Review Article

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Stem cell therapy: A novel & futuristic treatment modality for disaster injuries

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Stem cell therapy holds the potential to meet the demand for transplant cells/tissues needed for treating damages resulting from both natural and man-made disasters. Pluripotency makes embryonic stem cells and induced pluripotent stem cells ideal for use, but their teratogenic character is a major hindrance. Therapeutic benefits of bone marrow transplantation are well known but characterizing the potentialities of haematopoietic and mesenchymal cells is essential. Haematopoietic stem cells (HSCs) have been used for treating both haematopoietic and non-haematopoietic disorders. Ease of isolation, *in vitro* expansion, and hypoimmunogenecity have brought mesenchymal stem cells (MSCs) into limelight. Though differentiation of MSCs into tissue-specific cells has been reported, differentiation-independent mechanisms seem to play a more significant role in tissue repair which need to be addressed further. The safety and feasibility of MSCs have been demonstrated in clinical trials, and their use in combination with HSC for radiation injury treatment seems to have extended benefit. Therefore, using stem cells for treatment of disaster injuries along with the conventional medical practice would likely accelerate the repair process and improve the quality of life of the victim.

Key words Critical injuries - disasters - haematopoietic stem cells - mesenchymal stem cells - stem cell therapy

Introduction

Disasters whether natural (*e.g.* earthquake, volcanic eruption), man-made (like war, terrorism) or a result of human error/ignorance (such as nuclear reactor explosion, air and rail disasters) not only cause enormous loss of life and property, but also physical and psychological trauma to many people. Increasing terrorist activities and development of nuclear weapons of mass destruction demands the development of new treatment regimens to deal with victims of such events. In victims inflicted with critical injuries/disorders like cancer, burns, loss of immune cells, fractures and renal failure[1-5], transplantation of healthy functional cells which can repair or replace the damage through the process of regeneration, is likely to provide a permanent cure.

Isolation of differentiated cells from an autologous source and transplanting them to the damaged area (as in skin and bone grafting and autologous chondrocyte transplantation) is a good option, but it is associated with drawbacks like donor site morbidity and limited availability of amount of donor tissue, and unsuitability of using autologous tissue under certain situations such as renal failure and whole body

radiation exposure. Thus, allogeneic cells/tissues have been used for transplant, but under circumstances of a disaster which affects hundreds of thousands of individuals, availability of sufficient graft tissue is a challenge. The inability of differentiated cells to proliferate *in vivo* or *in vitro* is a major setback in regenerative medicine. Therefore, generation of functional cells with necessary characteristics and the development of technologies for their successful expansion while retaining the desired functions is of utmost importance. Stem cells have the ability to self-renew and undergo differentiation, and stem cell therapy, which involves transplant of normal or genetically modified stem cells, offers hope for treating thousands of survivors of various disastrous events taking place around the world.

Stem cells

Stem cells are a special class of cells characterized by their ability to self-renew (*i.e*. multiply to generate same kind of cells) and produce progenitor cells which are committed to give rise to fully differentiated cells. The quest for these master cells led to their isolation from various tissues at different stages of organism development. Stem cells were first found to be present in the bone marrow of mouse about 45 years ago[6]. Then came the stem cells known as haematopoietic stem cells (HSCs), which give rise to the cells of the haematopoietic lineage. Later, Friendenstein *et al* found another population of cells with stem cell-like characteristics present in the marrow and called them colony forming unit-fibroblast [now known as mesenchymal stem cells (MSCs), stromal stem cells][7]. Later on, such cells were found in almost every tissue of the body, and were broadly categorized into adult stem cells.

With the kind of potential these cells exhibited, the existence of such cells in the embryo was questioned. This led to the identification of mass of cells (inner cell mass) in the blastocyst, which exhibited indefinite self-renewal *in vitro* and differentiated into almost every cell type of the body (*i.e.* pluripotent). These cells are known as embryonic stem cells (ESCs) and first human ESCs were isolated in 1998 by Dr Thomson and colleagues from IVF clinic embryos[8]. Embryonic stem cells are best suited for the generation of any cell type by directed differentiation and in sufficient numbers but their use was hampered due to ethical issues, and the risk of teratoma formation and immune rejection upon transplantation.

