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Tonsil-derived Mesenchymal Stem Cells ameliorate Peritoneal Fibrosis by Inhibiting Oxidative Stress

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Objectives : Mesenchymal stem cells (MSCs) have regenerative capability and exert paracrine actions on damaged tissues and have recently received a new attention due to its preventive effect on organ fibrosis by inhibiting epithelial-to-mesenchymal transition (EMT). The EMT of mesothelial cells (MCs) is an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). This study was undertaken to investigate the role of Tonsil-derived MSCs (T-MSCs) in TGF β -induced EMT of human peritoneal mesothelial cells (HPMCs) and its mechanism.

Methods : Transwell co-culture system was used in which MCs were cultured with T-MSCs or T-MSC-conditioned medium (T-MSC-CM). EMT was evaluated by the changes in morphology and markers of epithelial and mesenchymal cells. ROS generation was assessed by DCF-DA and MitoSox^R staining. Animal model of PD was established by daily infusion of 4.25% glucose-based dialysate with methylglyoxal for 3 weeks via intraperitoneal catheter in Sprague-Dawley rats. T-MSC (1.0×10^7 cells, i.p.) was injected at 14 days of catheter insertion, and peritoneal tissue was isolated in 7 days of T-MSC injection. Markers of oxidative stress, ER-stress, apoptosis, and NLRP3 inflammasome were evaluated with peritoneal equilibrium test (PET) and histologic analysis.

Results : Co-culture of HPMC and T-MSC or T-MSC-CM inhibited TGF β -induced EMT (increased ZO-1 and E-cadherin and decreased α SMA) and oxidative stress (decreased ROS generation). In PD, T-MSCs alleviated EMT and peritoneal fibrosis and reduced Bax, cleaved caspase and increased Bcl-2, and also decreased 8-OHdG with an increase in GSH and SOD2. T-MSC led to a decrease in proteins of ER stress and NLRP3 inflammasome. T-MSCs treated rats had a higher D2/D0 glucose and a lower D2/P2 creatinine. Anti-human nuclei staining revealed scattered positive staining along peritoneal mesothelial layer.

Conclusions : T-MSCs represent a promising approach to prevent peritoneal fibrosis by providing anti-fibrosis and anti-oxidant effects in the peritoneal cavity and ameliorating the phenotype transition of peritoneal mesothelial cells.