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Stem/Progenitor-Cell-Based Approach for Restenosis after Percutaneous Coronary Intervention: Application of Bone Marrow Progenitors and Future Perspectives

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Abstract

Endothelial dysfunction and cell loss are prominent features of cardiovascular disease. Endothelial damage is a critical trigger of restenosis after percutaneous coronary angioplasty or stent implantation. Consequently, rapid re-endothelialization is essential for restoring normal vascular function and regulating neointimal hyperplasia. Bone-marrow-derived cell therapy has emerged as a therapeutic option for the treatment of ischemic cardiovascular diseases by virtue of its effects in enhancing endothelial capillary growth and collateral formation. It remains to be seen whether this cell therapy is also effective for the treatment of restenosis, but evidence suggests that it may be. Bone marrow stem/progenitor cells promote endothelialization and modulate immune response, processes that can lead to vascular repair after injury. Given the increased concern over late thrombosis after drug-eluting stents, therapeutic re-endothelialization by the bone marrow stem/progenitor cells seems both attractive and promising. In this review we focus on the therapeutic potential of endothelial progenitors and mesenchymal stem cells from bone marrow for the prevention of restenosis after coronary intervention. We describe the current status of this nascent therapy and perspectives on where it may lead in the future.

Keywords: Bone Marrow; Endothelial Progenitor Cells; Mesenchymal Stem Cells; Restenosis

Introduction

In recent years, angiogenic cell therapy with bone marrow (BM)-derived cells has emerged as a potential new strategy for the treatment of refractory cardiovascular diseases. Promising results from experimental studies prompted investigators to initiate clinical pilot trials. The Therapeutic Angiogenesis by Cell Transplantation (TACT) study first demonstrated that the angiogenesis stimulated by BM cell implantation was sufficient in magnitude to benefit patients with "no-option" chronic critical limb ischemia [1]. This study supported the notion that cell therapy may augment neovascularization and thereby restore oxygen supply to the tissue. Our group previously demonstrated the important contributions of the stem/progenitor cells among the BM mononuclear cells in improving limb ischemia [2]. In hearts, the infusion of BM mononuclear cells or BM–derived progenitor cells also enhances the tissue perfusion and improved function in patients after myocardial infarction [3-6].

Although drug-eluting stents have significantly reduced restenosis rates, delayed re-endothelialization and late stent thrombosis have emerged as major concerns [7]. It thus seems, even in the era of the drug-eluting stent, that a new type of stent or technology for percutaneous coronary intervention (PCI) will have to be developed for the abolishment of restenosis. BM stem/progenitor cells have properties that hold promise for the development of a safe and effective cell therapy for therapeutic re-endothelialization after PCI. Adult BM contains both hematopoietic lineage stem/progenitor cells (HSCs), including endothelial progenitor cells (EPCs), and non-hematopoietic progenitor subsets referred to as the mesenchymal stem/progenitor cells or multipotent stromal cells (MSCs). EPCs and MSCs have shown to strongly induce neovascularizaition compared with the freshly-isolated BM mononuclear cells in animal studies [8,9]. Both the progenitor cells have been used in several clinical trials as a "2nd-generation" cellular therapy [4,5,10]. Therefore, in this review, we focus on and discuss the potential roles and effects of EPCs and MSCs from BM in vascular repair.

EPCs have emerged as an important component of vascular injury response and offer the potential to accelerate vascular repair by promoting re-endothelialization [11-13]. CD34 antibody-coated stents have been clinically used to capture circulating EPCs at the injury sites and enhance re-endothelialization [14,15]. We will begin, here, by reviewing this topic as a current status of cell-based approach to coronary intervention. Yet the therapeutic potential of MSCs from bone marrow in restenosis following vascular injury has been poorly investigated so far. Accumulating evidence from animal studies has shown that MSC therapy is a promising strategy to treat refractory diseases and organ failures through the multiple mechanisms [16-18]. Thus, in the later part of this review, we suggest future perspectives that MSCs are useful therapeutic vectors to prevent restenosis after PCI.

