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Immunomodulatory and Anti-Inflammatory Therapeutic Potential of Mscs in Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus

(DM) and the main reason for end-stage renal diseases (ESRD). Currently, inflammation has been recognized as one of the underlying processes involved in the development and progression of kidney disease in the diabetic population. mesenchymal stem cell (MSC) therapy has been considered a promising strategy to ameliorate the progression of DN. They are multipotent and have immunomodulatory effects to assist in the recovery from tissue injury and the inhibition of inflammation. This review discusses recent experimental and clinical findings related to diabetic kidney disease, with a focus on the immunomodulatory and anti-inflammatory role of MSCs.

INTRODUCTION

Diabetes mellitus a metabolic disorder characterized by hyperglycemia is one of the world oldest disease (1). it has become a global health burden affecting 425 million people worldwide according to the International Diabetes Federation (IDF) (2). its complications are classified into '' macrovascular'' and ''microvascular'' representing involvement of arteries supplying heart , brain and lower extremities and damaging to small blood vessels respectively (3). Microvascular complications are grouped into retinopathy, neuropathy and nephropathy (4). approximately one third of all diabetic patient are affected by DN (5) which produces significant social and economic burdens (6) and constitutes the most frequent cause of end-stage renal disease (ESRD) (7, 8). In recent years, many researchers have been convinced that the inflammation pathways play central roles in the progression of diabetic nephropathy. Various molecules related to the inflammation pathways in diabetic nephropathy include transcription factors, pro-inflammatory cytokines, chemokines, adhesion molecules, and nuclear receptors, which are candidates for the new molecular targets for the treatment of diabetic nephropathy (9). Mesenchymal stem cells (MSCs) have immunomodulatory and regenerative effects in many organs, including the kidney. It is believed that their main anti-inflammatory and immunomodulatory effect is exerted through their soluble factors and extracellular vesicle which they secrete (10).

In this review, we summarize the present recognitions on inflammation in diabetic nephropathy and the potential immunomodulatory role of mesenchymal stem cell in diabetic condition induced kidney injuries.

INFLAMMATION IN DIABETIC NEPHROPATHY

the concept of underlying pathophysiologic process leading to DN has evolved tremendously suggesting that there is the involvement of a myriad of deviations from normal homeostasis, including hemodynamic abnormalities, that trigger the increase in systemic and intraglomerular pressure, metabolic abnormalities, oxidative stress, inflammation, fibrosis, and the activation of the renin–angiotensin system (RAS) (11, 12). researches over the past 10 years have shown that inflammation is being a key pathophysiological mechanism (13).in fact, large number of evidences support the role of inflammation in the early phases of clinical and experimental DN. Inflammation in diabetic nephropathy is proved to be as a result of innate and adaptive immune cells interaction with pro-inflammatory cytokines, chemokines and activated intracellular pathways (Figure-1) (14). In such circumstances, the identification of the role performed by innate and adaptive immune cells as well as inflammation-related molecules and pathways which are critically involved in the progression of diabetic nephropathy, would strongly enhance and promote the development of new therapeutic strategies (15, 16).

Macrophages, neutrophiles and TLR (Toll-like receptors) particularly TLR2 and TLR4 which are a family of pattern recognition receptors are responsible for the initiation of the innate immune responses in diabetic nephropathy pathogenesis (17).

Activated Tcells which are mainly found in the interstitium and consists of CD4+ and CD8+ cells have been shown to be

hallmark contributing factor of DN inflammation through their important functional role in adaptive immune response (13).

Diverse inflammatory molecules are involved in diabetic nephropathy including Chemokines and their receptors such as CCL2 (MCP-1) and its receptor, CCR2 CX3CL1 (fractalkine) and its receptor, CX3CR1 CCL5 (RANTES) and its receptor, CCR5, Adhesion molecules such as Intercellular adhesion molecule 1, Vascular cell adhesion protein 1, Endothelial cell-selective adhesion molecule, E-selectin (CD62E) and α-Actinin 4, Inflammatory cytokines such as IL1, IL6 and IL18, Tumour necrosis factor and Transcription factors such as (Nuclear factor κB) (16).

