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REVIEW

Genetically Modified Mesenchymal Stromal/Stem Cells: Application in Critical Illness

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Abstract

Critical illnesses including sepsis, acute respiratory distress syndromes, ischemic cardiovascular disorders and acute organ injuries are associated with high mortality, morbidity as well as significant health care system expenses. While these diverse conditions require different specific therapeutic approaches, mesenchymal stem/stromal cell (MSCs) are multipotent cells capable of self-renewal, tri-lineage differentiation with a broad range regenerative and immunomodulatory activities, making them attractive for the treatment of critical illness. The therapeutic effects of MSCs have been extensively investigated in several pre-clinical models of critical illness as well as in phase I and II clinical cell therapy trials with mixed results. Whilst these studies have demonstrated the therapeutic potential for MSC therapy in critical illness, optimization for clinical use is an ongoing challenge. MSCs can be readily genetically modified by application of different techniques and tools leading to overexpress or inhibit genes related to their immunomodulatory or regenerative functions. Here we will review recent approaches designed to enhance the therapeutic potential of MSCs with an emphasis on the technology used to generate genetically modified cells, target genes, target diseases and the implication of genetically modified MSCs in cell therapy for critical illness.

Keywords Mesenchymal stromal/stem cells · Critical illness · Gene therapy · Vector

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Introduction

Acute organ failure (AOF) can occur in patients with critical illnesses including severe infections, early sepsis and ischemic disorders necessitating admission to intensive care units (ICUs) [1, 2]. Sepsis can develop to more complex conditions leading to multiorgan dysfunction syndrome (MODS), which occurs as a response to pathophysiologic events and complicated interactions in body systems leading to immune, metabolic and hematologic dysfunctions [3, 4]. Sepsis associated with MODS is one of the leading causes of morbidity and mortality in ICUs worldwide [5]. In US, over 970,000 sepsis cases are admitted annually and sepsis accounts for more than 50% of hospital deaths [6]. Currently, aside from antibiotics and supportive care, there is no specific treatment for sepsis. Despite more than 104 Phase III clinical trials, no therapeutic intervention has emerged to reduce morbidity and mortality from sepsis and associated MODS [7, 8].

The morbidity and mortality rates due to ischemic disorders causing stroke, irreversible cardiomyopathy, kidney or liver failure and critical limb ischemia are also concerning [9, 10]. In an ICU setting, supportive strategies are applied to care for patients with critical illnesses including: hemodynamic resuscitation, mechanical ventilation, intravenous fluid therapy, pharmacotherapy using antibiotics, steroids, inotropes, sedatives, analgesics, anticoagulant and antipyretics, dialysis, endovascular procedures and organ transplantation. Although these interventions may improve the acute phase of the illness, in a majority of cases they fail to treat the latent pathophysiological changes causing organ failure [11, 12].

The evolution of organ failure in individual body systems occurs through the altered transcription of thousands of regulatory genes involved in immunity and metabolic-bioenergetic pathways leading to disruption of fundamental cellular processes or activation of cellular death pathways, including apoptosis, necrosis and autophagy in parenchymal and non-parenchymal tissues [13, 14].

Endothelial dysfunction has been described as a major predisposing factor in pathophysiology of most critical illnesses. Homeostasis in cardiovascular system, lung, kidney, brain and most major body systems is maintained by vascular endothelium [15, 16]. In the arterial vasculature, endothelial impairment contributes to the pathogenesis of complex disease processes such as atherosclerosis and its life-threatening complications, myocardial infarction and stroke [17, 18]. In severe infections, the complex interactions between the infecting organisms and the host immune leading to endothelial dysfunction are poorly understood [19]. It has been suggested that in sepsis, the interaction between endothelial cells and the cellular immune system affects the integrity of the endothelium. In most pathological conditions this effect can be further amplified when the coagulation and complement systems are activated, resulting in vasoregulatory dysfunction, microaggregation impairment and atherosclerotic plaque formation, reducing microvascular flow, creating local ischemia and hypoxia. As a consequence, this may impair cellular respiration and permeability of the endothelium, which enables the inflammatory cells and products to leave the circulation forming generalized edema [20]. It should be emphasized that hypoxia itself is a leading cause of cell death via apoptosis, resulting in organ failure. Different mechanisms have been proposed for hypoxia-induced apoptosis such as enhanced permeability of the inner mitochondrial membrane leading to deprivation of mitochondrial derived Adenosine triphosphate (ATP) and apoptosis mediated by reactive oxygen species (ROS) formation [21, 22]. Overall, there are similarities in underlying mechanisms in causing acute and chronic dysfunction in individual organs, however, the molecular basis of organ failure is more complex and requires further investigation.

