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MINIREVIEWS

New advances in the mesenchymal stem cells therapy against skin flaps necrosis

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Abstract

Mesenchymal stem cells (MSCs), multipotential cells that reside within the bone marrow, can be induced to differentiate into various cells, such as osteoblasts, adipocytes, chondrocytes, vascular endothelial progenitor cells, and other cell types. MSCs are being widely studied as potential cell therapy agents due to their angiogenic properties, which have been well established by *in vitro* and *in vivo* researches. Within this context, MSCs therapy appears to hold substantial promise, particularly in the treatment of conditions involving skin grafts, pedicle flaps, as well as free flaps described in literatures. The purpose of this review is to report the new advances and mechanisms underlying MSCs therapy against skin flaps necrosis.

Key words: Mesenchymal stem cells; Skin flaps; Endothelial progenitor cells

Core tip: Mesenchymal stem cells (MSCs) therapy appears to hold substantial promise in the treatment against skin flaps necrosis. This review involved four out of the top 10 innovations of the 20th century and four out of the 10 most important, current innovations. We hope that these contents could help you to pick up the new advances in the MSCs therapy against skin flaps necrosis.

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INTRODUCTION

According to the report by Hultman *et al*[1] from the American Council of Academic Plastic Surgeons and the Southeastern Society of Plastic and Reconstructive Surgeons, four out of the top 10 innovations of the 20th century were myocutaneous flaps, microsurgery, skin grafts, and transplantation, and four out of the 10 most important, current innovations are hand/face transplantation, fat grafting, stem cells, and perforator flaps. So these separately important contributions may lead to such a promising prospect by the combination of two or three or even more of them.

Mesenchymal stem cells (MSCs) mainly include widely applied bone marrow MSCs (BMSCs), adipose tissue-derived SCs (ADSCs), and Human umbilical cord matrix stem cells (HUCMSCs). Circulating BMSCs homed to perivascular sites in critically ischemic tissue, exhibited paracrine function and augmented microhemodynamics. These effects were mediated through arteriogenesis and angiogenesis, which contributed to vascular regeneration[2]. MSCs are relatively easy to isolate and expand in culture and therefore have potency as a therapeutic tool in ischemic disease and in transplantation. The current

dilemma is that MSCs may not have a long lifespan after administration[3,4]. A rapid disappearance of MSCs raises the question of how MSCs therapy might work. It is possible that partial administered MSCs escape from death and migrate to sites of injury and inflammation and that MSCs are able to rapidly pass on their effect to other cells that subsequently mediate tissue repair or immunomodulation. The dramatically decreased quantity of MSCs will absolutely affect their angiogenic and immunomodulatory function. Fortunately some authors have suggested that the combination of MSCs and gene therapy might generate a synergistic effect on stem cells therapy against skin flaps necrosis[5,6].

This review is willing to elicit the stem cells treatment of conditions involving skin grafts, pedicle flaps, as well as free flaps and stem cells immunomodulation in skin flaps therapy based on the published data.

MSCS THERAPY AGAINST FREE FLAPS NECROSIS

For majority of surgeons, one of the most amazing medical miracles is the total or partial human face transplantation. Dubernard *et al*[7] reported the encouraging outcomes 18 mo after the first human partial face transplantation which was performed on November 27, 2005. Then human face transplantation was successively reported.

Some free flaps combined with or without MSCs therapy already have clinical applications, but, for some cases they are lack of appropriate research models, and, for the remains the mechanisms are still disputed. A novel murine free flap model of acute hindlimb ischemia-reperfusion combined with Laser-Doppler Flowmetry, quantitative immunohistochemistry and immunofluorescence detection is maybe a suitable and reproducible experimental procedure of translational research that allows *in vivo* investigation of diverse molecular and cellular mechanisms[8]. Some authors considered the patient body as an ideal bioreactor to induce vascularisation in large volumes of grafted tissues. But, for volumes limited by the lack of vascularisation, engineering a bone free flap for maxillofacial reconstruction still exists technical restrictions[9].

It's good news for some patients who had undergone ablative tumor surgery, radiochemotherapy and primary reconstruction to receive the secondary reconstruction of the mandible by the prefabricated bony radial forearm flaps consisting of iliac crest and radial forearm flaps. And the iliac bone graft might be replaced with scaffold seeded with stem cells for further reduction of donor site morbidity[10]. And the fact that MSCs combine with growth factors therapy is extremely promising. MSCs transduced by stromal cell-derived factor-1α (SDF-1α) definitely augmented ischemic free flaps survival, which was initially reported by us previously[5]. Although the free flaps are versatile, they are deserted sometimes. For example, ADSCs enhance the survival of fat grafted into the face, and a microfat graft with simultaneous ADSCs injection may be utilized to treat Parry-Romberg disease without the need for microvascular free flap transfer by Koh *et al*[11], which has demonstrated the promising prospect by the combination of two current innovations.

