INTRAVENOUS ADMINISTRATION OF MESENCHYMAL STROMAL CELLS MODULATES RENAL LIPID METABOLISM IN RATS

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Introduction

- ✓ Mesenchymal stromal cells (MSC) represent a heterogeneous population of fibroblast-like adult multipotent cells
- ✓ MSC have anti-inflammatory, immune-regulatory and tissue repair properties
- ✓ MSC attenuate renal ischemia/reperfusion (I/R) injury in rodents
- ✓ The mechanisms of MSC-induced nephro-protection remain unclear

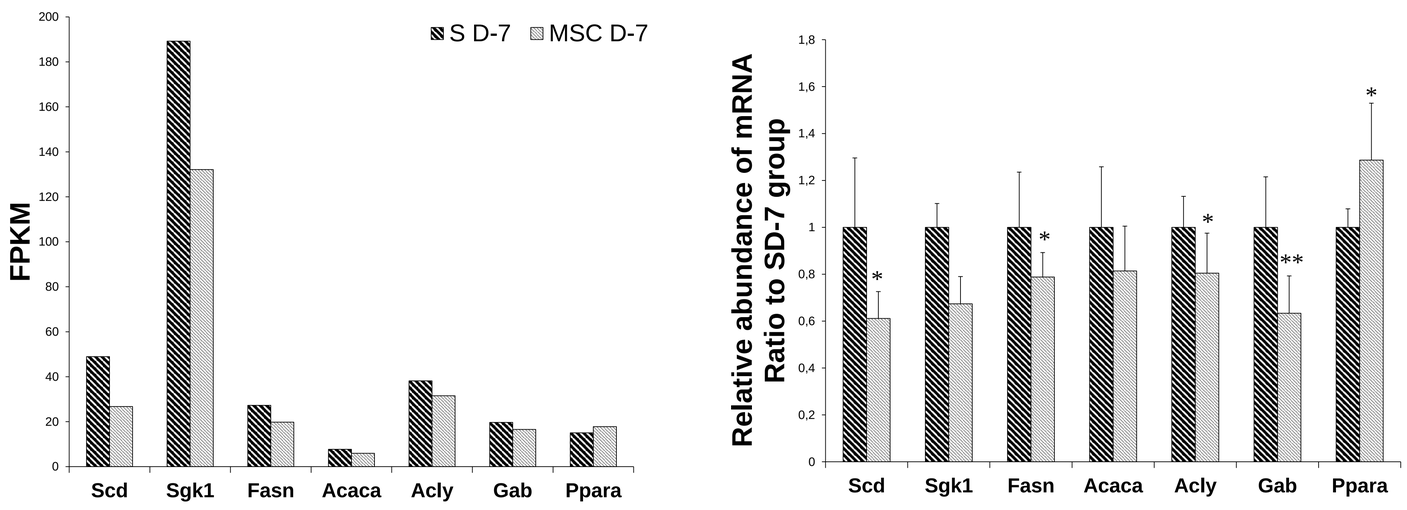
Materials and Methods

- ✓ Male 10-week-old *Lewis* rats were i.v. infused with bone marrow-derived MSC ($1.5x10^6$ cells in 1 ml saline; MSCD-7 group, n=6) or equivalent volume of saline (SD-7 group, n=6) 7 days before nephrectomy
- ✓ Messenger RNAs were extracted from kidneys. Libraries were prepared for each sample using Truseq mRNA stranded kit and sequenced on a Nextseq 500 sequencer (average of 20 million 2x75-bp reads per library)
- ✓ Reads were mapped onto the rat reference genome using TopHat. Resulting data were transferred to Cufflinks and Cuffmerge to generate a transcriptome assembly
- ✓ Identification of genes differentially regulated was performed with Cuffdiff
- ✓ Functional enrichment analysis was performed using WEB-based Gene SeT AnaLysis Toolkit
- ✓ Comparative real-time qPCR and immunoblotting were performed on kidney lysates of MSCD-7 *versus* SD-7 rats