Apart from immune cells and inflammatory molecules, renal tubular cells are also among the most important cell types contributing to the inflammation mediated acceleration of DN progression.in fact as a result of hyperfiltration along with accumulated high glucose and increased energy generation and consumption, cell stress will be provoked leading to free radical overgeneration (18) and subsequently activating DCs and macrophages to initiate a pattern of damage associated with inflammation (19).

Immune cells

Both adaptive and innate immune system have made a key contribution to the progression of DN (20). Apart from an increase in macrophage infiltration and overproduction of leucocyte adhesion molecules in innate immune response (21, 22). the induction of the pro-inflammatory cascade via TLR (Toll-like receptor) activation, specifically TLR2 and TLR4 in diabetic nephropathy can mediate inflammatory responses due to the fact that Ligand-induced signalling of TLRs ultimately induces the activation of NF-κB (nuclear factor κB), a transcription factor central in mediating inflammatory pathways, which then results in renal fibrosis and kidney failure (16, 23).

Researches have demonstrated that the development of DN was related to the infiltration of T cells (including CD8+ T cells) in the kidney (23-26) and their activation in the circulation (27). Activated T cells are thought to be part of an immune mediated Activated T cells are thought to be part of an immune mediated process associated with the development proteinuria in diabetic nephropathy (27). In the early stage of DN, T cells and macrophages migrate and accumulate in glomeruli and interstitium, due to the local release of adhesion molecules and chemokines (28). The process is initiated by cells infiltrating the kidney, which release proinflammatory cytokines (IFN-c, TNF-a and IL-1b) and reactive oxygen species (ROS), thus triggering stress-activated protein kinases, p38 MAPK, and JNK signalling pathways (29) Renal cells subsequently react by releasing chemokines (MCP-1 and CSF-1) and profibrotic factors such as TGF-b (30), thus establishing an inflammatory loop (21) which favours the deposition of extracellular matrix components including type I, II, IV collagen and fibronectin (31). Interestingly, recent evidence suggests that renal cells may ectopically express immune-related molecules. For instance, podocytes potentially express costimulatory molecules during hyperglycaemia in vivo (i.e., B7-1), as this has been shown in other diseases (e.g., focal segmental glomerulosclerosis) (32) thus triggering T-cell activation and maintaining inflammation (33).

DCs (dendritic cells) are critical for both adaptive and innate immune responses (34).Actually, renal DCs create a complicated network in tubule-interstitium, where they continually engulf antigens and present them to T lymphocytes. (35, 36).In kidney diseases, including DN, DCs prefer to migrate to the injury sites and express more chemokines, cytokines and co-stimulatory molecules, acting on renal cells and innate immune cells. Multiple studies have shown that DCs are pathogenic in different kidney diseases, suggesting that DCs are important for the initiation and progression of renal disease (37-40). Unfortunately however, the role for DCs in DN inflammation has not been well studied, in part due to difficulties associated with plasticity and the relative instability of cultured DC cell lines (41). To distinct from renal macrophages, renal DCs are defined as MHC-II+ CD11c+ F4/80− cell subsets in recent research (42) And renal DCs can be further divided into two subsets depending on the expression of CD103. Most importantly, CD103+ DCs accelerate renal injury via activating CD8 T cells in Adriamycin nephropathy (AN) (37) And suppression of CD103+ DCs with Flt3 inhibitor AC220 significantly alleviated renal injury in AN mice, which suggested that CD103+ DCs could be targeted as an effective treatment of CKD (43). more experiments are needed to verify the effect of CD103+ DCs in DN.

Chemokines and their receptors

Increased glomerular and interstitial infiltration of monocytes/macrophages (M/M) has been observed both in human biopsies and in animal models of diabetic nephropathy (44-47). M/M are central mediators of renal vascular inflammation, and their accumulation within the kidney is a characteristic feature in diabetic nephropathy (45, 48). MCP-1/CCL2 is believed to play a key role in mediating M/M and macrophage accumulation into kidney tissues of diabetic patients.(49-51) In addition to mononuclear cells, other non-leukocytic cellular elements, including renal resident cells, are able to synthesize this chemokine (50). several studies point to tumour necrosis factor (TNF)