Endothelial Progenitor Cells (EPCs) for Coronary Intervention

EPCs from bone marrow

The concept of BM cell implantation into ischemic tissues was originated from the discovery of EPCs derived from bone marrow and postnatal vasculogenesis. Adult EPCs were first identified in adult human peripheral blood by Asahara et al. [11] in 1997. Their study

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demonstrated that $CD34^+$ mononuclear cells gave rise to mature endothelial cells after ex vivo culture and contributed to endothelial recovery and new capillary formation after ischemia.

Though the strict definition is still controversial, EPCs are generally defined as cells that express HSC markers such as CD34 or CD133, along with an endothelial marker, vascular endothelial growth factor receptor 2 (VEGFR2). EPCs and HSCs share many surface marker antigens and probably descend from a common precursor, hemangioblast, during embryonic development [19,20]. In adult, bone marrow is a major source of EPCs such as HSCs, and the EPCs endogenously mobilize from the bone marrow into the peripheral blood in response to a physiologic and pathophysiologic need for neovascularization [20-22].

Therapeutic potential of EPCs for vascular repair

Therapies designed to mobilize EPCs or to increase their ability to home to the site of stent implantation and facilitate vascular repair are attractive and have the potential to improve clinical outcomes after PCI [12,13].

Injured vessels after angioplasty express increased levels of stromal-derived factor (SDF)-1α to promote vascular healing [23,24]. HSCs and EPCs express SDF-1α and its receptor CXCR4, both of which are crucial for cell recruitment to injured sites [25,26]. In a mouse model of injured carotid artery, intravenously administered EPCs inhibited neointimal hyperplasia by migrating into the injured vessel wall and promoting re-endothelialization [27]. Autologous EPC implantation also led to rapid re-endothelialization after balloon denudation of carotid arteries in rabbits [28]. Another study showed that transplanted EPCs were able to restore endothelial function in damaged vessels [29].

Exogenous mobilization of EPC from the bone marrow may provide a less cumbersome and potentially more effective strategy to enhance the re-endothelialization of damaged vessels. The administration of recombinant hematopoietic cytokines such as granulocyte-colony stimulating factor (G-CSF) mobilizes EPCs and HSCs, as well as mature hematopoietic cells. Several studies have demonstrated beneficial effects of G-CSF and erythropoietin on neovasucularization and re-endothelialization [30-33]. Kong, et al. [33], for example, reported that G-CSF treatment before balloon injury of rat carotid arteries led to accelerated re-endothelialization and a concomitant reduction in neointima of the injured vessels, in association with an increase in the number of circulating EPCs. Statin therapy [34] and estrogen [35] also increase the number of mobilized EPCs and reduce neointimal hyperplasia in animal models of arterial injury. The mechanism underlying these actions might be attributable to the stimulation of endothelial nitric oxide synthase.

These findings support the therapeutic concept of EPC-mediated re-endothelialization to inhibit restenosis after vascular injury.

EPC capture stent

Drug-eluting stents have dramatically reduced the rates of in-stent restenosis compared with bare-metal stents, but local antiproliferative therapy has been associated with delayed or maladaptive re-endothelialization, a process that leads to abnormal vascular homeostasis and late stent thrombosis [36].

A unique approach of the EPC-mediated re-endothelialization has recently been adopted for clinical use [14,15]. The Genous Bio-engineered R stent (OrbusNeich, Hong Kong), a device coated with monoclonal antibodies directed against CD34, is designed to attract circulating EPCs onto the stent surface to augment re-endothelialization and thereby prevent restenosis and thrombosis. Genous stents have already progressed to phase II and III clinical trials and have been deployed in >5,000 patients [13-15]. In the initial clinical trial [14,16] patients with de novo coronary lesions were implanted with EPC capture stents. Safety and feasibility were well demonstrated in the phase I study. Among the 4,939 patients in the e-HEALING registry, the 12-month cumulative event rates for the individual outcomes of cardiac death, myocardial infarction, and target lesion revascularization (TLR) were 1.7%, 1.9%, and 5.7%, respectively [15]. Notably, the incidence of late stent thrombosis (between 30 days and 12 months) was very low (0.2%). Comparisons between registries are hampered by the many differences in patient characteristics and practice patterns. Even so, the 5.7% incidence of clinically indicated TLR at 12 months compares well with the TLR rates for drug-eluting stents in the ARRIVE-1 registry (5.6%) [37] and E-FIVE registry (4.5%) [38]. The HEALING II registry reported that patients with normal $CD34^+VEGFR2^+$ EPC titers had lower rates of in-stent restenosis than patients with reduced circulating EPCs [39]. Intravascular ultrasound investigation in a subgroup analysis of this study demonstrated a regression of neointimal volume in patients with higher levels of EPCs.

