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The Mechanism of Mesenchymal Stem Cells for Treatment of Renal Interstitial Fibrosis: A Mini-Review

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ABSTRACT

Background: Although the efficacy and safety of mesenchymal stem cells (MSCs) in the treatment of kidney diseases have been preliminarily verified in clinical trials and animal experiments, the therapeutic mechanism of MSCs is still unclear.

Methods: The present study performed a mini-review focusing on the mechanism of MSCs for treatment of renal interstitial fibrosis combined with our previous works.

Results: Based on the mechanism of renal fibrosis, MSCs mostly participate throughout the renal fibrotic process. MSCs from bone marrow have been verified to exert anti-fibrotic effects in renal interstitial fibrosis and improve the renal function. The core mechanism down-regulated some anti-inflammatory cytokines, such as IL-6, ICAM-1, IL-1β, and TNFα, which inhibited inflammatory signal contributing to decreasing the sustained activation of myofibroblasts and extracellular matrix (ECM). MSCs also ameliorated renal tubular epithelial cells trans differentiation by decreasing key epithelial-mesenchymal trans differentiation (EMT)-inducing transcription factor, snail. The galectin-3 did not probably participate in the process of MSCs against NRK-49F fibrosis induced by TGF-β1, but participate in HK-2 fibrosis. The galectin-3 probably involved in the regulation of autophagy which is a promising approach for enlarging the biological properties of MSCs. MSCs delivery as early as possible in chronic kidney disease (CKD) onset is more effective than after disease occurrence.

Conclusions: Based on the mechanism of renal fibrosis, MSCs mostly participate throughout the renal fibrotic process. MSCs from bone marrow have been verified to exert anti-fibrotic effects in renal interstitial fibrosis and improve the renal function. The core mechanism down-regulated some anti-inflammatory cytokines, such as IL-6, ICAM-1, IL-1β, and TNFα, which inhibited inflammatory signal contributing to decreasing the sustained activation of myofibroblasts and extracellular matrix (ECM). MSCs also ameliorated renal tubular epithelial cells trans differentiation by decreasing key epithelial-mesenchymal trans differentiation (EMT)-inducing transcription factor, snail. The galectin-3 did not probably participate in the process of MSCs against NRK-49F fibrosis induced by TGF-β1, but participate in HK-2 fibrosis. The galectin-3 probably involved in the regulation of autophagy which is a promising approach for enlarging the biological properties of MSCs. MSCs delivery as early as possible in chronic kidney disease (CKD) onset is more effective than after disease occurrence.

Keywords: Galectin-3, MSCs, Renal interstitial fibrosis, Mechanism

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem, as demonstrated by increases in the mortality and the incidence of end- stage renal disease (ESRD) [1]. Renal fibrosis, as the fundamental pathological process of CKD, is characterized by inflammatory signaling stimulation, macrophage migration, endothelium injury, myofibroblast activation, and ECM deposition. So far, there is no specific drugs for CKD fibrosis. A great deal of evidence showed that stem cells have notable therapeutic effect in acute and chronic kidney diseases. Among them, MSCs are considered to be a most promising therapeutic tool due to their capacities for self-renewal, multilineage differentiation, immunomodulation, and have attracted great attention in regenerative medicine. At present, it is still recognized that a large number of cytokines secreted by MSCs is the main factor of their anti-fibrotic effect in acute and chronic kidney

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diseases. But the therapeutic mechanism of MSCs is still unclear. Therefore, this mini-review focuses on the possible mechanism of MSCs for treatment of renal interstitial fibrosis.

Mechanisms of fibrosis regression and resolution

From the various animal models of liver fibrosis and recovery, Introduced general principles of fibrosis inhibition [2].

1) Inhibition or termination of the underlying cause of tissue damage promotes regenerative pathways in parenchymal cells and avoids further activation of myofibroblasts [3].

2) Deactivation of inflammatory pathways and establishment of an anti-inflammatory microenvironment [4-6].

3) Restoration of myofibroblast sensitivity to apoptosis, killing/elimination of senescent cells, deactivation and elimination of myofibroblasts [7,8].

4) Disruption of collagen-matrix cross-links, augmentation of matrix proteolytic activity, and the clearance of degraded matrix molecules by cellular uptake and autophagy [8,9].

5) Targeting chromatin dysregulation in organ fibrosis: using the DNA methylation-modifying drugs, HDAC inhibitors, and small molecule inhibitors by nanotechnology-based delivery systems [10]. The pathological features of fibrosis were almost similar in different organs, the same can referred to renal fibrosis.