Mesenchymal Stromal/Stem Cells (MSCs)

MSCs are multipotent adult stromal cells with the capacity to differentiate into multiple cell types such as osteoblasts, adipocytes, and chondroblasts [23]. MSCs can be isolated from different sources including bone marrow, adipose tissue, umbilical cord, peripheral blood, heart and various other organs [24]. MSCs are adherent to plastic in standard culture conditions, express the surface molecules CD105, CD73 and CD90, but lack the expression of CD45, CD34, CD14, CD11b, CD79alpha, CD19 and HLA-DR [25]. Allogeneic MSCs are especially attractive due to their potential to provide an 'off-the-shelf' therapeutic cell product for immediate infusion to patients with acute critical illness and organ dysfunction. This is favoured by biological characteristics including convenient isolation, rapid expansion in culture and minimal immunogenicity. In terms of their low immunogenicity, the question has been raised as to whether these cells are immune evasive rather than immune privileged [26]. The prevailing dogma has been that allogeneic MSCs are immune privileged, but few studies have assessed and controlled for matched or mismatched major histocompatibility complex (MHC) molecule expression in vivo. While a few published studies that controlled for MHC donor and recipient haplotypes suggest that adult MHC-mismatched MSCs may in fact not be immune privileged, a systematic review of MSC-based clinical trials that described over 1000 patients who had received MSCs for various clinical conditions including ischemic stroke, Crohn's disease, cardiomyopathy, myocardial infarction, graft versus host disease, as well as healthy volunteers found these cells to be safe for human administration. Specifically, meta-analysis of the randomized clinical trials included did not detect an association between acute infusional toxicity, organ system complications, infection, death, malignancy or evidence of

significant immune dysregulation. There however was a significant association between MSCs and transient fever [27].

MSCs are purported to home to the wounded or damaged tissue sites [28]. This is driven by the expression of 'homing factors', for example, stromal cell derived factor 1/CXCR4 pathway that can mediate traffic of MSCs to ischemic or hypoxic tissues [29], or by CD44 expressed on MSCs that may interact with hyaluronic acid where interstitial matrices are exposed after an injury [30]. When administered intravenously, MSCs become entrapped in the capillary beds – primarily in the lung and liver [31]. The biological meaning of MSC entrapment is not clear [32, 33]. As a therapeutic strategy for acute critical illness, we and others have shown that enhanced anti-bacterial and pro-survival advantage does not depend on cell-cell contact as cell engraftment with differentiation [34, 35], trans-differentiation, or cell fusion are not required for therapeutic effect [36]. In fact, it was suggested that MSCs do not even have to be viable to confer a beneficial advantage [37].

The vast majority of infused MSCs reside transiently in the lungs, becoming undetectable within 96 h [38]. Currently, it has been suggested that MSC-derived paracrine mediators and extracellular vesicles (EVs) deliver effector molecules including mRNAs, miRNAs, DNA, proteins, and lipids that regulate function in recipient cells [39–41]. Indeed, EVs can account for many of the therapeutic effects of MSCs [42]. The number, size, and content of MSC- derived EVs vary based on the microenvironmental conditions [43, 44].

EVs are derived from different cellular compartments such as early endosomes and cell membrane and can be categorized into exosomes (30–150 nm) and large vesicles such as microvesicles (MVs) (50–1000 nm), apoptotic bodies (500–5000 nm), or Golgi vesicles [45–47]. In the pulmonary vasculature, MSCs release EVs and mediators that have both local (pulmonary) and systemic effects. MSCs administered in preclinical models of pulmonary injury and sepsis release anti-inflammatory mediators [48–51] and EVs containing signaling-relevant nucleotides, proteins and possibly lipids [52].

The strong immunoregulatory properties of MSCs, affecting both adaptive and innate immune systems have been characterized in several studies [53]. MSC administration results in an overall modulation of the host transcriptional response, characterized by a down-regulation of inflammation and an up-regulation of genes involved in phagocytosis, bacterial killing [54]. MSC administration results in transcriptional reprogramming of the host response to injury and repair [55]. By modulating response in recipient cells, MSCs can change the activity of various immune cells like T-cells, B-cells, neutrophils, NK cells, dendritic cells and macrophages. In T-cells, MSCs suppress activation and proliferation; inhibit monocyte differentiation, and block proliferation of B-cells [56, 57]. MSCs also inhibit B lymphocyte proliferation via G0/G1 phase arrest [58, 59], leading to inhibition of antibody production [60]. An intriguing property of MSCs is their ability to enhance bacterial phagocytosis and killing [34, 48]. We have demonstrated that treatment with MSCs enhances gene expression related to antigen presentation and bacterial killing in sepsis model [34, 54, 61]. Moreover, it has been proposed that MSCs may be "educated" to enhance specific phenotypes [62] . MSC phenotype and the potential effect exerted on the immune system is dependent upon the microenvironment as MSCs may be induced to develop a pro- or an anti-inflammatory phenotype [63]. Pro-inflammatory MSCs are associated with early stage infection and inflammation, such as through Toll Like Receptor 4 (TLR 4) activation by LPS. However, activation of TLR3 with poly I:C or dsDNA results in an alternative MSC phenotype characterized by secretion of immunosuppressive mediators [64]. Recent studies have suggested a role for macrophages in the reduction of inflammation and promotion of tissue repair [65]. MSCs secrete lipoxins, specialized proresolving lipid mediators that limit excessive inflammation, induce resolution, and protect from leukocyte-mediated tissue damage. Previous studies suggested that aspirin-triggered 15-epi-LXA4 induced neutrophil apoptosis and facilitates resolution of pulmonary inflammation [66]. In a murine model of LPS induced lung injury, a LXA4 receptor antagonist reversed the beneficial effect of MSCs on survival and pulmonary edema resorption. Thus, there are several mechanisms by which MSCs may improve host response during critical illness. Based on the pathophysiology and molecular basis of target disease and the goal of therapy, the therapeutic functions of MSCs may be modulated by performing appropriate genetic modifacations.