The results from the registries hold promise, but large randomized studies to evaluate the long-term safety and efficacy of this stent are still underway. On a cautionary note, a recent preclinical study with a porcine model found that the EPC capture stent improved re-endothelialization at the early stage but ultimately conferred no effect on the neointimal thickness compared with control stents over long-term observation [40]. Restenosis with CD34 capture stents may occur as a consequence of nonspecific binding with non-EPCs. CD34 is common to a number of progenitors, including smooth muscle progenitor cells, as we and others have previously shown [41,42]. Circulating smooth muscle progenitor cells are poorly characterized, but they are known to contribute to neointimal hyperplasia [31,43].

Mesenchymal stem/progenitor cells (MSCs) for coronary intervention

MSCs from bone marrow: Compared with EPCs, MSCs from bone marrow can be easily isolated and expanded in culture system. The first MSCs in the BM were reported in 1976 [44]. Friedenstein et al. [45] described clonal, plastic adherent cells from BM capable of differentiating into osteoblasts, adipocytes, and chondrocytes. Thus, MSCs are typically defined as adherent, fibroblastoid-like cells that differentiate to osteoblasts, adipocytes, and chondrocytes *in vitro*. MSCs *in vitro* express the surface receptors CD29, CD44, CD49a-f, CD51, CD73, CD105, CD106, CD166, and Stro1, and lack expression of the definitive hematopoietic lineage markers CD11b, CD14, and CD45 [18]. In the bone marrow, MSCs localize along the endosteal surface of the bone (an HSC niche) and also in a vascular-associated niche [46]. MSCs play a critical role in regulating HSC proliferation, differentiation, and quiescence *in vivo* by signaling via the "stem cell niche synapse" through which growth factors, cytokines, and immunomodulatory factors are exchanged [47,48]. In addition to regulating hematopoiesis, some nonhematopoietic progenitor cells may enter the blood stream and circulate as "continuous reservoirs" of replacement cells and/or reparative cells for nonhematopoietic tissues [49].

MSCs are isolated from the mononuclear layer of the bone marrow after separation by discontinuous density gradient centrifugation. The mononuclear layer is simply cultured and MSCs adhere to the culture plastic. Typically, MSCs recovered from a 2-mL bone marrow aspirate can be expanded 500-fold over about 3 weeks [50]. The cells generally retain their multipotentiality for at least 6–10 more passages.

Thus, the MSCs provide attractive opportunities for cell-based therapy in various diseases and organ failures. Indeed, the administration of exogenous cultured MSCs has proven to be significantly efficacious in experimental animal models of lung injury [51], kidney disease [52], diabetes [53], stroke [54], and myocardial infarction [55].

Cardiac repair by MSCs: Like EPCs, there has been considerable interest in the development of a new therapy with MSCs from bone marrow in cardiac repair or regeneration. Favorable effects of MSCs on jeopardized myocardium have been frequently reported [55-63]. MSCs can express phenotypic characteristics of cardiac myocytes [58]. This property prompted investigators in earlier studies to explore the ability of engrafted MSCs to differentiate into cardiac lineage cells [56,59]. Yet MSCs influence cardiac repair in spite of the low or transient levels of engraftment they show *in vivo*. We and others have shown that MSC treatment improves cardiac function in acute and chronic myocardial infarction models, in part through paracrine action [55,60-63]. Paracrine factors released from MSCs into the surrounding tissue direct a number of restorative processes, namely, myocardial protection [60], neovascularization [61], matrix remodeling [62], and differentiation of resident progenitors [63]. The capacity of MSCs to secrete soluble factors that alter the tissue microenvironment may play a more prominent role in tissue and organ repair than the cell transdifferentiation [18].

