Albumin-induced apoptosis of tubular cells is modulated by BASP1

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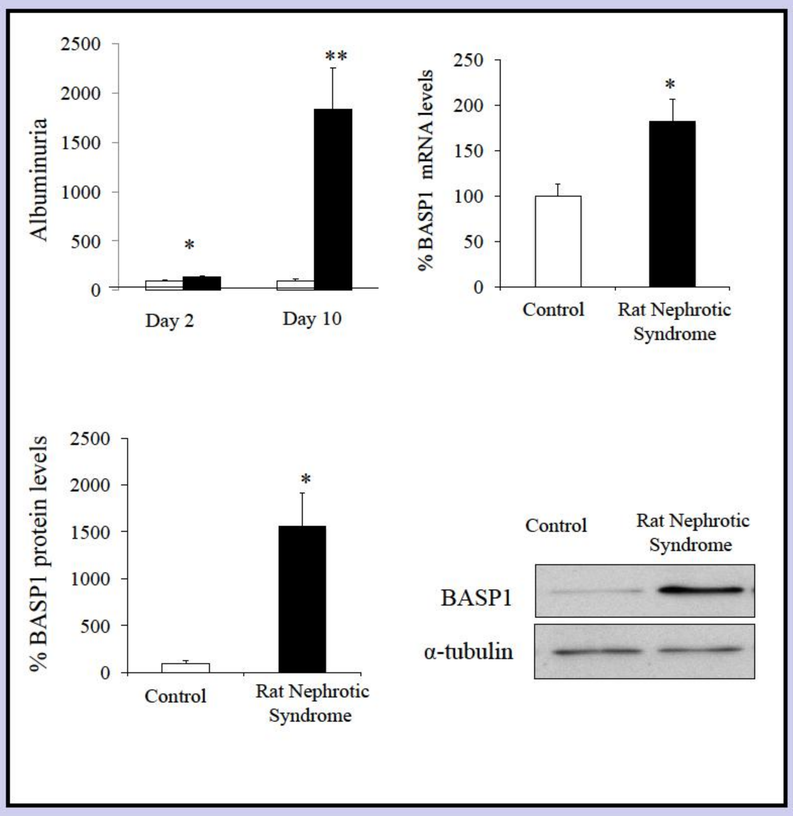
Background and Aims

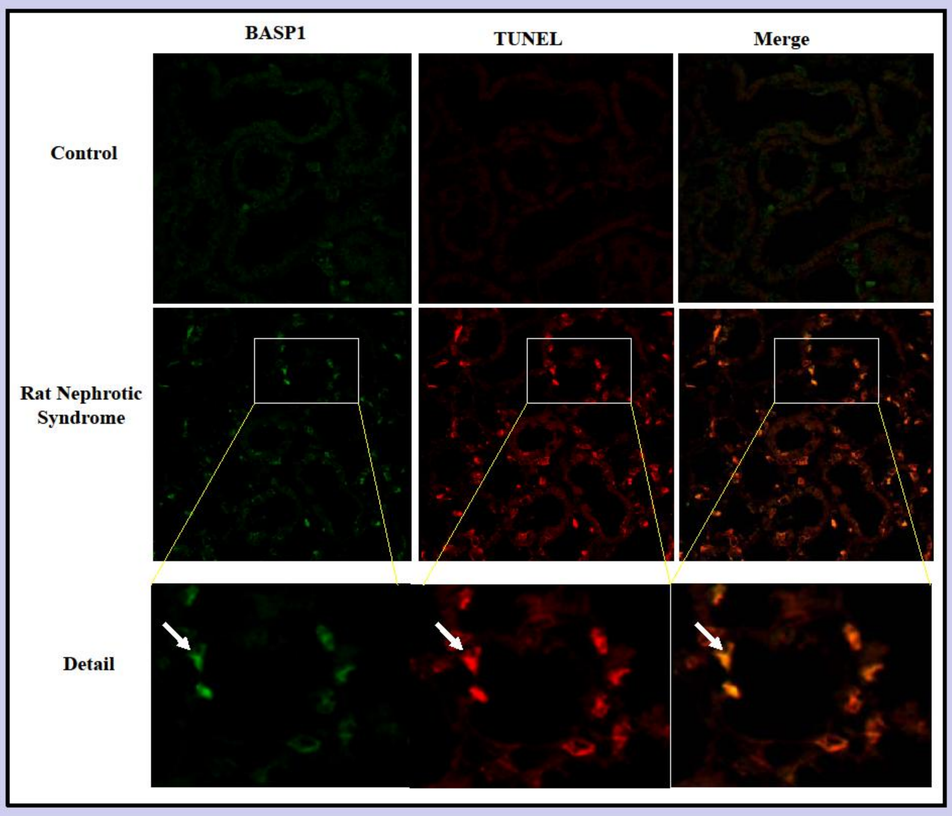
Albuminuria promotes tubular injury and cell death and is associated with faster progression of chronic kidney disease (CKD) to end-stage renal disease. However, the molecular mechanisms regulating tubular cell death in response to albuminuria are not fully understood. Brain abundant signal protein 1 (BASP1) was recently shown to mediate glucose-induced apoptosis in tubular cells.

