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Adipose derived mesenchymal stem cells and their role in management of kidney diseases

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ABSTRACT

Kidney diseases are universal and researchers are trying to figure out how to manage them. Meanwhile, stem cells are a promising source of therapy that has been considered for various kinds of illnesses. Here, we are going to present the newest studies allocated to the role of adipose-derived stem cells in the management of kidney diseases (e.g. acute and chronic kidney diseases, diabetic nephropathy, and rejection). By searching in PubMed, 34 paper related to the topic were reviewed. Various diseases and pathophysiologic aspects of them have been considered in their presentation, as well. Route of injection, combination therapy, and scaffolds are among the other subjects.

Keywords: Adipose-derived mesenchymal stem cells, Extracellular vesicles, Diabetic nephropathy, Nephrotoxicity, Renal ischemia

Review

Implication for health policy/practice/research/medical education:
Adipose-derived mesenchymal stem cells are a promising source for the management of kidney diseases.
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Introduction

Hypertension, diabetes mellitus, and obesity; components of metabolic syndrome and their consequences e.g. kidney diseases are growing worldwide. However, their managements are unsatisfactory. One of the promising fields in this era is "stem cells related management".

Mesenchymal stem cells (MSCs) are multipotent cells that can differentiate into quite a lot of cell types, for example, chondrocytes, adipocytes, and osteoblasts. They are fibroblast-like cells that primarily were derived from bone marrow (BM) in the 1960s. MSCs are considered as exceedingly encouraging cells for allogeneic cell rehabilitation. The MSCs' assets include astonishing self-renewal ability, immunomodulation, and perhaps the most important, secretory characteristic which modifies cellular dysfunctions. The prerequisite to substitute or restore injured tissues is growing. The use of stem cells is acknowledged to be more valuable than differentiated cells since stem cells can be acquired without difficulty and in higher sizes, have a much upper proliferation capacity, undertake senescence later, and can be differentiated into a varied range of anticipated cell phenotypes. In tissue engineering in vitro, this differentiation can be induced by growing the cells on scaffolds with proper composition. There are three types of stem cells containing embryonic stem cells, induced pluripotent stem cells, and adult stem cells. MSCs can be isolated from neonatal tissue, including umbilical cord MSCs and human umbilical cord blood MSCs. These cells have received considerable attention due to better immunomodulatory characteristics and proliferation rate as compared to bone marrow-derived stem cells (BMSCs). MSCs can be separated from peripheral blood, synovial fluid (SF-MSCs), and dental pulp (DMSCs) as well. MSCs can be recognized by a unique panel of positive cell surface antigens (CD29, CD73, CD90, and CD105) and negative cell surface markers (CD14, CD11b, CD19, CD34, CD45, CD79, and HLA-DR) (1,2).

For the first time, adipose-derived mesenchymal stem cells (ADMSCs) were separated from fat aspirate by a special enzyme in 2001. There is both white and brown adipose tissue, which acting different natural roles. Brown adipose tissue is recognized for its thermogenic properties. In humans, the volume of brown adipose tissue largely shrinkages through growing ages and approximately is lacking in adults. White adipose tissue is mutually an

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energy storage location and an endocrine organ. Especially, the stem cells in white adipose tissue may have superior differentiation potential. ADMSCs are established in the perivascular region of white adipose tissue, which contains subcutaneous fat deposits. Meanwhile, there is adequate of it, and could be isolated easily, therefore ADMSCs have been considered for requests in regenerative medicine (3).

There are many animal and human studies as well, which show encouraging results in the field of kidney diseases management via ADMSCs transplantation. In the current paper, a couple of these studies are reviewed (Figure 1).

Acute kidney injury

A systemic review including seventy-two animal studies about ischemia-reperfusion injury, achieved by Shang et al showed that ADMSCs were the most-researched stem cells, and they possibly hold the highest therapeutic potential (4).

Acute kidney injury (AKI) is a multipart medical disorder allied with substantial morbidity and mortality and without an actual cure. In a study, ischemia-reperfusion injury caused a significant decline in creatinine clearance. This change was reduced by the use of ADMSCs and was accompanied by meaningfully dropped injury scores. This outcome shows that the use of ADMSCs improves renal injury and dysfunction related to ischemia (5).