MSCS THERAPY AGAINST PEDICLE FLAPS NECROSIS

At the very beginning, flap anti-necrosis therapy might be performed without directly division and culture of MSCs. For example, an intramedullary muscle flap could improve the functional results of joints reconstructed with partially demineralized and lyophilized osteochondral allografts by providing both vascularity and an increased population of MSCs capable of responding to bone morphogenetic proteins[12]. By far the major pathway of cranial defects repair induced by implantation of demineralized bone matrix is by the direct induction of resident MSCs to osteoblasts and by the direct formation of bone through upgrading osteocalcin and Collagen type I mRNA[13].

A series of endogenous growth factors and chemokines may do great contribution to flaps survival. A positive correlation existed between MVD and the high expression of SDF-1 and Chemokine receptor type 4 (CXCR4) following hyperbaric oxygen treatment in promoting neovascularization, which might be explained by the upregulation of SDF-1 and CXCR4 expression in the skin flaps of rats[14]. Human umbilical cord mesenchymal stem cells (HUCMSCs) could improve the survival of ischemic skin flaps by promoting vascularization, which might be attributed to the increased expression of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)[15]. Hypoxia preconditioned BMSCs or ADSCs transplantation improved ultra-long random skin flaps survival *via* promoting angiogenesis by upgrading VEGF[16,17]. ADSCs could enhance the survival of random-patterned skin flaps in streptozotocin-induced diabetic mice *via* elevated expression of hypoxia-inducible factor-1α[18], be capable of promoting flap prefabrication by VEGF-A[19], and prevent ischemia-reperfusion injury, mainly by regulating the growth factors, such as VEGF, bFGF and transforming growth factor-beta (TGF-β)[20]. However, the angiogenic effect by ADSCs is still controversial. Although the mean survival area ratios in the ADSCs treatment group and in the BMSCs treatment group had no significant difference, higher levels of bFGF and VEGF were found in the BMSCs transplantation group[21]. In addition, ADSCs also had a significantly angiogenic response[22], better immune compatibility and potential for enhancing the blood supply. These together suggest that both ADSCs and BMSCs have proangiogenic effect, but their promoting angiogenesis mechanisms may be quite different.

A large sum of exogenous stem cells and growth factors are utilized to promote flaps survival. An optimal delivery route should have been screened through a lot

of researches. There are mainly five methods to deliver MSCs: (1) intravenous injection; (2) subcutaneous injection; (3) intramuscular injection; (4) application with collagen sponge seeding; and (5) application with fibrin glue seeding. Hu *et al*[23], as many did, suggested that intravascular delivery of BMSCs increased wound healing and promoted flap survival following ischemia-reperfusion injury of cutaneous tissue flaps. Lee *et al*[24] suggested that the collagen sponge method delivered ASCs most effectively within the flaps and increased flap vascularity. VEGF and MSCs had synergetic effect when they were used together[6], as we suggested the synergetic effect by SDF-1α and MSCs co-application[5], which could help rebuilding the blood circulation of the ischemic region in random flaps.

Recent advances about the flap anti-necrosis therapy should not neglect the prefabricated flaps and/or tissue engineering flaps. The prefabricated groin flaps with skin substitutes provided a useful vehicle for the implantation of MSCs to serve as an autologous microvascular bioscaffold[25]. Poly(L-lactic-co-glycolic acid) or poly(ε-caprolactone) scaffolds seeded with co-cultured chondrocytes and BMSCs, were wrapped in a pedicle muscle flaps[26].

MSCS THERAPY AGAINST SKIN GRAFT NECROSIS

Autologous transplantation of BMSCs was a promising therapeutic strategy for prevention of skin-graft contraction[27]. A typical combined graft consisting of a free full-thickness skin graft and cultured autologous fibroblast-like BMSCs was effectively implanted and healed on the facial soft tissue defect[28]. Some scholars suggested that the autologous ADSCs transplantation increased full-thickness skin graft survival and showed promise for use in skin graft surgery. This might be both due to in situ differentiation of ADSCs into endothelial cells and increased secretion by ADSCs of growth factors, such as VEGF and TGF-β3 that enhanced angiogenesis[29].

The most vital role of skin graft may not only be to repair a defect, but also to study the immunomodulatory mechanisms. Human MSCs have immunomodulatory properties. They inhibited lymphocyte (especially, T-cell) proliferation to mitogens and alloantigens *in vitro* and prolonged skin graft survival *in vivo*[30,31]. MSCs increased interleukin (IL)-2 and soluble IL-2 receptor in MSCs and lymphocyte co-cultures and antibodies against IL-10 further suppressed proliferation, that is to say, MSCs induced suppression was a complex mechanism affecting IL-2 and IL-10 signaling and might function differently, depending on T-cell stimuli[30]. Alloreactivity was marked by pronounced CD45+ T-cell infiltration consisting of CD4+ and CD8+ T cells and increased skin graft IFN-γ expression which was significantly inhibited by both BMSCs and ADSCs[32].

