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).

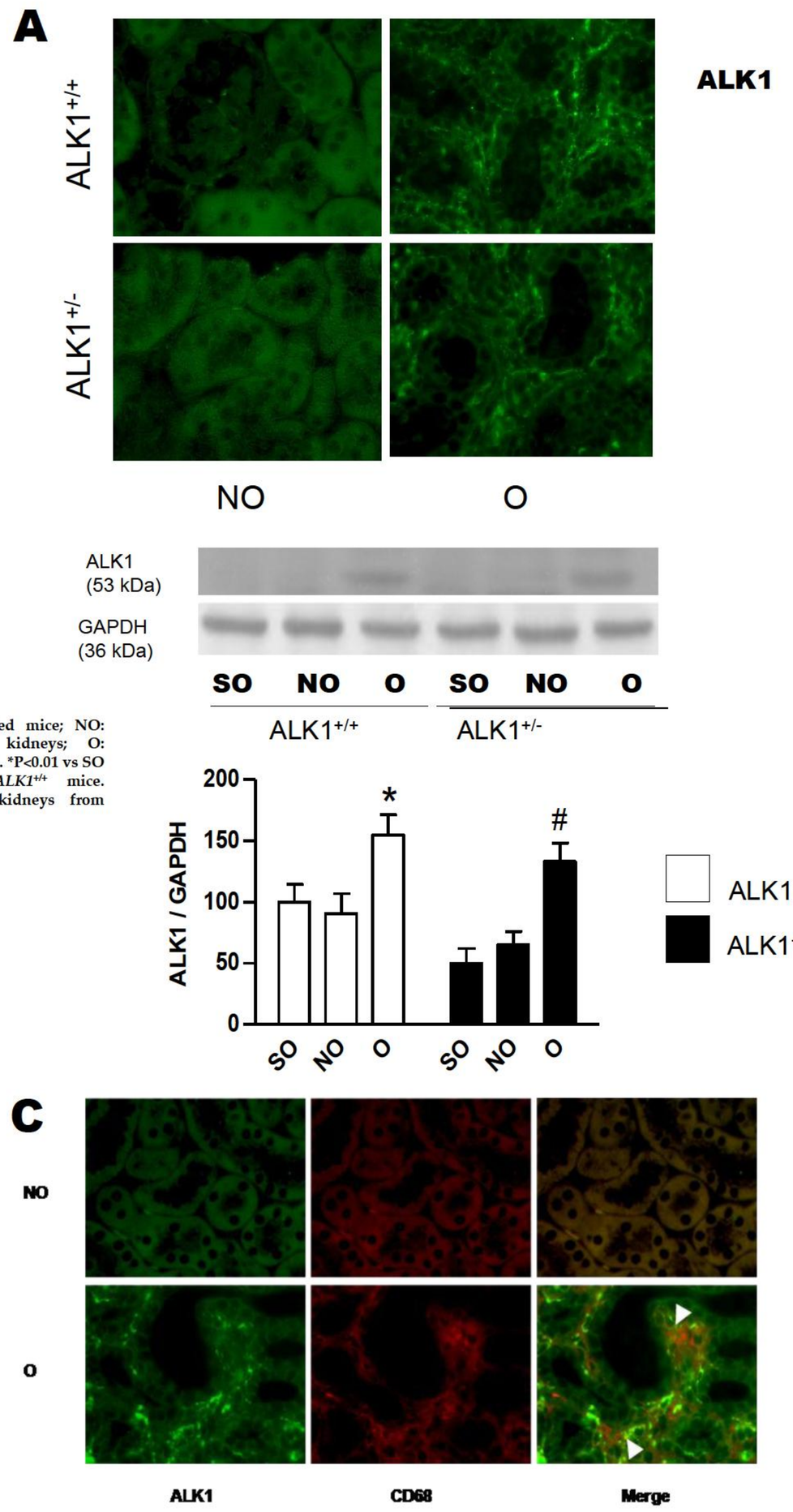
[3] Health Science Institute of Castilla y León (IECSCYL), Research Unit, University Hospital of Salamanca, Salamanca, Spain.