as the most potent inducer for MCP-1 protein expression (52). In diabetic patients, MCP1 is upregulated in the glomerular and renal tubular epithelium (48, 53). Immunohistochemical studies and in situ hybridization analyses have revealed that upregulation of CCL2 occurs in the tubulointerstitial lesions of patients with diabetic nephropathy (48). this protein has been proposed as a novel biomarker of tubulointerstitial changes and as predictor of renal progression and prognosis in patients with diabetes (52). it has also suggested that its urinary levels are strongly associated with the decline of renal function (54). CXCL (CXC chemokine ligand) 12, also known as stromal cell- derived factor-1) is a homoeostatic chemokine with multiple functions including cell homing, tumour metastasis, angiogenesis and tissue regeneration after acute injuries. CXCL12 is produced by podocytes, contributing to podocyte loss, and specific inhibitors ameliorated proteinuria and glomerulosclerosis in db/db mice (55) Renal CSF1(The chemokine colony-stimulating factor 1)is highly expressed in type 2 diabetic db/db mice (56).

Interestingly, decreasing the levels of renal CSF1, by deletion of the codifying gene in mice, attenuates the infiltration and proliferation of macrophages during renal inflammation(57). CX3CL1 (CX3C chemokine ligand 1; also known as fractalkine) exists in two forms as a membrane-anchored or as a shed 95-kDa glycoprotein. The soluble CX3CL1 has potent chemoattractant activity for T-cells and monocytes and induces adhesion between activated endothelial cells, which express its receptor CX3CR1 (CX3C chemokine receptor 1). Up-regulation of CX3CL1 and CX3CR1 was reported in the glomeruli of STZ-induced diabetic rat kidneys (58).

Adhesion molecules

Adhesion molecules are cell-surface proteins involved in binding cells together or attaching them to the extracellular matrix. Several studies have clearly shown increased expression of cell adhesion molecules in patients with diabetic nephropathy. Upregulation of ICAM1 and VCAM1 occurs in response to proinflammatory cytokines, specifically TNF (59, 60). In mice models, the deletion of the ICAM1 gene ameliorates renal inflammation indicating that ICAM1 contributes to the pathogenesis of DN (61).

Pro Inflammatory cytokines

In diabetic nephropathy, inflammatory cytokines such as IL (interleukin)-1, IL-6, IL-18 and TNF (tumour necrosis factor) are critically involved in pathogenesis (16).

IL-6

Kidneys of patients with DN also present increased expression levels of IL6 in infiltrating cells from the mesangium, interstitium, and tubules. Diverse abnormalities at kidney level have been associated with the raise in the expression of IL6 including changes in the permeability of glomerular endothelium, expansion of the mesangium , increased fibronectin levels (62, 63), and thickness of the glomerular basement membrane (64, 65) urinary concentration of this cytokine is associated with the development of renal hypertrophy (66, 67).

IL-18

IL-18 is a potent proinflammatory cytokine implicated in different actions, including the release of interferon- (IFN-) which stimulates functional chemokine receptor expression in human mesangial cells (68). Serum and urinary levels of interleukin- (IL-) 18 have been reported to be higher in patients with DN than in control subjects, showing significant positive correlations with UAE rate in DN patients (69-71) another functions include: the increase in the expression of ICAM1, and the apoptotic process in endothelial cells (72-74). Renal tubular cells express increased levels of IL18 in patients with DN which has been related to the triggering of mitogen-activated protein kinase (MAPK) pathways secondary to the action of TGFβ (75). Moreover, infiltrating cells in the renal tissue also produce this cytokine (76, 77).

IL-1

IL-1A and IL-1B are structurally distinct forms of IL-1 and they are synthesized by a variety of cell types, including macrophages, B-cells and fibroblasts, and are potent mediators of inflammation and immunity. Increased expression of IL-1 in animal models of diabetes have been demonstrated and they are associated with increased expression of ICAM1, VCAM1 (vascular cell adhesion molecule 1) and SELE (selectin E; also known as E-selectin) (78, 79).

TNF-α

The cytokine TNF is mainly produced by monocytes but also, in a lower extent, by renal cells (endothelial, epithelial, mesangial, and tubular cells) (80-82). Many clinical studies in patients with DN have reported that the serum and urinary concentrations of TNF- are elevated as compared with nondiabetic individuals or with diabetic subjects and kidneys and that these concentrations increase concomitantly with the progression of DN. These findings indicate a potential relationship between the elevated levels of this inflammatory cytokine and the development and progression of renal injury in DM (66, 69). Hypertrophy and hyperfiltration are prominent signs in DN and both have been related to increased TNF expression levels Several harmful effects are elicited in the kidney by TNF including cytotoxicity (83), apoptosis, and necrotic cell death (84, 85). Experimental researches have shown that TNF- induces the activation of NADPH oxidase in isolated rat glomeruli through the activation of the intracellular pathways protein kinase C/phosphatidylinositol-3 kinase and MAPK (86). Finally, in vivo studies in diabetic rats found an enhanced urinary excretion of TNF- excretion, which was related to sodium retention and renal hypertrophy (87, 88).

