Mesenchymal stem cells in kidney inflammation and repair

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ABSTRACT:
Mesenchymal stem cells are a heterogeneous population of fibroblast-like stromal cells that have been isolated from the bone marrow and a number of organs and tissues including the kidney. They have multipotent and self-renewing properties and can differentiate into cells of the mesodermal lineage. Following their administration in vivo, mesenchymal stem cells migrate to damaged kidney tissue where they produce an array of anti-inflammatory cytokines and chemokines that can alter the course of injury. Mesenchymal stem cells are thought to elicit repair through paracrine and/or endocrine mechanisms that modulate the immune response resulting in tissue repair and cellular replacement. This review will discuss the features of mesenchymal stem cells and the factors they release that protect against kidney injury; the mechanisms of homing and engraftment to sites of inflammation; and further elucidate the immunomodulatory effect of mesenchymal stem cells and their ability to alter macrophage phenotype in a setting of kidney damage and repair.

KIDNEY STEM CELLS AND REGENERATION
Understanding the process of endogenous kidney regeneration is important for the development of new therapeutic strategies. Tissue stem/progenitor cells play a vital role in maintaining homeostasis, a process of self-renewal.1 The rate at which this occurs varies among tissues. For example, epithelial cells of the intestine1 and skin2 have a high cell turnover rate and can completely self-renew within days. In contrast, the kidney has a considerably lower cell turnover rate, with proliferative abilities that differ depending on the specialized cell type.3,4 Unlike mammalian kidneys, where the formation of nephrons ceases at birth, cartilaginous fish have the capacity to form new nephrons after birth through de novo nephrogenesis.5 Moreover, following partial nephrectomy, skate fish show proliferation of progenitor cells that results in ongoing kidney development.6 In contrast, mammalian adult kidneys undergo compensatory hypertrophy following uninephrectomy without the formation of new nephrons. The mammalian kidney, therefore, has a limited capacity to undergo endogenous cellular replacement and tissue remodelling under normal conditions. Nevertheless, in response to acute injury the adult kidney does have some capacity for repair and remodelling that can ultimately lead to restoration of renal structure and function.7
Acute insults to the kidney such as exposure to toxins, sepsis or ischemia can lead to apoptotic cell death and/or necrosis of the tubular epithelial cells and glomerular podocytes.3,8 The kidney’s repair response, consisting of cellular replacement of the injured tubular epithelium, is most likely mediated by surviving epithelial cells that neighbour the sites of injury.9,10 These epithelial cells dedifferentiate and migrate to injured sites of apoptosis, necrosis and cell detachment, where they subsequently proliferate and redifferentiate into functional tubular epithelial cells.3,11 In a setting of chronic injury, glomerular repair is less impressive. Ongoing damage to glomerular cells results in the progressive loss of nephrons, leading to the expansion of the interstitium and development of fibrosis.
It is currently unclear if the kidney contains resident stem cells,12 although recent reports suggest that progenitor cell population/s originally identified in embryonic kidneys (CD24+CD133+Oct-4+Bmi-1+) exist within the urinary pole of the glomerular parietal epithelium of the Bowman’s capsule.13,14 These cells, expressing CD24, a surface antigen commonly used for the identification of human stem cells,16,17 and CD133, a surface antigen specific for a variety of...
adult stem cells, may represent a residual kidney progenitor cell population within the parietal epithelium. The CD24+CD133+podocalyxin+ cells localized to the urinary pole of the parietal epithelium may be responsible for podocyte replacement after injury, a cell type once thought to be post-mitotic and unable to divide.

Cellular loss most often leads to the infiltration of bone marrow (BM)-derived inflammatory cells that may contribute to both tissue destruction or repair depending on the extent of injury. Mesenchymal stem cells (MSC), derived from the BM, have initiated considerable excitement in their role to promote kidney repair and tissue remodelling through the paracrine secretion of mitogenic and angiogenic factors.

**MESENCHYMAL STEM CELLS**

Mesenchymal stem cells were originally identified in the BM stroma by Friedenstein and colleagues. MSC therapy has since been reported to ameliorate kidney injury and promote structural repair. These undifferentiated adult stem cells are of mesodermal origin and constitute only 0.001–0.01% of the total BM cell population. They can be easily isolated from other BM cells due to their propensity to adhere to plastic and their ability to extensively proliferate in vitro. Furthermore, these characteristics allow for the cell expansion of adequate numbers of MSC for potential therapeutic use. However, as the extensive expansion of MSC in culture can lead to alterations in both phenotype and function, it remains uncertain if in vitro cultured MSC differ significantly from the in vivo populations.