Genetic Modification of Mesenchymal Stromal/Stem Cells

Although, MSCs possess various favorable biological activities, the diseases-specific therapeutic efficacy and immunomodulatory properties of these cells and their derivatives such as EVs can be further optimised. Gene modification can improve the natural function of MSCs in different aspects such as tissue regeneration, repairing organ injury and immunemodulation [51]. These critical functions can be augmented by reprogramming MSCs via upregulation or downregulation of their native genes resulting in a controlled production of their own natural specific desired products such as pro/anti-inflammatory mediators and cytokines, or by introducing critical foreign genes that modulate the therapeutic effects of MSCs or enable them to express non-native products for specific therapeutic applications [67, 68]. In recent reports, a novel approach using MSCs as gene or drug delivery vehicles has been described, which emphasizes other potential application of genetically-modified MSCs [69, 70]. This can greatly broaden the spectrum of diseases for which MSCs could

provide therapeutic benefits. Overall, gene modification may be applied to generate: 1. Disease-specific potent MSCs with improved immunomodulatory or regenerative properties, 2. MSCs as vehicles for gene delivery or manufacturing specific therapeutic proteins, 3. Loading of therapeutic cargo into MSC-derived extracellular vesicles (EVs) as potent therapeutic or vehicles for gene, mRNA and protein delivery.

Genetic modification of MSCs can be facilitated by different tools and techniques that introduce particular genes or sequences to the genomic content or tailor the native genetic material using molecular engineering techniques called "gene editing" [71].

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 is a novel gene-editing technology in which, a complex made of Cas9 nuclease and a small guide RNA produces a target-specific break in the genome followed by insertion of a new sequence mediated by homology-directed repair that can be used to correct a gene mutation, introduction of a knock-in or knock out mutation or silencing of a specific gene [72]. CRISPR/Cas9 has been employed to some extent for gene editing of MSCs [73, 74]. The gene expression machinary can also be manipulated at the cytoplasmic level by RNA interference technology using siRNAs or microRNAs that inhibit the expression of messanger RNA of target genes in a sequence specific manner [75].

Nucleic Acid Delivery Systems

Delivery of therapeutic genes or sequences for genetic manipulation in target cells or tissues can be accomplished using viral and nonviral delivery systems with different characteristics, as discussed below:

Viral Vectors

Viral vectors are promising tools for nucleic acid delivery in pre-clinical and clinical applications. Almost 70% of clinical gene therapy trials around the world conducted are based the use of viral vectors such as lentiviral/retroviral, adenoviral and adeno-associated viral vectors [76]. Several fundamental features of viral vectors including high transduction efficiency and tropism for a broad range of target cells and tissues, high safety profile, and establishment of a long-term transgene expression have made them attractive systems for gene therapy. Drawbacks for therapeutic application of viral vectors include their immunogenicity, limited loading capacity and potential insertional mutagenesis described for integrating types [77, 78]. Among the different types of viral vectors, recombinant lentiviral vectors as a subgroup of retrovirus family have been the most frequently used systems due to the high tropism and transduction efficiency and stable expression of transgene in MSCs [79, 80]. Also, lentivectors have a high loading capacity which is a great advantage allowing transferring large genes (up to 8 kb) into target cells/tissues. Furthermore, current generations of lentiviral vectors have a convincing safety record proven repeatedly in several analytical studies and clinical trials worldwide [81].

Adeno-Associated Viral (AAV) vectors with different serotypes have shown significant promise for gene therapy. The high transduction efficiency of these vectors in a broad range of target cells and tissues as well as their excellent safety profile and a minimal inflammatory toxicity have made them an attractive choice for gene therapy applications [82, 83]. Although, AAVs suffer from a limited loading capacity for exogenous DNA (up to 4 kb), overall, they are known as efficient gene therapy tools being employed in clinical applications [84]. Several studies have shown that AAV vectors can efficiently transduce MSCs [85, 86]. Adenoviral vectors (AdVs) have long been used as efficient non-integrating gene therapy vectors that induce a transient gene expression in both dividing and quiescent cells [87]. AdVs offer an excellent safety profile and account for >20% of all gene therapy trials worldwide. The immunogenic nature of AdVs has proved beneficial for the development of anticancer immunotherapies as well as vaccines, where the goal is inducing immunity against the cancer cells [88].

