Adipose derived stromal cells in cardiovascular regenerative medicine

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Mesenchymal Stem Cells: promising for myocardial regeneration?

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Abstract

The pandemic of cardiovascular disease is continuously expanding as the result of changing life styles and diets throughout the Old and New World. Immediate intervention therapy saves the lives of many patients after acute myocardial infarction (MI). However, for many this comes at the price of adverse cardiac remodeling and heart failure. Currently, no conventional therapy can prevent the negative aftermath of MI and alternative treatments are warranted. Therefore, cardiac stem cell therapy has been put forward over the past decade, albeit with modest successes. Mesenchymal Stem Cells (MSC) are promising because these are genuine cellular factories of a host of secreted therapeutic factors. MSC are obtained from bone marrow or adipose tissue (ADSC). However, the heart itself also contains mesenchymal-like stem cells, though more difficult to acquire than ADSC. Interestingly, mesenchymal cells such as fibroblasts can be directly or indirectly reprogrammed to all myocardial cell types that require replacement after MI. To date, the paracrine and juxtacrine mechanisms of ADSC and other MSC on vessel formation are best understood. The preconditioning of, otherwise naïve, stem cells is gaining more interest: previously presumed deleterious stimuli such as hypoxia and inflammation, i.e. causes of myocardial damage, have the opposite effect on mesenchymal stem cells. MSC gain a higher therapeutic capacity under hypoxia and inflammatory conditions. In this review, mesenchymal stem cells and their working mechanisms are put into the perspective of clinical cardiac stem cell therapy.
**Introduction**

Cardiovascular disease (CVD) has developed into a pandemic over the past decades. Dramatic changes in life, changes to high caloric diets, lack of exercise, smoking and increased socioeconomic stress all contribute to increased risk for CVD, in particular as comorbidity of obesity, overweight and type 2 diabetes (1). The vascular system responds to the constant exposure of the CVD risk factors with endothelial dysfunction which is underlying atherosclerosis. In end-stage atherosclerosis, branches of the coronary arteries may occlude and cause an acute myocardial infarction (MI). Downstream of an occluded coronary artery the myocardium is severely ischemic. Prolonged ischemia causes death of cardiomyocytes and surrounding vasculature. Subsequently, the death signals from apoptotic and necrotic cells induce an inflammatory reaction (2-5). In experimental MI in mice, the inflammation dominates the early post-MI cardiac microenvironment with a rapid influx of neutrophils, followed by macrophages that clear debris, dead cells and that promote the wound healing process. Macrophages are known to shift their phenotype from the classically polarized (inflammatory macrophages) to alternatively polarized (anti-inflammatory macrophages) in the transition process from inflammation to scar formation after MI (6). Indeed, the systemic depletion of macrophages led to impaired wound healing and delayed, if not prevented, remodeling after myocardial injury (4). The highest inflammatory cellular influx after the MI is within seven days and followed by increased numbers of myofibroblasts that facilitate the formation of a rigid scar (7). Unfortunately, the limited proliferation capacity of adult cardiomyocytes cannot meet the demands to replace lost cardiomyocytes and hence the cardiac damage is beyond adequate repair. The functional repair comprises of a rigid scar that prevents the ventricular wall from rupture. The loss of cardiomyocytes and the lack contractility of the scar together cause a compensatory reaction which features hypertrophy of the surviving cardiomyocytes. This is the onset of a secondary remodeling process that causes cardiac fibrosis. Without appropriate intervention, these events lead to cardiac dilatation, deterioration of cardiac function and eventually heart failure. To prevent this adverse cardiac remodeling, it is essential to provide the damaged myocardium with a source of cardiomyocytes and to revascularize the damaged microenvironment. To obtain optimal regeneration, initiation of the regenerative processes must occur in an early post-MI inflammatory phase i.e. immediately after MI and before appearance of scar tissue. This leaves no more than a small window of opportunity for intervention with stem cells. Recent findings indicate that cardiac tissue has an endogenous repair capacity too. During healthy life, cardiomyocytes are replaced every eight years, this frequency is even accelerated after insults such as MI (8,9). In spite of attempts to differentiate cardiomyocytes from stem cells(10) or to tissue engineer entire cardiac constructs(11) or even hearts(12), the observation that postnatal cardiomyocytes show physiological turnover is of no less importance. Obviously, this is an opportunity for novel therapeutic treatments that engage on the stimulation of the proliferation of the surviving cardiomyocytes. Thus, application of therapeutic stem cells that modulate the post-MI microenvironment is desirable, in particular to increase the proliferation of cardiomyocytes that surround the damaged area. This would circumvent the need to form a scar and it would prevent subsequent adverse cardiac remodeling and the onset and progression of heart failure. In this review, we discuss the opportunities of mesenchymal stem cell therapy for the treatment of MI, in the light of the microenvironmental influence on stem cells and their function. A main focus is on mesenchymal stem cells from adipose tissue (ASDC).