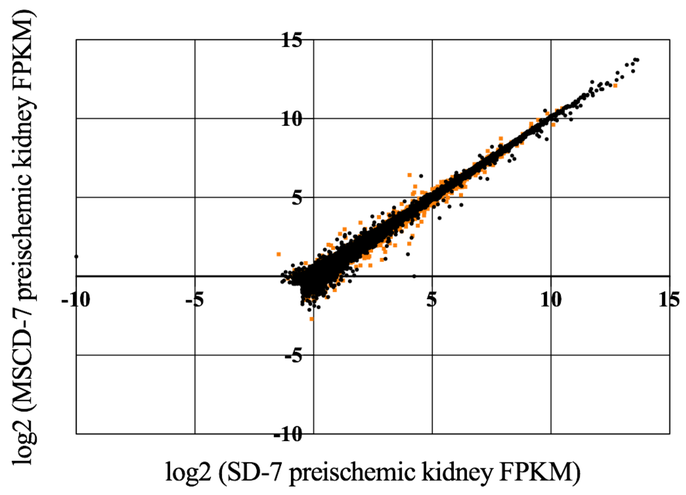
Results

Pathway name	Number of genes /reference genes in each category	*p*
Downregulated pathways		
Adipogenesis	10/129	5 x10 $^{-7}$
Insulin signaling	9/158	1.36 $^{-5}$
Fatty acid biosynthesis	5/28	1.36 $^{-5}$
IL-6 signaling pathway	7/114	0.0001
B cell receptor signaling pathway	8/199	0.0003
ErbB signaling pathway	5/60	0.0003
IL-3 signaling pathway	6/110	0.0004
Upregulated pathways		
Nuclear receptors in lipid metabolism and toxicity	4/ 39	0.0001
Proteasome degradation	2/59	0.0480
Translation Factors	2/47	0.035

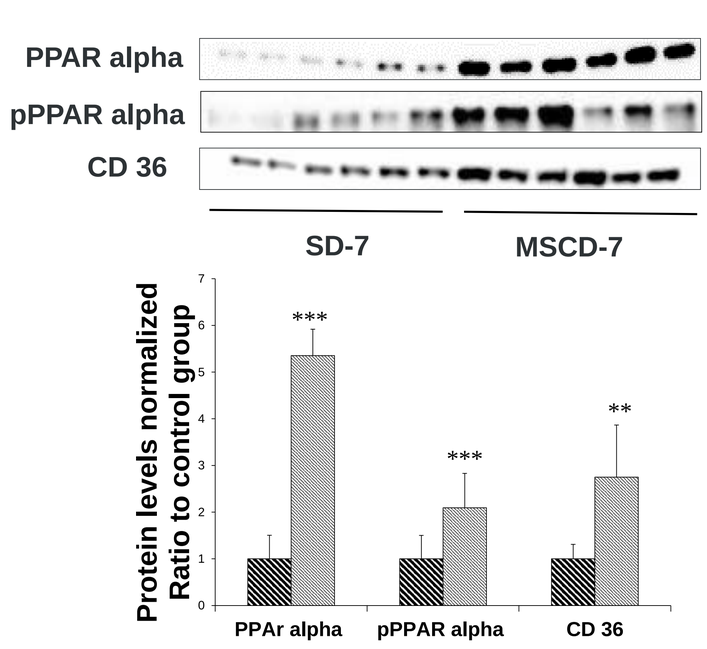
Metabolic pathways involved in MSC-mediated conditioning based on the high-throughput RNA seq



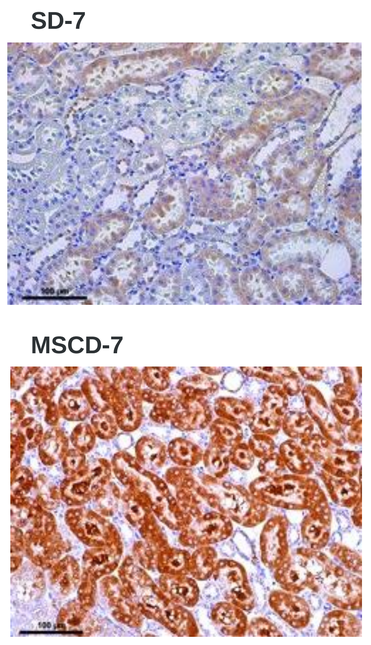
Significantly differentially expressed genes involved in fatty acid biosynthesis and nuclear receptor in lipid metabolism pathways in MSCD-7 and SD-7 on the basis of the high-throughput RNA-sequencing and corresponding RT-qPCR analysis of the genes



Scatter plot of the log2 (Fragments per Kilobase of sequence Per Million mapped reads, FKPM) counts of genes for SD-7 and MSCD-7 kidneys. Dots represent the 25908 genes differentially assessed, with orange dots corresponding to the significantly differentially expressed genes (FDR<0,05).



Immunoblotting of PPARα, phospho-PPARα and CD36 expression in MSCD-7 and SD-7 kidneys



Immunohistochemistry for FAT/CD36

Conclusions

✓MSC infusion is associated with critical modifications of lipid metabolism in renal parenchyma, including down-regulation of fatty acid (FA) biosynthesis and activation of PPARα pathway

✓MSC infusion may be associated with a prioritization of FA as sources of energy in proximal tubular cells, which may eventually prevent lipid peroxidation and attenuate renal I/R damage

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Experimental AKI I
Francois Jouret
DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.