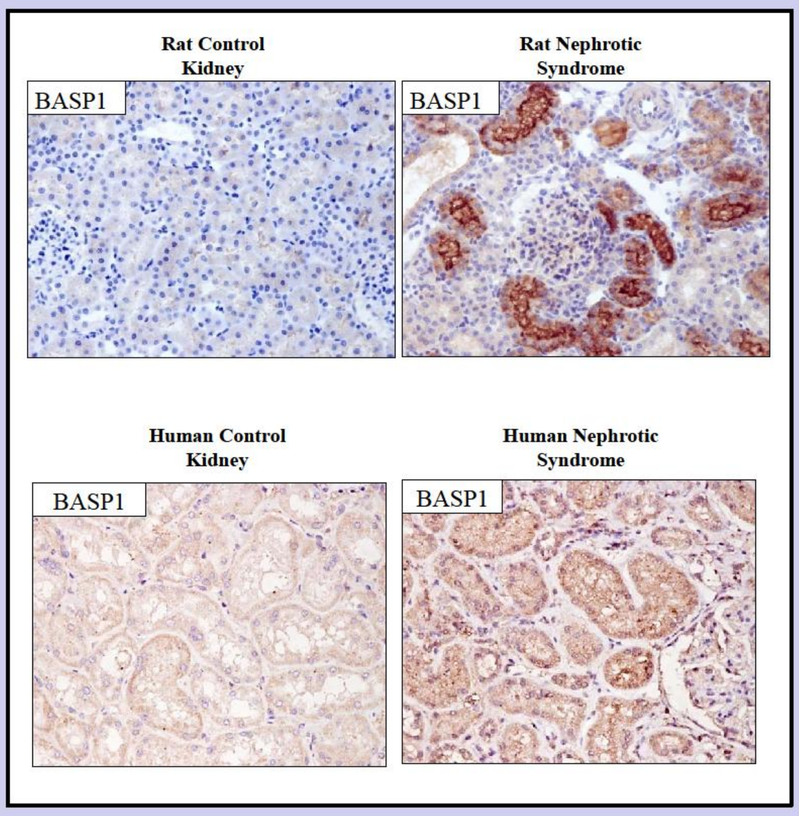
AIM: To study the role of BASP1 in albumin-induced tubular cell death

