Mesenchymal stem cells-derived magic bullets for burns

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Mesenchymal stem (stromal) cells (MSCs), being divided into embryonic and adult cells, which are obtained and isolated from many different sources, such as adipose, bone marrow, Wharton's jelly, cervical tissue placentae, skeletal muscle tissue, amniotic fluid, liver tissue, dental pulp, synovial membranes, saphenous veins, lung, dermal tissues, periodontal ligaments, human umbilical cord, and human umbilical cord blood, are a heterogeneous population of progenitor cells that possess differentiation ability, in vitro expansion, release of trophic materials, as well as angiogenic, anti-apoptotic, and immune-modulatory properties.[1–7] MSCs are suitable candidates for tissue repair and/or regenerative medicine, and in the treatment of various disease, such as diabetes, organ transplantation, burns, inflammatory and as well as many organ diseases.[1–7]

Human umbilical cord MSCs might be one of the best and preferred candidates for the aforementioned purposes, based on their potential advantages, such as cells obtained by a minimally invasive isolation method, the use with absence of ethical concerns, cells with lower immunogenicity, cells with faster self-renewal ability, cells with relatively stable doubling time, and cells with higher proliferation potency.[1,7–9] Although MSCs are powerful, certain limitations impede the widespread use of MSCs in modern medicine. For example, MSCs cost much to maintain their biological activity; the quantification of bioactive substances (low cell dosage) is always present, and the logistics delivery (the possibility of delayed engraftment) is complicated; all these constitute key obstacles.[1] Therefore, significant efforts to search for an alternative in place of original cell therapy with all advantages of human umbilical cord MSCs as well as the same output and efficacy have consistently been made by physicians and researchers.

Among these, MSCs derived-exosomes, spherical particles with a size of 40–100 nm in diameter and a density of 1.13–1.19 g/mL, produced after the fusion of multivesicular bodies, which are endocytic organelles containing many luminal vesicles with the plasma membrane (two-lipid layers containing sphingomyelin, cholesterol, ceramide, phosphatidyl choline, and phosphatidyl ethanolamine), might be one of the most promising magic bullets.[1,4,8,9] MSCs-derived exosomes have the capacity to transfer or deliver bioactive molecules, such as deoxyribonucleic acid, protein, messenger ribonucleic acid (mRNA), micro RNA (miRNA or miR), lipid, and organelles, from their originating cell to the recipient cells, leading to genetic information exchanges, host cell reprogramming and cellular communication.[1,4,8,9] More and more evidences reveal that exosomes mediate the effects of parental cells via miR delivery.[4] miRs, a cluster of naturally occurring small non-coding RNA molecules of 19–24 nucleotides in length, control gene expression post-transcriptionally by binding to a specific site at the three prime untranslated region (the 3′-UTR) of target mRNA, resulting in mRNA cleavage and translation repression, contributing to at least 60% of the human transcriptome, and playing an important regulators of cellular differentiation and dedifferentiation.[10]

We are happy to introduce the study by Liu et al,[11] published in the last December issue of the *Journal of the Chinese Medical Association*, on the investigation of the value of human umbilical cord MSC-derived exosomal miR-451 on the burn-induced acute lung injury. The authors used an animal model to produce the burn in rats, and found that the lung function of these rats with burns could be successfully preserved while human umbilical cord MSC-derived exosomal miR-451 was applied; and by contrast, this protection of lung function in rats after burn was dramatically inhibited while miR-451 inhibitors were used simultaneously.[11] In addition, the authors evaluated the expression of inflammatory markers, such as tumor necrosis factor (TNF) alpha, interleukin (IL) 1β, and interleukin 6 to support their findings. We congratulated the successful publication of Liu et al.. Since this study is interesting, it is worthy of discussion.

At first, as shown by our previous editorial comment published in the last October issue of the *Journal of the Chinese Medical Association*,[3] stem cell therapy, regardless of what are resources obtained, is a promising and potentially high effective method in the management of burns because stem cells may provide the cell regeneration directly, such as wound healing at the burn site and may influence immune-modulation to minimize the catastrophic events during the healing process after burns, including flare up of severe inflammatory cascade and overwhelming destruction process.[12,13] Care of the burns is not easy, because besides the burn wound, burns also induce systemic effect on hosts. Burn itself not only has a direct damage on the skin and/or respiratory system but also activates the systemic fulminant inflammatory reaction of all organs in the whole body. The former needs an activation of repair system, such as wound-healing process, including inflammation, proliferation, and remodeling phase.[14,15] The latter needs

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tightly orchestral guide and direction, since overproduction of inflammatory mediators, such as TNF alpha, IL-6, may not accelerate the recovery from injury, and by contrast, it may deteriorate the homeostasis of the body, resulting in more harmful effects in the injured body.[16] Liu et al[11] used these inflammatory markers to provide additional evidence to support the beneficial effects in rats with burns treated with MSCs-derived exosomes with high expression of miR-451. In fact, the authors have provided the evidence of functional capacity of the lung in rats with burns after the aforementioned treatment and this effect could be blocked by the adding miR-451 inhibitors into MSCs-derived exosomes for these rats.[11]

Second, it is well known that miR plays an important role for modification of gene function, but we believe that positive or negative effects on diseases may be varied by different types of miRs and they may be also affected by the different amounts. Sequence analysis showed that only 13% of the total RNA content of exosomes is miR, although this estimation might be varied in exosomes derived from different resources.[8] However, sorting of these certain-type miRs from MSCs-derived exosomes with appropriate amount (dosage) may be one of key steps in the successful treatment. As shown by authors, miR-451 was significantly upregulated in human umbilical cord MSCs-derived exosomes.[11] Therefore, the strategy of the authors to test the beneficial role of miR-451 of exosomes on acute lung injury was the transfected miR-451 inhibitors into the exosomes, and the authors confirmed that the protective effect of acute lung injury was significantly impaired in exosomes with deficiency of miR-451, as expected.[11] We did not argue the study design of the authors. However, is there any correlation between the amount of exosomes or their content of miR-451 and effectiveness of decrease or prevention of burn-induced acute pulmonary injury? In addition, was the concentration of 800 μg (RNA concentration) human umbilical cord MSCs a minimal requirement to produce the effect in the reduction of burn-induced acute lung injury? We believe all of them might be interesting and worthy of further evaluation to test the efficacy of MSCs-derived exosomes and their contents-miR in the management of burn-related systemic reaction, including acute pulmonary injury.

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