NF-kB

NF-κB is activated by a wide variety of stimuli such as cytokines, oxygen radicals, inhaled particles, ultraviolet irradiation and bacterial or viral products. In diabetic kidney disease, proteinuria itself is the important activator for NF-κB and is an important pro-inflammatory stimulus for tubular cells (89) in vivo studies demonstrated that temporal changes in NFκB activity occur with the evolution of experimental diabetic nephropathy, and that NFκB seems to be an important mediator of the effects of angiotensin II, predominantly via the type-1 angiotensin II receptor. These effects of NFκB result in an increase in both CCL2 expression and macrophage infiltration in the early stages of experimental diabetic nephropathy. Second, results from in vitro studies have shown that aldosterone increases the transcriptional activity of NFκB in cultured mesangial and epithelial cells (90). The blockade of RAS in diabetic rats provides Reno-protective anti-inflammatory effects through the suppression of NF-κB-dependent pathways, beyond the control of blood pressure and proteinuria (90). In addition, recent experimental studies indicate that suppression of NF-κB activation by various agents, such as 1,25-dihydroxyvitamin D3 (91).

INTRACELLULAR SIGNALLING PATHWAYS

Systemic and local inflammatory cytokines have been shown to activate several intracellular stress pathways in diabetic

nephropathy including c-jun N terminal kinases (JNK) (92), which are members of the family of stress activated protein kinases (SAPK), the JAK2 (Janus kinase 2) and STAT (signal transducer and activator of transcription)-1, -3 and -5 pathway (93), the p38 MAPK signalling pathway, activation of PKC (Protein kinase C) (94), Rho-Kinase Signaling (95), and the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) as the most important regulators of oxidative stress (96, 97).

c-jun N terminal kinases (JNK)

JNK a member of the family of stress activated protein kinases (SAPK) whose Activation of JNK has been described in human diabetic neuropathy is composed of 3 members, of which both JNK1 and JNK2 are implicated in diabetes (92). the role performed by this pathway in mediating inflammatory responses in DN is through both distinct transcription factors (i.e. c-Jun/AP-1) and ones that are shared with p38MAPK (98).

JAK-STAT signalling

it has been shown that the activation of JAK proteins is caused by ROS under high glucose conditions (99). results of different studies demonstrated that overexpression of suppressors of cytokine signalling (SOCS-1 and -3), which are negative feedback regulators of JAK-STAT signalling, reduces activation of STAT1 and STAT3, macrophage infiltration, expression of proinflammatory molecules, renal injury and loss of renal function in rodents with diabetic nephropathy (100, 101) and this may reflect the pathway's role in protecting from inflammation and injury in diabetic kidneys.

the p38 MAPK signalling pathway

activation by the p38 MAPK signalling pathway stimulated by Hyperglycaemia, oxidative stress and ligation of several cell membrane proinflammatory receptors (e.g., IL-1R, TNF-αR and RAGE) in DN translocate to the nucleus where it can modulate a variety of transcription factors via phosphorylation and induce gene expression of proinflammatory molecules(98). According to results of a study, mice deficient in mitogen-activated protein kinase kinase 3 (Mkk3/Map2k3 – an

upstream activator of p38 MAPK) have reduced phosphorylation of p38 MAPK in the kidney, which is associated with suppression of interstitial macrophage accumulation, Ccl2 gene expression, albuminuria and renal dysfunction (102).

activation of PKC (Protein kinase C)

Activation of protein kinase C (PKC) isoforms has also been implicated in diabetic nephropathy. PKC consists of a family of enzymes that phosphorylate serine and threonine residues on intracellular proteins involved in a range of cellular functions (103) including expression of growth factors (104)and regulation of basement membranes. activation of PKC by high glucose or AGEs promotes expression of inflammatory mediators Intercellular Adhesion Molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM-1) and MCP-1, suggesting a role for PKC in diabetic nephropathy (94).