Mesenchymal stem cells form a heterogeneous population in culture that consists of small immature rapidly self-renewing cells, large, more mature, slowly replicating cells and in some confluent cultures, cuboidal cells. Interestingly, it has been shown that single cell-derived clones of MSC can vary in phenotype, gene expression and their differentiation abilities. The Mesenchymal and Tissue Stem Cell Committee of the International Society of Cellular Therapy have outlined a combination of morphological, phenotypical and functional characteristics that are required to define these cells. As part of their definition, it is essential that MSC adhere to plastic in standard tissue culture conditions, exhibit a fibroblast-like morphology and have the ability to undergo extensive proliferation, resulting in the formation of colonies of fibroblastic cells, termed colony-forming unit-fibroblasts (CFU-F; Fig. 1A). Furthermore, MSC should express the surface antigens CD73, CD90 and CD105 and lack the expression of the hematopoietic markers CD45, CD34, CD14 or CD11b, CD79a or CD19 and major histocompatibility complex (MHC) class II. They also typically express intermediate levels of MHC class I and are negative for the co-stimulatory molecules CD40, CD80 and CD86. However, when exposed to inflammatory stimuli, such as interferon (IFN)-γ, their expression of MHC class I and II has been reported to be upregulated. Finally, when exposed to the appropriate differentiation conditions, MSCs should have the capacity to differentiate into adipocytes, osteocytes and chondrocytes in vitro (Fig. 1B–D). More recently MSC have also been detected in adipose, umbilical cord and a number of postnatal organs and tissues, including the kidney, and they have shown a promising ability to protect
against tissue injury and facilitate endogenous tissue repair.57–60 Unlike embryonic stem cells and induced pluripotent stem cells, MSC do not form teratomas following transplantation in rodents.61

MESENCHYMAL STEM CELLS IN TISSUE REGENERATION AND REPAIR

Mesenchymal stem cells have been found to exert a therapeutic effect in a wide array of diseases, acting through their unique immunomodulatory abilities that can alter the pro-inflammatory course of injury. This may involve the secretion of paracrine factors that dampen inflammation and in turn promote tissue remodelling and repair.59 Their ability to modulate the immune response in vivo was first reported by Bartholomew et al.,42 who demonstrated that the intravenous administration of allogeneic MSC to baboons resulted in prolonged skin-graft survival. MSC have also been reported to be beneficial in an autoimmune disease setting. In a mouse model of multiple sclerosis termed autoimmune encephalomyelitis (EAE), the administration of MSC at the onset of disease induced peripheral T-cell anergy against the pathogenic peptide myelin oligodendrocyte glycoprotein (MOG), resulting in the amelioration of the progression of injury.43 Furthermore, the administration of MSC to mice with diabetes type 1 resulted in the recovery of damaged insulin producing pancreatic islets and β-cells and decreased blood glucose levels.44 Two mechanisms appear to be aiding this recovery. In addition to the production of trophic growth factors, MSC also inhibit the β-cell specific T-cell immune reaction.45 In a mouse model of lung fibrosis, MSC reduced local inflammation, collagen accumulation and consequently fibrosis.46 Subsequent studies demonstrated that MSC conferred this protection by inhibiting the release of interleukin (IL)-1α and tumour necrosis factor (TNF)-α through the secretion of IL-1 receptor antagonist (IL-1RA).47 The local injection of MSC to mice following coronary ligation induced the regeneration of cardiac tissue and improved myocardial function.48 Following intravenous administration, MSC preferentially homed to the infarct site where they promoted angiogenesis and myogenesis and mediated myocardial repair via paracrine mechanisms.49 The first phase I clinical trial in humans involved the intravenous infusion of MSC into patients with hematologic malignancies in complete remission resulting in no adverse events.50

MESENCHYMAL STEM CELLS IN ACUTE KIDNEY DISEASE

Despite the current data showing clinical efficacy, the precise manner in which MSC confer renoprotection is not understood. Initial experimental studies carried out by Morigi et al.58 and Herrera et al.59 reported that the exogenous administration of MSC to mice with acute renal injury could promote both structural and functional renal repair via the transdifferentiation of MSC into tubular epithelium. However, follow up studies revealed that only 2.0–2.5% of the injected MSC showed engraftment,59 opposed to a previously reported 22% of cells.51 These reports demonstrate that the direct engraftment of exogenously administered, transdifferentiating MSC is not the predominant mechanism in which MSC enhance renal repair.

