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COMMENTARY

Therapeutic effects of mesenchymal stem cells on renal ischemia–reperfusion injury: a matter of genetic transfer?

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Abstract

Accumulating evidence indicates that the protective effect of mesenchymal stem cells in models of tissue injury is related to the endocrine/paracrine release of factors. The delivery of growth factors, cytokines, prostaglandins, enzymes or extracellular vesicles from mesenchymal stem cells to target cells may induce cell reprogramming and *de novo* expression of factors involved in tissue proliferation and repair. A recent paper showed that Wharton jelly-derived mesenchymal stem cells interact with injured renal tubular epithelial cells, inducing the expression of native and foreign hepatocyte growth factor necessary for renal repair and fibrogenesis inhibition. The genetic exchange between resident and mesenchymal stem cells, probably mediated through microvesicles, therefore appears instrumental in mesenchymal stem cell therapeutic effects.

In virtue of their anti-inflammatory and tissue-regenerating properties, mesenchymal stem cells (MSCs) appear a promising approach for the treatment of renal tissue injury. The possible mechanisms involved are under deep investigation.

In this context, the paper published by Tao Du and colleagues provides evidence that human Wharton jelly-derived mesenchymal stem cells (WJ-MSCs) delay epithelial–mesenchymal transition and alleviate renal fibrosis in a model of renal ischemia and reperfusion injury in the rat [1]. In the search for underlying mechanisms, the authors identify the relevance of the hepatocyte growth factor (HGF)/transforming growth factor beta 1 balance in this process, HGF being able to inhibit epithelial–mesenchymal transition and to block fibrogenesis [1]. Indeed, after *in vivo* administration of WJ-MSCs, HGF gene expression and protein release was upregulated in tubular epithelial cells. Of interest, human HGF mRNA was also detected by real-time PCR, indicating that WJ-MSCs induce *in vivo* both native and foreign HGF expression in injured tubular cells. Accordingly, conditioned medium produced by WJ-MSCs induced *in vitro* HGF mRNA upregulation and protein release of both rat and human origin in hypoxic rat tubular epithelial cells. These data indicate that human HGF gene transcript, released by WJ-MSCs, is delivered to tubular cells and then translated into protein. The explanation proposed by the authors is that a genetic transfer mediated by WJ-MSC-released microvesicles (MVs) may support the tubular induction of human HGF in the rat [1].

Accumulating data indicate that MVs released from many cells target specific cells from other tissues. Indeed, MVs have been recently described as new mediators of cell-to-cell communication that may re-program target cells through the active transfer of proteins, functional mRNAs and miRNAs [2]. As a consequence of the active genetic transfer, MVs derived from bone marrow (BM) MSCs were shown to promote tissue regeneration in different experimental animal models of renal injury. In particular, therapeutic administration of a single dose of MSC-derived MVs accelerated the morphological and functional recovery in glycerol-induced acute kidney injury and prevented lethality in cisplatin-induced acute kidney injury [3-5]. In addition, administration of multiple doses of BM MSC-derived MVs, at different time points after injury, improved mice survival and prevented chronic renal injury [4,5]. MSC-derived MVs also displayed protection against renal injury in the mouse model of 5/6 subtotal nephrectomy, preventing renal fibrosis [6].

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The *in vitro* and *in vivo* effects of MVs have been attributed to RNA delivery, as inactivation of RNA diminishes their properties [3-5]. Reis and colleagues have also recently reported that whole conditioned medium or purified MVs from BM MSCs ameliorated gentamicin-induced acute kidney injury, effects that were blunted after incubation with RNase, confirming that the regenerative properties of MSCs were mediated by MV-carried RNAs [7]. Although it is likely that single mRNA, miRNA or protein act in concert to gain the MSC therapeutic effect, the paper by Du and colleagues identifies the genetic transfer of HGF to resident cells as instrumental for inducing renal repair and for avoiding fibrogenesis in renal ischemia–reperfusion injury [1]. In parallel, a native HGF induction in tubular epithelial cells induced by other factors was reported [1]. Another recent study points out the involvement of insulin growth factor 1-receptor mRNA transferred through BM MSC-derived MVs in promoting the proliferation of damaged proximal tubular cells [8].

