Mesenchymal Stem Cells and Diabetic Nephropathy

Bing Liu, Guanqiao You, Li-na Zhang, Lin Tao, Hui Chen, Feng-min Shao

Department of Nephrology, Henan Provincial People's Hospital, Zhengzhou, Henan 450003, China
Email: bingliu6699@126.com

【**Abstract**】 Mesenchymal stem cells (MSCs) are a class of self-renewing, multilineage differentiation potential, immune regulation and low immunogenic cells. MSCs are able to differentiate into osteoblasts, chondrocytes, adipocytes, muscle (tendon) cells, hepatocytes, neurons and other cells. Because of their immunomodulatory ability, capacity for self-renewal, and differentiation into mesodermal tissues, MSCs are described as new choice in the treatment of various diseases, including diabetes mellitus, diabetic nephropathy. In this article, we review the research progress for MSCs therapy in diabetes nephropathy.
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MSCs are an extensive source of multipotent progenitor cells, and can be obtained from bone marrow, umbilical cord blood, or adipose tissue, various tissues. The shape of MSCs is similar to fibroblasts. MSCs show variable expression levels of several molecules: CD105, CD73, Stro-1, CD44, CD90, CD166, CD54/CD102 and CD49[1,2], MSCs lack the expression of surface markers characteristic for hematopoietic stem cells CD14, CD45, CD11a/LFA-1, erythrocytes (glycophorin A), platelet and endothelial cell markers (CD31)[3].Very low expression levels of MHC-I antigen, lack the expression of MHC-II antigen and FasL. Therefore, MSCs cells also have the characteristics of low immunogenicity.

The main functional characteristics of MSCs are their immunomodulatory ability, capacity for self-renewal, and differentiation into tissues of mesodermal origin. MSCs are able to differentiate into several cell types, including cardiomyocytes, vascular endothelial cells, neurons, hepatocytes, epithelial cells, and adipocytes. MSCs can inhibit T lymphocyte proliferation induced by MAPK, antibody or antigen stimulation, through direct contact between cells and the secretion of soluble cytokine, [4,5,6]. MSCs can promote B cell proliferation and immunoglobulin secretion[7], inhibit the maturation of dendritic cells and the diversion for lymph[8]. MSCs can induce extracellular matrix formation, lymphocytes homeostasis and hematopoietic precursor cell differentiation, support and update the immune system, involved in immune regulation, immune tolerance[9]. Because of these biological properties, MSCs are described as the choice of treatment of various diseases, including diabetes mellitus. In this review, we discuss the research progress for MSCs therapy in diabetes nephropathy.

1. Mesenchymal stem cells and type 1 diabetic nephropathy

Type 1 diabetes mellitus is an organ - specific T cell mediated autoimmune diseases. Islet auto antibodies is produced due to the role of genetic, environmental and other factors under the body .The infiltration of T lymphocytes damages the islet beta cell, which resulting in the absolute lack of insulin secretion. The incidence of type 1 diabetes is increasing in recent years, because of the serious complications of the diabetes heart disease, nephropathy, neuropathy and retinopathy, has become an important problem threatens human health [10].Once type 1 diabetes happens the lifelong insulin is required. Islet transplantation can achieve insulin independent effect, but the rejection and the shortage of donor limit its clinical application. Because of its potential of multi-directional differentiation and immune regulation function, MSCs has the ability to treat patients with type 1 diabetes and its chronic complications. Diabetic nephropathy is a common and serious complication of diabetes. It is a progressive renal disease caused by glomerular disease. And there are less effective interventions.

Lee *etal*[11]found that by the transplantation of human bone marrow mesenchymal stem cells (hMSCs) to a small dose of streptozotocin (STZ) NOD / SCID mice with type 1 diabetic nephropathy, the mice blood glucose levels decreases, murine insulin level is higher, mesangial is thickening and macrophage infiltration is reduced. Migration to the kidney of human bone marrow MSCs could differentiate into vascular endothelial cells CD31+ after transplantation. But after one month only a small amount of hMSCs differentiate into glomerular endothelial cells, which suggested that MSCs transplanted into the kidney could not proliferate. May be it improves renal function by scavenging cytotoxic molecules in vivo or promoting angiogenesis. In mice with T1DM induced by the administration of five low doses of streptozotocin, Ezquer *et al*[12] showed that the intravenous administration of

syngeneic MSCs (≈20x106/kg body weight) results in the reduction of microalbuminuria an d the preservation of normal renal histology. By contrast, untreated diabeticmice remained albuminuric and presented glomerular hyalinosis and mesangial expansion.

It is suggested that bone marrow derived mesenchymal stem cell transplantation can be used as a cell therapy for the treatment of type 1 diabetes mellitus and renal complications, preventing the progression of renal disease. The study indicated that MSCs transplantation to diabetic nephropathy mice, promote necrosis kidney tissue reconstruction, glomerular structure restoration, renal function improvement.

2. Mesenchymal stem cells and Type 2 diabetic nephropathy

Type 2 diabetes is generally considered to be a heterogeneous disease with a genetic or more genetic. Environmental factors include obesity, lack of activity and aging etc. The main performance of the clinical symptoms is insulin resistance and inadequate insulin secretion. Although many drugs have good effects for lowering blood glucose, controlling blood pressure and correcting the disorder of lipid metabolism, Prevention and treatment of complications caused by T2DM is still not ideal. Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD), accounting for 40% -50% of patients with ESRD[13,14]. Early damage of DN performs the ability of self-regulation decreased, especially the elasticity decline of the afferent arteriole make the kidney High filtration and high perfusion. Many studies have shown that prostaglandins, nitric oxide, and vascular endothelial growth factor, TGF-β, renin-angiotensin system, especially angiotensin - Ⅱ changes involved in the excessive production of mesangial matrix, basement membrane thickening, podocyte damage and increased protein leakage and glomerular sclerosis [15].

