BET BROMODOMAIN INHIBITION AMELIORATES EXPERIMENTAL INFLAMMATION IN THE KIDNEY

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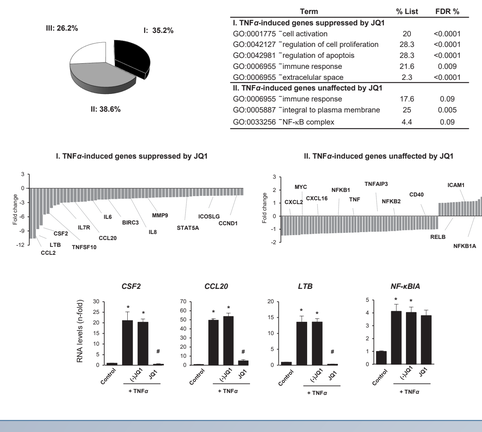
INTRODUCTION: Selective bromodomain inhibitors block the interaction between bromodomain and extraterminal domain (BET) proteins and acetylated proteins. These inhibitors have beneficial effects on malignancy and experimental inflammation in mouse models, but information about renal diseases is scarce. Our aim was to investigate whether BET inhibition could modulate renal inflammation.

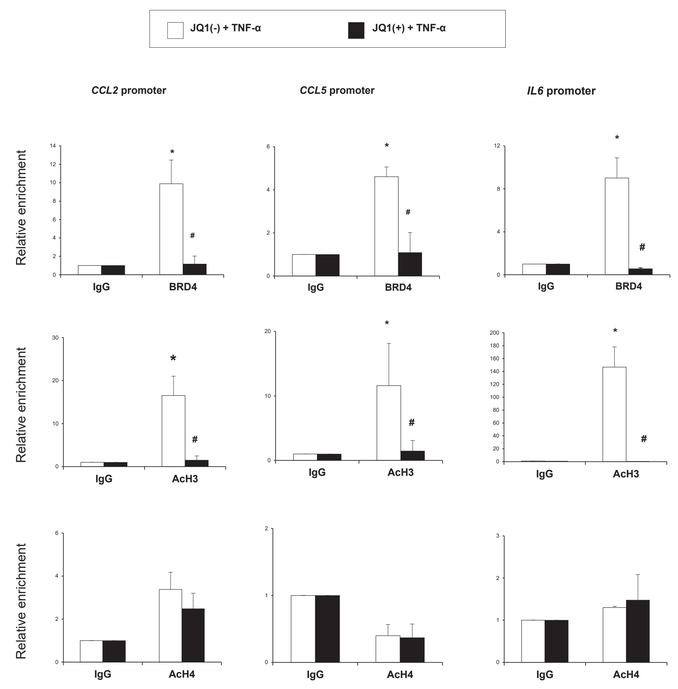
METHODS: In vitro studies were done in human renal proximal tubular epithelial cells (HK2 cell line), stimulated with the proinflammatory cytokine TNF-α in the presence of the BET bromodomain inhibitor JQ1 or its inactive stereoisomer. For in vivo studies, we used several models like the model of unilateral ureteral obstruction (UUO), Angiotensin II infusion model and Glomerular Basement Membrane model (GBM), and mice were treated with JQ1 (100 mg/ mouse/day, starting 1 day before UUO; n=6-8 mice per group).

JQ1 downregulates proinflammatory gene expression in cultured renal cells.

