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Adipose tissue-derived mesenchymal stem cells: a fat chance of curing kidney disease?

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Abstract

Many kidney diseases are associated with inflammation and altered immune response. Mesenchymal stem cells are known for their anti-inflammation and immune-modulation. Demonstration that phenotype and immunosuppressive ability of adipose tissue-derived mesenchymal stem cells (AD-MSC) are not affected by human kidney disease and uremic serum could have potential clinical significance if autologous AD-MSC can be tested to prove their long-term safety and efficacy in treating kidney disease.

Mesenchymal stem cells (MSC) are adult stem cells with the capacity of self-renewal and trilineage differentiation into adipocytes, chondroblasts, and osteoblasts. They were first isolated from the bone marrow of guinea pigs in 1970 by Friedenstein and colleagues based on their properties of adherence to plastic and formation of fibroblast colonies. (1)MSC have since been isolated from virtually every organ in mice including fat, liver, spleen, pancreas, kidney, lung, muscle, and brain. Human MSC have also been isolated from umbilical cord tissue and cord blood, placenta and joints. However, there is no unique cell surface marker distinguishing MSC from other stem cells. The International Society of Cell Therapy has suggested the following minimal criteria to define human MSC: "1) MSC must be plastic-adherent when maintained in standard culture conditions; 2) MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules; and 3) MSC must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro.*" (2) Although these criteria have been adopted to identify MSC isolated from other animal species, murine MSC are known to express a different set of markers. As cells are expanded in culture dishes, the surface molecules and their level of expression may change as well.

Bone marrow-derived MSC (BM-MSC) constitute the major source of MSC and are best studied. The widely used method for isolation of BM-MSC involves density gradient centrifugation to obtain nucleated cells, removal of non-adherent hematopoietic cells from plastic-adherent MSC, and expansion of MSC in culture. A similar method is used to isolate and expand MSC from other organs. The resulting cells are usually heterogeneous with

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variable self-renewal and differentiation capacities. Many of the cells represent mesenchymal stromal cells, thus raising the concern of “stemness” or true stem cell property in the mixed population. Although MSC isolated from different sources share a considerable degree of overlap in their surface molecular expression profile, they are known to have variations in the pattern and level of expression at different times in culture. For example, MSC isolated from human adipose tissue are known to express CD34 initially, but later CD34 expression is down-regulated in culture. Presently, there are no uniform markers that identify MSC isolated from all sources.

Roemeling-van Rhijn et al. (3) isolated MSC from the adipose tissue of humans with end-stage renal disease (MSC-RD) (mean GFR of 10.3 ml/min/1.73 M^2) and control subjects (mean GFR of 76.8 ml/min/1.73M^2) using culture method (Figure 1A). The immunophenotype, adipogenic and osteogenic differentiation, immuno-modulation, and genetic stability of MSC-RD were compared with control MSC. The authors did not find any differences in the above characteristics. One interpretation of the results would be that the biological properties of adipose tissue-derived MSC are not affected by renal failure. However, derivation of MSC requires weeks of cultures in medium containing 15% fetal bovine serum, so it is also possible that cells from either source may have undergone adaptations in culture. To exclude this possibility, the authors performed flow cytometric analysis on freshly isolated $CD34^+$ and $CD73^+$ non-hematopoietic and non-endothelial cells from adipose tissue. No difference in the expression of CD90, CD105 and CD166 was detected between MSC isolated from controls and patients with renal disease, thus providing some reassurance in surface molecular expression. It remains unknown whether freshly isolated MSC from either renal patients or control subjects exhibit self-renewal and trilineage differentiation. The small number of cells before culture expansion limits further studies to answer this question.

Using mixed lymphocyte cultures, the authors showed that MSC-RD inhibited the proliferation of activated peripheral blood mononuclear cells (PBMC). To address whether this immunosuppressive ability was affected by uremia, the authors tested the effects of MSC-RD in the presence of uremic serum and discovered that cell proliferation was inhibited similarly in the presence of uremic serum or control serum. This result could have clinical significance if autologous MSC are used to induce or modulate immunosuppression in renal failure patients who need kidney transplantation. Animal and human studies have shown that the number and function of endothelial progenitor cells (EPC) are reduced in renal failure. (4) Although studies presented here by Roemeling-van Rhijn did not examine whether uremic condition influenced the initial number of cells expressing markers commonly used to identify MSC, the cells isolated from controls and patients with renal failure showed similar population doubling time when both were maintained in culture conditions up to 70 days. Taking a step further, the authors tested the population doubling time of MSC-RD in cultures supplemented with 10% control human serum or sera obtained from pre-dialysis and dialysis patients. No difference in the proliferative capacity was detected, further supporting the conclusion that uremia does not affect the growth of MSC in culture. Although the cells could be maintained in culture for months, the studies presented here did not address whether they were true stem cells that could self-renew and proliferate from a single cell colony.