Mesenchymal stem cells for treatment of homing type 1 diabetic nephropathy in the pancreas and kidney, by way of increase insulin secretion, to decrease blood glucose, promote kidney recovery, and improve renal function. So for the type 2 diabetic nephropathy, how does mesenchymal stem cell effect? Zhou *et al* [16] use CD29, CD44, CD105 surface marker positive and CD34, CD45-negative ,bone marrow mesenchymal stem cells were identified 2 × 106 MSCs/200ul by cardiac injection after in vitro expansion culture transplanted into diabetic nephropathy rats, MSCs were cultured in vitro antigen expression of mesenchymal cell phenotype, can have more differentiation, osteogenic, adipogenic cells. Chemokines in vivo to the damaged kidney, but found no proliferating cells in the stem cell colonization parts. After 1 week of the stem cell therapy, transplant group compared with diabetic nephropathy control group get lower blood glucose. Until 2.8 week, the transplant group compared with diabetic nephropathy in the control group, 24 h urinary protein decreased, but the difference was not statistically significant. Stem cell transplantation group creatinine clearance rate is lower than the control group of diabetic nephropathy, two weeks after treatment, and the difference was statistically significant. In the first two weeks, stem cell transplant group owned lower renal hypertrophy index compared with diabetic nephropathy control group, but higher than the normal control group. Conclusion that MSCs cultured in vitro markers after in vivo chemotaxis to diabetic nephropathy, diabetic nephropathy can temporarily improve. Liu *et al*[17] used the transplantation of bone marrow-derived mesenchymal stem cell to therapy diabetic nephropathy rats by small doses of Chain urea streptozotocin (STZ) plus high fat diet induced. Negative surface markers such as CD34, CD45, and CD44, CD71, CDl05 positive identification of bone marrow mesenchymal stem cells with BrdU and successful to the mark. Immunofluorescence detection of post-transplant insulin and BrdU-labeled cells of rats: STZ islet destruction obvious, the islet increased after implantation of bone marrow mesenchymal stem cells; the STZ group serum insulin to maintain a high level, insulin levels decreased after treatment, serum adiponectinhormone increased, blood glucose decreased, reduced urinary albumin excretion, glomerular average cross-sectional area and the mean glomerular volume are reduced. Visible BrdU labeling-positive cells in the pancreas, kidney tissue. Conclusion that via the tail vein injection of bone marrow mesenchymal stem cells can be positioned in the type 2 diabetic rat pancreas and kidney, and repair the damage to the pancreas and kidney, lower blood glucose, reduce urinary albumin excretion and reduce serum insulin levels, to improve the content of serum adiponectin and improve insulin resistance.

To determine whether the renoprotective effect of MSCs is indirect, i.e. due to hyperglycemia correction, or direct, i.e. due to protection/regeneration of renal tissue, Ezquer *et al*[18,19] administered syngeneic MSCs in a mouse model that develops severe diabetes after the infusion of a single high dose of streptozotocin. Despite not sharing the etiology of either T1DM or T2DM, these animals showed a rapid progression of renal failure and developed most of the pathognomonic signs of DN. In these diabetic mice, MSC administration did not result in hyperglycemia correction; however, renal failure did not progress. In contrast, in untreated diabetic mice microalbuminuria gradually increased and renal histopathological alterations were evident at the end of the study period. Interestingly, at least up to three months after MSC administration donor cells were found in the kidney of severe diabetic mice. Park *et al*[20] application of cord

blood stem cells in the treatment of STZ-induced diabetic nephropathy rats, observed after the success of the model, diabetic nephropathy FN, α-SMA expression and the control group compared to up-regulate E-cadherin down-regulated. Given umbilical cord blood stem cells 1×10^6cells/rat, diabetic nephropathy rats via the tail vein injection of transplantation in the treatment group, reduce proteinuria, reducing kidney expression of FN 、 α-SMA upregulation and E-cadherin downregulation, while blood glucose was no significant difference between groups. The conclusions suggest that the umbilical cord blood stem cells are able to slow the progress of diabetic kidney damage.

3. Conclusion

Because of their immunomodulatory ability, self-renewal, and differentiation capacity, MSCs are expected to become a promising therapeutic agent for improvement of diabetic nephropathy. Among stem cells, MSCs have several advantages for therapeutic use, such as, they are able to home into damaged organs where they may protect the parenchyma from noxa, organize endogenous regenerative mechanisms and/or differentiate into tissuespecific cells. MSCs have the characteristic of immunomodulatory ability, better safety after infusion of allogeneic MSCs. The application of human embryonic stem cells is related to ethical issues. However, there are several outstanding problems about MSCs including potential risk of malignant transformation, differentiation efficiency, the optimal dose, and the cellular and molecular mechanisms behind MSC renoprotection in a diabetic environment, which should be elucidated before the application of MSCs as a novel and efficient therapeutic agent in the treatment of DN.

Corresponding author:
LIU Bing,
Email: bingliu6699@126.com

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