Vasculoprotective potential of MSCs: Vascular injury triggers local inflammation in a vessel wall. Macrophages and vascular smooth muscle cells release cytokines and growth factors, resulting in neointimal hyperplasia with phenotypic change, migration, and proliferation of smooth muscle cells. Rapid re-endothelialization after injury is important for restoring normal vascular function, reducing vascular inflammation, and preventing adverse remodeling and neointimal formation [64].

An analysis of transcriptome in human and murine MSCs revealed that the cells express transcripts encoding proteins that regulate a broad range of biological activities, including wound healing, angiogenesis, and immunity [55,65]. Thus, we hypothesize that MSCs modulate healing processes after vascular injury via the secretion of factors (Figure 1). Anti-inflammatory effect of MSCs: Several experimental and clinical studies have shown that MSCs are highly immunosuppressive [66]. MSC-mediated immunosuppression has been variously demonstrated to involve IL-10 [67], nitric oxide [68], prostaglandin E2 [69], and tumor necrosis factor-α stimulated gene/protein 6 (TSG-6), a protein recently shown by Prockop's group to have multifunctional anti-inflammatory properties [70]. IL-10, nitric oxide, and prostaglandin E2 are well known to confer immunosuppressant effects. The TSG-6 protein reduces nuclear factor-κB signaling in the macrophages and thereby modulates the cascade of proinflammatory cytokines [66]. Our group previously reported that intracardiac administration of human MSCs inhibited macrophage infiltration and neointimal formation in carotid artery after ligation in immunodeficient mice [71]. We were also interest to find, in the same series of experiments, that MSC administration reduced the serum levels of monocyte chemoattractant protein-1 in mice fed an atherogenic diet. Proangiogenic effect of MSCs: MSCs differentiated to endothelial cells in one of our earlier experiments with infarcted porcine myocardium, but the extent of