There is increasing evidence that MSC can elicit repair through paracrine and/or endocrine mechanisms, where they release trophic growth factors that modulate the immune response and consequently mediate repair.57–64 The ability of MSC to inhibit the release of pro-inflammatory cytokines and secrete a variety of trophic growth factors that, promote angiogenesis, mitogenesis and proliferation while reducing apoptosis may collectively mediate the protective and regenerative effects in the kidney of laboratory rodents (summarized in Table 1).54–70

Recent studies have shown that the administration of MSC following ischemia-reperfusion (IR) injury result in a significant downregulation of the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, IFN-γ and suppression of inducible nitric oxide synthase (iNOS) at 24 h post-IR injury. This was coupled with an upregulation of the...
anti-inflammatory cytokines IL-4, IL-10, basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-α and Bcl-2, which resulted in a reduction in renal injury, increased tubular epithelial proliferation and improved renal function. These findings indicate that MSC are capable of modulating the inflammatory immune response soon after the initiation of injury, shifting it from a pro-inflammatory Th1 profile to an anti-inflammatory Th2 one.\(^6\)\(^{62}\) Moreover, the areas of the kidney where MSC were still present at 24 h post-IR injury were associated with reduced apoptosis compared to regions that no longer contained these cells.\(^5\)\(^9\) This suggests that MSC are capable of secreting anti-apoptotic factors that protect surrounding renal cells from undergoing apoptosis following renal insult. To further elucidate their protective mechanisms, MSC, were co-cultured in vitro with cisplatin-treated proximal tubular epithelial cells (PTEC).\(^5\)\(^9\) These co-culture assays, using Transwell membranes, showed that the protective effects of MSC on PTEC proliferation were not due to cell-to-cell contact but more likely the production of MSC-derived trophic factors.\(^5\)\(^9\)

### Table 1  Summary of studies using mesenchymal stem cells (MSC) isolated from various sources to treat acute kidney injury