Human MSCs and their stromal cell antigen 1 Stro-1 positive [Stro-1(+)] subgroup possess immunosuppressive properties. Stro-1(+) MSCs induced greater prolongation of skin graft in mice than unsorted MSCs[33]. Transplantation of allogeneic bone marrow-derived flk-1+Sca-1- MSCs led to stable mixed hematopoietic chimerism, permanent donor-specific immunotolerance in allogeneic host and long-term allogeneic skin graft acceptance[34]. The co-infusion of MSCs with unmodified donor bone marrow limited the toxicity of allogeneic bone marrow transplantation, treated graft *vs* host disease (GVHD), enhanced mixed chimerism and improved vascularized skin graft survival[35]. The high level of TNF-α also demonstrated a possible immunogenic role for donor (allogeneic) MSCs against skin allograft rejection[36]. Lee *et al*[37] suggested that ADSCs and their secretome had the potential to induce immunologic tolerance in full-thickness skin allotransplantation model. Moreover, the immunosuppressive properties of ADSCs were mediated by the ADSCs secretome. However, these chimerism induced tolerance theories were still disputed, for example, as Carrier *et al*[38] suggested, microchimerism did not lead to the induction of a high degree tolerance after utero transplantation but instead lead to the development of alloreactivity to donor cells.

Furthermore, infusion of MSCs exosomes enhanced the survival of allogenic skin graft in mice and increased Tregs to help MSCs to show their immunosuppressive characters[39]. In addition, infusion of ADSCs dramatically increased skin allograft survival by inhibiting the Th-17 pathogenic immune response and enhancing the protective Treg immune response[40]. However, this viewpoint might be controversial. Co-administration of allogeneic hematopoietic stem cells and third-party myeloid progenitor (MP) transplantation simultaneously with placement of a MP-matched skin graft demonstrated that the organ donor matched Treg was not essential for tolerance but MP did[41].

Donor specific immune tolerance could be effectively induced by intra-bone marrow-bone marrow transplantation combined with BMSCs treatment without any additional cytoreductive recipient treatment, which provided a promising allograft transplantation strategy whenever the donor bone marrow was available[42]. Moreover, third-party BMSCs transplantation could prolong skin graft survival time by inhibiting T lymphocyte activation and proliferation[43]. Third-party MSCs were able to suppress allo-specific antibody production *in vitro*, and they might rescue patients with life-threatening GVHD *in vivo*[44]. Likewise, the donor haematopoietic stem cells had the capacity to reduce the risk of GVHD[45]. A split-thickness skin graft from the donor was accepted, however, a third-party graft was rapidly rejected without the help of the third-party MSCs[46]. And all dogs received donor bone marrow at the time of vascularized composite allograft (VCA) transplantation were tolerant to their donor skin graft and promptly rejected the third-party skin grafts. These data demonstrated that donor-specific tolerance to all components of the VCA could be established through simultaneous allogeneic hematopoietic third-party stem

cells transplantation[47].

For some extreme situations, such as diabetic and radiation-induced tissue defects, stem cells therapy shows their unique advantages. Autologous ADSCs transplantation could enhance skin graft survival in diabetic rats through differentiation, vasculogenesis, and secretion of growth factors, such as VEGF and TGF-β3. This might represent a novel therapeutic approach in skin graft surgery for diabetic wounds[48]. MSCs combined with plastic surgery or skin graft therapy may be a promising therapeutic approach for improving radiation-induced skin and muscle damages[49].

Recently, tissue engineered skin graft develops rapidly when taking micro-environment into consideration. Chitosan-modified poly(3-hydroxybutyrate-co-3-hydroxyvalerate) scaffold loaded with HUCMSCs or unrestricted somatic stem cells could significantly contribute to full-thickness skin defects repair and be potentially used in the tissue engineering[50,51]. Laser microporous porcine acellular dermal matrix, which provided a "cell niche-like" micro-environment for the migration and differentiation of the BMSCs population, could induce exogenous differentiation of BMSCs *in vivo* and achieve the reconstruction of skin appendages, when combining with the split-thickness skin graft[52].

CONCLUSION

Thanks to all published data, we have to acknowledge that we yet know little about how MSCs therapy against skin flaps necrosis works. Further studies aimed at exploring angiogenic signaling pathway after administration and optimal treatment approach will shine light on effective MSCs therapy against skin flaps necrosis.

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