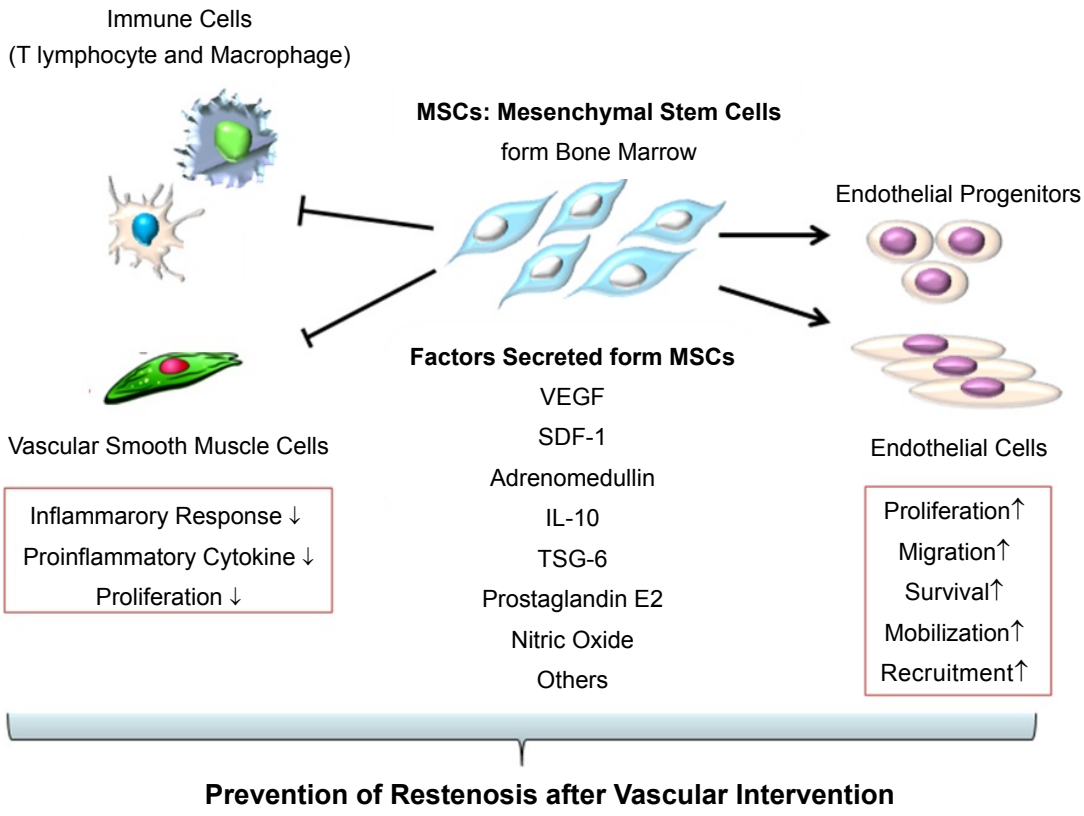

Figure 1: Modulation of vascular-related cells by MSCs. Secreted factors from MSCs activate endothelial cells and EPCs and suppress activation of immune cells and vascular smooth muscle cells, which leads to prevention of restenosis after vascular intervention.

differentiation was far too low to account for the significant increases in the vessel numbers [61]. MSCs express a number of proangiogenic factors, as well as proteins that modulate endothelial cell migration [55,61]. Several of these factors, such as VEGF and SDF-1, have been shown to not only induce endothelial proliferation and capillary growth, but also mobilize HSCs and EPCs from the marrow and induce them to proliferate [72]. And in experiments comparing cultured human MSCs with HSCs, we found that the former expressed higher mRNA levels for proangiogenic factors such as VEGF and adrenomedullin [55]. We previously examined the culture system to confirm the angiogenic and endothelial protective effects of factors from MSCs. In our in-vitro angiogenesis assay, co-culture with human MSCs induced prominent capillary network formation [61]. We also found that conditioned medium from the MSCs rescued human umbilical vein endothelial cells from cell death during hypoxia exposure [55].

Again, these findings suggest that MSCs have vasculoprotective potential against restenosis after PCI via anti-inflammatory effects and re-endothelialization promoted by factors the cells secrete. We also found that conditioned medium from the MSCs directly and significantly attenuated the proliferation of vascular smooth muscle cells exposed to platelet-derived growth factor-BB (unpublished data).

Future perspective on MSC therapy for the prevention of restenosis after PCI

As long as the specific cell surface markers on MSCs *in vivo* remain poorly defined, it will probably be difficult to develop an MSC capture stent. Yet recent advances of tissue engineering make it possible to directly seed cultured MSCs from the BM on stainless steel stents coated with gluten and polylysine [73]. Scanning electron microscopy elegantly demonstrated faster and more complete re-endothelialization on the MSC seeded stents, compared with unseeded control stents, within 1 month of implantation in rabbit femoral arteries. If this technology is available for clinical use, autologous MSC therapy will emerge as an option for the prevention of restenosis in individual patients undergoing PCI. Based on our observations, we further propose that the development of a stent coated with concentrated proteins and peptides secreted from the MSCs may become a more effective "off-the-shelf" strategy in interventional cardiology.

Conclusions

Bone marrow stem/progenitor cells have drawn interest for their ability to promote proper healing by modulating vascular response after injury.

EPC-based technologies and strategies have attracted considerable interest in the field of interventional cardiology. However, EPC capturing stents have a technological limitation as described above. Henceforth, further technological advances and a fuller understanding of the behavior of each BM progenitor such as EPCs and smooth muscle progenitors will be required before the outcomes after PCI can be improved.

MSCs seem promising as a cell source for an effective treatment modality for restenosis, though basic research on the MSC biology and paracrine biology remains to be done. As tissue engineering technologies evolve, it will be possible to apply stem cell biology to endovascular techniques beyond drug-eluting stents.

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