<table>
<thead>
<tr>
<th>Injury model</th>
<th>MSC source</th>
<th>Administration</th>
<th>Features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol-induced kidney injury</td>
<td>1 × 10^6 GFP+ mouse BM-MSC – female C57BL/6j mice</td>
<td>i.v. injection</td>
<td>↑ proliferation, ↑ morphological recovery, ↑ renal function</td>
<td>54</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>2 × 10^6 mouse BM-MSC – male C57BL/6j mice</td>
<td>i.v. injection</td>
<td>↑ renal function, ↑ tubular proliferation, ↑ morphological recovery</td>
<td>55</td>
</tr>
<tr>
<td>40 min bilateral IR</td>
<td>1.5 × 10^6 rat BM-MSC – Sprague-Dawley rats</td>
<td>Infused into thoracic aorta via a carotid artery</td>
<td>↑ renal function, ↓ injury score, ↑ preservation of proximal tubular brush border</td>
<td>68</td>
</tr>
<tr>
<td>40 min bilateral IR</td>
<td>1 × 10^6 rat BM-MSC</td>
<td>Intra-aortic delivery via left carotid artery</td>
<td>↑ renal function, ↑ proliferative indexes, ↓ apoptotic indexes, ↓ renal injury, ↓ IL-1β, TNF-α, IFN-γ, INOS, ↑ IL-10, bFGF, TGF-α, Bcl-2</td>
<td>62</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>2 × 10^6 mouse BM-MSC – male C57BL/6j mice</td>
<td>Tail vein or i.p. injection</td>
<td>↑ renal function, ↑ tubular cell proliferation, ↑ renal function, ↓ tubular cell apoptosis</td>
<td>57</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>1 × 10^6 mouse CD44+ or CD44- BM-MSC – C57BL/6j or Cd44tm1Hbg/J mice</td>
<td>Tail vein</td>
<td>CD44+ BM-MSC: ↑ morphological and functional recovery</td>
<td>56</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>2 × 10^6 mouse IGF-1 gene silenced BM-MSC – male C57BL/6j mice</td>
<td>i.v. injection</td>
<td>Limited protection of renal function (BUN) and tubular injury</td>
<td>59</td>
</tr>
<tr>
<td>60 min bilateral IR</td>
<td>2 × 10^6 rat BM-MSC – male Wistar rats</td>
<td>i.v. injection</td>
<td>↓ serum creatinine and plasma urea, ↑ PCNA nuclei in MSC treated kidneys, ↑ IL-4, ↓ IL-1β</td>
<td>70</td>
</tr>
<tr>
<td>30 min unilateral IR</td>
<td>1 × 10^6 rat MSC</td>
<td>Intra-arterially infused</td>
<td>↓ apoptosis in kidney regions with MSC still present in microvasculature 24 h post-IR</td>
<td>63</td>
</tr>
<tr>
<td>40 min bilateral IR</td>
<td>1 × 10^6 Kallikrein-modified BM-MSC – male Wistar rats</td>
<td>Intra-aortic delivery via left carotid artery</td>
<td>↓ serum creatinine and urea nitrogen, ↓ apoptosis, ↓ tubular injury</td>
<td>67</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>5 × 10^6 human BM-MSC</td>
<td>Tail vein</td>
<td>↑ renal function, ↑ proliferative score, ↓ proximal tubular epithelial cell injury, ↓ apoptotic score, ↓ mortality</td>
<td>69</td>
</tr>
<tr>
<td>60 min bilateral IR</td>
<td>2 × 10^6 rat BM-MSC – male Wistar rats</td>
<td>i.v. injection</td>
<td>↓ serum creatinine, ↑ renal function, low expression of IL-1β, IL-6, TNF-α, high expression IL-4 and IL-10</td>
<td>60</td>
</tr>
<tr>
<td>58 min bilateral IR</td>
<td>VEGF knockdown BM-MSC – hPAP transgenic F344 rats</td>
<td>Intra-aortic delivery via left carotid artery</td>
<td>↑ mortality, delayed functional recovery</td>
<td>61</td>
</tr>
<tr>
<td>60 min bilateral IR</td>
<td>1 × 10^6 human umbilical cord-MSC</td>
<td>Intra-aortic delivery via left carotid artery</td>
<td>↓ serum creatinine and urea nitrogen, ↓ caspase-3, il-1β and TNF-α, ↑ proliferative score</td>
<td>65</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>5 × 10^6 human BM-MSC</td>
<td>i.p. injection</td>
<td>Prolonged survival, ↓ urea nitrogen, ↓ apoptosis, ↑ proliferation</td>
<td>66</td>
</tr>
<tr>
<td>Cisplatin-induced kidney injury</td>
<td>5 × 10^6 VEGF-HMSC</td>
<td>Tail vein</td>
<td>↑ proliferation, ↓ apoptosis, ↑ renal function, improved morphology and prolonged survival</td>
<td>64</td>
</tr>
<tr>
<td>60 min bilateral IR</td>
<td>1 × 10^6 human umbilical cord-HGF-MSC</td>
<td>Intra-aortic delivery via left carotid artery</td>
<td>↓ apoptosis, ↓ tubular casts, ↑ proliferation, ↑ renal function</td>
<td>58</td>
</tr>
</tbody>
</table>

bFGF, basic fibroblast growth factor; BM-MSC, bone marrow-mesenchymal stem cell; BUN, blood urea nitrogen; HGF, hepatic growth factor; IGF, insulin-like growth factor; IL, interleukin; INOS, inducible nitric oxide synthase; i.p., intraperitoneal; IR, ischemia reperfusion; i.v., intravenous; PCNA, proliferating cell nuclear antigen; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.
Importantly, the administration of MSC-conditioned medium to mice with cisplatin-induced injury was also found to reduce tubular cell apoptosis and improve kidney structure and function. This further supports the notion that MSC secrete factors that mediate renoprotection in a paracrine manner. MSC-conditioned medium has been reported to contain hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). Both HGF and IGF-1 have anti-apoptotic and mitogenic properties that can accelerate cellular repair when administered to mice with kidney IR injury. In addition to the cellular survival effects of VEGF that decrease apoptosis and promote endothelial and epithelial proliferation, VEGF can also mediate vasodilation, matrix remodelling, monocyte chemotaxis and angiogenesis.

Imberti et al. provided in vitro evidence that MSC-derived IGF-1 is the principle mediator responsible for renal repair. The addition of an anti-IGF-1 antibody to MSC and PTEC co-cultures resulted in the attenuation of PTEC proliferation. Furthermore, the co-culture of IGF-1 silenced MSC and PTEC also resulted in the attenuation of PTEC proliferation and increased apoptosis. The in vivo administration of IGF-1 silenced MSC to mice with cisplatin-induced injury resulted in limited improvements in renal regeneration and repair.

