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Tonsil-derived Mesenchymal Stem Cells preserve Renal Function and Fibrosis in Gentamicin-induced Acute Kidney Injury (AKI) by Alleviating Oxidative Stress and Apoptosis

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Objectives : The therapeutic effect of mesenchymal stem cells (MSCs) in repairing damaged renal cells in AKI has been demonstrated. Tonsil-derived MSCs (T-MSCs) derived from tonsillar tissues are reported to be effective in acute liver injury. The aim of this study is to investigate the therapeutic potential of T-MSCs in gentamicin-induced AKI.
Methods : Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, intraperitoneal injection for 10 days for 10 days), GM+T-MSCs ($1x10^7$ cells, intravenous injection at 1 day after the 1st GM injection), and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H_2O_2 generation, NOX mRNA expressions with DCF-DA staining.
Results : The infusion of T-MSCs in animal model of GM-induced AKI preserved renal function with a decrease in proteinuria and tubulointerstitial fibrosis. T-MSCs injection decreased apoptotic cells and the expression of Bax, cytochrome C, and cleaved caspase and increased Bcl-2. T-MSCs suppressed oxidative stress as reflected by a decrease in the level of urinary 8-OHdG with an increase in antioxidant enzymes (glutathione peroxidase and catalase) in the renal tissue. Anti-human nuclei and PHK-26 staining demonstrated the localization of T-MSCs in the tubules of renal cortex. In-vitro study revealed that T-MSC or T-MSC-conditioned media ameliorated GM-induced NOX-1 expression, H_2O_2 generation, and apoptosis of NRK cells.
Conclusions : T-MSCs ameliorate GM-induced AKI, which is mediated by direct engraftment into the damaged renal tubules and paracrine effects of T-MSCs, exerting anti-apoptotic and anti-oxidative effects.