The implication of MSC-derived MVs is considered a general mechanism, as shown in other experimental models such as myocardial ischemia–reperfusion injury [9]. In addition, as shown by the paper from Du and colleagues [1], MSC types other than BM MSCs share this communication property. The interaction of tissue-localized MSCs and injured cells might also present more complex dynamics. The microenvironment, possibly MVs or growth factors, released from injured cells has been proposed to perhaps modify MSCs localized into tissues, thus inducing a bidirectional mechanism to promote tissue repair [10]. Strategies to mimic these possible MSC modifications induced by the injured microenvironment include MV collection by cells placed under stress.

All together, these data show that the beneficial effects of MSCs can be attributed, at least in part, to communication mechanisms involving MVs. During MSC therapy, the delivery of proteins, mRNA and miRNA to tubular epithelial cells may induce cell reprogramming and *de novo* expression of factors involved in tissue proliferation and repair, such as HGF [1]. The modifications in target cells appear to be stable and result in significant functional effects. However, several issues still need to be elucidated on the effects of MSCs in renal repair, including the mechanisms of MV uptake and action and, for a possible therapeutic use of MVs themselves, their bio-distribution and dosage.

Abbreviations

BM: Bone marrow; HGF: Hepatocyte growth factor; miRNA: microRNA; MSC: Mesenchymal stem cell; MV: Microvesicle; PCR: Polymerase chain reaction; WJ-MSC: Wharton jelly-derived mesenchymal stem cell.

Competing interests

The authors declare that they have no competing interests.

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References

1. Du T, Zou X, Cheng J, Wu S, Zhong L, Ju G, Zhu J, Liu G, Zhu Y, Xia S: **Human Wharton jelly-derived mesenchymal stromal cells reduce renal fibrosis through induction of native and foreign hepatocyte growth factor synthesis in injured tubular epithelial cells.** *Stem Cell Res Ther* 2013, **4:**59.
2. Camussi G, Deregibus MC, Bruno S, Grange C, Fonsato V, Tetta C: **Exosome/microvesicle-mediated epigenetic reprogramming of cells.** *Am J Cancer Res* 2011, **1:**98–110.
3. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F, Morando L, Busca A, Falda M, Bussolati B, Tetta C, Camussi G: **Mesenchymal stem cell-derived microvesicles protect against acute tubular injury.** *J Am Soc Nephrol* 2009, **20:**1053–1067.
4. Bruno S, Grange C, Collino F, Deregibus MC, Cantaluppi V, Biancone L, Tetta C, Camussi G: **Microvesicles derived from mesenchymal stem cells enhance survival in a lethal model of acute kidney injury.** *PLoS One* 2012, **7:**e33115.
5. Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, Camussi G: **Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia–reperfusion-induced acute and chronic kidney injury.** *Nephrol Dial Transplant* 2011, **26:**1474–1483.
6. He J, Wang Y, Sun S, Yu M, Wang C, Pei X, Zhu B, Wu J, Zhao W: **Bone marrow stem cells-derived microvesicles protect against renal injury in the mouse remnant kidney model.** *Nephrology* 2012, **17:**493–500.
7. Reis LA, Borges FT, Simoes MJ, Borges AA, Sinigaglia-Coimbra R, Schor N: **Bone marrow-derived mesenchymal stem cells repaired but did not prevent gentamicin-induced acute kidney injury through paracrine effects in rats.** *PLoS One* 2012, **7:**e44092.
8. Tomasoni S, Longaretti L, Rota C, Morigi M, Conti S, Gotti E, Capelli C, Introna M, Remuzzi G, Benigni A: **Transfer of growth factor receptor mRNA via exosomes unravels the regenerative effect of mesenchymal stem cells.** *Stem Cells Dev* 2013, **22:**772–780.
9. Lai RC, Arslan F, Lee MM, Sze NS, Choo A, Chen TS, Salto-Tellez M, Timmers L, Lee CN, El Oakley RM, Pasterkamp G, de Kleijn DP, Lim SK: **Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury.** *Stem Cell Res* 2010, **4:**214–222.
10. Del Tatto M, Ng T, Aliotta JM, Colvin GA, Dooner MS, Berz D, Dooner GJ, Papa EF, Hixson DC, Ramratnam B, Aswad BI, Sears EH, Reagan J, Quesenberry PJ: **Marrow cell genetic phenotype change induced by human lung cancer cells.** *Exp Hematol* 2011, **39:**1072–1080.

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