CD362+ MESENCHYMAL STEM CELL TREATMENT OF KIDNEY DISEASE IN TYPE 2 DIABETIC LEPR DB/DB MICE

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Introduction and Aims: Mesenchymal stem cells (MSC) are extensively studied as potential therapeutic modulators of disease. CD362/Syndecan-2 is a heparan sulphate proteoglycan identified as a functional marker for MSC isolation and therapeutic development. These are present in both bone marrow derived MSC and umbilical cord stem cells. However, their therapeutic potential in diabetic nephropathy is yet unclear. We speculated that a single dose of CD362+ MSC could have benefits in diabetic kidney disease.

Methods: LepRdb/db type 2 diabetic male mice were procured from Taconic Biosciences (DK-8680 Ry, Denmark). Uninephrectomy was done at 6 weeks of age to accelerate diabetic kidney disease via increased hyperfiltration. At 4 months proteinuric mice were randomized to either a single intravenous dose of 250,000 CD362+ MSC or saline. 56 days later kidneys were collected for immunostaining, flow cytometry, ELISA and RT-PCR. Proteinuria was assessed as albumin to creatinine ratio in spot urine samples. Also we evaluated the efficacy of CD362+ umbilical cord stem cells (UCSC) in uninephrectomized mice treated with high fat diet to further aggravate diabetic kidney disease. Bio-distribution of MSC after injection was studied in various organs at 4, 14, 28, and 56 days by detecting human DNA (ALU) sequences in mouse tissues.

Results: LepRdb/db type 2 diabetic male mice showed increased urine albumin/creatinine ratio, plasma creatinine, BUN levels and decreased GFR levels versus baseline. This was associated with diffuse glomerulosclerosis. Renal IL-6, TNF-α, and iNOS mRNA expression were significantly increased in vehicle-treated mice. CD362+ MSC-treated mice revealed a significant reduction in glomerulosclerosis, albuminuria, plasma creatinine, BUN levels, and showed a significantly increased GFR. The markers of inflammation were significantly compared to vehicle-treated mice and reached baseline level. However, the observations in high fat diet-fed mice treated with UCSC are not in accordance of MSC results. In these UCSC-treated group, elevated clinical and functional parameters remained unaffected. Human DNA was not detectable in any organ tissue at 4 days after injection or later.

Conclusions: Human CD362+MSC do not persist 4 days or more upon injection in diabetic mice. Nevertheless, CD362+ MSC were able to protect the type 2 diabetic mice with kidney disease through modulation of inflammation. Our result with UCSC in high fat diet-fed mice were not significantly protective, which may relate to their different origin or to the high fat diet-related aggravation of renal inflammation. Our studies were based on single MSC injections. As the MSC did not persist in the tissue, repetitive injections might be even more effective. We conclude that the our results clearly demonstrate the role of CD362+ MSC in diabetic nephropathy treatment and allow us to formulate the stem cell based therapeutic intervention for the treatment of diabetic kidney disease.