Ischemia/reperfusion (I/R) is the most prevalent etiology of AKI. Glomerulus, tubules, and capillaries are injured during I/R. Inflammation leads finally to necrosis and apoptosis. Monteiro et al showed that during kidney infarction made by renal artery obstruction, lesser grade of necrosis and upper tubular vascularization are observed in the groups treated with ADMSCs, predominantly in the group cured with intrarenal ADMSCs 48 hours following damage. Hussein et al on the other hand showed that ADMSCs treatment significantly increases stromal cell-derived factor 1 (SDF-1α) and Hypoxia-inducible factor 1 (HIF-1α) expressions. Besides, it initiated a significant decrease in caspase-3 in the kidney compared with the control group ($P < 0.05$) (6,7).

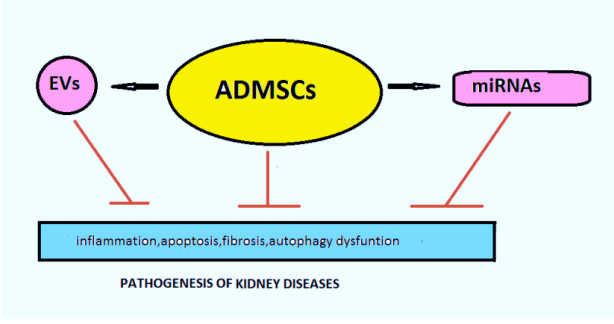

Figure 1. Adipose derived mesenchymal stem cells adapt the pathogenesis of kidney diseases through different mechanisms. EVs, Extracellular vesicles; ADMSC, Adipose derived mesenchymal stem cells.

Renal cells lose their proteostatic capability following offensive circumstances which activates the unfolded protein response or ER stress. Apoptosis began when the cells cannot maintain protein homeostasis. Accordingly, gentamicin and cisplatin nephrotoxicity lead to apoptosis of tubular cells in the kidney. ADMSC treatment as He et al showed improved tissue damage and endoplasmic reticulum stress in gentamicin-induced AKI in mice and dogs (8).

Acute kidney injury predisposes to chronic injury. Experimental folic acid (FA) induced AKI leads to kidney fibrosis similar to medical observation. Conversely, Burgos-Silva et al evaluated the effect of ADMSCs in a trial model of nephrotoxicity persuaded by FA in mice. They disclosed that ADMSCs treatment reduced interstitial collagen deposition (9).

Cisplatin is well known nephrotoxic agent. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein. It's Up-regulation on the surface of proximal tubular epithelial cells is an indicator of AKI. ADMSCs could improve renal function in cisplatin-induced nephrotoxic as Begum et al showed. It could decrease KIM-1 expressions in the kidney of mice exposed to cisplatin (10).

Hyaluronic acid is a polysaccharide in the extracellular matrix (ECM) and attaches to CD44 receptors. CD44 receptor has a vital role in cellular proliferation, migration, and adhesion. Moreover, CD44 and its major ligand -hyaluronic acid- enhanced the transfer of MSCs in AKI. Likewise, the CD44 gene is upregulated in the renal tubular epithelium during I/R injury. In a study, treatment with either ADMSCs or hyaluronic acid +ADMSCs triggered a decrease in, inducible nitric oxide synthase (iNOS) and malondialdehyde (MDA) concentrations and on the other hand increase in reduced glutathione (GSH)and superoxide dismutase (SOD) concentrations compared to the control group. Furthermore, hyaluronic acid + ADMSCs group showed substantial improvement in these parameters regarding ADMSCs group. These results suggest that preconditioning of ADMSCs with hyaluronic acid enhanced their cytoprotective effect by suppression of oxidative stress and apoptosis (11).

Hyperbaric oxygen (HBO) therapy decreases circulating amounts of inflammatory cytokine and recovers the blood flow in the ischemic region. The latest observation has moreover confirmed that HBO therapy protected against ischemia-reperfusion damage chiefly through inhibiting oxidative stress and augmenting angiogenesis. A study by Ko et al presented that combined HBO and autologous ADMSCs therapy was superior to either alone at protecting renal function against oxidative stress. The expressions of dystrophin and zonula occludens (ZO-1) glomeruli, two integrity markers of podocyte components, are meaningfully higher in I/R-HBO-ADMSC compared to I/R-HBO and I/R-ADMSC. Moreover, the expression of nephrin, another indicator of podocyte component integrity in glomeruli, predominantly in the renal tubule,

displayed an identical pattern to ZO-1 among the groups. Likewise, the protein expressions of inflammatory (TNF-α) and apoptotic (mitochondrial-Bax) markers displayed an equal arrangement to blood urea nitrogen (BUN)/creatinine (12).