**Stem cell-guided cardiac regeneration**
Alternative therapies for treatment of the consequences of myocardial infarction are still in high demand, because conventional pharmaceutics do not provide repair or regeneration. On the other hand, heart transplantation is the ultimate replacement therapy, yet the number of patients by far exceeds the donor heart availability. Thus, late mortality due to the heart failure continues to increase. Stem cell-based or progenitor cell-based therapies have emerged as an alternative treatment of cardiovascular diseases such as MI. Stem cell therapy aims on the induction of angiogenesis as well as on induction of myogenesis, the latter of which is inefficient. The restoration of blood flow to ischemic regions by itself appears to help reduce scar formation and improved the contractile activity of the damaged myocardium. In the early days, research on the regeneration of the damaged heart focused on the healing properties of fetal and neonatal cardiomyocytes and cardiac progenitor cells. Many of these studies reported that those cells could functionally integrate and improve cardiac function in various animal models for MI (13,14). The efficiency of these integrations was generally low. Recent findings by Kaushal and co-workers indicate that cardiac stem cells from newborns have a higher regenerative capacity to restore cardiac function compared to adult cardiac stem cells (15). Although the embryonic or neonatal stem cell therapies show beneficial influence on the regenerative process after MI, the cells are difficult to obtain and are ethically compromised (16-18). The advent of inducible pluripotent stem cells (iPSC) (19) paved the way to generate autologous ‘repair’ cells. By using the patient’s own fibroblasts, reprogramming can be achieved by introduction of no more than four transcription factors that are pivotal in maintenance of a primitive i.e. embryonic stem cell state. The iPSC technology solved the potential immune rejection of embryonic stem cell-derived myocardial cells, yet leaves the possibility that teratomas develop unsolved as yet. A giant leap forward was achieved by retroviral delivery of a specific set of cardiac developmental transcription factors, which directly reprogrammed fibroblasts into cardiomyocytes albeit it with low efficiency(20). Meanwhile, iPSC technology has progressed from gene delivery by permanently integrating retroviruses to transient overexpression by plasmid-encoded defined (cardiac) factors or even delivery of microRNA to yield mature and functional cardiomyocytes (20-24). In vivo, iPSC-derived cardiomyocytes ameliorated cardiac function in rodents after myocardial infarction (25-27). Remarkably, highly proliferative cardiomyocytes could be generated through derivation of iPSC from neonatal cardiomyocytes and their redifferentiation to cardiomyocytes (28). The authors attributed this efficient ‘cycling’ of reprogramming to the maintenance of the cardiomyocyte epigenetic status (28). Reprogramming is primarily based on rewiring the epigenome of the source cells, but the epigenetic makeup is at least partly maintained in reprogrammed fibroblasts (29-31). Therefore, the use of fibroblasts for cardiac reprogramming deserves caution because fibroblasts are also the culprit cells in heart failure and cardiac fibrosis.

Unfortunately, most, if not all, studies in which stem cell-derived cardiomyocytes were employed to treat MI were performed in small animals such as mice. The task to scale up stem cell differentiation, administration and integration of cardiomyocytes into the human heart, which may require billions of cardiomyocytes, is formidable. However, as the heart in principle is a specialized muscle, therapies have been investigated that made use of skeletal myoblasts. Myoblasts are easy to obtain and are readily expanded in vitro to the large numbers required for cardiac cell therapy. Unfortunately, the patients that received the intramyocardial transplantation of skeletal myoblasts experienced severe tachycardia. This was due to the lack of electromechanical coupling with the host cardiomyocytes (32,33).
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Taken together, the application of stem derived-derived cardiomyocytes as replacement therapy is still in its infancy, despite significant scientific breakthroughs.