The mechanisms of MSCs for treatment of renal interstitial fibrosis

Based on the mechanism of renal fibrosis, MSCs mostly participate throughout the renal fibrotic process [11]. MSCs from different sources [12,13], conditional medium of MSCs (MSCs-CM) [17], MSCs in serum-free medium (SF-MSCs) [18], and extracellular vehicles (EVs) or exosomes secreted by MSCs [19] have been verified to exert anti-fibrotic effects in renal fibrosis diseases and improved the renal function. Mechanistically, it is the recognized by far that the growth factors such as VEGF [20], FGF-2 [21], IGF [22] and HGF [23] derived from MSCs via paracrine signaling recruit leucocytes or repair intrinsic cells, and may participate in AKI or CKD repair or the AKI-CKD transition with hardly integrated with the hosts [24]. MSCs have the potential to address both aspects, either reducing the severity of AKI and CKD or promoting the regenerative process towards beneficially adaptive repair pathways [25]. In addition, EVs secreted by MSCs are regarded as another special form of paracrine/endocrine response, which are rich in a broad variety of biologically active molecules, including lipids, proteins, and nucleic acids (e.g., mRNAs, miRNAs, and lncRNAs) [25]. Likewise, it has been verified repeatedly that MSCs also have the potent anti-inflammatory, immunosuppressive, antioxidative, anti-apoptotic, and pro-angiogenic properties resulting from the various growth factors secreted by MSCs in fibrosis-related diseases or other diseases. In our previous studies [17], on the one hand, MSCs probably established an anti-inflammatory microenvironment by decreasing inflammatory cytokines, such as IL-6, IL-1β, ICAM-1, and TNFα, and then avoided further activation of myofibroblasts and decreased ECM deposition. On the other hand, MSCs decreased the key EMT-inducing transcription factor, Snail, by inhibiting galectin-3/Akt/GSK3β signaling which reducing the amount of myofibroblasts. Meantime, MSCs also rebalanced enzyme system which regulated the production and degradation of extracellular matrix by augmenting matrix proteolytic activity (e.g., Down-regulated TIMPs/MMPs ratio), and the clearance of degraded matrix molecules. Our studies unconsciously conformed to the principle of fibrosis regression and resolution.

However, in most researches, the anti-fibrotic effect of MSCs is limited, and partially improved, requiring the repeated administration to maintain a long anti-fibrotic effect. Our studies indicated that only 40 proteins in kidney tissues existed significantly statistical differences compared with Adenine+MSCs group and Adenine group, which partly interpreted the limited therapy of MSCs anti-fibrosis. Valuably, one of the important goal for the treatment or management of fibrosis is to diagnose the risk factors or the biomarkers in an early stage [10]. Finding specific biomarkers of renal fibrosis would definitely help developing the most promising treatment in humans, since they would be used as primary end-points in addition to GFR and proteinuria in clinical trials [26]. So far, such biomarkers don't exist, but promising candidates include procollagen III amino-terminal pro-peptide (PIIINP), galectin-3 and periostin [26]. Galectin-3 (molecular weight: 26 kDa) is filtered through the glomerular basement membrane and its plasma levels inversely correlate with renal function and GFR [27]. Therefore, the significance of galectin-3 levels disappears when adjusted for GFR. Galectin-3 variation within the plasma has been also shown to increase before the onset of CKD: in 2450 participants of the Framingham Heart study, higher plasma galectin-3 levels associated with a rapid GFR decline and a higher risk of incident CKD [28]. According to the biomarker of the onset of CKD, such as galectin-3 levels in the plasma, MSCs delivery as early as possible before CKD onset will adequately enlarge the biological effects of MSCs against renal fibrosis, which avoid low survival rates due to unsuitable microenvironment. The results also confirmed this view in vivo and in vitro. Therefore, in the early stage of disease development, MSCs treatment as early as possible is more effective than after disease occurrence.

In addition, there are still many unanswered questions. Using untargeted proteomic analysis showed that armadillo repeat containing 1 (Armc1), was the most significantly up-

regulated protein compared with Adenine MScs group and Adenine group (fold changes: 3.521). According to the molecular function, Armc1 is in association with mitochondrial contact site and cristae organizing system (MICOS) complex components and mitochondrial outer membrane sorting assembly machinery (SAM) complex components may regulate mitochondrial dynamics playing a role in determining mitochondrial length, distribution and motility. Mitochondrial dysfunction also plays a key role in the etiology, progression, and pathophysiology of CKD [29]. We guess that MSCs maybe ameliorate mitochondrial dysfunction to regulate the balance of proinflammatory and anti-inflammatory microenvironment. Further research is needed on this point.