The physiological function of BM-MSC is to provide extracellular matrix, cytokines and growth factors that are needed for the normal development, maintenance and differentiation of hematopoietic stem cells. MSC are a rare population in the bone marrow representing less than 1 in 30,000 nucleated cells. Under culture conditions, MSC isolated from various tissues can be expanded within weeks to achieve the numbers needed for potential clinical application. In the last two decades, studies have explored the use of MSC as immune-modulators, cell replacement agents or delivery vehicles for therapeutic purposes (Figure 1B). There are currently 225 registered clinical trials (www.clinicaltrails.gov) using MSC to treat various conditions including wound healing, bone defects, graft-versus-host disease, inflammatory diseases, organ ischemic injury and diabetes. To date, most trials are in the recruitment phase and have not had sufficient data to demonstrate sustained effects. Animal studies have shown that administration of MSC improves renal structure and function after acute kidney injury. The mechanism of renal protection is largely due to paracrine effects that inhibit pro-inflammatory cytokines and stimulate anti-inflammatory cytokines. (5) Although differentiation of MSC into tubular epithelial cells has been reported,(6) most studies indicate that intravenously injected MSC show minimal homing to renal tubules and have limited survival in the kidney environment.(7) A ossible approach to enhance the therapeutic value of MSC would be to increase homing to the kidney, e.g., by overexpressing CD44.(8) Another interesting area of research is to use MSC in conjunction with induction immunosuppression in renal transplant recipients to modulate immunity. A pilot study of two patients who received intravenous injection of autologous bone marrow-derived mesenchymal stromal cells 7 days after living-related kidney transplantation showed increased Treg engraftment in the peripheral blood and modulation of memory CD8 T cell function. After one year of follow up, both patients have stable renal function, and a protocol biopsy in one patient showed normal graft.(9) Further long-term studies in larger populations are required to confirm safety and efficacy.

Safety is a key issue in developing MSC-based therapies. Intra-arterial injection of BM-MSC in kidneys of a rat model of anti-Thy1.1 mesangioproliferative glomerulonephritis results in the appearance of adipocytes in 20% of glomeruli. The affected glomeruli show increased matrix deposition and sclerosis. (10) The undesired adipocyte differentiation in the kidney offsets the initial beneficial effects in preserving glomerular structure and reducing proteinuria. Like many other reports, this animal study raises important safety concerns that must be addressed before moving MSC into clinical trials. Furthermore, injected MSC have been shown to lead to tumor formation in multiple organs, which are thought to be due to chromosomal abnormalities that arise during expansion in culture. Roemeling-van Rhijn et al. examined three samples of culture-expanded MSC-RD using SNP-based whole genome analysis and did not detect any significant changes. Fluorescence in situ hybridization (FISH) of MSC isolated from five controls and three renal failure patients indicated that >95% of the cells had a normal karyotype. However, a small number of tetraploid cells were detected after 10 population doublings, an amount of expansion that is often required to obtain sufficient number of cells for clinical applications.

The studies by Roemeling-van Rhijn et al. demonstrated that the phenotype of adipose tissue-derived MSC isolated from renal failure patients and control subjects is similar. While maintaining enthusiasm in utilizing our own fat tissue-derived MSC for potential treatment

of kidney disease, it is critical that we perform thorough testing in animal models before conducting human studies and continue long-term monitoring for safety and efficacy.

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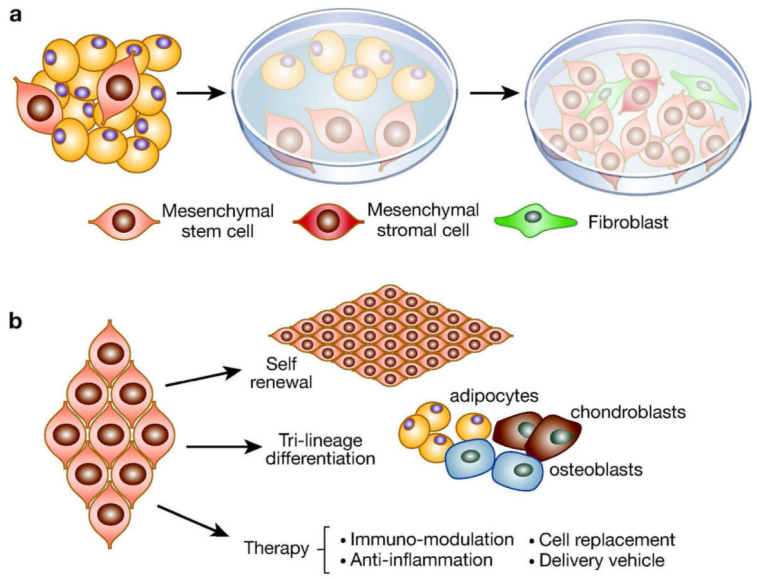

Figure 1.

Mesenchymal stem cell isolation, characterization and potential therapeutic use. A. Adipose tissue-derived stem cells can be isolated by culture expansion of plastic-adherent cells followed by cell characterization. Please note that cells in culture are heterogeneous. They include mesenchymal stem cells, stromal cells and fibroblasts. B. Mesenchymal stem cells are characterized by their properties of self-renewal and differentiation into adipocytes, chondroblasts and osteoblasts. The cells could potentially be used to treat diseases by providing immuno-modulation, anti-inflammation, cell replacement as well as delivering therapeutic agents.