I receptor for TGF-β1 with a pivotal role in endothelial proliferation and migration. ALK1 promotes Smad1/5 signaling and is a lateral antagonist of ALK5/Smad2/3 signaling in endothelial cells. ALK1 potentiates ECM protein synthesis in scleroderma fibroblasts. Nevertheless, the role of ALK1 in obstructive nephropathy is unknown.



METHODS

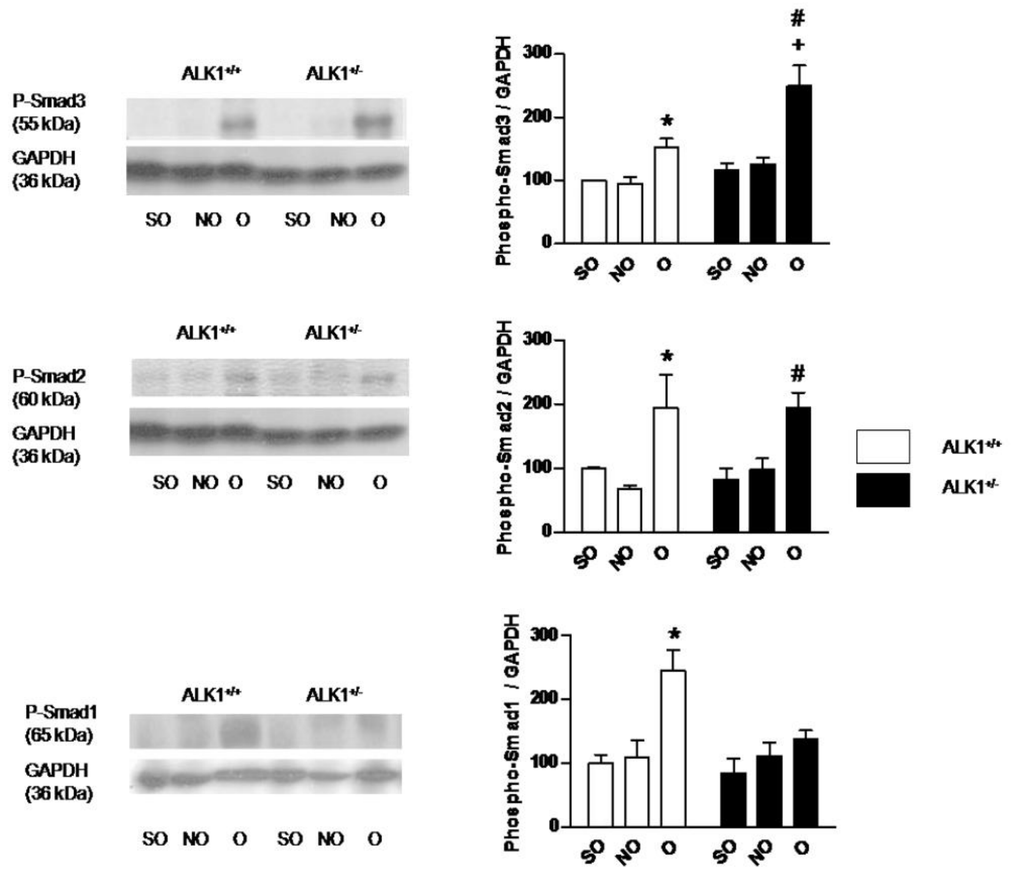
We performed unilateral ureteral obstruction (UUO), an obstructive nephropathy experimental model, in haploinsufficient ($ALK1^{+/-}$) and control ($ALK1^{+/+}$) mice in order to analyze the role of ALK1 haploinsufficiency 15 days following ureteral obstruction. Kidney ultrastructure was analyzed by hematoxylin-eosin staining. We analyzed tubulointerstitial fibrosis by Masson's trichrome and Red Sirius staining. Phospho-Smad1, phospho-Smad2 and phospho-Smad3 expression was evaluated by western blot and immunostaining.

RESULTS

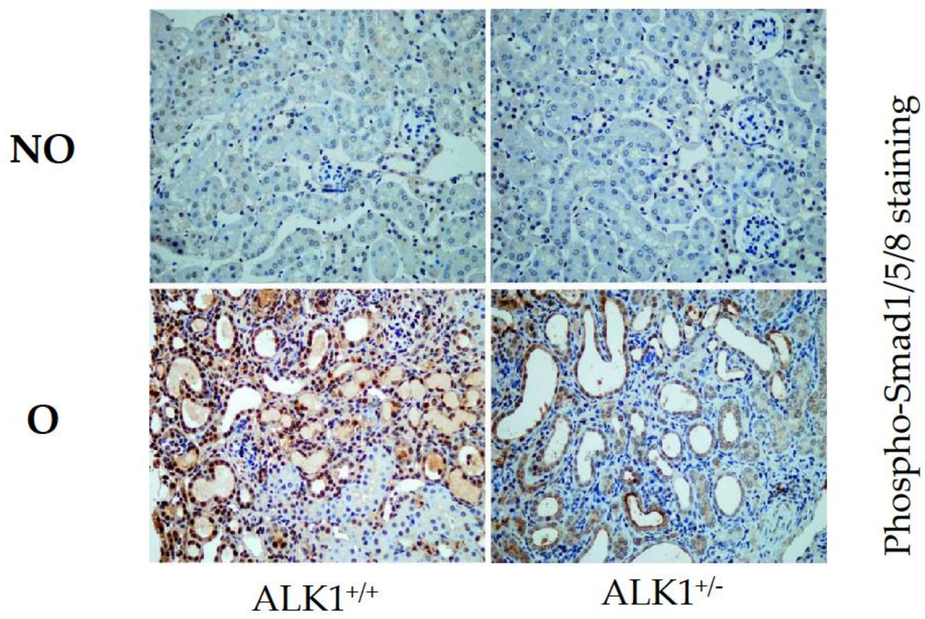
Phospho-Smad1, phospho-Smad2 and phospho-Smad3 expressions were increased following UUO in both $ALK1^{+/+}$ and $ALK1^{+/-}$ obstructed kidneys. Phospho-Smad1 expression was lower, while phospho-Smad3 was higher in obstructed kidneys from $ALK1^{+/-}$ mice than in $ALK1^{+/+}$ mice. No differences were found in Smad2 phosphorylation between obstructed kidneys from $ALK1^{+/+}$ and $ALK1^{+/-}$ mice. Tubulointerstitial fibrosis is higher in obstructed kidneys from $ALK1^{+/-}$ mice.