Another opinion, conversely describes that hypoxia can expand the healing potential of ADMSCs, reduces their apoptosis, and induces their proliferation and anti-inflammatory possessions. Moreover, hypoxia surges the discharge of elements accompanied by immunomodulation. The study by Collino et al revealed that hypoxia rises the ADMSCs capability to secrete extracellular vesicles (EVs) that promote higher anti-oxidative stress reactions, immunomodulatory and antiapoptotic effects in renal tissue compared with EVs secreted in normoxia (13).

Chronic kidney disease

Progressive interstitial fibrosis is the main pathological component of obstructive kidney injury. At the early stage, inflammatory cell infiltration into the renal interstitial compartment is mediated by chemokine production. Renal expression of transforming growth factor beta 1 increases progressively after the onset of obstruction which stimulates fibroblasts, resulting in collagen deposits in the renal ECM. Subsequently, glomerulosclerosis is observed in patients with ureteropelvic junction obstruction. Interestingly, ADMSCs administration alleviates kidney damage in laboratory animals by lowering TGF-β1 concentration (14).

Systemic lupus erythematosus (SLE) is a devastating autoimmune disease that has inadequate management options. In SLE, antigen-antibody complexes are formed and consequently trapped in the basement membrane zone of many tissues including kidneys. mTOR is an abundant serine/threonine kinase that controls cell growth and proliferation which is activated in SLE. Elevated IL-17 cytokine production, intervened by mTORC1 (mechanistic target of rapamycin complex 1), has an important role in disease pathogenesis. During a study in the murine model of SLE, it was shown that compared with the control group, the ADMSCs transplanted group had a significant improvement in histologic abnormalities. Moreover, a substantial reduction of renal IL-17 expression was observed in the latter group (15).

Sepsis

Sepsis syndrome is the general inflammatory reaction accompanying infections. Sepsis syndrome is the most important reason for mortality in cases admitted to hospitals. Kidneys are frequently injured in sepsis syndrome situations. Chang et al verified both healthy ADMSCs-derived exosomes and apoptotic -ADMSCs-derived exosomes, induced by 12 hours hypoxia/12 hours starvation were comparably effective at alleviating sepsis syndrome. The expressions of inflammation markers (TNF-α/ matrix metalloproteinase-9) and oxidative stress, in the renal parenchyma, demonstrated an equal form of inflammatory intermediaries (16). Eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, is an impressive inflammation regulator that modulates the secretion of inflammatory agents. EPA preconditioned ADMSCs and nonpreconditioned cells revealed comparable viability and differentiation capacity, collective mainly in the lungs and kidneys following systemic administration as Silva et al observed. Nevertheless, Compared to the latter group, EPA-preconditioned ADMSCs reduced acute tubular necrosis and caused an augmented secretion of pro-resolution and anti-inflammatory mediators [resolvin D1 (RvD1), prostaglandin E2, interleukin 10 (IL-10), and TGF-β (transforming growth factor-beta)] (17).

Angiotensin receptor blockers (e.g., valsartan) as well as melatonin are strong scavengers of reactive oxygen and nitrogen species and inhibit inflammation and oxidative stress. The latest observations have revealed that ischemia/reperfusion damage can be successfully managed by melatonin. Besides, studies have displayed that the cell stress signaling of PI3K/Akt/mTOR is regularly triggered by chronic kidney disease (CKD) circumstances. Yang et al demonstrated that ADMSCs accompanied by melatonin and valsartan conserve the residual renal function in CKD rats by upregulating PI3K/Akt/mTOR axis. Besides, Oxidative-stress, fibrosis, and apoptosis are prohibited (18).

Diabetic nephropathy

The existing management for diabetic nephropathy (DN) predominantly consists of blocking the renin-angiotensin-aldosterone axis which is not satisfactory. A study by Hao et al identified that ADMSC-derived exosomes hold the potential to alleviate DN pathogenesis. They diminished urine albumin/creatinine ratio and repressed fibrosis in DN rats. The exosomes also inhibited the synthesis of IL-6, glomerular mesangial cells hyperplasia, and promoted cell apoptosis (19).