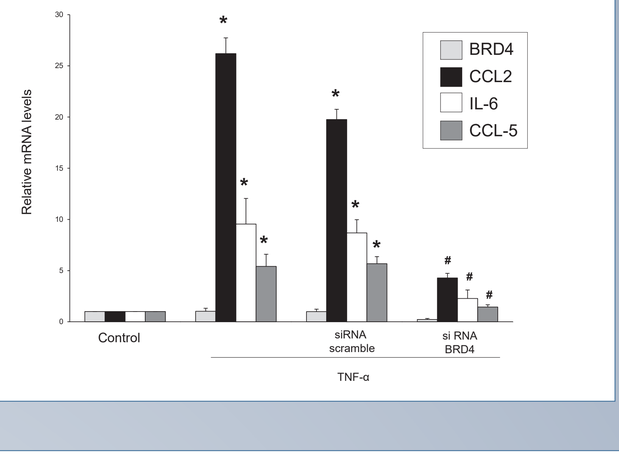


Term	% List	FDR %
I. TNFα-induced genes suppressed by JQ1		
GO:0001775 ~cell activation	20	<0.0001
GO:0042127 ~regulation of cell proliferation	28.3	<0.0001
GO:0042981 ~regulation of apoptois	28.3	<0.0001
GO:0006955 ~immune response	21.6	0.009
GO:0006955 ~extracelular space	2.3	<0.0001
II. TNFα-induced genes unaffected by JQ1		
GO:0006955 ~immune response	17.6	0.09
GO:0005887 ~integral to plasma membrane	25	0.005
GO:0033256 ~NF-κB complex	4.4	0.09

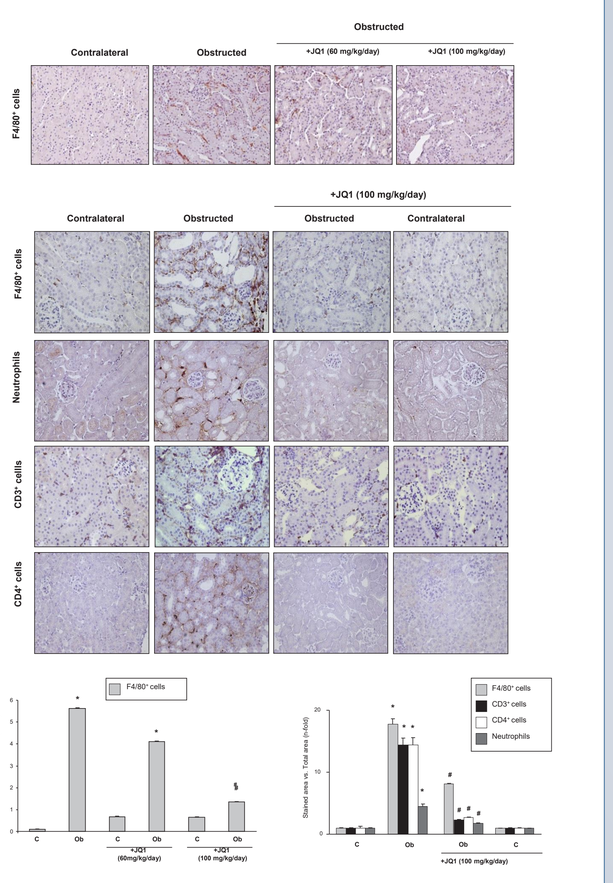
JQ1 inhibits the direct binding of BRD4 at the CCL-2, CCL-5 and IL-6 promoters through histone acetylation in renal tubular epithelial cells.



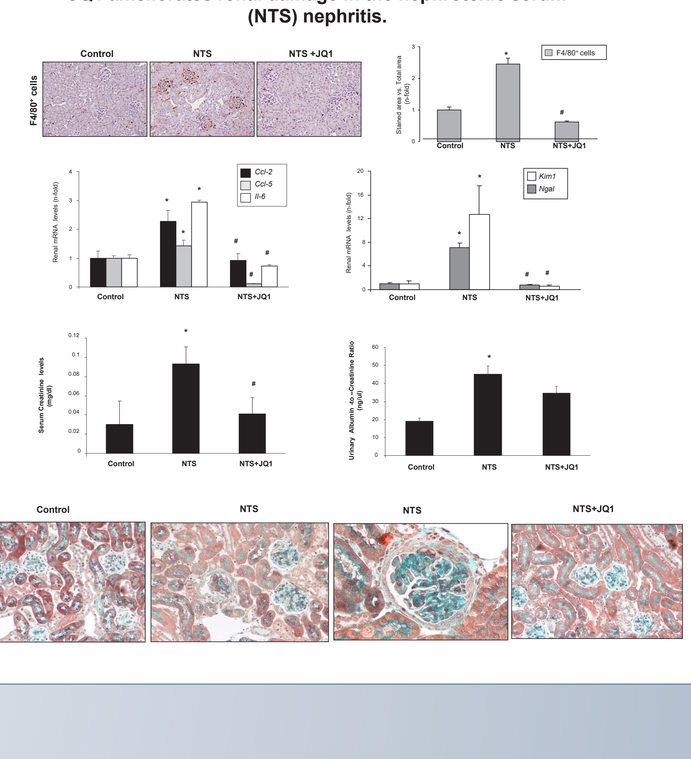
BRD4 disruption inhibits TNF-α-induced upregulation of proinflammatory genes in renal tubular epithelial cells.