Nonviral Delivery Systems

Nonviral delivery systems such as plasmid DNA, DNA minicircles, nanoplasmids, liposomes and polymers have been extensively studied for gene delivery applications [89–91]. The main advantage of using nonviral vectors is their limited immunogenicity, enhanced biosafety and high loading capacity. However, the application of nonviral systems in gene therapy has been limited due to their low transfection efficiency and transient expression of the transgene [92]. Liposomes and polymers are among traditional nonviral delivery systems shown that transiently transfect MSCs [90, 93–95]. Minicircles are small DNA-based vectors lacking prokaryotic backbone sequences that are typically present in conventional plasmid vectors. When compared to traditional plasmid vectors, minicircles have demonstrated less toxicity and immunogenicity, higher transfection efficiency and longer transgene expression, in vitro and in vivo [90, 96–98]. A number of reports suggest that minicircles can efficiently and stably transfect MSCs [99, 100].

Therapeutic Effects of Genetically Modified MSCs in Critical Illness

The choice of the appropriate genetic modulation in cellular-based gene therapy is a critical determinant of the therapeutic outcomes, as the impact of such intervention will be directly observed in functionality and therapeutic effects of transplanted cells. Table 1 provides an overview of cell

Table 1 An overview of cell therapy studies based on the application of genetically modified mesenchymal stromal cells in animal models of critical illness (*BM-MSC* bone marrow Mesenchymal stromal cell, *UC-MSC* Umbilical cord Mesenchymal stromal cell, *A-MSC* Adipose Tissue Mesenchymal stromal cell, *AF-MSC* Amniotic Fluid Mesenchymal stromal cell, *h* from human, *m* from mouse, *p* from pig, *r* from rat, *rb* from rabbit, *s* from sheep)

Critical Illness	Modified genomic target	Strategy/Method	Cells	Animal Model
SEPSIS/ARDS/ALI	ANGPT1	Overexpression with eletroporation	mBM-MSC	Mouse Model of LPS-Induced ALI [49]
		Overexpression with lentiviral vector	mBM-MSC	Mouse Model of LPS-Induced ALI [102]
	FGF-2	Overexpression with lentiviral vector	mBM-MSC	Mouse Model of LPS-Induced ALI [103]
	KGF	Overexpression with lentiviral vector	mBM-MSC	Mouse Model of LPS-Induced ALI [104]
	KGF	Transfection with Nucleofection	mBM-MSC	Mouse model of hemorrhagic shock and trauma (ARDS) [105]
	ACE2	Expression using lentiviral vector	hUC-MSC	Mouse model of Bleomycin-induced lung fibrosis-injury [108]
	ST2	Overexpression with lentiviral vector	hA-MSC	Mouse model of LPS-Induced ALI [114]
Ischemia and Reperfusion (I/R)	IL-10	Overexpression with retroviral vector	rBM-MSC	Rat model of lung ischemia induced by clamping [115]
	AKT	Overexpression with lentiviral vector	rbAF-MSC	Rabbit model of myocardial I/R [116]
	Gremlim-1	Overexpression with lentiviral vector	mMSC	Mouse model of ischemic hindlimb [118]
	CXCR4	Overexpression with lentiviral vector	rBM-MSC	Rat model of transient MCAO (middle cerebral artery occlusion) followed by reperfusion [119]
	ANGPT1	Overexpression with Adenoviral vector	hBM-MSC	Rat model of transient MCAO (middle cerebral artery occlusion) followed by reperfusion [120]
	ANGPT1 and VEGF	Overexpression with Adenoviral vector	hBM-MSC	Rat model of transient MCAO (middle cerebral artery occlusion) followed by reperfusion [121]
AMI	AKT	Overexpression with retroviral vector	rBM-MSC	Rat model of myocardial ischemia [122]
	Akt/ANGPT1	Overexpression with Adenoviral vector	rBM-MSC	Rat model of acute myocardial infarction [124]
	Bcl-2	Overexpression with nonviral transfection system jetPEI®	rBM-MSC	Rat model of myocardial infarction [125]
	SDF-1	Overexpression with Adenoviral vector	rBM-MSC	Rat model of myocardial infarction [126]
	Prostaciclin Synthase	Overexpression with Adenoviral vector	mBM-MSC	Mouse model of unilateral hindlimb ischemia [117]
	TNFR	Expression with Adeno-associated viral vector	rBM-MSC	Rat model of acute myocardial infarction [129]
	Oxygen-resistant form of HIF1-α	Minicircle vector	sBM-MSC	Ovine model of acute myocardial infarction [130]
	IGF-1 and HGF	Overexpression with lentiviral vector	pA-MSC	Pig model of acute myocardial infarction [131]
	miR-377	Overexpression or Knocking-down with lentiviral vector	rA-MSC	Rat model of acute Myocardial infarction [132]
AKI	Lcn2	Overexpression with nonviral transfection system FuGENE	rBM-MSC	Rat model of Cisplatin-induced AKI [135]
	Nrf2	Overexpression with Adenoviral vector	hBM-MSC	Rat model of Cisplatin-induced AKI [137]
ALF	CXCR4	Expression with lentiviral vector	hBM-MSC	Mouse model of Acute Liver Failure by i.p. administration of CCL_4 [143]
	c-Met	Overexpression with lentiviral vector	rBM-MSC	Fulminat Hepatic Failure model by i.p. administration of Galactosamine and LPS [144]
	US6, US11	Expression with MSCVneo retrovirus	h-MSC	Pre-immune fetal sheep recipient [146]
	IL-1R	Overexpression with lentiviral vector	hAF-MSC	Fulminat Hepatic Failure model by i.p. administration of Galactosamine and LPS [153]

therapy studies based on application of genetically modified MSCs in animal models of critical illness.