Ethical issues associated with use of ESCs can be overcome by the technique known as somatic cell nuclear transfer[9]. This generates custom-made, patient-specific ESCs which can be induced to differentiate and then transplanted without immune rejection since they have the genetic material of the patient. However, the technique is very labour-intensive. Since it demonstrates the ability to reprogramme adult cells, Takahashi and colleagues identified four important transcription factors (Oct-4, Sox2, KLF4 and c-Myc) that could induce fibroblasts to become embryonic like-stem cells known as 'Induced pluripotent stem cells' (iPSCs)[10,11]. These cells exhibit properties of embryonic stem cells such as pluripotency and *in vitro* expansion, and do not have immune problems. But one potential drawback with both these approaches is the likely presence of inherited or accumulated mutations in the genome from older adult cells that would predispose them to senescence or cancer.

Adult stem cells (ASCs) like cardiac, neural, intestinal, though used in animal studies, represent significant challenge in clinics due to constraints of their location (source) and low occurrence. Epithelial tissues such as intestine, skin, mammary gland, and cornea require continuous replenishment of new cells to maintain tissue homeostasis and are shown to possess stem cells[12,13]. Limbal stem cells and keratinocyte stem cells grow well in culture and can be expanded *ex vivo*. However, these have not been demonstrated to exhibit multipotent character and therefore, have restricted application.

Apart from epithelial tissues, bone marrow is a rich source of stem cells in the adult. It harbours two stem cell populations, haematopoietic and mesenchymal. Haematopoietic stem cells (HSCs) constitute the non-adherent cells and are responsible for replenishing the blood cells. These are isolated based on the expression of several identified surface molecules such as CD34, c-kit, Thy-1, *etc*[14]. Even though HSCs can be isolated in good number, their *in vitro* expansion has not been very successful and these cells encounter immune responses upon allogeneic transplantation[15-17]. However, HSC transplantation has been successfully used over the years for the treatment of haematopoietic disorders in humans[15] due to ease of isolation.

Mesenchymal stem cells (MSCs) present in bone marrow overcome limitations imposed by ESCs and other tissue-specific stem cells. These constitute an adherent, fibroblast-like cells present in the

marrow, which are involved in maintenance of the mesenchymal tissues. Like ASCs, these occur at a very low frequency (0.001 - 0.01% in bone marrow mononuclear cells), but proliferate *in vitro* for about 30-40 population doublings while retaining their differentiation potential[18,19]. These can also be isolated from other tissues such as peripheral blood, periosteum, umbilical cord blood, synovial membrane, trabecular bone and adipose tissue[20]. Naturally differentiating into cells of bone, cartilage, skeletal muscle, tendons, fat and stroma, these have been demonstrated to give rise to cardiomyocytes, hepatocytes, and neural and epithelial cells *in vitro*[21-25]. These multipotent cells do not express HLA class-II antigens and co-stimulatory molecules CD40, CD80 and CD86, making them immune privileged and hence, suitable for allogeneic transplantation[26,27]. These features along with their ability to home to injury sites[28,29], modulate immune responses[27] and facilitate tissue regeneration[30,31], make them appropriate for stem cell-based therapy. But it is important to decipher and understand the signaling network regulating proliferation and differentiation of tissue-specific stem cells to fully exploit their potential and develop new efficient and effective strategies.

Stem cell therapy and its applications

Stem cell therapy involves the transplantation of stem cells (normal or genetically modified) or stem cell-generated grafts for the treatment of various damages/ disorders. HSCs have been in clinical use for a long time. Several clinical studies have been performed in recent years documenting safe use of MSCs but lack sufficient evidence to support their therapeutic benefit.

Haematopoietic disorders

Haematopoietic system is particularly affected in case of radiation disasters due to radiosensitivity of haematopoietic cells[32,33]. A dose of 2 or more Gy of ionizing radiation results in haematologic syndrome characterized by depletion in the lymphocyte, granulocyte and platelet counts, thus making the victims susceptible to infections. It also causes mutations leading to increased incidence of development of leukemia, as was observed among the survivors of Hiroshima and Nagasaki atomic bomb attacks[34]. Thus rapid regeneration of the depleted myeloid cells is necessary to impart immune tolerance to cope with radiation-induced damage. Since the haematopoietic stem cell pool is also affected, transplantation of HSC has been suggested for victims severely affected with acute radiation syndrome (*i.e*. exposed to 7 to 10Gy)[1,35]. Due to damage to endogenous HSCs, allogeneic HSCs need to be transplanted raising the risk of graft-versus-host disease (GVHD). The incidence and severity of GVDH can be reduced by transplantation of MSCs as demonstrated in preclinical studies[36]. Human clinical trials using MSCs for treatment of severe, steroid-resistant GVHD have shown positive results[37,38]. Also, intravenous infusion of MSCs in patients suffering from leukemia resulted in HSC engraftment, rapid platelet recovery and low incidence of GVHD[39,40]. The modulation of immune cell responses by MSCs probably via secretion of transforming growth factor-beta (TGF-β), prostaglandin E2 and indoleamine 2,3-dioxygenase results in suppression of T-cell proliferation and activation[27,41], thereby reducing GVHD. Allogeneic MSCs have been used to reduce tissue toxicity in patients undergone allogeneic HSC transplantation[42] due to their ability to modulate the immune responses.