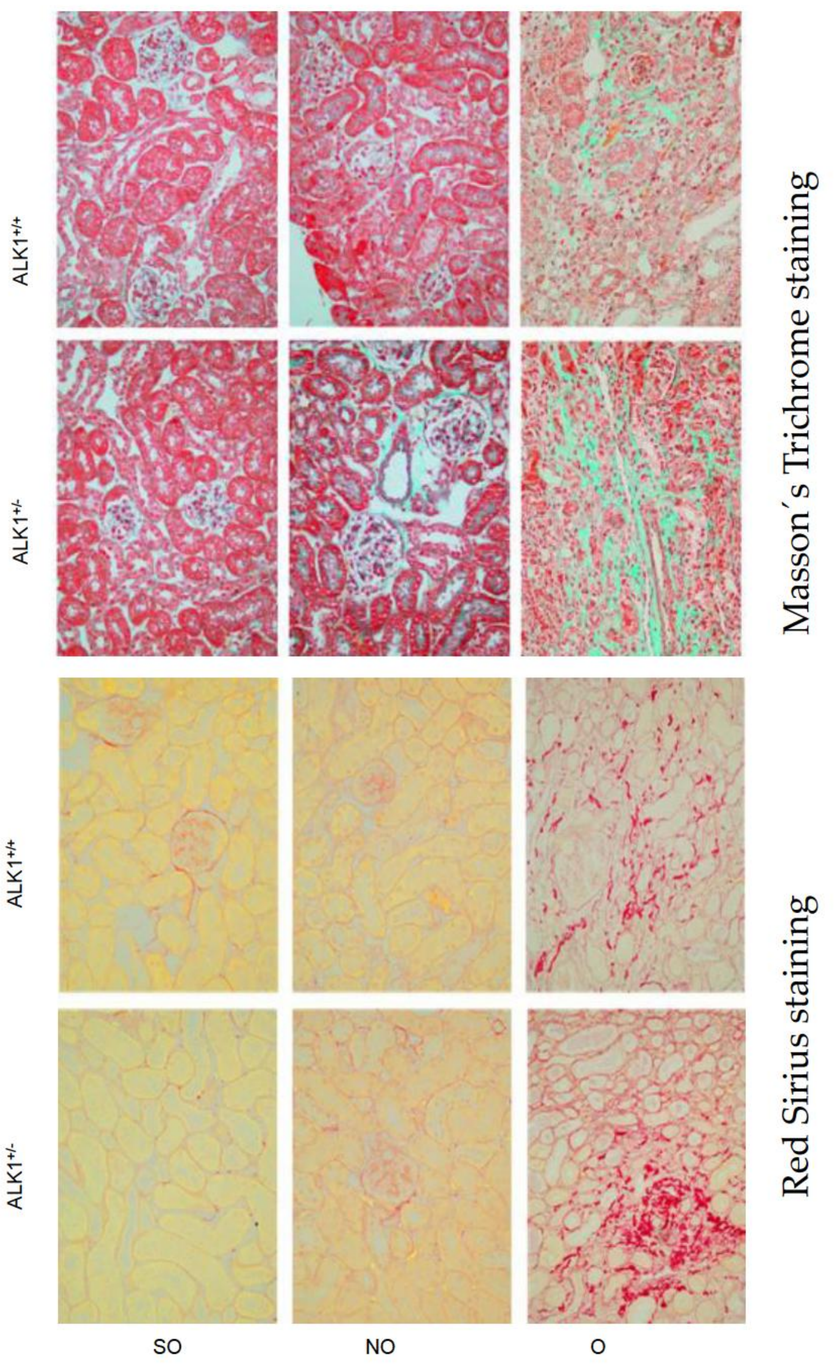
CONCLUSIONS

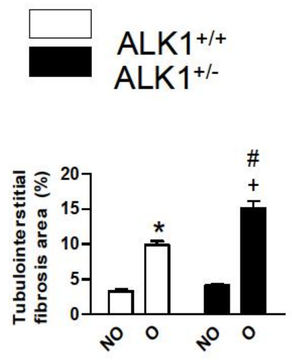
ALK1 heterozygous disruption promotes TGF-β/Smad signaling leading to increased renal fibrosis after 15 days of ureteral obstruction.



SO: Sham operated mice; NO: non obstructed kidneys; O: obstructed kidneys. *P<0.01 vs SO kidneys from *ALK1*$^{+/+}$ mice. #P<0.01 vs SO kidneys from *ALK1*$^{+/-}$ mice. +P<0.05 vs O kidneys from *ALK1*$^{+/+}$ mice.







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