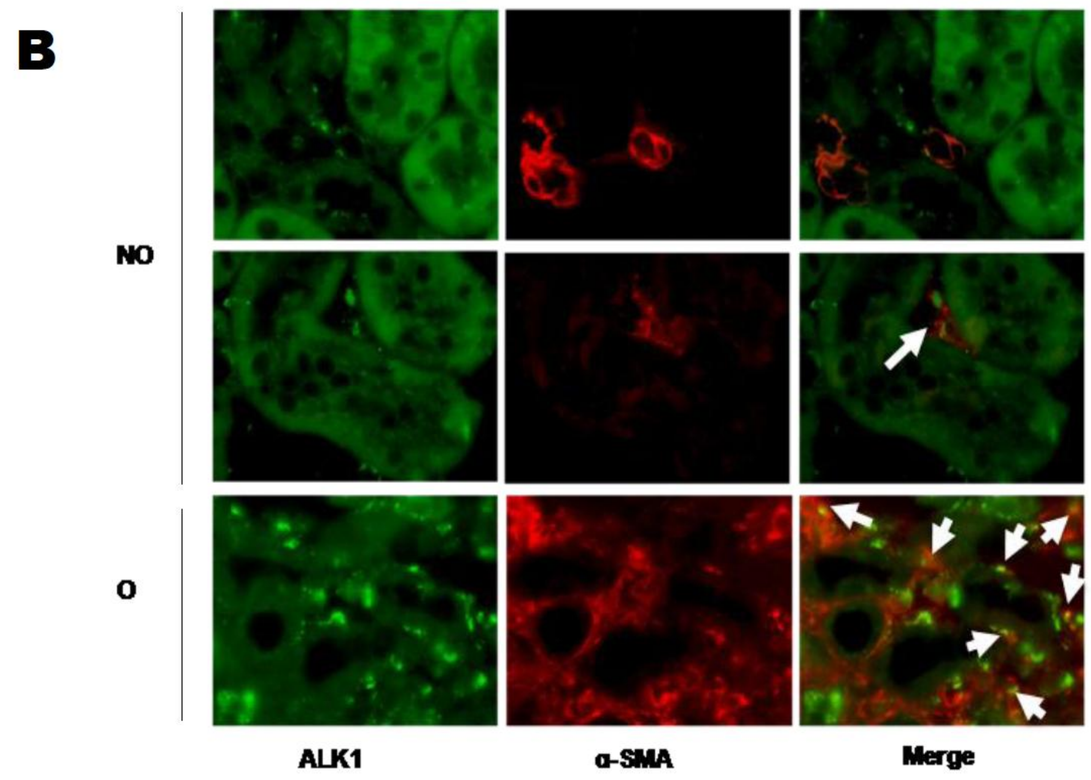
UP-REGULATION OF ALK1 IN MOUSE KIDNEY FOLLOWING URETERAL OBSTRUCTION

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

INTRODUCTION 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. Others receptors such as ALK5 and endoglin are overexpressed in experimental models of renal fibrosis. Nevertheless, the expression and the role of ALK1 in renal fibrosis is unknown.





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.

METHODS

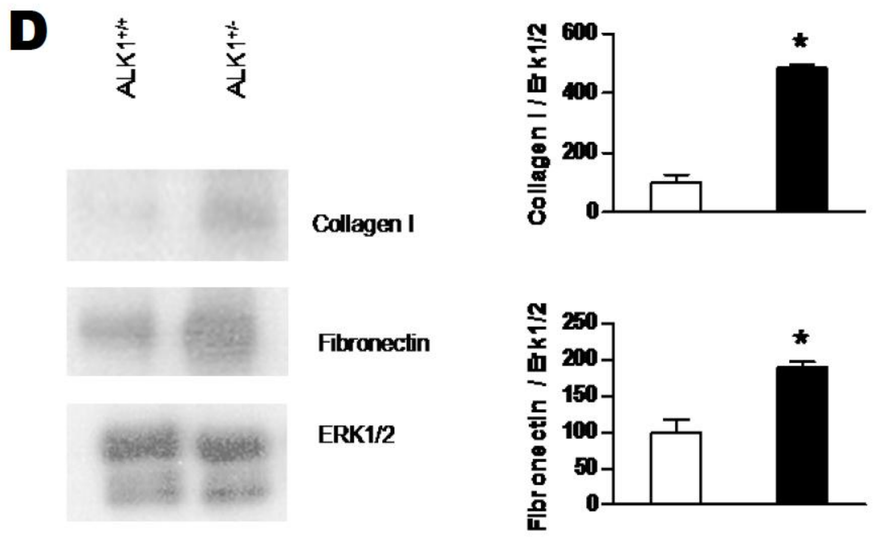
We performed unilateral ureteral obstruction (UUO), an experimental model of obstructive nephropathy in mice in order to analyze the expression of ALK1 following ureteral obstruction. We analyzed the expression of this receptor by western-blot and immunofluorescence. We have assessed the expression of ALK1 with other proteins such as α-SMA (myofibroblast marker) and CD68 (macrophage marker) in order to elucidate which cells expressed ALK1 after UUO.
On the other hand we have cultured renal fibroblasts from haploinsufficient (ALK1+/-) and control (ALK1+/+) mice in order to analyze the expression of ALK1 in these cells and the role of ALK1 in ECM protein expression. We analyzed ECM proteins such as collagen I and fibronectin, and the expression of ALK1 by Western-blot.

RESULTS

There was an increase in ALK1 expression following UUO. In non obstructed kidneys, the expression of ALK1 is restricted to some interstitial fibroblasts and smooth muscle cells of small blood vessels (A).
In obstructed kidneys, the expression of ALK1 was mainly located in the tubulointerstitial área. Double immunostaining with ALK1/α-SMA (B) and ALK1/CD68 (C) showed that ALK1 is expressed in myofibroblasts and infiltrated macrophages .
Cultured renal fibroblasts express the ALK1 receptor. Moreover, ALK1 heterozygous renal fibroblasts express more collagen I and fibronectin (D), suggesting that ALK1 negatively regulates ECM protein expression.

CONCLUSION

ALK1 upregulation following UUO may be considered as a protective mechanism against renal fibrosis due to its ability to downregulate ECM protein expression.



*P<0.01 vs *ALK1*$^{+/+}$ renal fibroblasts .

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Experimental models of CKD
Jose M Lopez-Novoa
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