Mesenchymal stem cells in cardiac therapy

The great discovery in cardiovascular research that bone marrow-derived stem cells are able to differentiate not only into blood cells but also into muscle, cardiomyocytes, vascular components, liver and brain cells opened new opportunities for cardiac tissue regeneration (34-37). Besides hematopoietic stems, the bone marrow contains stromal cells which harbor stem cell-like features. These mesenchymal stromal cells or mesenchymal stem cells (MSC) were first isolated and characterized by Caplan and co-workers, who opened up new opportunities for cardiac stem cell therapy (38-40). MSC are isolated from many different sources such as bone marrow, adipose tissue, cord blood or amniotic fluid. They can be easily obtained in clinically relevant numbers, rapidly expanded in vitro and cultured in simple media (41). The benefit of mesenchymal stem cells has been shown in animals models to improve cardiac function and reduce adverse remodeling (35,42,43). Bone marrow-derived mesenchymal stem cells (BM-MSC) appear to contribute to the regeneration of cardiac tissue after the MI, albeit modest (44,45). Interestingly, every organ in the body appears to harbor a set of mesenchymal-like stem cells that are more or less predisposed to a cellular fate of that organ. Also the heart is a source of cardiac stem cells (46) or cardiac progenitor cells, some of which resemble hematopoietic stem cells while others resemble mesenchymal stem cells (47). These endogenous cardiac stem cells (CSC) are usually isolated using a typical surface marker such as c-Kit, Sca-1, Islet-1 or SSEA-1, while mere plastic adherence of aggregation growth as cardiospheres is employed too. Finally, the heart contains so-called side population cells which are negatively FACS-sorted based on dye-exclusion through an ABC transporter (CSC are excellently reviewed in (48).

Mesenchymal stem cells in clinical trials.

Ever since bone marrow-derived stem cells and cardiac stem cells were isolated, they have been exploited in clinical trials to evaluate their therapeutic potential after myocardial infarction. Readouts generally comprise of general clinical features, functional cardiac parameters and quality of life. Several clinical trials demonstrated improved cardiac function after administration of bone marrow-derived stem cells, both hematopoietic stem cells and MSC, such as cardiac c-kit stem cells in the SIPIO trial or cardiospheres in the CADUCEUS trial (49,50). Recently, the POSEIDON clinical trial showed a beneficial effect of after acute MI. Remarkably, in this trial administration of autologous and allogeneic BM-MSC was compared and it was shown that they had similar therapeutic benefit (51). This is an important study, because it shows for the first time, that cardiac stem cell therapy does not depend on the patient’s own cells. This allows for standardization and better control of future therapies. In addition, a dose comparison study was performed in the POSEIDON trial. Surprisingly, the investigators observed an inverse relation between therapeutic outcome and the number of administered stem cells: a mere twenty million cells resulted in better improved cardiac parameters compared to two hundred million cells (51). Low dose concentration of MSC resulted in greater reduction of left ventricular volumes (LV) and increased ejection fraction (EF). Yet, this remarkable inverse dose response must be further studied in larger clinical trials. Although, bone marrow-derived stem cells lead to the functional improvement of a damaged cardiac tissue, their isolation is cumbersome and associated with donor site morbidity. In addition, the number of BM-MSC that can be
isolated is limited and may demand culture expansion, although Hare and colleagues may contradict this (51). Expansion of (stem) cells *in vitro* always bares the risk of reduced genome stability and may have long-term adverse effects after administration. Yet, this risk may not be present as yet, because the retention of stem cells after their administration is low. In an acute MI model in pigs, retention of mesenchymal-like stem cells was higher than of bone marrow-derived mononuclear stem cells (52). Yet, within one hour after intramyocardial injection the majority of administered cells had left the heart (52). Nevertheless, over the past decade mesenchymal stem cells emerged as the most promising type of stem cell for the cardiovascular regeneration. Besides bone marrow and heart, scientists focused on other tissue sources for mesenchymal stem cells with a high regenerative potential (53). Adipose tissue is rich in MSC too, while it is easier accessible than bone marrow. The biology of adipose tissue-derived stem cells or ADSC will be addressed in the following section. ADSC have rapidly reached the clinic. The APOLLO double-blind randomized clinical trial for treatment of acute myocardial infarction employs autologous ADSC. These ADSC are harvested from lipoaspirates and enriched through processing with the Celution system of Cytori. This closed system procedure takes only a few hours which allows for administration of the ADSC during the conventional treatment of the acute MI. The clinical trial involved ten patients that received ADSC and four placebo group 36 h after the infarction occurred. So far, APOLLO showed two important benefits for the intraoperative use of ADSC. Firstly, an up to sixty percent reduction of infarct size was observed and secondly an improved revascularization of the ischemic tissue was observed which ameliorated blood flow. In addition, contractility was improved, while no arrhythmias (54). According to the investigators not only the short term follow up (six months) but also the long term follow up (eighteen months) of the APOLLO clinical trial showed a persistent benefit for the patient that had been treated with ADSC. This substantiates the need for further development of the ADSC-based therapies for cardiac regeneration. Meanwhile, ADVANCE has started which is a follow-up clinical trial focusing to prevent heart failure. It includes a near 375 patients that will be treated with ADSC within twenty-four hours after acute myocardial infarction. Whereas several trials focus on early intervention, other clinical trials, like PRECISE and ATHENA, focus on the aftermath of myocardial infarction i.e. treatment of chronic myocardial ischemia with ADSC (reviewed in mortality) (55). Thus, the coming years will be high in anticipation for the long-term efficacy of ADSC-based cardiac stem cell therapy.