The galectin-3 did not probably participate in the process of MSCs against NRK-49F fibrosis induced by TGF-β1

According to our studies, we speculate that galectin-3 maybe involve in the process of MSCs against renal fibrosis, which was probably not only a new biomarker of CKD onset, but also a promising anti-fibrosis target. Notwithstanding, our previous results supported this opinion, the evidence is still weak. However, the origin of the myofibroblast population has long been debated. Cellular sources that have been traditionally proposed to give rise to the interstitial myofibroblasts population include resident fibroblasts, bone marrow-derived fibroblasts, tubular epithelial cells, endothelial cells, pericytes, Gli1+ perivascular mesenchymal stem cell-like cells, and other specialized cell types [30, 31]. Adenine mainly leaded to the interstitial fibrosis with the characteristic of 2, 8-dihydroxyadenine (DHA) crystal deposition in the tubular lumen and interstitium of the kidney [32]. The resident fibroblasts seem to be the most important ancestors of myofibroblasts in renal interstitial fibrosis [33]. Our studies only proved that MSCs ameliorate renal fibrosis by galectin-3/Akt/GSK3β/Snail signaling pathway in HK-2 fibrosis induced by TGF-β1. So, we further verified whether the galectin-3 also involve in the process of MSCs against NRK-49F fibrosis induced by TGF-β1, and expect to obtain similar results as in HK-2 fibrosis.

MSCs began to exert anti-fibrotic effects at 24 h after MSCs treatment in NRK-49F fibrosis induced by TGF-β1. α-SMA expression showed significant decreases in TGF-β1+MSCs-CM group compared with TGF-β1 group, lower than TGF-β1+MEM group **(Figure 1A)**. MSCs also notably inhibited the TGF-β1/Smad signaling pathway in NRK-49F **(Figure 1B)**, and obviously reduced galectin-3 concentration in the supernatant after MSCs treatment by galectin-3 ELISA kit **(Figure 1C)**. To further prove the relationship of MSCs and galectin-3 in NRK-49F fibrosis induced by TGF-β1, the galectin-3 knockdown (KD Gal-3) and overexpression (OE Gal-3) were established by lentivirus vector transfection in NRK-49F and verified by western blot **(Figures 1D-1F)**. The results showed that TGF-β1 obviously increased the expression of galectin-3 and α-SMA proteins in the TGF-β1 group compared with the control group. No matter KD Gal-3 or OE Gal-3 in NRK-49F, MSCs-CM ameliorated TGF-β1-induced fibrosis in NRK-49F, better than TGF-β1+MEM group which were consistent with those in HK-2 fibrosis induced by TGF-β1, but also observed that α-SMA expression was not affected by galectin-3 knockdown or overexpression **(Figures 1G & 1H).** MSCs against NKR-49F fibrosis induced by TGF-β1 seem to be through other mechanism, which need further research. Taken together, we seem to draw a preliminary conclusion that the galectin-3 did not probably participate in the process of MSCs against NRK-49F fibrosis induced by TGF-β1, but did HK-2 fibrosis. Now, a new problem has arisen. Whether does the galectin-3 also influence the progress of MSCs against TGF-β1 induced fibrosis in other origins of myofibroblasts which have been proposed in renal interstitial fibrosis, such as bone marrow-derived fibroblasts, endothelial cells, pericytes, and $Gli1^+$ perivascular mesenchymal stem cell-like cells? Which specific cells the galectin-3 affects remains an unresolved question. More experiments are needed to confirm this problem.

Why has the galectin-3 a significant regulation in MSCs against HK-2 fibrosis induced by TGF-β1? The answer may lie in cell-specific localization and biological function of the galectin-3. Galectin-3 is a β-galactoside-binding lectin which is important in numerous biological activities in various organs, including cell proliferation, apoptotic regulation, inflammation, fibrosis, and host defense. Galectin-3 is widely distributed in epithelia, including the simple columnar epithelium in the gut, stratified squamous epithelium in the gut and skin, and transitional epithelium and several regions in nephrons in the urinary tract [34,35]. Galectin-3 is predominantly located in the cytoplasm and expressed on the cell surface, and then often secreted into biological fluids, like serum and urine. It is also released from injured cells and inflammatory cells under various pathological conditions. Galectin-3 can be secreted extracellularly, but also can shuttle into the nucleus. Extracellular galectin-3 modulates important interactions between epithelial cells and the extracellular matrix, and plays a vital role in the embryonic development of collecting ducts and nephrogenesis [36,37]. Thus, the regulation of the galectin-3 in HK-2 can have great influences on interstitial fibrosis induced by TGF-β1, and have a negligible effect on fibroblasts. Our results also confirmed this opinion.

