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Matsuura S, Tadachi K, Shimoda N, Tsuchiya N, Sato K, Ohyama C, Kato T
Department of Urology, Akita University School of Medicine

BLADDER FIBROSIS ASSOCIATED WITH THE INTERACTION BETWEEN HEPATOCYTE GROWTH FACTOR (HGF) AND TRANSFORMING GROWTH FACTOR-B (TGF-β) IN URETHRAL-LIGATED RATS

Aims of Study

Hepatocyte growth factor (HGF), a ligand for the c-Met receptor tyrosine kinase, is known to have a critical role in tissue protection and repair (Nakamura-T et al., Nature 342: 440-443, 1989). In chronically damaged organs, HGF decreases in a manner reciprocal to the increase in expression of transforming growth factor-β (TGF-β), a key player in tissue fibrosis. Decrease in endogenous HGF and increase in TGF-β augment the susceptibility to the onset of organ fibrosis and dysfunction. On the other hand, it has been reported that exogenous HGF supplement activates “simple duplication system” and enhances regeneration and remodelling of tissue fibrosis. These facts indicate the therapeutic efficiency of HGF on various disorders induced by fibrosis (e.g. liver cirrhosis, chronic allograft nephropathy) (Azuma-H et al. J Am Soc Nephrol. 12: 1280-1292, 2001; Ueki-T et al., Nature Med. 5(2): 226-30, 1999). Clinically, HGF therapy could be an alternative for patients with severe “low compliance bladder” who have no choice except bladder augmentation surgery. To make a first step, the present study was designed to clarify whether HGF and TGF-β interact each in injured mammal bladder.

Methods

Female S-D rats, weighing 200-250 g, were used (n=24). The urethra was completely ligated to produce a bladder over-distension, and the animals were harvested 6, 12, 18 and 24 hours after the surgery. Sham-operated rats were used as controls. HGF, TGF-β1 and c-Met expression in the bladder was quantified by enzyme-linked immuno-sorbent assays (rat HGF-ELISA kit, Institute of Immunology, Tokyo, Japan; TGF-β1 ELISA kit, R&D Systems, MN, USA) and western blot analysis (rat c-Met antibody: Santa Cruz, CA, USA), respectively.

Results

A slight decline of HGF expression was observed within 24 hours after the surgery, compared to bladder HGF level in controls (285.4±21.4 ng/mg protein, mean±SD). Level of bladder TGF-β1, however, markedly increased at 6 hours (14.9±3.5 ng/mg: little detection in controls) and was sustained until 24 hours (7.1±5.0 ng/mg). In contrast, the level of c-Met expression decreased and almost vanished at 24 hours.

Conclusions

Although this is a study of acute phase, we confirmed that bladder injury induces a rapid increase of TGF-β1 and decrease of c-Met protein in this organ. Supplement of exogenous HGF increases the level of endogenous HGF and c-Met protein in the rat liver (Ueki-T et al., Nature Med. 5(2): 226-30, 1999). Therefore, we expect that HGF therapy (recombinant HGF administration or HGF gene transfection) may elicit “simple duplication system” also in the bladder, and could prevent or even improve the progression of bladder fibrosis.