NERVE GROWTH FACTOR EXPOSURE PROMOTES TUBULAR EPITHELIAL-MESENCHYMAL-TRANSITION *via* TGFβ1 SIGNALING ACTIVATION

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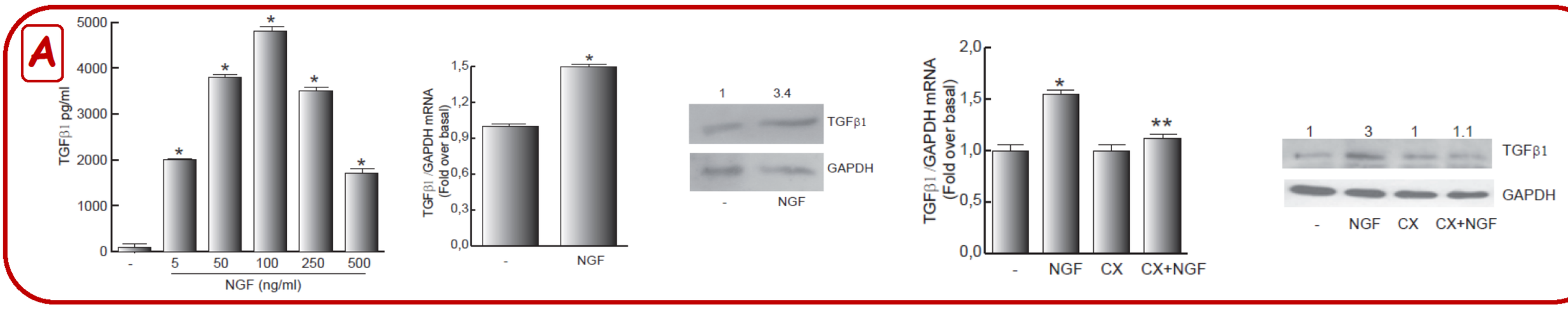
BACKGROUND AND AIM

The Nerve Growth Factor (NGF) is a neurotrophin that plays a critical role in development, survival and function of cells localized within and outside the peripheral and central nervous system, through the activation of two receptor types: the pro-survival tropomyosin-related kinase-A receptor, TrKA, and the death receptor p75NTR. Recent clinical studies showed that renal expression and serum levels of NGF are increased in some progressive renal diseases histologically characterized by glomeruli and tubule-interstitium fibrosis, a pathologic processes in which the cytokine TGFβ-1 mediates all key events leading to the tubular epithelial-mesenchymal transition (EMT). However the consequences that high NGF levels produce in chronic kidney diseases have not yet been elucidated. Therefore, in this study we investigated the effects that the exogenous administration of NGF exert in tubular epithelial cells, HK-2.

MATERIALS AND METHODS

Immortalized human proximal tubular renal cells, HK-2; enzyme-linked immuno-sorbent assay (ELISA), Real-time RT-PCR assay, Western Blot Analysis, Immunoprecipitation studies, Wound-healing scratch assay, RNA interference (RNAi), Transient transfection assay, Statistical analysis.



RESULTS

We found that in HK-2 cells increasing doses of NGF up-regulated TGFβ1 secretion and expression levels in a transcriptional dependent-manner (A) via both its receptors $p75^{NTR}$ and TrKA (B). We observed that NGF promoted the up-regulation of EMT markers via TGFβ1 that was prevented when TGFβ1 knocked-down gene occurred (C). Moreover, ourr results evidenced that NGF exposure activated TGFβ-1/SMAD signaling rather than non-canonical pathway (D). Finally, we demonstrated that SMAD pathway activation dependent by TGFβ1, as it was strongly mitigated when TGFβ1 knocked-down gene occurred (E upper panel) and that NGF induced TGFβ-1/SMAD signaling since the pretreatment with an antibody anti-NGF mitigated the nuclear translocation of pSMAD3/SMAD4 functional complex (E lower panel).

CONCLUSIONS

Our results highlight for the first time that NGF promoted renal fibrosis via TGFβ-1, suggesting that increased NGF serum and tissue expression could represent a precocious marker of renal fibrosis.

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