Moreover, galectin-3 in the cytoplasm could recruit endosomal sorting complexes required for transport (ESCRT) components, Alix, to damaged lysosomes for repair and restoration of their function [38]. Meantime, Galectin-3, via interaction with TRIM family proteins, such as TRIM16, recognizes membrane damage and direct autophagic homeostasis of lysosomal and phagosomal organelles in an Unc-51-like kinase 1 (ULK1)-dependent

manner [39]. The regulation of autophagy is a promising approach for improving the biological properties of MSCs. More in-depth investigations about the role of autophagy in MSCs anti-fibrotic process are required to contribute to the clinical application of MSCs.

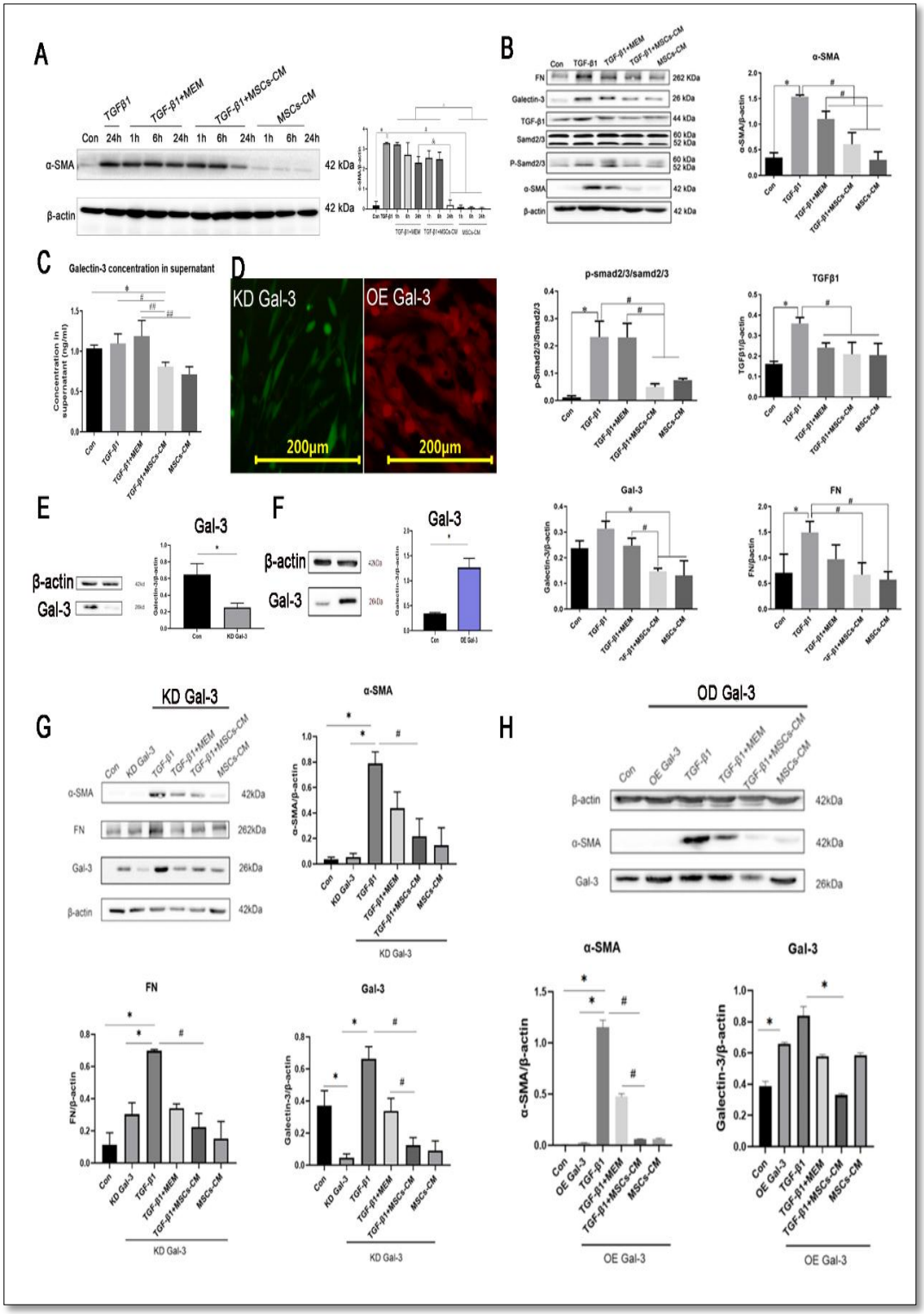

Figure 1. The galectin-3 did not possibly participate in the process of MSCs against renal interstitial fibroblast (NRK-49F) fibrosis induced by TGF-β1.

After human recombinant TGF-β1 (20 ng/mL) was used to induce renal interstitial fibrosis in NRK-49F, MSCs-CM treated for 24 h to estimate the relationship of the galectin-3 in MSCs anti-fibrosis. MSCs began to exert anti-fibrotic effects at 24 h after MSCs treatment in TGF-β1-induced NRK-49F fibrosis. α-SMA expression showed significant decreases in TGF-β1+MSCs-CM group compared with TGF-β1 group, lower than TGF-β1+MEM group (A). MSCs also notably inhibited the TGF-β1/Smad signaling pathway in NRK-49F (B), and obviously reduced galectin-3 concentration in the supernatant after MSCs treatment by galectin-3 ELISA kit (C). To further prove the relationship of MSCs and galectin-3 in TGF-β1 induced NRK-49F fibrosis, galectin-3 knockdown (KD Gal-3) and overexpression (OE Gal-3) by lentivirus vector transfection were established in NRK-49F cells and verified by western blot (D, E, and F). The results showed that TGF-β1 obviously increased the expression of galectin-3 and α-SMA proteins compared with the control group. No matter KD Gal-3 or OE Gal-3 in NRK-49F, MSCs-CM ameliorated NRK-49F fibrosis induced by TGF-β1, better than TGF-β1+MEM group which were consistent with those in HK-2 fibrosis induced by TGF-β1, but also observed that α-SMA expression was not affected by galectin-3 knockdown or overexpression (G and H). Data are presented as mean ± SD, and analyzed by one-way ANOVA (GraphPad Software, San Diego, CA, USA), followed by the Tukey post hoc testing to analyze differences between groups. $P < 0.05$ was considered significant.

