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COMMENTARY

Regenerating the injured kidney with human umbilical cord mesenchymal stem cell-derived exosomes

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Abstract

Transplantation of adult stem cells is being used to facilitate repair or regeneration of damaged or diseased tissues. However, in many cases, the therapeutic effects of the injected stem cells are mediated by factors secreted by stem cells and not by differentiation of the transplanted stem cells. Recent reports have identified a class of microvesicles, termed exosomes, released by stem cells that are able to confer therapeutic effects on injured renal and cardiac tissue. In this issue of *Stem Cell Research & Therapy*, Zhou and colleagues demonstrate the ability of exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs), but not non-stem cell-derived exosomes, to improve acute kidney injury induced by cisplatin in rats. The authors demonstrate that hucMSC exosomes can reduce cisplatin-mediated renal oxidative stress and apoptosis *in vivo* and increase renal epithelial cell proliferation in culture. These results suggest that stem cell-derived exosomes, which are easy to isolate and safer to use than the parental stem cells, could have significant clinical utility.

In this issue of *Stem Cell Research & Therapy*, Zhou and colleagues [1] provide insight into how adult stem cell populations – in particular, mesenchymal stem cells (MSCs) derived from human umbilical cord (hucMSCs) – are able to regulate tissue repair and regeneration. Adult stem cells, including MSCs from different sources, confer regenerative effects in animal models of disease and tissue injury and are in phase I and II trials for limb ischemia, congestive heart failure, and acute myocardial infarction [2]. However, in many cases in which stem cells mediate therapeutic effects, the presence of the transplanted stem cells in the regenerating tissue is not observed. This suggests that the predominant therapeutic effect of stem cells is conferred through the release of therapeutic factors. Indeed, conditioned media from adult stem cell populations are able to improve ischemic damage to kidney and heart, confirming the presence of factors released by stem cells in mediating tissue regeneration after injury [3,4]. Moreover, the secretion of factors such as interleukin-10 (IL-10), indoleamine 2,3-dioxygenase (IDO), interleukin-1 receptor antagonist (IL-1Ra), transforming growth factor-beta 1 (TGF-β1), prostaglandin E_2 (PGE_2), and tumor necrosis factor-alpha-stimulated gene/protein 6 (TSG-6) has been implicated in conferring the anti-inflammatory effects of stem cells [5], consistent with positive clinical effects of MSCs in treating Crohn's disease and graft-versus-host disease [6]. Muscle-derived stem/progenitor cells, related to MSCs, also are able to extend life span in a mouse model of progeria through a paracrine mechanism following systemic injection [7]. However, it is unclear what factors released by functional stem cells are important for facilitating tissue regeneration after injury, disease, or aging and the precise mechanism through which these factors exert their effects.

Recently, several groups have demonstrated the potent therapeutic activity of microvesicles, termed exosomes, released by stem cells [8-12]. Exosomes are a type of membrane vesicle with a diameter of 30 to 100 nm released by most cell types, including stem cells [13]. They are formed by the inverse budding of the multivesicular bodies and are released from cells upon fusion of multivesicular bodies with the cell membrane [13]. Exosomes are distinct from larger vesicles, termed

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ectosomes, that are released by shedding from the cell membrane. The protein content of exosomes reflects that of the parental cell and is enriched in certain molecules, including adhesion molecules, membrane trafficking molecules, cytoskeleton molecules, heat-shock proteins, cytoplasmic enzymes, and signal transduction proteins. Importantly, exosomes also contain functional mRNA and microRNA (miRNA) molecules. The role of exosomes *in vivo* is hypothesized to be for cell-to-cell communication, transferring proteins and RNAs between cells both locally and at a distance.

To examine the regenerative effects of MSCs derived from human umbilical cord, Zhou and colleagues used a rat model of acute kidney toxicity induced by treatment with cisplatin. After treatment with cisplatin, rats show increases in blood urea nitrogen and creatinine levels and decreases in apoptosis, necrosis, and oxidative stress in the kidney. Injection into the renal capsule of exosomes purified from hucMSCs, termed hucMSC-ex, resulted in decreases in these indices of acute kidney injury and promoted proliferation of rat renal tubular epithelial cells in culture. These results suggest that hucMSC-ex have the ability to reduce oxidative stress and apoptosis as well as promote proliferation. What is not clear is the mechanism of action through which these potent microvesicles from hucMSCs modulate oxidative stress, apoptosis, and proliferation. Zhou and colleagues provide evidence that hucMSC-ex can reduce Bax and increase Bcl-2 levels in the kidney to modulate apoptosis and stimulate Erk1/2 to increase proliferation. Another group has reported roles for miRNAs and antioxidant proteins contained in stem cell-derived exosomes for repair of damaged renal and cardiac tissue [14]. In addition, MSC exosome-mediated delivery of glycolytic enzymes to complement the ATP deficit in ischemic tissues was recently reported to play an important role in repairing the ischemic heart [15]. Clearly, stem cell exosomes contain many factors, including proteins and miRNA, that can contribute to improving the pathology of damaged tissues.

The significance of the results of Zhou and colleagues and others is that stem cells may not need to be used clinically to treat diseased or injured tissue directly. Instead, exosomes released from the stem cells, which can be rapidly isolated by centrifugation, could be administered easily without the safety concerns of aberrant stem cell differentiation, transformation, or antigenicity. Also, given that human umbilical cord exosomes are therapeutic in a rat model of acute kidney injury, it is likely that allogeneic stem cell exosomes would be effective in clinical studies.

Despite the interesting results of Zhou and colleagues, a number of important questions remain. What are the key pathways targeted by stem cell exosomes to regenerate injured renal and cardiac tissue? Are other tissues as susceptible to the therapeutic effects of stem cell exosomes? Do all stem cells release similar therapeutic vesicles, or do certain stem cells release vesicles targeting only specific tissue and regulate tissue-specific pathways? How can the therapeutic activity of stem cell exosomes be increased? What is the best source of therapeutic stem cell exosomes? Despite these important remaining questions, the demonstration that hucMSC-derived exosomes block oxidative stress, prevent apoptosis, and increase cell proliferation in the kidney makes stem cell-derived exosomes an attractive therapeutic alternative to stem cell transplantation.

Abbreviations

hucMSC: Human umbilical cord mesenchymal stem cell; hucMSC-ex: Exosomes purified from human umbilical cord mesenchymal stem cells; miRNA: MicroRNA; MSC: Mesenchymal stem cell.

Competing interests

The authors declare they have no competing interests.

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