Rho-Kinase Signaling

The activation of the Rho-kinase signaling which is a serine-threonine kinase involved in the regulation and cell proliferation, contraction, and migration of cells by acting on the cytoskeleton increases MCP1 levels and the chemotaxis of monocytes toward glomerular cells, and regulates CSF1 production suggesting that its blockade constitutes a new therapeutic anti-inflammatory intervention in diabetic nephropathy pathogenesis (105).

MESENCHYMAL STEM CELL (MSC) THERAPY IN DIABETIC NEPHROPATHY (DN)

Mesenchymal stem cells (MSCs) are multipotent cells with the abilities of self-renewal, regeneration, and multilineage differentiation with respect to tissues such as bone, muscle, and adipocyte (106) MSCs can be isolated from different kinds of tissues, including bone marrow, adipose tissue, umbilical cord, amniotic fluid, and placenta (106). MSCs have been shown to ameliorate renal injury in a number of kidney disease models, including acute kidney injury (AKI), chronic kidney disease (CKD), and diabetic nephropathy (107). The therapeutic effects of MSC-based therapy are associated with characteristics including multipotency, self-renewal, secretion of factors related to proliferation and survival, immunomodulation, and homing (108-110) . Emerging evidence have shown that the role of MSCs in ameliorating DN is mainly mediated by paracrine effect rather than differentiation mechanism.(107, 111-113) of course, a study performed by Tsai et al demonstrated that mesenchymal stem cells were differentiated into new pancreatic cells alleviated the increase in blood glucose in diabetic group(114) and different other studies also confirmed the increased blood glucose was associated with the decreased insulin secretion in the diabetic rats when compared with the non-diabetic rats and it was improved after treated with MSCs(115, 116) however on the contrary, many other studies suggested that MSCs in an animal model did not result in hyperglycemia correction and there was no improvement in blood sugar levels(117) . In rodent models of DM, intravenous injection of MSCs is reported to result in preservation of renal structure and amelioration of the symptoms of DN (117, 118). studies have shown that mesenchymal stem cell (MSC) therapy reduces blood glucose, microalbuminuria and ameliorates glomerular injury, MSC transplantation was also beneficial to the inhibition of oxidative stress in kidney with diabetes (119, 120).

In terms of renal fibrosis in animal model of DN results of a study found that BMSCs could significantly reduce the expression of plasminogen activator inhibitor-1 (PAI-1) in DN rats, decrease the accumulation of extracellular matrix and delay the process of renal fibrosis. These results suggested that BMSCs could decrease expression of PAI-1 protein and significantly delay renal fibrosis due to the fact that expression of PAI-1 inhibited degradation of glomerular and tubular ECM, which resulted in progressive accumulation of ECM. BMSC also downregulated TGF-b1/Smad3 signaling pathways and It has been suggested that expression of PAI-1 is associated with

TGFb1/ Smad3 signaling pathways (121). Another recent study revealed that MSC–MV-miR-451a could inhibit cell cycle inhibitors P15 and P19 to restart the blocked cell cycle andimprove EMT by regulating

E-cadherin and a-SMA and thus making miR-451a potential new target for DN therapy(122).

Results of an experiment performed by Juan Jin et al in 2019 indicated that miR-486 of ADSCs-Exo acted the key improvement role on podocyte apoptosis in rat model of diabetic nephropathy through weakening mTOR activation-mediated autophagy via directly targeting smad1(123). As Snail (gene name: SNAI1) is considered to be an initiator of EMT10,44.

Snail modulates tubulointerstitial fibrosis by repressing the expression of E-cadherin and by inducing the expression of a-SMA, fibronectin and collagen I in myofibroblasts4 (124),results of a recent study on therapeutic effect of mesenchymal stem cell derived extracellular vesicle (MSC EV) and its miRNA content on the progression and reversion of fibrosis in a mouse model of diabetic nephropathy conducted by Cristina Grange et al suggested that stem cell-derived EVs specifically prevented and reverted the progression of glomerular and interstitial fibrosis, through down-regulating Snail and collagen 1 expression in renal tissues(125) These studies suggest that exosome secreted From mesenchymal stem cells is the key paracrine regulator for cell/ tissue repair in diabetic nephropathy.