Methods and Results

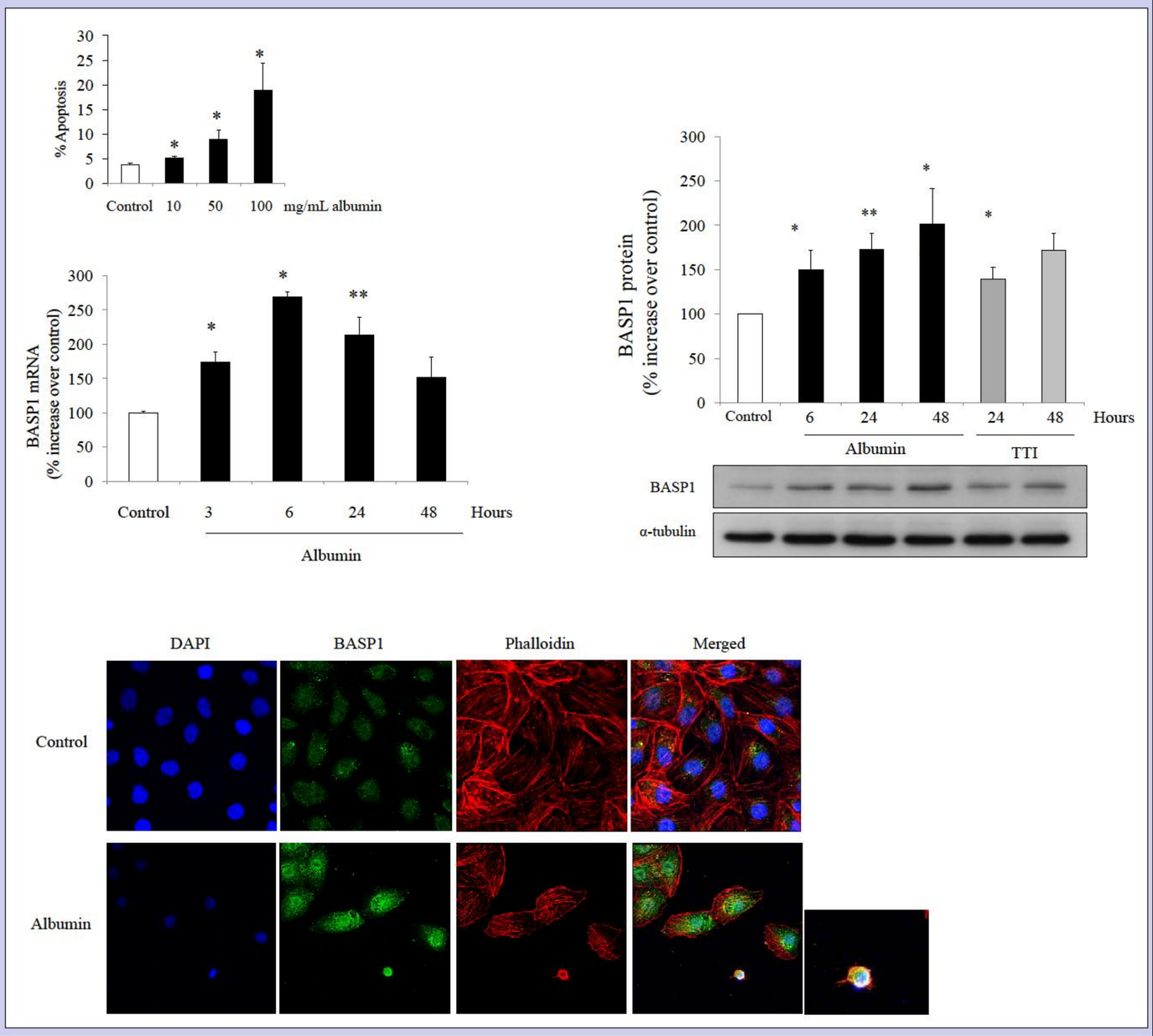
PAN induces nephrotic syndrome and BASP1 expression in the rat kidney and in human proteinuric nephropathy. Systemic PAN administration causes podocyte injury in rats leading to an increased urinary protein excretion at day 2 and severe albuminuria at day 10. Increased whole kidney BASP1 mRNA and protein expression was noted 10 days post-PAN injection. BASP1 protein was localized to tubular epithelial cells by immunohistochemistry. Furthermore, tubular cell BASP1 expression colocalized with TUNEL positive cells, indicating expression of BASP1 by tubular cells undergoing apoptosis. In human proteinuric nephropathy immunohistochemistry identified BASP1 positive tubular cells while minimal BASP1 staining was observed in tubules from control kidney samples



