THE BET BROMODOMAIN INHIBITOR JQ1 DIMINISHED RENAL FIBROSIS

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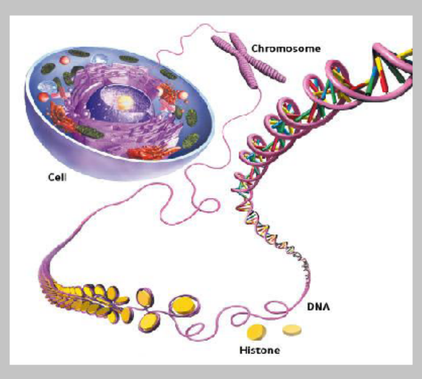
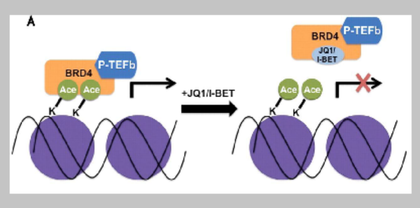
INTRODUCTION

Epigenetic mechanisms, especially DNA methylation and histone modifications, are dynamic processes and mediate the diversified gene expression profiles in normal and diseased states. Oxidative stress, proinflammatory cytokines and uremic toxins might induce epigenetic modifications involved in alterations of immune response, fibrosis and cardiovascular disease in renal patients. The bromodomain and extraterminal (BET) protein family (BRD2, BRD3, BRD4 and BRDT) participate in tumor development, infections, autoimmunity and inflammation. Bromodomains in BET proteins bind to acetylated lysine residues on histones and other nuclear proteins to regulate the transcriptional program. Selective bromodomain inhibitors block the interaction between bromodomain and extraterminal domain (BET) proteins and acetylated proteins. BET inhibitors, such as JQ1, have demonstrated beneficial effects on cancer and in murine pulmonary fibrosis, by modulating proliferation and matrix production, but there is no data in renal diseases.

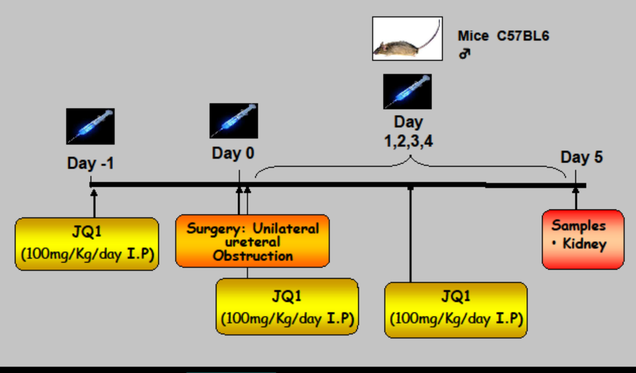




METHODS

The effect of JQ1 in vivo was studied in a model of renal damage in C57BL6 mice. The model of unilateral ureteral obstruction (UUO) consist on the ligation of the left ureter, and its cut to prevent urinary tract infections. Mice were treated with the BET bromodomain inhibitor JQ1 at the dose of 100mg/kg/day, i.p. starting 24 hours before of surgery. In vitro studies were done in mesangial cells and renal fibroblasts stimulated with the profibrotic cytokine TGF-β in the presence of JQ1 or its inactive stereoisomer.

UNILATERAL URETERAL OBSTRUCTION MODEL



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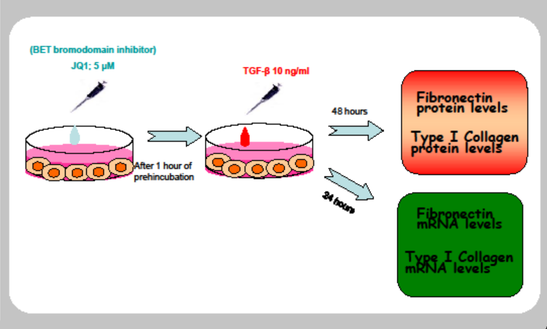
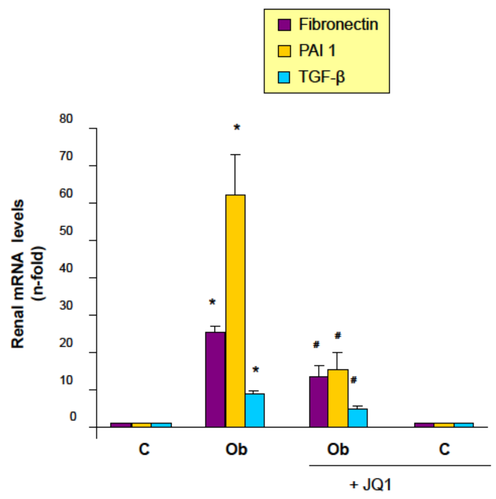


AIM

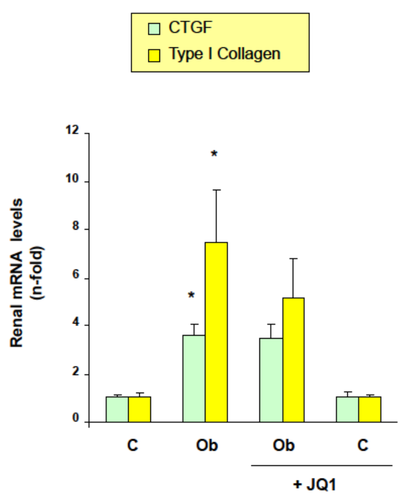
To investigate whether BET inhibition could modulate experimental renal fibrosis.