Genetically Modified MSCs for the Treatment of Acute Lung Injury

Angiopoietin 1 (ANGPT1) is known as a vascular endothelial stabilization factor that mediates maturation of the vasculature and maintains their permeability. In two separate studies on LPS-induced acute lung injury mouse model [49, 101], the administration of ANGPT1-overexpressing bone marrow MSCs (BM-MSCs), modified by electroporation/plasmid or lentivectors, led to a much higher reduction in pulmonary inflammation and vascular endothelial permeability when compared to wild-type MSC treatment. It was noted that MSCs-ANGPT1 had a more potent therapeutic effect, not only by reducing extravasation of plasma proteins and inflammatory cells, but also by further reducing the levels of various inflammatory cytokines and chemokines including IFNγ, TNF-α, IL-6, IL1β and Cxcl2 in the bronchoalveolar lavage (BAL) fluid. Zhao et al. delivered BM-MSCs transduced with a lentivector carrying the gene for basic fibroblast growth factor (FGF2), an angiogenic factor, for the treatment of LPS-induced lung injury in mice. Treatment with FGF2-modified MSCs attenuated the inflammatory response and vascular leakage as well as suppressed the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in LPS-induced lung injury model [102].

Keratinocyte growth factor (KGF), also known as FGF-7, is a potent mitogenic factor for alveolar epithelial cells. It is known that the clinical effectiveness of exogenous recombinant (rh) KGF is limited due to rapid degradation. However, using a different approach, Chen et al. [103] transduced MSCs overexpressing KGF and showed the modified MSCs exerted their immunomodulatory functions via sustained expression of KGF in injured lung tissues, resulted in a significant alleviation of alveolar inflammation and permeability and improvement of lung injury. Recently, it was reported that the conditioned medium of KGF-modified MSCs resulted in similar therapeutic effects as MSC therapy [104].

The protective role of Angiotensin-converting enzyme 2 (ACE2) in acute lung injury was demonstrated previously [105, 106]. Min et al. used a lentivector encoding for ACE2 and showed that treatment of a mouse model of bleomycin-induced lung injury, with human umbilical cord-derived MSCs (UC-MSCs) overexpressing ACE2, led to efficient therapeutic effects by improving the inflammatory profile. Importantly, MSCs expressing ACE2 had a more robust therapeutic effect than application of recombinant ACE2 or naïve MSCs [107].

In a similar approach, He et al. [108] used BM-MSCs transduced with a lentivector overexpressing ACE2 and transplanted into wild type and ACE2 knockout mice following LPS-induced lung injury and showed that MSC-ACE2 efficiently alleviated lung injury at 24 and 72 h post-transplantation when compared to naïve MSCs.

Recent studies have investigated the therapeutic effects of MSCs in the novel coronavirus 2 (SARS-CoV-2)-induced ARDS and organ failure [109–111]. In a pilot trial, Leng et al. performed intravenous transplantation of ACE2-overexpressing MSCs into seven patients with COVID-19 pneumonia. Two days after MSC administration, a significant improvement of pulmonary function and symptoms was observed in all patients. The results of this study show an increase in the number of regulatory T lymphocytes and dendritic cells (DCs), an increase in IL-10 and a decrease in TNF-α after MSC treatment [112].

The IL-33/IL-1 receptor–like–1 (ST2) axis has been suggested to function as an alarm system in lungs, which is released upon endothelial or epithelial cell damage [113]. Gonzalez et al. [114], generated adipose tissue–derived MSCs (A-MSCs) overexpressing soluble IL-1 receptor–like–1 (sST2) using a lentiviral vector. Treatment of mouse LPS-induced lung injury model with these cells resulted in a decrease in lung airspace inflammation and vascular leakage, characterized by reductions in protein leakage, differential neutrophil counts, TNF-α, IL-6, and macrophage inflammatory protein 2 in bronchoalveolar lavage fluid of treated animals. Lungs showed preserved alveolar architecture, absence of apoptosis, and minimal inflammatory cell infiltration.

Genetically Modified MSCs for the Treatment of Acute Ischemia Reperfusion Injury

Ischemia–reperfusion (IR) injury is a critical condition that may occur in the vasculature of different organs, mainly lung and heart. This pathologic condition is characterized in lung by nonspecific alveolar damage, edema formation, and hypoxemia. Manning et al., administered IL-10-overexpressing BM-MSCs as a delivery system for IL-10, to prevent lung IR injury in rats. They applied a retrovirus carrying IL-10 cDNA for genetic engineering of MSCs. It was shown that as early as 4 h post-IR injury, blood oxygenation was significantly improved in animals treated with MSC-IL-10 in comparison to untreated animals. Moreover, MSC-IL-10-treated animals had fewer CD4(+) and CD8(+) T cells in bronchoalveolar lavage fluid compared to untreated control animals [115].