Exenatide is broadly used in diabetic type 2 cases. It stimulates glucagon-like peptide-1 (GLP-1) receptors. Remarkably, the therapeutic effects of GLP-1 receptor agonist particularly their co-administration with mesenchymal stem cells exhibited notable development of kidney function in acute and chronic kidney injury prototypes. On the other hand, a study by Habib et al revealed that exenatide enhances ADMSCs renoprotective effects in DN by suppressing inflammation, apoptosis, and fibrosis (20).

Rejection

Kidney transplantation has enhanced the survival of renal end stages cases. Nevertheless, it is accompanied by several side effects including infection as well as cancer. Thus, it is essential to create new approaches such as cell-founded treatments to modify the immune reaction, stimulating a

state of graft tolerance. In a rat model of kidney rejection, Ramirez-Bajo et al displayed that autologous ADMSCs rather than their EVs, prolonged recipient and graft survival. The improvement of graft function might be related to improvement in tubular injury. Moreover, the application of donor-derived ADMSCs was risky, and all rats died earlier than the end of the protocol (21).

Costimulation blockade is a developing plan in transplantation that avoids the necessity for permanent immunosuppressive administration by preventing the motivation of the immune system. OX40 and OX40 ligands are costimulatory receptors on activated T cells and antigen-presenting cells respectively, persuading cytokine production and cell proliferation. It has been verified that the blockade of the OX40-OX40L pathway can encourage antigen-specific T cell anergy in acute kidney allograft rejection. Besides, Liu et al proposed that ADMSCs therapy and OX40 costimulation blockade noticeably prolongs the mean survival time of renal grafts and considerably downregulates the (IFN-γ) and upregulates IL-10, TGF-β, and forkhead box protein 3 (Foxp3) (22).

Nephrolithiasis

Nephrolithiasis is a public health problem. Several causes containing genetics as well as environmental factors involve in its pathogenesis. Urinary tract stones are commonly made of calcium oxalate (CaOx). Observations displayed that miR-20b-3p is down-regulated in rat kidney stone formers. Handling with miR-20b-3p-enriched exosomes from ADMSCs as showed by Shi et al protected ethylene glycol-induced hyperoxaluria in rats and cell experiments established that co-culture with miR-20b-3p-enriched exosomes, lessened oxalate-induced cell over- stimulated autophagy and inflammation (23).

Route of injection

The value of renal injury rehabilitation by stem cell, have been confirmed by numerous observations. Intravenous (IV), intra-arterial and intraparenchymal injections have been experienced in animal models of renal injury. While IV delivery is non-invasive, pulmonary entrapment diminishes the mass of stem cells in the renal parenchyma. Intra-arterial supply resolves this problem. Nevertheless, it is invasive and has the risk of vascular occlusion. Direct renal parenchyma injection is invasive as well. In a study achieved by Thin et al, ADMSCs were injected into the renal artery using ultrasound guidance. Imaging and histology results established that ultrasound-guided renal artery injection is feasible in mice and can effectively convey an enormous percentage of cells within the kidney (24).

Combination therapy

Combined ADMSCs and ADMSCs-derived exosome therapy as Lin et al verified, protected rat kidney from acute ischemia-reperfusion (IR) injury. The protein expression of oxidative stress, inflammatory and apoptotic biomarkers revealed that combined exosome-ADMSCs therapy was superior to either one for keeping the kidney safe from acute I/R injury (25).

Extracellular vesicles

Extracellular vesicles are membrane-bound packages. They are released by many cells types, including MSCs (26,27). EVs were thought to function solely as the "dumpster" of cells, a way to organize undesirable proteins, however, they have now appeared as one of the important mediators in cell–cell communication for various processes such as differentiation, proliferation, immune response, and angiogenesis. There are three known EVs: apoptotic bodies, microvesicles, and exosomes.

Human urine-derived stem cells (USCs) can be appropriately attained noninvasively. Solitary clones of USCs may grow to a massive quantity. Exosomes secreted by urine-derived stem cells as Jiang et al revealed have the potential to endorse renal restoration by blocking podocyte apoptosis, surge glomerular endothelial cell proliferation, and discontinue the caspase-3 production in diabetic rats (28).

