Microvesicles Secreted by Mesenchymal Stem Cells Exhibit a Renoprotective Effect by miRNA-Mediated Reprogramming of Tubular Epithelial Cells

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INTRODUCTION: Acute kidney injury (AKI) is associated with elevated mortality rates (80%) and currently has limited treatment options. Mesenchymal stem cells (MSC) have powerful immunotherapeutic properties beyond act as effector agents in the modulation of gene expression by microvesicles loaded with miRNAs (MVs-MSC). AIM: In this present study we assessed the global expression profile of miRNAs as well as the molecular and cellular mechanisms involved in MSC-mediated renoprotection, using an experimental model of nephropathy. RESULTS: Both MSCs and MVs-MSC treatments, exerted a local renoprotective effect with improvement of renal parameters, low tubular apoptosis rate, elevated proliferation index, less oxidative stress and a reduction of pro-inflammatory cytokines levels. Furthermore, the treatments significantly increased the level of anti-inflammatory molecules and renoprotective genes beyond reduced the mitochondrial oxidative stress in tubular cells. In addition, we found that both local and systemic immunoregulation were directly associated with specific inhibition of the NFKB pathway in renal cells by modulation of signaling proteins (IKK-α, IκBα, p65), cell receptors (TNFR, TLRs) and pro-inflammatory molecules (C3, Csf3, Egr-1, IL-6, IFNg, IL-1β and TNF-α). Moreover, in order to investigate the specific mechanism, the miRNAs profile was evaluated in renal tissues, which 464 were similarly expressed, 61 were up-regulated and 3 were down-regulated after MSC treatment. In addition, proteins involved in the miRNAs biosynthesis (Dicer, Drosha, Argonaut) were up-regulated in renal injury and down-modulated after MSC injection. The pre-treatment with RNAses, abrogated the MVs-MSC effect and the use of DNAse and proteases did not change the phenotype. DISCUSSION AND CONCLUSIONS: This work demonstrated that the MSC-associated renoprotection could involve epigenetic reprogramming of tubular cells by miRNA modulation. In the future, we hope characterize the precise mechanism related with MSC regenerative process, as well as identify potential miRNAs biomarkers of injury or tissue regeneration, facilitating their translation to clinical practice.

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