In a study by Wang et al. [116], the cardioprotective effect of genetically modified MSCs was evaluated after ischemia-reperfusion (I/R) injury in heart. In this study, amniotic fluid-derived mesenchymal stromal cells (AF-MSCs) overexpressing Akt, a serine-threonine kinase involved in survival and proliferation of MSCs as well as in survival and cell cycling of cardiomyocytes, were transplanted into the ischemic myocardium of rabbits prior to reperfusion. Three weeks post-

transplantation, a significant decrease in myocardial inflammation, ultrastructural damage and cardiomyocyte apoptosis as well as a marked augmentation in left ventricular function was observed in animals treated with AF-MSC-Akt when compared to control group.

Ishii et al. [117], assessed the therapeutic effects of genetically modified MSCs in a mouse model of critical limb ischemia (CLI) which is characterized by a markedly reduced blood-flow in the limb, due to severe arterial blockage. Using an adenoviral vector, they overexpressed the vasoregulatory protein, prostacyclin synthase (PGIS) in BM-MSCs and transplanted the mice after inducing hindlimb ischemia. It was shown that by administering PGIS-overexpressing MSCs they were able to obtain reperfusion of the ischemic limb within 7 days of inducing ischemia, suggesting enhanced proangiogenic function of genetically modified MSCs had a fundamental effect on outcomes. Moreover, in this report, MSC-induced overexpression of PGIS resulted in higher expression levels of the antiapoptotic mediators phosphorylated Akt and Bcl-2.

Gremlin1 (GREM-1) is an extracellular antagonist of the bone morphogenetic proteins (BMPs), acting as a regulator of growth, differentiation and development. GREM-1 has been identified as a novel proangiogenic factor. In a recent study by Xiang et al. [118], the therapeutic effects of BM-MSCs overexpressing GREM-1 was investigated in a mouse model of ischemic hindlimb. Transduction of MSCs with a lentivirus overexpressing GREM-1 showed enhanced survival when exposed to peroxide (H_2O_2), attributed to enhanced in vivo survival of genetically modified MSCs and their effects on the viability of endothelial cells in the ischemic area.

Yu and colleagues took advantage of CXCR4 role in MSC chemotaxis and hypothesized that MSCs overexpressing CXCR4 can promote their own recruitment around the ischemic core. Using lentiviral vector, they generated rat MSCs overexpressing the CXCR4-eGFP fusion protein. They treated the animals following a left middle cerebral artery occlusion for 2 h and then reperfusion was performed. One week post treatment, there was an increased number of eGFP-positive cells surrounding the infarct areas in the CXCR4-MSC group when compared to the naïve MSC group. Treatment with CXCR4-MSCs also resulted in an increase in the capillary vascular volume of the peri-infarct area, reduction in the volume of the cerebral infarction and improved neurological function when compared to control groups [119].

Kocsis's group used human BM-MSCs transduced with an adenoviral vector carrying a human Angiopoietin 1 (ANGPT1) cDNA, for the treatment of permanent middle cerebral artery occlusion (MCAO) in rats. They demonstrated that treatment with these cells presented a better outcome in terms of neovascularization and regional cerebral blood flow, and improved functional recovery in the treadmill stress test in comparison to naïve MSCs [120]. In a similar study, the same group expanded the gene modification strategy and transduced hBM-MSCs with adenoviral vectors carrying a human ANGPT1 gene and VEGF gene and investigated whether the combination of ANGPT1 and VEGF gene-modified MSCs (ANGPT1-VEGF-hMSC) contributed further to functional recovery in a rat MCAO model. It was noticeable in the MRI and behavioral experiments that animals which received ANGPT1-VEGF-hMSCs showed the greatest structural–functional recovery when compared to all the other control groups [121].

Genetically Modified MSCs for the Treatment of Acute Myocardial Injury

In the case of MSC therapy for acute myocardial infarction (AMI), most of the applied genetic modification approaches were based on enhancing the survival, migration and retention properties of MSCs as well as reprograming them to produce angiogenic and regenerative factors. Mangi et al. [122] overexpressed Akt in BM-MSCs using a retroviral vector followed by transplantation of these cells into the ischemic rat myocardium. This was associated with a remarkable reduction of infarct size and myocardial remodeling as well as improved left ventricular function. Importantly, the hypothesis that MSCs differentiate into cardiomyocytes was challenged by new reports, indicating that the therapeutic function of MSCs was due to the enhanced production of anti-inflammatory as well as pro-repair factors [123]. Shujia et al. [124], improved the duration of the beneficial effects of MSC therapy up to 3 months by co-transducing MSCs with two adenoviral vectors encoding for Akt or the pro-angiogenic protein Angiopoietin 1 in a rat AMI model.