RESULTS

JQ1 inhibits the renal fibrotic response in the unilateral ureteral obstruction model (UUO).



* p< 0,05 vs Contralateral
\# p < 0,05 vs Obtructed



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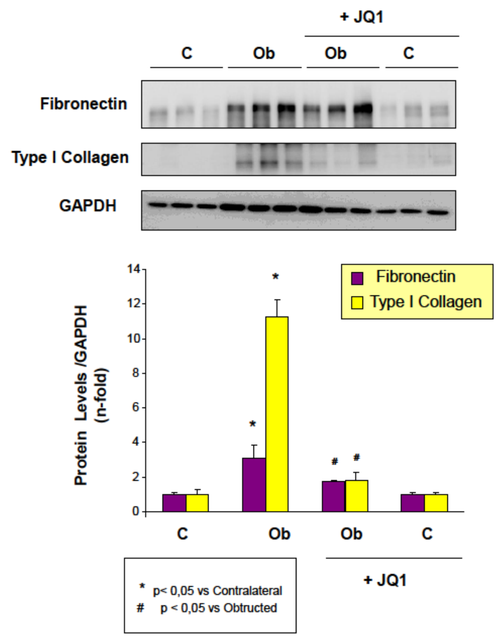

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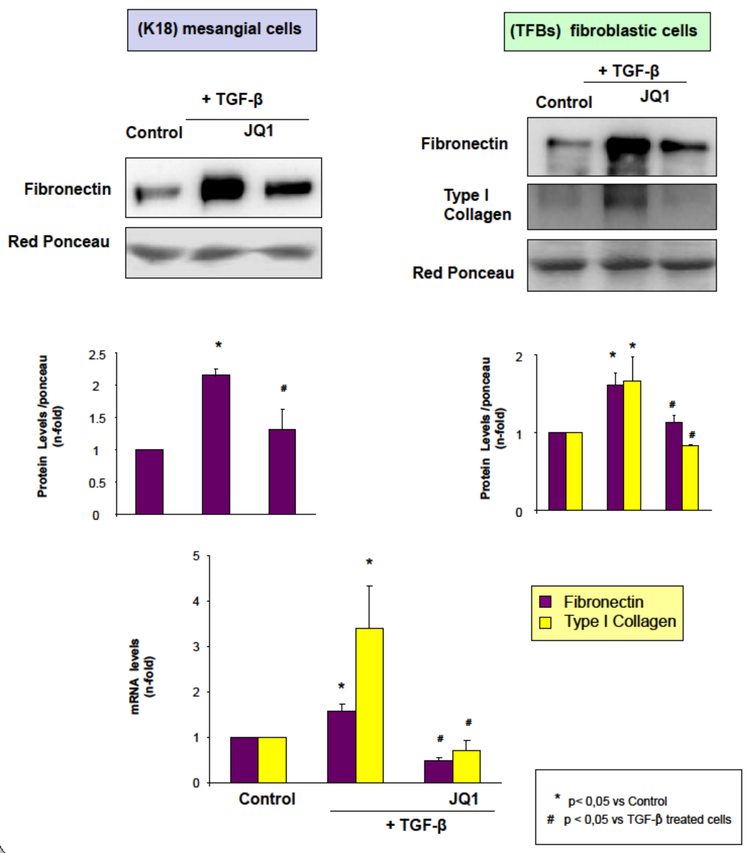
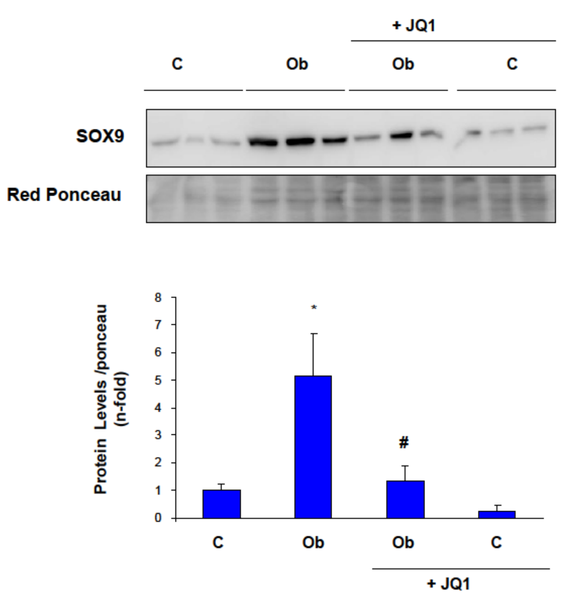
JQ1 inhibits overexpression of extracellular matrix proteins response induced by TGF-β in fibroblasts and mesangial cells.