A clinical trial also showed a stabilized or improved glomerular filtration rate (GFR) after the treatment with allogenic MSCs transplantation in patients with DN (126).

These studies along with several other experiments highlight the therapeutic potential of MSCs in different pathways associated with the progression of diabetic nephropathy.

IMMUNOMODULATORY AND ANTI-INFLAMMATORY EFFECT OF MSC IN DN

Various studies have demonstrated the extensive immunomodulatory potential of MSCs and the ability of infused MSCs to resolve inflammation and promote tissue repair in models of diseases such as GvHD (127) systemic lupus erythematosus (SLE) (128), multiple sclerosis (129) kidney injury (130), diabetic nephropathy(131) arthritis (132) ischemic stroke(133) and diabetes .(134) A large number of experimental and clinical studies revealed that most of MSC-base immunomodulatory effects were attributed to the immunoregulatory properties of MSC-sourced secretome, which consists of a soluble component and encapsulated extracellular vesicles (MSC-EVs): apoptotic bodies, micro vesicles and exosomes (MSC-Exos)(135) the soluble components are mainly divided into three types:

growth factors

HGF (hepatocyte growth factor) and LIF (leukemia-inhibitory factor)

cytokines and chemokines

TGFb, IL-10, IL-6, IL-7, CCL2

anti-inflammatory mediators

inducible nitric oxide synthase (iNOS), indoleamine-2,3-dioxygenase (IDO), PGE2, TSG6

Besides trophic factors,

extracellular vesicles (EVs)

which also have the ability to communicate with target cells by transferring their cargo of mRNA, miRNA, DNA, and proteins are secreted from MSCs.(136-138)

Several studies have shown that mesenchymal stem cell therapy can ameliorate diabetic nephropathy through suppressing the expression of inflammatory cytokines and chemokines (118, 139) or they can interact with different adaptive and innate immune cells engaged in the progression of inflammation in DN pathogenesis (140, 141).gather together, we investigated the recent experiments on the Immunomodulatory and anti-inflammatory role performed by MSCs in cells and molecules related to the inflammation pathway in diabetic nephropathy.

INTERACTION WITH IMMUNE CELLS

immunosuppressive property of MSCs has been described in a great number of literature studies, including inhibition of the proliferation of CD8+ and CD4+ T lymphocytes and natural killer (NK) cells, inhibition of maturation of dendritic cells (DCs), and stimulation of the proliferation of regulatory T cells. (142). increasing evidence has suggested that MSCs have the effect of immune modulation via direct interactions with immune cells, including macrophages, dendritic cells, T cells, and NK cells (111, 143-145). Multiple studies recently showed that MSCs had inhibitory effects on DCs (146, 147) MSCs suppress the migration and the antigen (Ag)-presenting function of DCs, serving as an immunoregulator. Previous studies demonstrated that early intervention with MSCs prevents renal injury in DN rats via improving the hyperglycaemia-induced endothelial injury and inflammatory microenvironment.(131, 148) a recent study showed that the protective effect of MSCs are partly related to their immunosuppression of CD8+ T cell proliferation and activation mediated by CD103+ DCs in the kidney of DN rats(140).

INTERACTION WITH INFLAMMATORY CYTOKINES, CHEMOKINES AND ACTIVATED INTRACELLULAR SIGNALLING

It is well revealed that hepatocyte growth factor (HGF) inhibits inflammation and fibrosis. (149, 150) HGF has shown that can inhibit the differentiation of TH1 and TH17 cells(151, 152) Lv et al. found that MSC-derived HGF reduces macrophages infiltration by inhibiting expression of monocyte chemotactic protein-1 (MCP-1), thus down-regulating expression of pro-

inflammatory cytokines such as IL-1β, IL-6, and TNFα in renal tissue of diabetic rat (144) a recent study has demonstrated that early treatment with MSC could upregulate serum anti-inflammatory cytokines IL-10 and EGF and it could also inhibit lipopolysaccharide (LPS)-stimulated rat peritoneal macrophage activation via the downregulation of inflammatory-related cytokines such as IL-6, MCP-1, tumor necrosis factor-α (TNF-α) and IL-1β suggesting that early intervention with MSCs prevented renal injury via immune regulation in diabetic rats. (131)