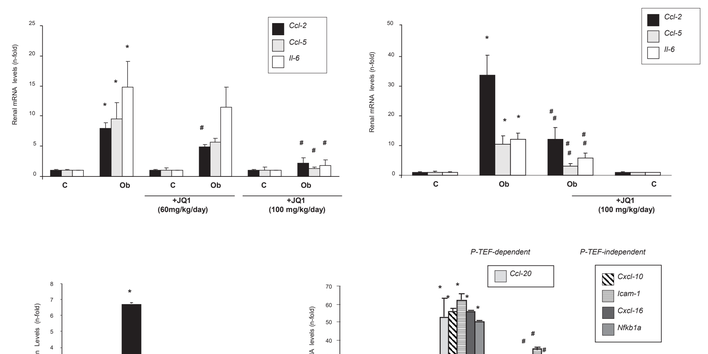
JQ1 reduces renal inflammation in the experimental models of unilateral ureteral obstruction.



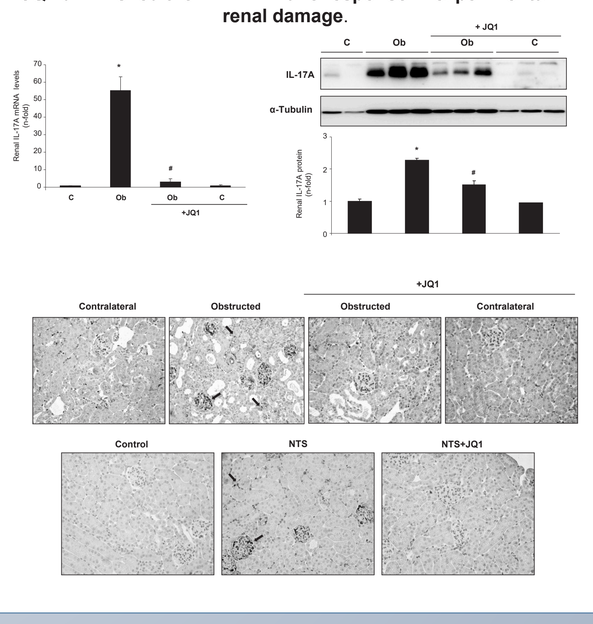
JQ1 ameliorates renal damage in the nephrotoxic serum (NTS) nephritis.



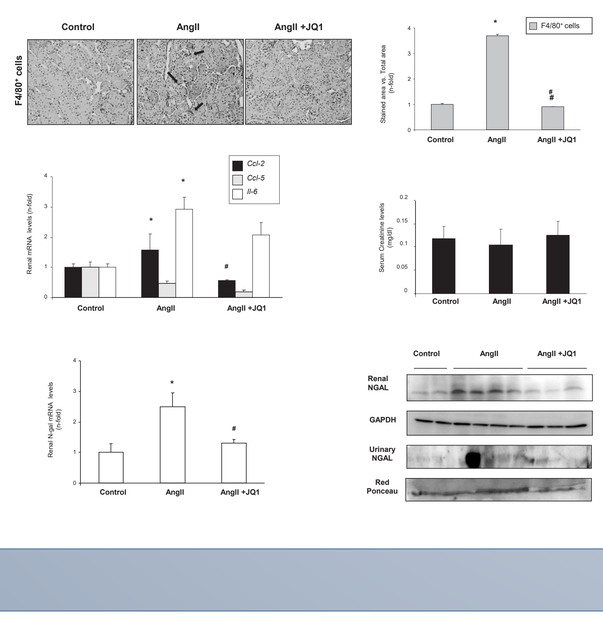
JQ1 attenuates gene expression of proinflammatory factors in obstructed kidneys.