The existed problems of MSCs in anti-fibrosis therapy

How much MSCs could exert the anti-fibrotic effects in renal fibrosis diseases largely depends on the source, delivery method and quantity, the age of the donator, various preconditioning strategies, genetic modification or not, and repeated administration of MSCs which directly determined their survival, paracrine, migration, and host integration ability. The various strategies are ultimately to improve MSCs survival and paracrine ability, augmenting their beneficial effects. The limited efficacy of MSCs against renal fibrosis existed the four main problems, including the lower engraftment, poor survival rate, impaired paracrine ability, and delivery time of MSCs [40]. Given that special role of galectin-3, it is necessary to clarify how the galectin-3 regulate renal fibrosis induced by TGF-β1 in different origins of myofibroblasts in MSCs anti-fibrosis. Therapeutic regimens based on MSCs still have a promising future in kidney or other organ fibrosis.

CONCLUSIONS

This mini-review focused on the mechanism of MSCs for the treatment of renal interstitial fibrosis. MSCs constitute a very promising therapy for renal fibrosis via paracrine signaling based on a variety of growth factors secreted by MSCs to maintain an anti-inflammatory environment. MSCs exerted anti-fibrotic effects by down-regulating some anti-inflammatory cytokines to inhibit sustained activation of myofibroblasts, decreasing their amounts by reducing key EMT-inducing transcription factor, Snail, and rebalancing the enzyme system which regulated the production and degradation of the ECM. MSCs probably ameliorated renal interstitial fibrosis by inhibiting galectin-3/Akt/GSK3β/Snail signaling pathway in HK-2 fibrosis, not NRK-49F fibrosis induced by TGF-β1. Additionally, we speculate that galectin-3 probably involves in MSCs anti-fibrotic progress which is possibly related to the regulation of the autophagy enlarging the biological properties of MSCs. Finally, we will further explore the unresolved issues we mentioned above. In brief, we may conclude that MSCs can provide a useful therapy in the field of renal fibrosis.

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