MSCs can promote the polarization of macrophages from a pro-inflammatory phenotype to an anti-inflammatory phenotype through the production of immunosuppressive molecules and metabolites, such as prostaglandin E2 (PGE2) (153), tumor necrosis factor (TNF)-stimulated gene 6 protein (TSG6)(154-156), lactate(156), kynurenic acid(155) and spermidine(157). Moreover, MSCs can inhibit the infiltration of macrophages, monocytes and neutrophils into sites of inflammation in a TSG6-dependent manner. This mechanism is critical to the ability of MSCs to alleviate acute lung injury (147) corneal injury (158) and kidney injury. In fact anti-fibrotic factor tumor necrosis factor α stimulated gene 6 (TSG-6) from bm-MSCs ameliorates tubular inflammation and fibrosis in albumin-induced chronic kidney disease (CKD) models(159) in addition, another study on animal model of acute kidney injury showed that TSG-6 plays a key role in the treatment of IRI-AKI with BMSC, due to its effect on promoting renal tubular epithelial cells proliferation by modulating inflammation(160).

According to the size and source of production, EVs are divided into three general type: exosomes (40–100 nm), apoptotic bodies (50-500 nm), and microvesicles (200– 1000 nm)(161, 162) MSC-EVs-dependent renal protection is relied on the inhibition of apoptosis, necrosis and oxidative stress in renal tubular epithelial cells as well as suppression of detrimental immune response in the kidneys (163) MSC-sourced mRNAs, miRNAs and immunosuppressive factors were mainly responsible for beneficial effects of MSC-EVs in alleviation of acute and chronic renal inflammation (163-165)

MSC-sourced miRNAs, particularly let-7c, targeted pro-fibrotic genes (collagen IV_1, TGF-_1 and TGF_R1) in inflamed kidneys, crucially contributing to the therapeutic effects of MSC-EVs in renal fibrosis and diabetic nephropathy (166, 167)

Zhong et al. reported that miR-451 in MSC-EVs ameliorated diabetic kidney injury through the inhibition of EMT, and the effect relied on the improved cell cycle arrest and the downregulation of P15INK4b (P15) and P19INK4d (P19)

Recently Juan Jin has suggested that Exosome secreted from adipose-derived

stem cells (ADSCs-Exo) vividly ameliorated DN symptom by enhancing the expression of miR-486 which led to the inhibition of Smad1/mTOR signalling pathway in podocyte.(123)

Kanna Nagaishi has shown that administrating MSC-conditioned medium (MSC-CM) as renal trophic factors to high-fat diet (HFD)-induced type 2 diabetic mice and streptozotocin (STZ)-induced insulin-deficient diabetic mice could suppress the excessive infiltration of BMDCs into the kidney by regulating the expression of the adhesion molecule ICAM-1. Proinflammatory cytokine expression (e.g., TNF -a) and fibrosis in tubular interstitium.(168) another study has revealed that administration of Bone marrowderived mesenchymal stem cellconditioned medium could attenuate tubulointerstitial fibrosis by inhibiting monocyte mobilization in an irreversible model of unilateral ureteral obstruction.(169) in another uuo animal model the results suggested that hucMSC-CM (as trophic factors) has protective effects via anti-inflammatory effects through inhibiting TLR4/NF-κB signalling pathway activation. (170) E Xiang showed that UC-MSC conditioned medium and UC-MSC-derived exosomes decreased the production of pro-inflammatory cytokines (IL-6, IL-1β, and

TNF-α) in high glucose-injured renal tubular epithelial cells, and renal glomerular endothelial cells.(171).

CONCLUSION

The burden of global diabetes is predicted to increase dramatically in the coming decade. One of the most important microvascular complications of diabetes is nephropathy, which substantially increases cardiovascular morbidity and mortality, determining a considerable impairment in the quality of this group of patients. Therefore, the need to find therapeutic targets and strategies for treating DN is clearly evident. Recent studies suggest that inflammation is a key factor in the development and progression of DN. Stem cell-based therapy holds promise for DN treatment and they have found to exert their immunomodulation effect through their secretomes rather than direct differentiation. The understanding that inflammation plays an important role in the initiation and advancement of DN and that mesenchymal stem cells have anti-inflammatory and immunomodulatory properties may widen the field to generate a novel and improved therapy.

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