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ROLE OF WNT PATHWAY ON MESENCHYMAL STEM CELL THERAPY TARGETED TO INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Interstitial cystitis is a devastating disease with no reliable treatment modality. Stem cell therapy could be a option to manage this disease. On injury, Shh expression increase and elicits increased stromal expression of Wnt protein signals, which in turn stimulate the proliferation of both urothelial and stromal cells. This study is to evaluate the therapeutic efficacy of mesenchymal stem-cells (MSCs) for the treatment of interstitial cystitis (IC) rat induced by HCl and investigate the possible role of Wnt protein signalling in the therapeutic mechanisms involved in MSC therapy.

Study design, materials and methods

IC rat was induced by instillation of 0.1M HCl via urethra catheter in 20 female 7-week-old Sprague-Dawley rats. Ten rats underwent sham operations (Sham). One-week after inducing IC, 20 IC rats were divided into 2 groups received a single transplantation of human adipose-derived MSCs (IC+MSC) or PBS (IC). Cystometric parameters, histological examination, immunostaining for cytokeratin, toluidine blue, s100, CD34, Oct4, and Stella, and the transcriptional activity levels for stemness and stem-cell trafficking genes, B-cathenin for Wnt genes were measured at 1 week after intervention..

Results

Cystometry showed the voiding interval was shortest in IC group followed by IC+MSC and Sham (210.0±111.1 vs 405.0±135.1 vs 430.0±139.0 sec, p=0.007). Compared to Sham, denudation of epithelium, increase of inflammatory response, mast cell count, neural cell count and decrease of angiogenesis were found in IC group. However IC+MSC group showed recovery of epithelium, decreases of inflammatory response, mast cell and neural cell counts, increase of angiogenesis compare to IC group. The bladders that received MSCs increased the transcription of *Oct4* and *Stella*, which are surrogate markers of pluripotent stem-cells. In addition, MSCs enhanced the expression levels of several Wnt genes.

Interpretation of results

Here we showed in IC rat that the proliferative response of MSCs to chemical injury within the bladder is regulated by Wnt signal. We demonstrated that these stem cells capable of regenerating all cells within the urothelium are marked by expression of Wnt.

Concluding message

These results indicate that the transplantation of MSCs can restore bladder function, recover the epithelium and inflammatory response in IC rat. One of repairing mechanisms in IC rat bladder is Wnt signal pathway.

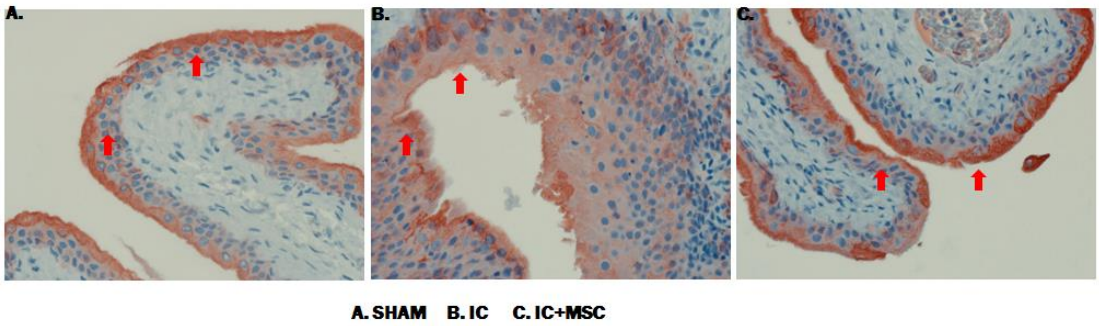

Fig 1. Improvement in the bladder epithelial layer by the transplantation of MSCs. (A) Staining for Cytokeratin (magnification 400)

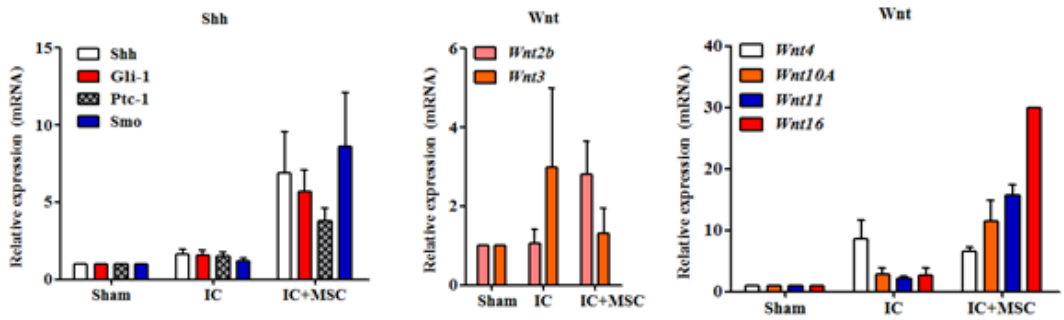

Fig 2. Emergence of Shh and Wnt 2b, Wnt10A, Wnt11, Wnt 16 in MSCs that were transplanted into rat bladders. RQ-PCR analysis of various Wnt genes using rat sequence-targeted primers in the indicated bladder tissues.

Disclosures

Funding: no **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Asan Institutional Animal Care and Use Committee