Not only restricted to haematopoietic cells, the supportive stroma in the marrow is also irreversibly damaged by ionizing radiation[43,44]. This results in reduction of the engraftment efficiency of transplanted HSCs[45]. Recently, spindle-shaped, N-cadherin expressing osteoblasts (SNO) have been demonstrated to form part of the haematopoietic niche[46]. Following a 4Gy dose of whole body irradiation to mice, a significant decrease in osteoblasts including SNO was observed, highlighting damage to the haematopoietic niche[47]. Therefore, co-transplantation of MSCs and HSCs has been tested to facilitate HSC engraftment. Studies have shown improved HSC engraftment upon co-infusion[48-51], even in acute radiation syndrome (ARS) model[52], which can be employed in clinics as well although the underlying mechanism needs to be elucidated.

Acute radiation syndrome

Exposure to penetrating ionizing radiation (particularly, doses >0.5Gy) leads to physiological derangements, collectively known as ARS or radiation sickness. The survivors of Hiroshima and Nagasaki attacks and Chernobyl nuclear reactor incident are sufferers of ARS. In the present scenario, soldiers are likely to be exposed to radiation during war, and developing radiation sickness. Depending on radiation dose and duration of exposure, different complications can develop requiring replacement of transformed and dead cells to prevent fatality. Almost all casualties receiving more than 4Gy die within 30 days without

any medical treatment[53]. Stem cells are likely to offer hope for ARS victims.

HSC transplantation has been used for treating victims of nuclear accidents demonstrating bone marrow failure[54-56]. For instance, of the 13 victims, exposed to dose between 5.6-13.4Gy during the Chernobyl nuclear accident, receiving bone marrow transplants only two survived more than 3 years after the accident[55]. The damage to other organ systems such as skin burns, renal failure, respiratory distress syndrome, graft-versus-host disease resulted in mortality. HSC transplantation alone is not sufficient and improvement in current treatment regimes is warranted.

Studies in animal models subjected to lethal dose of irradiation have demonstrated the ability of MSCs to specifically home to sites of injury[28,29,52]. NOD/SCID mice irradiated at a dose of 3.5Gy were infused with human MSCs. Total body irradiation increased engraftment levels of MSCs in the brain, heart, bone marrow and muscles[28,29]. Moreover, localized irradiation of the abdomen and leg increased engraftment in the exposed areas. Such engraftment also contributes to reparative process either directly or indirectly. Though the exact mechanism of homing is not yet known, release of certain chemotactic factors by damaged cells is one possibility[57]. Deciphering such signals will help in improving MSC-based treatment regimens, and fasten their progress from laboratory to the clinic for treating ARS victims. As already discussed, co-infusion of HSC and MSC seems a better option for treating radiation victims since it combines the haematopoietic reconstitution ability of HSCs and the paracrine effects of MSCs[58].

Musculoskeletal injuries

Injuries of the bone like fractures and cartilage are very common during earthquakes and wars. Critical fractures are of prime concern since these do not heal by themselves. Though bone grafting is used, it is not ideal due to insufficient graft material, donor site morbidity, inconsistent remodelling in the graft and risk of transmission of disease (in case of allograft)[59,60]. MSCs being the precursors of osteoblasts have therefore, been used for treating fractures. Combined with biomaterials to provide support in the bone defect, MSCs have been successfully demonstrated to repair the critical size bone defects in animal models[61,62]. Repair of nonunions and large bone defects have also been reported in clinical trials. Bone defects in patients were implanted with culture expanded MSCs seeded on hydroxyapatite scaffold[63,64]. All patients showed callus formation and integration of implant at 2 months and complete repair by 15 months with restoration of normal limb function.

