Adenovirus-mediated expression of the NF-E2-related factor 2 (Nrf2) protein within the MSCs alleviated cisplatin-induced acute kidney injury in rat

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Abstract

Background and objectives:
Poor MSCs survival after transplantation is one of the major challenges in their therapeutic application. Therefore, it is necessary to augment MSCs in order to improve the efficacy of cell therapy. In this study, we manipulated MSCs with a cytoprotective factor i.e Nrf2 and evaluate its efficiency flowing MSCs transplantation to cisplatin-induced acute kidney injury in a rat model.

Materials and methods:
Mesenchymal stem cells were isolated from bone marrow. Nrf2 was isolated and TOPO cloned into the pENTR vector. The recombinant vector was transferred into pAD/CMV/V5-DEST vector by gateway technology. Recombinant adenovirus was produced in AD293 cells, followed by infecting into MSCs. The Nrf2 engineered MSCs were exposed to hypoxic, serum deprived and oxidative stress conditions followed by evaluation of the cells viability and apoptosis. Finally, Nrf2-MSCs were transplanted to cisplatin-induced acute kidney injury in rats and their therapeutic efficacy was assayed by blood urea nitrogen, creatinine determination and morphologic analysis.

Results:
Nrf2 was successfully expressed in MSCs. Nrf2-MSCs retained their multi-differentiation capacity. Comparing to the controls, following exposure of the Nrf2 transduced cells to hypoxia, serum deprivation and oxidative stress conditions, cell viability was found to be higher, while their apoptosis rate was lower. Nrf2 alleviates cisplatin-induced acute kidney injury.

Conclusions:
Our findings are good demonstration of how an understanding of the cellular stress response can be leveraged for practical application. Enhanced anti-apoptotic and anti oxidative capabilities of MSCs following Nrf2 infection via adenoviral vectors, could be a graft cell death prevention strategy in transplantation and may emerge an alternative plan for stem cell therapy.

Key words:
Mesenchymal stem cells, Nrf2, Adenoviral Vector, Oxidative stress, Cisplatin, Kidney injury