* p< 0,05 vs Control
\# p < 0,05 vs TGF-β treated cells

JQ1 inhibits SOX9 nuclear traslocation in the kidney of UUO mice.



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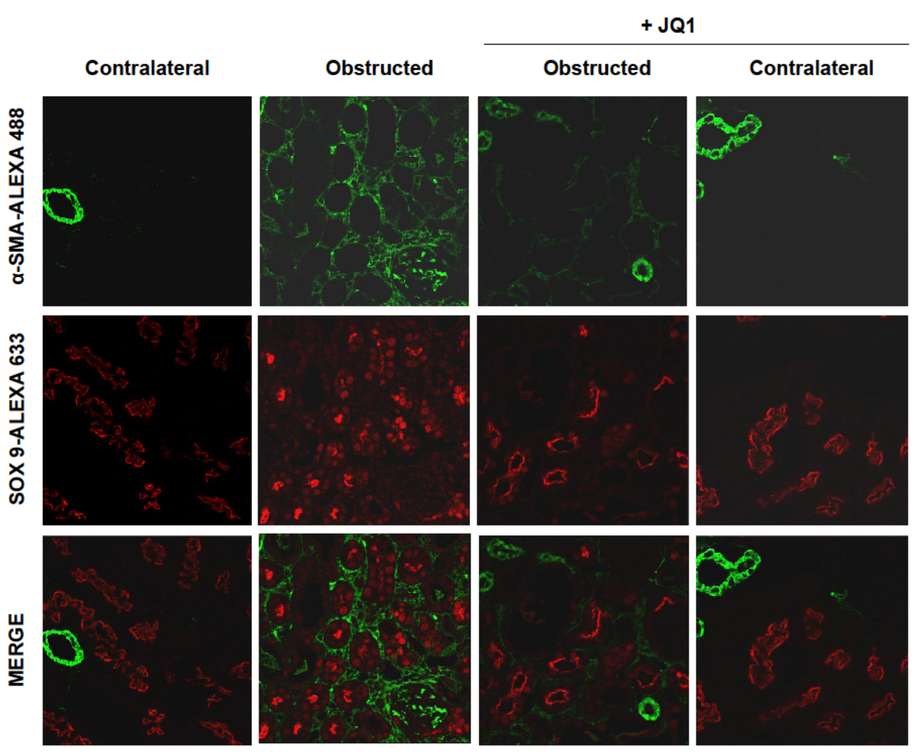
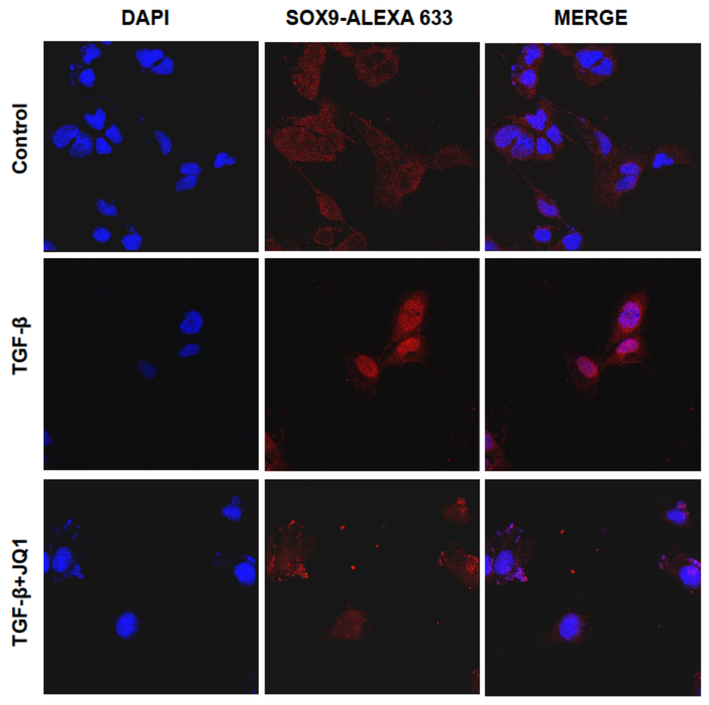
JQ1 inhibits SOX9 nuclear translocation and reduces fibrotic markers in the kidney of UUO mice.



JQ1 inhibits SOX9 nuclear traslocation in mesangial cells.



CONCLUSION

Our results demonstrate that the BET inhibitor JQ1 regulates profibrotic and matrix-related components and reduces experimental renal fibrosis. These results suggest that BET inhibitors could have important therapeutic applications in chronic kidney diseases.

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53 ERA
Renal pathology. Experimental and clinical.
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