Genetic modification of MSCs has also been employed to enhance their functionality. MSCs transduced with bone morphogenetic protein 2 (BMP2) and BMP4 have been shown to possess greater osteogenic potential than untransduced MSCs and repair bone defects in animals[65-67]. Apart from BMP family members which are potent inducers of osteoblast differentiation, overexpression of transcription factors like Runx2[68] and Osterix[69] has also been utilized. Runx2-modified bone marrow stromal cells loaded onto scaffold made of polycaprolactone and type I collagen were implanted into critical size segmental defects in rat[70]. Overexpression of Runx2 accelerated the healing of critical sized defects, reducing the recovery time compared to rat implanted with unmodified cells. Combination of genes can also be used to aid in successful regeneration of defect. For instance, MSCs were genetically modified to overexpress BMP2 and vascular endothelial growth factor (VEGF) and systemically transplanted in mouse model of segmental bone defect created in the tibia of athymic nude mice[71]. The group receiving BMP2/VEGF-overexpressing MSCs demonstrated enhanced bone formation and increased vascularity. Repair of femoral condyle and patella have also been demonstrated using MSCs in rabbits[72,73]. Autologous MSCs dispersed in collagen type-I gel repaired full thickness defects on weight bearing surface of medial femoral condyles in rabbit[72], while MSC transplantation enhanced repair of patellar defect[73].

Such approaches are likely to be useful in advent of nuclear warfare since radiation leads to deterioration of bone quality by destruction of type-I collagen[74] and suppression of osteoblast proliferation[75,76]. A single dose of 2Gy has been shown to result in about 30 per cent loss of trabecular bone volume in mouse approximately 3 months post-irradiation[77]. MSC pool in the marrow is shown to be reduced upon total body irradiation in mice and the surviving MSCs have decreased osteogenic differentiation ability[47], emphasizing the need for transplantation of MSCs possessing enhanced osteogenic ability.

Spinal cord injury

Damage to the spinal cord results due to being hit by falling debris during earthquakes[78]. Spinal cord injury

can result in paralysis if the nerve cells are extensively damaged. Thus, regeneration of neurons and repair of fractured bone can only result in functional recovery. Neural progenitor cells are capable of differentiating into neurons, astrocytes and oligodendrocytes. In rat model of contusion injury, transplantation of murine green fluorescent protein (GFP)-expressing neural stem cells into spinal cords demonstrated integration of cells into the host tissue and expression of markers for neurons, astrocytes and oligodendrocytes[79]. The cells appeared to migrate to the lesion site but no functional recovery was observed. Studies using neural stem cells have been performed only in animal models and are less likely to find application in human due to limited availability and limited range of cell types generated[80].

Since MSCs have been shown to differentiate into neurons *in vitro*[22], their ability to repair spinal cord damage and restore normal function has been tested in animal models[81-83]. Results from animal model studies are controversial and all do not support differentiation of MSCs into neural cells. *Hofstetter et al*[82] did not observe any differentiation of transplanted MSCs into neuron-like cells in rats rendered paraplegic due to spinal cord injury. However, they observed improved recovery as a result of formation of bundles bridging the lesion and acting as guiding strands for nerve growth following incorporation of astrocytes into MSC bundles.

The ability of MSCs to support host axonal growth was also reported by *Lu et al*[83]. Increased local concentrations of nerve growth factor and brain derived neurotrophic factor (BDNF) in the cellular matrix secreted by MSCs provided neuroprotective environment[83]. Extensive axonal growth was observed upon transplantation of BDNF-overexpressing MSCs, demonstrating the feasibility of using MSCs as delivery vehicles to facilitate endogenous tissue repair by providing a suitable growth environment and stimulating host cells[83].

Autologous bone marrow stem cell transplantation in spinal cord injury patients has been documented to be safe and improve their quality of life[84]. During the 2 year follow up, no tumour formation and infection or increased pain were observed. Transplantation of human cord blood-derived MSCs have been shown to be useful for a spinal cord injury patient, who was paraplegic for 16 yr[85]. MSCs were injected into the subarachnoid space and diffuse into the intradural and extradural space of the injured spinal cord without any immunosuppressive regimen. Improvement in motor activity (sensory perception) and movement in hips and thighs were observed in the patient within 41 days of transplantation, and no adverse immune responses were noticed. Though the mechanism of action of MSCs, mediated by released cytokines or by direct differentiation, is not clear, MSC transplantation led to expansion of the atrophied spinal cord[85].