The promotion of autophagy flux is a goal in preventing podocyte damage in DN. On the other hand, the mTOR signaling initiation leads to augmented podocyte damage in diabetic renal injury which theoretically proposes the inhibition role of mTOR on the autophagy phenomenon of podocytes. A new study emphasized the role of exosomes derived from ADMSCs in contradiction of the development of DN. It was demonstrated that ADMSCs-Exosomes intensely improved DN symptoms by augmenting the expression of miR-486 which led to the inhibition of the Smad1/mTOR signaling pathway in the podocyte (29).

Toll-like receptor 4 (TLR4), is a receptor for lipopolysaccharides and takes part in the pathogenesis of DN as well. Furthermore, it is recognized as a downstream target gene of miR-26a-5p. Upregulation of nuclear factor kappa B (NF-κB) by TLR4 on the other hand, can stimulate the expression of vascular endothelial growth factor A (VEGFA), which induces albuminuria in DN. Duan et al exhibited that miR-26a-5p is extremely expressed in EVs derived from MSCs. Loss of miR-26a-5p led to the progress of DN in streptozotocin-induced diabetic mice. They postulated that ADMSCs-derived EVs transferred miR-26a- 5p to other cells modifying the development of DN by pointing TLR4 and modulating NF-κB and VEGFA (30).

Conclusively, these studies propose that exosome secreted from stem cells is the main paracrine regulator for cell/tissue repair.

Scaffolds

Extracellular matrix scaffold can be arranged by

decellularization of natural tissues. Decellularized scaffolds significantly participate in the cell adhesion, proliferation and differentiation of stem cells into various types of kidney cells.

Choi et al explored the co-culture of rat bone marrow mesenchymal stem cells (rBMSC) and its glomerulus endothelial cell (rGEC) to grow microvascularization in the kidney scaffold. Co-cultured cells were inserted through a decellularized kidney scaffold artery. Appropriate flow rate (1 mL/min) was selected based on inflammation/endothelialization proteins expression level. The optimized perfusion rate under rGEC+rBMSC co-culture conditions bring about an improved ECM-derived implantable renal scaffold (31).

ECM hydrogel (ECMH) can be a perfect transport scaffold for partial stem cell transplantation. Zhou et al established an adapted plan to make the ECMH. They arranged a renal ECMH from natural ECM constituents by a revised procedure of kidney decellularization and a new approach of gelation, which could optimize the usage of bioactive components in the ultimate ECMH. In vivo and in vitro evidence designated that the kidney ECMH could progress the retention and survival rate, along with multiple biological functions of ADMSCs. As expected, it repaired the histological and functional loss of injured kidneys persuaded by ischemia-reperfusion (32).

Human studies

There are few studies about the management of kidney diseases by ADMSC. One of them showed that renal arterial infusion of ADMSC modifies atherosclerotic renovascular disease and post-stenotic kidney tissue injury. ADSMC infusion increased renal blood flow and reduced cortical hypoxia. Furthermore, glomerular filtration rate remained stable contrary to the control group (33).

Another one describes the portal infusion of ADMSC and hematopoietic stem cells (HSC) to kidney transplanted recipients as superior to HSC-only infusion because of higher both case and graft survival rates. Besides, both groups needed reduced immunosuppression compared to controls (34).

Conclusion

Various types of kidney diseases are spreading worldwide, however, satisfactory managements are not available, so it is worth discussing the pros and cons of their management utilizing stem cell transplantation and its future. In the current paper, MSCs and their mechanisms of action are described. Furthermore, a couple of studies related to the management of different kidney diseases by ADMSCs transplantation are reviewed.

They are arranged by different diseases and diverse pathophysiologic aspects as well. Rout of injection, combined therapy, extracellular vesicles, and scaffolds are likewise discussed.

Authors' contribution

Conceptualization: Farahnaz Dadras.
Data curation: Farhad Khoshjou.
Investigation: Farhad Khoshjou.
Methodology: Farahnaz Dadras.
Project Administration: Farhad Khoshjou.
Supervision: Farhad Khoshjou.
Visualization: Farahnaz Dadras and Farhad Khoshjou.
Writing–original draft: Farahnaz Dadras and Farhad Khoshjou.
Writing–review & editing: Farahnaz Dadras and Farhad Khoshjou.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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