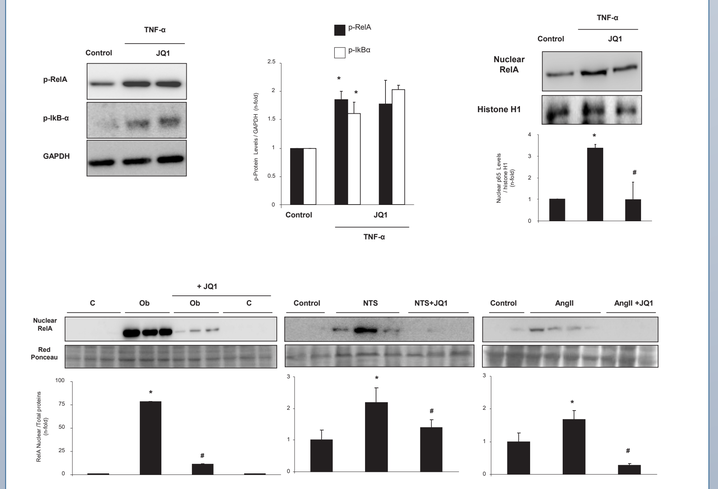
JQ1 diminished the Th17 immune response in experimental renal damage.



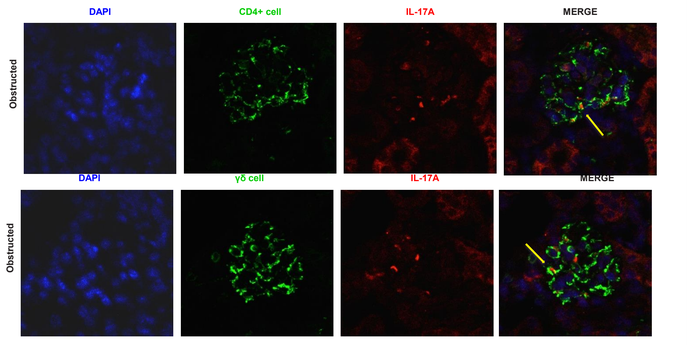
JQ1 ameliorates renal damage in the Angiotensin II infusion model



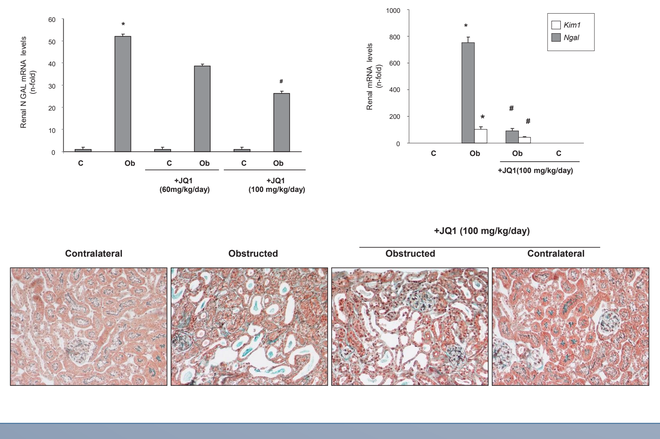
JQ1 inhibits NF-κB pathway activation in renal cells and murine damaged kidney.



JQ1 diminished the Th17 immune response in experimental renal damage



JQ1 reduces renal damage in experimental models of unilateral ureteral obstruction.



CONCLUSIONS: Our results demonstrate that BET inhibition reduces renal inflammation by three mechanisms: 1) chromatin remodelling in promoter regions of specific genes, 2) blocking of NF-κB pathway activation, and 3) modulation of the Th17 immune response. These results suggest that BET inhibitors could have important therapeutic applications in inflammatory renal diseases

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