Burns and skin injuries

Hot molten lava from volcanic eruption, forest fires and air and rail accidents result in skin burns. Exposure to high dose of radiation also causes radiation burn. Moreover, various skin injuries occur during wartime as a result of bullets, missile and landmine blasts. Treatment of these severe injuries requires grafting of skin to replace the damage.

Fathke *et al*[86] demonstrated using a chimeric mouse model in which bone marrow from enhanced GFP (EGFP) transgenic mice was transplanted into normal C57BL mice that 15-20 per cent of spindle shaped cermal fibroblasts were $EGFP^+$ and two-third of these cells were $CD45^-$. Both haematopoietic and mesenchymal populations provided long term reconstitution and produced collagen I and III. BM-MSCs and endothelial progenitor cells likely enhanced cutaneous repair and $CD45^+$ fibrocytes caused fibrosis[87].

MSCs have been shown to undergo differentiation into keratinocyte *in vitro* and hence aid in regeneration of skin in cutaneous wounds[88-90]. Deep burn wounds in rats undergo accelerated formation of blood vessels and granulation tissue and decreased inflammation following transplantation of MSCs[91]. Even upon intravenous injection, MSCs were found to home to the wound site[89] and accelerate the ongoing repair process probably via secretion of chemotactic and angiogenic factors like VEGF-α, EGF, keratinocyte growth factor and angiopoietin-1[31,90], which attracted macrophages, keratinocytes and endothelial cells to the site. The studies emphasize the role of MSCs in reducing the inflammatory response and attracting accessory cells to site of damage rather themselves undergoing differentiation.

In a case report, a very severe buttock radiation burn (2000 Gy at the center of the lesion) of a 27 year old victim was treated using combination of physical techniques, surgical procedures and autologous culture expanded MSCs[92]. Injection of clinical-grade expanded MSCs following surgical excision of muscular fibrotic tissue and skin autografting, led to elimination of pain

and facilitated wound repair with no recurrence of radiation burn during 11 months follow up. The healing was complete without any functional impairment at 5.5 months post-irradiation (75 days post-cell therapy). Using conventional therapy (without using MSCs) it takes much longer time to heal or does not heal at all[92]. In another case report of a patient having extremely severe radiation burn caused due to exposure above 70Gy on the arm, conventional surgical therapy was ineffective and was followed by five local administration of autologous, culture-expanded MSCs in combination with skin autograft[93]. During the 8 month follow up, the clinical evolution was favourable and no recurrence of lesion was observed even after three years. The ability of MSCs to modulate the inflammatory responses by secretion of various factors is likely the underlying mechanism[93]. Thus, supplementing conventional regimen with MSC therapy provides a novel approach for treatment of severe radiation burn injuries.

Gastrointestinal damages

Abdominal injuries due to gunshots and bomb blasts during wartimes are quite prevalent. War victims with intestinal injuries have a higher mortality rate as a result of haemorrhage and septicaemia[94]. Also, radiation overexposure (>6 Gy) causes death of the intestinal mucosal stem cells, haemorrhagic shock and enterocolitis, thereby being fatal for the victim[32,33]. MSC infusion has been shown to be beneficial for treating radiation-induced intestinal injury in mice[95]. PCR analysis confirmed low levels of MSC implantation (0.17%) in small intestine as well as other sites of local irradiation (stomach, kidney and spleen). Structural recovery was observed within 3 days following irradiation and was accompanied with increase in villus height[95]. Infused MSCs homed to sites of damage and stimulated repair by proliferation of epithelial cells, suggesting the possibility of using MSC for treatment of radiation-induced intestinal injury.

A study was undertaken in experimental colitis rat model to compare the population and repair ability of HSC and MSC following allogenic stem cell transplantation[96]. Rats receiving only MSC or HSC exhibited similar population ability in the colons on histological analysis. Combination of HSC and MSC resulted in improved gross morphology 21 days post-transplant, slightly better than HSC and MSC alone, thus highlighting the therapeutic relevance of co-transplanting MSCs.