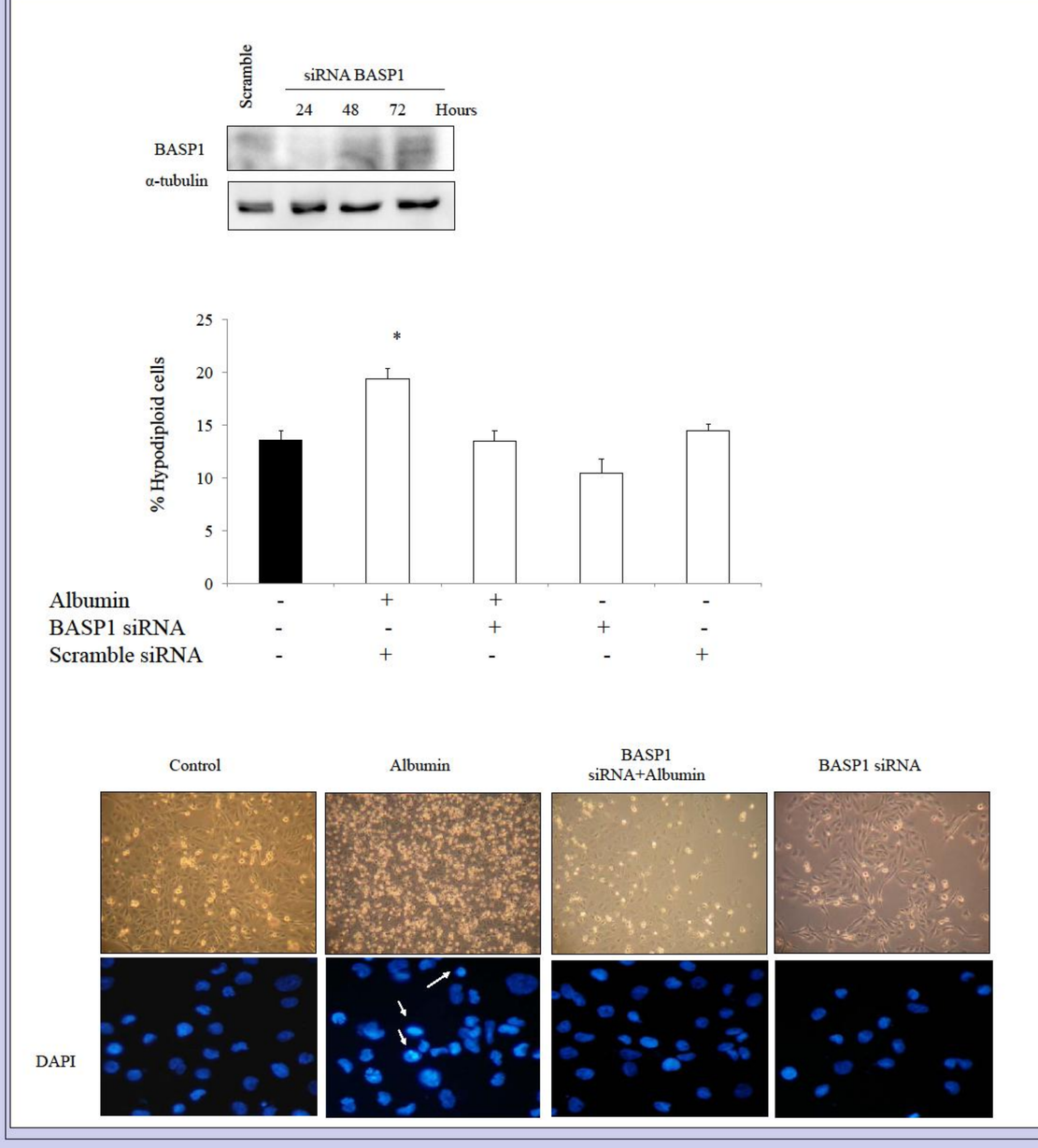




Albumin induces a time-dependent increase in BASP1 mRNA and protein expression in tubular cells. Flow cytometry of DNA content showed that abumin increased the number of apoptotic proximal tubular cells. At concentrations that promoted tubular cell apoptosis, albumin increased BASP1 mRNA and protein expression in a time-dependent manner. Confocal microscopy localized the increased BASP1 expression in albumin-treated cells mainly to the perinuclear area, where it colocalized with actin .



Inhibition of BASP1 expression protects against albumin-induced apoptosis. BASP1 targeting protected from albumin-induced apoptosis quantified by flow cytometry of cell DNA content. Morphological studies disclosed the presence of pyknotic nuclei characteristic of apoptosis among cells exposed to albumin and protection of albumin-exposed cells from apoptosis by BASP1 siRNA



Conclusions

The data presented in this study show that exposure to albumin, as may occur in vivo in proteinuric nephropathies, increases BASP1 expression and promotes BASP1-dependent tubular cell apoptosis. This information may be used to design novel therapeutic approaches that slow CKD progression by protecting tubular cells from the adverse consequences of albuminuria in patients not fully responding to current anti-proteinuric agents. These novel approaches may include interfering with BASP1 function in tubular epithelium by using specific siRNAs.

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L) Renal pathology. L1) Experimental pathology.
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