Dipeptidyl Peptidase IV Inhibitor Teneligliptin Accelerates Recovery from Cisplatin-Induced AKI by Promoting the Proliferation of Proximal Tubular Epithelial Cells

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INTRODUCTION AND AIMS: Dipeptidyl peptidase-4 (DPP-4) inhibitors can have renoprotective effects in some acute kidney injury (AKI) models, but the mechanisms of action and their role in tubule recovery upon AKI remains speculative. We hypothesized that the DPP-4 inhibitor teneligliptin can accelerate tubular re-epithelialization after cisplatin-induced AKI by triggering cell cycle entry and completion of mitosis, i.e., proliferation of tubular epithelial cells.

METHODS: Isolated primary tubular cells were screened with a drug library to identify potential candidates to accelerate proliferation by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Proliferation of tubular cells was evaluated with cell cycle analysis and cell counting by flow cytometry. AKI was induced in rats by injecting 5mg/kg of cisplatin intravenously. Oral administration of 10mg/kg of teneligliptin once a day, was started just before injecting cisplatin or from day 5 after cisplatin injection.

RESULTS: In vitro, teneligliptin and its optimal dose were selected based on the MTT screening assay (Fig.1). Teneligliptin promoted cell cycle entry into S/G2/M phase in primary tubular cells (Fig.2), which increased cell number (Fig.3). In vivo, the levels of serum creatinine (sCr)/blood urea nitrogen (BUN) and cell death evaluated with the terminal uridine nick-end labeling (TUNEL)+ cells peaked at day 5 after cisplatin injection. The levels decreased at day 10, comparing to that of day 5; however, the increased levels sustained until day 14. Pretreatment of teneligliptin prevented the elevation of sCr/BUN level and decreased TUNEL+ cells at day 5. Post treatment of teneligliptin from day 5 decreased BUN level (Fig.4), kidney injury molecule-1 (kim-1) expression (Fig.5) and collagen deposition (Fig.6) at day 14.
CONCLUSIONS: The DPP-4 inhibitor teneligliptin accelerates recovery after toxic AKI by facilitating the proliferation of tubular cells.