Severe intestinal damage during wartime can lead to sepsis due to entry of bacteria into the bloodstream. Since no cure for sepsis exists, it is a life-threatening condition. However, MSCs have been demonstrated to attenuate sepsis in a murine model as a result of their immunomodulatory functions[97]. Binding of prostaglandin E2 released from MSCs to prostaglandin EP2 and EP4 receptors on macrophages stimulated the production and release of interleukin (IL)-10, which prevents neutrophils from migrating into tissues and causing oxidative damage. The increased neutrophils levels in blood help fight bacteria more efficiently. As MSCs have been used safely in humans so far, these are likely to provide a treatment for sepsis as well, which needs to be evaluated.

Liver damage

Abdominal injuries resulting in damage to the liver are common during wartimes[98]. Animal model studies have documented the generation of donor-derived hepatocytes following HSC transplantation[99]. However, the issue of true differentiation remains controversial, since cell fusion events have also been reported[100]. Comparison of different HSC phenotypes has revealed that human BM $CD34^+$ Lin^- $CD38^-$ cells generated more hepatocytes *in vivo*[101].

MSCs can be differentiated into hepatocytes in culture[24,102], however *in vivo* trans-differentiation potential is controversial. Major therapeutic beneficial effects of MSCs in treating damaged liver are mediated by secretion of factors that stimulate regeneration of endogenous parenchymal cells[103,104]. *Colletti et al*[105] demonstrated true differentitation of MSCs into hepatocytes within liver expressing hepatic markers as early as 24-48 h post-transplantation.

Clinical trials using HSC and MSC have been performed on small scale as feasibility studies. Autologous transplantion of BM-derived CD133+ cells in patients undergone parital hepatectomy for liver cancer showed 2.5-fold higher proliferation rate[106]. In a small study of 5 patients suffering from cirrhosis, infusion of autologous CD34+ cells resulted in improvement of serum bilirubin in 4 of 5 pateints for upto 6 months[107]. There was marginal increase in serum bilirubin in three patients at 12 months. The study demonstrated absence of focal lesion and no tumour formation till 12 months post-transplatation. In a recent study enrolling 30 liver cirrhosis patients, transplantion of autologous bone marrow (BM) mononuclear cells resulted in improvement in albumin

and bilirubin levels[108]. However, the improved liver function persisted only for 90 days post-transplant.

Use of MSCs has also been tried in liver cirrhosis patients. In a study of 8 patients, infusion of autologous MSCs improved liver function as assessed by Model for End-stage liver disease score and serum creatinine, albumin and bilirubin levels during 6 months follow up[109]. No adverse effects were noted. All these studies involving HSC and MSC have documented safety and transient improvement. However, long-term studies enrolling more number of patients have to be performed to assess long term effects. It would be of interest to evaluate the possibility of multiple injections to improve the therapeutic benefit.

Kidney damage

Loss of kidney function has been reported among severely injured casualties during war[110,111] and earthquake[112]. Recovery of renal function following MSC infusion in mice model for acute renal failure has been documented[113]. MSC engraft in the kidney and differentiate into tubular epithelial cells. In another study performed in rat model, the kidney recovery rate was higher in rat transplanted with MSCs than the control group and the injured renal tissue was observed to induce differentiation of MSCs[114]. However, in other studies utilizing rat model of glomerulonephritis[115] and ischaemia-reperfusion model of acute renal failure[116], paracrine factors secreted by MSCs were reported to mediate recovery. Radiation-induced nephropathy is very likely upon accidental radiation exposure due to radiosensitivity of renal tubular epithelial cells and damage to blood vessels[117]. Based on animal studies, use of MSC transplant can be of help for treating radiation nephropathy, though no study has been reported.

Transfusing HSCs or mobilizing them using granulocyte colony-stimulating factor (G-CSF) in animal models of renal dysfunction has shown beneficial effects as determined by improvement in structure, function and animal survival[118,119]. However, MSCs appear to be more promising than HSCs in kidney regeneration[120]. Clinical trials for assessing the safety and efficacy of MSCs in renal diseases are in progress[121].

Conclusions

Stem cell therapy, particularly employing MSCs, holds tremendous potential to stimulate or accelerate reparative processes and provides sufficient graftable cells for treating disaster victims suffering from critical injuries. Use of MSCs in combination of other ASC transplantation or conventional treatment is likely to have enhanced therapeutic benefit. However, certain problems need to be resolved before it becomes a routine clinical practice. Culture conditions, dose of cell infusion, number of infusions and route of cell delivery need to be optimized. Long-term studies to assess the survival and fate of transplanted cells are warranted. An understanding of the immune response and paracrine mechanism is essential to assess feasibility of allogeneic transplantation.

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