Furthermore, human umbilical cord-derived MSC (hMSC) overexpressing HGF (HGF-hMSC) showed enhanced therapeutic effects when administered to mice with IR injury, compared to hMSC treatment. In addition, Yuan et al. demonstrated that the in vitro co-culture of human embryonic MSC overexpressing VEGF (VEGF-hMSC) with cisplatin-injured tubular epithelial cells (TCMK-1) resulted in enhanced protection, in comparison with co-cultures involving hMSC. Moreover, the administration of VEGF-hMSC to mice with cisplatin-induced injury, resulted in decreased apoptosis and increased proliferation, enhanced functional recovery and prolonged survival compared to hMSC treated mice. Togel et al. also demonstrated that the administration of VEGF knockdown MSC to animals with IR injury resulted in a decline in the rate of functional renal repair and increased mortality rates.

While results in the laboratory have shown great potential for MSC to exert immunomodulatory effects and promote regeneration and repair following disease, it should not be ignored that some studies have demonstrated that the therapeutic effect of MSC can vary.

**HOMING OF MESENCHYMAL STEM CELLS**

In steady state, intravenously injected MSC migrate to the BM. In the setting of inflammatory damage, MSC preferentially home to the site of inflammation where they then migrate across the endothelium and enter the injured organ, to some extent analogous to leukocyte trafficking (Fig. 2). The in vivo tracking of fluorescently labelled MSC have demonstrated that these cells infiltrate the peri-tubular capillaries and glomeruli of kidneys with IR injury within 10 min of injection, with no cells evident by 72 h. The precise mechanisms of MSC homing to sites of tissue injury are not fully understood. However, Bi et al. reported that the beneficial effects of administering MSC to mice with cisplatin-induced injury were also observed when MSC-conditioned media was administered without the cells. This implies that the mechanisms in which MSC confer protection is not entirely attributed to their ability to home and engraft to the site of kidney damage. The study highlights that MSC are also capable of mediating protection via an endocrine manner.

Mesenchymal stem cells have numerous chemokine receptors that may assist in their migration to sites of inflammation. Following ischemic injury, the expression of the chemokine stromal cell-derived factor-1 (SDF-1), also known as CXCL12, is upregulated within the kidney. MSC express the SDF-1 receptor CXCR4, which is further upregulated under hypoxic conditions. In addition, when MSC are pre-incubated with TNF-α they show an increased migratory capacity towards SDF-1 indicating that a SDF-1/CXCR4 interaction may mediate the localization of exogenously injected MSC to sites of tissue injury. Ponte et al. tested the ability of MSC to home towards 16 different growth factors and chemokines in vitro and found that platelet-derived growth factor-AB (PDGF-AB) and IGF-1 were the most potent chemoattractants for MSC. CD44 is another candidate that has been shown to play a vital role in MSC trafficking. CD44 on MSC binds to hyaluronic acid (HA), which is significantly upregulated in the kidney following ischemic injury. Supportive studies by Herrera et al. show that the injection of either MSC derived from CD44 null mice, or MSC incubated with a CD44 blocking antibody or soluble HA, did not migrate to the kidney following glycerol induced damage. However, MSC homing was restored when these CD44-negative cells were transfected with wild-type CD44, indicating that CD44/HA interactions are required for the migration of MSC to the kidney following injury.

**DO MESENCHYMAL STEM CELLS ACT VIA MACROPHAGES?**

Monocyte-derived macrophages comprise a heterogeneous population of cells that play a fundamental role in immune and non-immune-mediated renal disease, host defence and allograft responses. Macrophages are key regulators of the innate immune system, where they can detect, phagocytose and destroy foreign antigens. Apart from tissue destruction, it is now known that macrophages also play an important role in tissue homeostasis, cellular replacement and repair through the clearance of apoptotic cells and cellular debris. They also produce mediators that downregulate inflammation and promote remodelling and regeneration.
The immunomodulatory effects of MSC on T lymphocytes, B lymphocytes, natural killer cells and dendritic cells have been extensively investigated (for review 34,92). However, less is known about their ability to modulate macrophage phenotype and function. The activation state that governs macrophage function is dependent on the inflammatory stimuli received from the tissue microenvironment. As the process of repair shifts from the initial inflammatory phase to that of remodelling, macrophages subsequently exhibit varying polarization states and exert a diverse range of functional activities. 93 Although a variety of classification methods have been proposed, macrophages are typically believed to exist in one of two opposing polarization states, that is, the M1 ‘classically activated’ subset or M2 ‘alternatively activated’ subset. 94

