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VESICAL FIBROSIS FOLLOWING CHRONIC BLADDER OUTLET OBSTRUCTION: POSSIBLE ROLE OF HEPATOCYTE GROWTH FACTOR AND TRANSFORMING GROWTH FACTOR-BETA 1 INTERACTION

Aims of Study

Hepatocyte Growth Factor (HGF), a ligand of the c-Met receptor tyrosine kinase, is considered a crucial factor for tissue protection or repair of variety of organ damages, e.g. liver cirrhosis, renal failure, and pulmonary fibrosis. In damaged organs, HGF decreases in a manner reciprocal to the increase in expression of transforming growth factor-beta 1 (TGF-beta 1), and it has been reported that administration of exogenous HGF can dramatically prompt the damaged tissue to be regenerated (Ueki T et al., Nature Med. 5(2): 226-30, 1999). Patients with severe low compliance bladder, that results in a fibrous change of the bladder, have no other than bladder augumentation surgery, but HGF therapy could be used as an alternative for these patients. We thus investingated whether the interaction between HGF and TGF-beta 1 takes part in the vesical fibrosis following bladder outlet obstruction (BOO) in the rats.

Methods

Female S-D rats, weighing 150-200 g, were used (n=128). Under the anesthesia, partial urethral ligation was placed to produce BOO. Sham-operated rats as controls. The urinary bladders were harvested on 1, 3, 5 days and at 1, 2, 4, 8, 12, 16, 20, 28 weeks postoperatively for biochemical analysis. HGF, TGF-beta 1 and c-Met expression in the bladder was quantified by enzyme-linked immunosorbent assays (Rat HGF ELISA kit, Institute of Immunology, Tokyo, Japan; TGF-beta 1 ELISA kit, R&D System, MN, USA) and western blotting (c-Met antibody: Santa Cruz, CA, USA), respectively. Mann-whitney U test was used for statistical analysis (P value less than 0.05 as significant).

Results

Bladder weight in BOO rats significantly increased after 4 week postoperatively, and a thickened connective tissue was histologically confirmed in BOO bladder. HGF and TGF-beta 1 expression in the BOO bladder peaked at 5 days (14.0 ng / bladder; approximately 4 times higher compared to shams) and at 1 day (1727.4 pg/ bladder; approximately 10 times to shams), respectively, and declined thereafter. No significant increase in HGF and TGF-beta 1 expression was observed after 12 week. On the other hand, c-Met expression decreased soon after the BOO onset, and almost vanished at 1 week. C-Met protein in the BOO bladder maintained such a low expression throughout the experiment.

Conclusions

Our findings suggest that HGF and TGF-beta 1 interaction is involved in the fibrous changes of the BOO bladder. The increased expression of TGF-beta 1 in the acute phase of BOO may trigger the fibrosis. On the other hand, the increase of endogenous HGF, partly derived from other organs, may be insufficient for tissue protection and repair, thus resulting in progression of the bladder fibrosis. Interestingly, although HGF and TGF-beta 1 expression settles down to the control level, fibrous changes of the bladder advance. This could be so because expression of c-Met, HGF receptor protein, maintained its lower level throughout the observation. This study suggests the possibility that exogenous HGF therapy, recombinant HGF administration or HGF gene transfection, may evoke c-Met expression and could generate tissue repair even in the fibrous bladder.