In a study by Li et al. [125], Bcl-2, a pro-survival antiapoptotic gene was overexpressed in rat BM-MSCs using polymeric delivery system, polyethylenimine (PEI). Intracardiac injection of transfected MSCs in a rat model of AMI resulted in reduction of infarct size and a better left ventricular function compared to control group. Furthermore, this study demonstrated that the therapeutic effects of Bcl-2-overexpressing MSCs was partly due to an increase in vascular endothelial growth factor (VEGF). Also, overexpression of Bcl-2 enhanced the in vivo survival of MSCs.

Stromal-derived factor-1 alpha (SDF-1alpha) plays an important cardioprotective role by homing of stem cells to the injured heart tissue [126]. Tang et al. [127], overexpressed SDF-1α in MSCs using an adenoviral vector, followed by intramyocardial transplantation in a rat model of myocardial infarction. Four weeks following transplantation, these investigators were able to show reduced infarct size and fibrosis, greater vascular density and thicker left ventricular wall in the Ad-SDF-MSC group compared to rats treated with naïve MSCs. Moreover, it was reported that transplanted MSCs were partly positive for the cardiac marker troponin-T,

suggesting that transplanted MSCs can differentiate into cardiomyocytes. In a follow up study by the same group, dual overexpression of VEGF and SDF-1α in MSCs using adenoviral vectors demonstrated additive therapeutic benefits in experimental model of AMI [128].

Bao et al. [129], investigated the therapeutic effect of BM-MSCs overexpressing tumor necrosis factor receptor (TNFR), mediated by a recombinant AAV vector, in a rat model of AMI. It was demonstrated that treatment with genetically modified MSCs improved cardiac inflammation and left ventricular function 2 weeks post-MI. This therapeutic effect was attributed to the anti-apoptotic and anti-inflammatory function of TNFR-overexpressing MSCs.

Hypoxia-inducible factor 1-α (HIF1-α) is known to upregulate various cardioprotective genes during ischemia. Hnatiuk et al. [130] used a minicircle vector encoding a stable, oxygen-resistant form of HIF1-α for transfection of BM-MSCs followed by intramyocardial delivery of the cells in a sheep model of AMI. Over a 2-month follow-up study, it was shown that treatment with modified MSCs reduced infarct size and improved LV systolic performance compared to naïve MSCs, attributed to increased neovascularization and cardioprotective effects induced by HIF1-mediated overexpression of paracrine factors and enhanced retention of injected cells.

In a study by Gomez et al. [131], pig MSCs derived from adipose tissue were transduced with lentivectors encoding for insulin-like growth factor 1 (IGF-1) or hepatocyte growth factor (HGF). These cells were used to improve cardiac function in a porcine model of intramyocardial transplantation. Overexpression of either IGF-1 or HGF improved left ventricular ejection fraction (LVEF), cardiac output, and stroke volume, and reduction in heart rate and infarction size compared to naïve MSCs.

Wen and colleagues [132], searched for the most important microRNAs associated with angiogenic properties in MSCs. Using microRNA microarray analysis, they found that the expression of microRNA-377 was reduced in hypoxia-treated MSCs. The group further reported that VEGF is a direct target of microRNA-377. Using lentivectors, they knocked-down miR-377 in MSCs and administered these cells in a rat model of AMI. Four weeks after transplantation of miR-377 depleted MSCs into the infarcted rat hearts, the vessel density was increased in the heart, and this was accompanied by reduced fibrosis and improved myocardial function due to promotion of MSC-induced angiogenesis in the infarcted myocardium.

Genetically Modified MSCs for the Treatment of Acute Kidney Injury

Recent studies capitalized on the application of genetically modified MSCs for the treatment of Acute kidney injury (AKI) [133, 134]. In a recent study by Roudkenar et al. [135], overexpression of Lipocalin-2 (Lcn2) in MSCs enhanced their therapeutic effects in a cisplatin-induced AKI rat model. Lcn2, a neutrophil gelatinase-associated lipocalin, is a secretory protein discovered in neutrophils which accumulates in blood and urine after acute kidney injury due to bacterial infection [136]. Overexpression of Lcn2 in MSCs using FuGENE transfection reagent efficiently enhanced the therapeutic properties of these cells leading to improvement in renal function. Treatment with MSC-Lcn2 resulted in upregulation of HGF, IGF, FGF and VEGF growth factors following cisplatin-induced AKI. In addition, a reduction in molecular biomarkers of kidney injury such as KIM-1 and Cystatin C and elevation of the markers of proximal tubular epithelium such as AQP-1 and CK18 was observed.

In a study by Mohammadzadeh et al. [137], overexpression of nuclear factor erythroid-2 related factor 2 (Nrf2), a critical cytoprotective transcription factor, in BM-MSCs protected rats against AKI by restoring renal tubule structure and improving renal function. Additionally, Nrf2-MSCs were resistant to apoptosis and produced higher amount of growth factors.

Genetically Modified MSCs for the Treatment of Acute Liver Injury

Acute liver failure (ALF) is a clinical syndrome characterized by hepatocellular necrosis observed after acute injuries due to assaults such as viral infections, hepatotoxic drugs, autoimmune responses and veno-occlusive disease. The only definitive treatment for ALF is liver transplantation, which is limited because of financial aspects, shortage of donor, and immunosuppression-related complications [138].