M1 polarization is achieved through a combination of events. The first ‘priming’ step involves exposure of the macrophage to IFN-γ. 93 The second signal requires the exposure to either a microbial product, such as lipopolysaccharide (LPS), or proinflammatory cytokines, such as TNF, to the macrophage, resulting in M1 activation. 94 M1 macrophages are characterized by their enhanced ability to phagocytose and present antigen through the upregulation of MHC class II and the co-stimulatory molecules CD80 and CD86. 95 They secrete numerous pro-inflammatory cytokines, particularly IL-12 and IL-23, which induce the downstream production of the toxic intermediates nitric oxide and reactive oxygen species (ROS) as well as promoting the killing and degradation of intracellular microorganisms. 91,96

It was previously believed that Th2 derived cytokines had a deactivating effect on macrophages. 97 However, in 1992, Stein et al. 98 demonstrated that macrophages exposed to IL-4 took on an ‘alternative’ phenotype, characterized by reduced secretion of proinflammatory cytokines. It has since been reported that exposure to IL-13, IL-10, TGF-β, glucocorticoids and immune complexes in combination with IL-1β or LPS can also induce an M2 alternative polarization state. 94 In contrast to their classically activated counterpart, M2 macrophages are involved in dampening the inflammatory response, while exhibiting enhanced scavenging abilities that promote tissue remodelling and repair. It has recently been shown that M2 macrophages produce several factors that promote angiogenesis, mediate wound healing, extracellular matrix (ECM) deposition and tissue remodelling. For example, they express high levels of IGF-1, which provides signals for repair and stimulates re-epithelialization;
fibronectin (FN)-1, which mediates ECM deposition; and the TGF-β matrix associated protein MP78/70 (BIG-H3) that promotes fibrogenesis.99–101

Recent studies have demonstrated that MSC interact with macrophages and have the potential to promote M2 polarization.102–106 The in vitro co-culture of human MSC and macrophages resulted in an alternatively activated macrophage phenotype described as mannose receptor (MR) high, IL-10 high, IL-6 low, TNF-α low and IL-12 low with enhanced phagocytic activity.102,106 In addition, it has been shown that MSC-conditioned medium can promote macrophages to adapt a regulatory-like M2 phenotype characterized by a significantly reduced production of pro-inflammatory cytokines and an enhanced production of IL-10 and phagocytic function.103

The in vivo treatment of wounds with BM-MSC conditioned medium has been reported to enhance wound healing, a process associated with an increased infiltration of macrophages.107 Following the systemic administration of human gingiva-derived MSC (GMSC) to mice with an excisional skin wound, GMSC homed to the wound site and were found in close propinquity with macrophages. Subsequent analysis of this macrophage phenotype revealed an increased expression of the M2 macrophage markers Fizz1 and arginase-1, highlighting the ability of MSC to interact with macrophages and promote M2 polarization.106 In a mouse model of transient global ischemia, the administration of BM-MSC resulted in neuroprotection. Further investigation demonstrated an upregulation of the M2 markers Ym-1, IGF-1, galactin-3 and MHCII in the microglia/macrophages.105 Moreover, Nemeth et al.104 showed that MSC administered to mice with cecal ligation and puncture (CLP)-induced sepsis homed to the lung where they were found surrounded by macrophages. To further support the argument for the importance of macrophages in the MSC reparative response, when MSC were administered to mice with CLP-induced sepsis following macrophage depletion, injury protection was lost.104

CONCLUSION

Since the initial excitement surrounding the multilineage potential and self-renewal properties of MSC, their therapeutic potential to elicit tissue regeneration has now been exploited both experimentally and in a wide range of potential clinical applications. MSC can home to damaged tissue where they exert potent immunosuppressive effects and secrete soluble factors that modify the pro-inflammatory cascade to promote tissue remodelling and cellular replacement, which subsequently protects the kidney from further injury. The interaction of MSC with macrophages may play a vital role in their downstream anti-inflammatory and immunomodulatory effects. However, the specific cell cross-talk between MSC and damaged kidney cells and the molecular mechanisms responsible for their unique immunogenicity remain poorly defined. Furthermore, the optimal delivery methods for engraftment, long-term safety and their ability to modify the tissue microenvironment in a setting of fibrosis require additional consideration.

REFERENCES