The therapeutic function of genetically modified MSCs in acute liver injuries are partially based on their regenerative properties and differentiation into hepatocyte-like cells (HLCs) [139–142]. Therefore, the key element for better therapeutic outcomes in liver injury is an efficient targeted delivery and homing of MSCs in the injured area.

Hu-Cheng Ma and colleagues [143] hypothesized that overexpression of CXCR4 (chemokine CXC receptor 4), a receptor for SDF-1α involved in MSC homing - would enhance the engraftment of MSCs in the injured liver and improve liver regeneration. In this study, liver injury was induced using hepatotoxic chemical carbon tetra chloride CCL4. Both in vitro *and* in vivo experiments showed that CXCR4 MSCs present better migration capability than null-MSCs toward the injured area and prevented cell death in hepatocytes. In vivo fluorescence imaging demonstrated the presence of CXCR4 MSCs in liver at days 1 and 5 after liver injury. Moreover, CXCR4 MSC group presented a longer lifetime and better liver function and histology.

In a study by Wang et al. [144], in order to enhance the migration ability and homing properties of bone marrow

MSCs in acute liver injury, c-Met, a member of tyrosine protein kinase family – was overexpressed using a lentivector. Hepatocyte growth factor (HGF) is known as the ligand of c-Met and the HGF/c-Met signaling pathway is considered to play an important role in the homing ability of MSCs to the liver [145]. In this study, in vitro assays showed that c-Met-MSCs had a higher migration activity in comparison with control MSCs. Transplantation of c-Met-MSCs into rats with ALF resulted in an improved homing ability of the MSCs to the injured liver, ameliorated liver injury with reduced hepatic activity index (HAI) scores and enhanced survival.

Another approach to improve the success of MSC therapy is to make MSCs look as invisible as possible to the recipient's immune system. Soland and colleagues [146], genetically engineered human MSCs using MSCVneo retrovirus to express human cytomegalovirus proteins that are known to downregulate HLA-I expression (US2, US3, US6 and US11). After this genetic modification, they tested if these MSCs were protected from cytotoxic T lymphocyte and Natural killer cell attack. From the 4 different proteins they tested, only US6 and US11 reduced HLA-I expression. This reduction in HLA-1 expression was accompanied by a decrease in human and sheep mononuclear cell proliferation after a mixed lymphocyte reaction. Transplantation of MSC-US6 or MSC-US11 cells into pre-immune fetal sheep resulted in an increased liver engraftment when compared to control MSCs.

Poor in vivo cell viability of MSCs has been a limiting factor for their therapeutic effects [147, 148]. In order to make MSCs more resistant to apoptosis and enhance their in vivo survival, Zhou et al. overexpressed Akt1 – a pro-survival signal protein – in MSCs. The in vivo survival and hepatoprotective effects of Akt1-MSCs was investigated after transplantation into a rat model of acute liver injury induced by concanavalin A. When compared to control MSC groups, a higher survival rate and significantly lower serum AST, ALT, TNF-α and IFN-γ levels and less histopathological abnormalities was observed in Akt1-MSCs treated animals. In addition, Akt1-MSCs treated mice had significantly higher serum concentrations of IL-10, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF).

Fulminant hepatic failure (FHF) is a lethal inflammatory liver disease with elevated serum levels of immuno-inflammatory cytokines like IL-1, TNF, IL-6 and IL-8 [149, 150]. Uncontrolled hepatic immunoactivation has been proposed as the primary pathological mechanism of FHF [151]. IL-1Ra is a cytokine member of the IL-1 family known to prevent biological response to IL-1 by competing for its receptor. IL-1Ra presents hepato-protective effects [149] and play an anti-inflammatory role in acute and chronic inflammation [152]. Zheng and collaborators tested whether IL-1Ra overexpressing MSCs could protect injured livers in a rat FHF model. They used a lentivector to overexpress IL-1Ra in AF-MSCs and demonstrated that treatment of a rat model of FHF with these cells prevented liver failure and improved survival. The presence of engrafted cells and their progeny in the injured livers was shown using Fluorescent imaging [153].

Concluding Remarks

MSCs possess strong regenerative, pro-inflammatory, anti-inflammatory and drug delivery properties. These features introduce MSCs as attractive cell-based therapeutics for critical medical conditions with inflammatory basis such as sepsis, ARDS, ALI, AKI, ALF, AMI and ischemia. Several studies based on experimental models of critical illness, have demonstrated that proper genetic modifications can enhance the therapeutic potency of MSCs in terms of improvement in mortality and morbidity. Genetic manipulations in MSCs can be mediated by advanced techniques and delivery systems, mainly gene therapy viral vectors, in order to efficiently induce expression, up-regulation or down-regulation of specific genes or pathways. Clinical translation of advances in genetically engineered MSCs requires detailed investigations on the safety and potency of each strategy in short- and long-term cell therapy studies in clinically relevant animal models of critical illness as reviewed in this report.

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