**Mesenchymal stem cells from adipose tissue**

Adipose tissue is an abundant source of mesenchymal stem cells, known as adipose tissue-derived stem or stromal cells (ADSC) (56). By definition, ADSC are the plastic adherent fraction of the stromal vascular fraction of adipose tissue. In our experience, several tens of millions of ADSC can be easily isolated from as little as one liter of lipoaspirate (Przybyt, unpublished). This sheer abundance of cells almost contradicts them being named as stem cells. Also their limited number of population doublings supports the suggestion to call ADSC adipose tissue-derived stromal cells, more than stem cells. Not uncommon for ‘stem’ cells, the origin of ADSC is debated. In fact, multiple types of stromal-derived *cum* vascular bed-associated cells may give rise to ADSC, (57). Similar to all other types of MSC, ADSC are per definition *in vitro* culture (d) artifacts that acquire a phenotype that may strongly differ from their *in vivo* phenotype. To date, the vasculature of adipose tissue is thought to give rise of at least three types of multipotent precursor cells. Firstly, at luminal side these are endothelial precursor cells, while both other types are either supra-adventitial (58) or
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These perivascular ADSC are likely a subfraction of the pericytes, while the supra-adventitial ADSC may relate to a specific subset of adventitial fibroblasts. Others, provide evidence that ADSC originate from perivascular and adventitial vascular regions but are more similar to smooth muscle cells. It is likely that the cells in these locations form a continuum, while the local microenvironment dictates their resident phenotype. Once disrupted from their original environment these cells appear to show a high degree of interchangeability. In comparison to BM-MSC, ADSC yields are consistently higher, while the growth rate of ADSC in a simple mesenchymal medium is higher too. In vitro, ADSC have a mesenchymal phenotype and a morphology that is virtually indistinguishable from ‘common’ fibroblasts. Unanimous markers or marker panels that discriminate between mesenchymal stem cells and fibroblasts do not exist. However, surface markers expressed by cultured ADSC include CD90, CD105, CD29, CD44, CD73, CD271, while others are absent such as the endothelial markers CD31 or CD34 and hematopoietic markers such as CD45, CD14 among others. Other criteria may differentiate between ADSC and fibroblasts, because MSC are multipotent. As such ADSC are generally assessed for their multipotency through differentiation to the typical trilineage of adipocyes, chondrocytes, osteoblasts. Furthermore, ADSC also easily differentiate into smooth muscle cells, which comes as no surprise in view of their vascular origin. Interestingly, both fibroblasts and ADSC are amenable to reprogramming into iPSC. Yet, this process is by far more efficient in ADSC. In the previous section we discussed the use of freshly isolated ADSC for clinical experimental therapy. Yet, cultured ADSC have proven beneficial in several animal models for acute MI too.

Requirements for cardiac regeneration

Myocardial infarction causes dramatic spatiotemporal changes in the ventricular wall. This hostile microenvironment is characterized by lack of perfusion and massive cell death and thus is a non-attractive playground for therapeutic stem cells. By definition, stem cells are ‘naïve’ and are readily persuaded to change their phenotype upon microenvironmental stimuli. Therefore, the concept to use stem cells to adjust a damaged and hostile tissue microenvironment would appear naïve too. The fact that therapeutic benefits have been reached is likely caused by the relatively large numbers of stem cells that are administered in cardiac stem cell therapies. In the future, major improvements could be reached by educating stem cells prior to their administration, while their retention should be improved too e.g. by using biomaterial-based delivery systems.

In the post-infarct period, the major processes that occur are cell death, inflammation, wound healing, followed by need for the formation of blood vessels. These processes are all tightly associated but, importantly, ADSC can influence all four of them. As mentioned earlier, a major ‘flaw’ of the mammalian heart after infarction is the almost complete absence of proliferation of cardiomyocytes. Despite their being naïve stem cells, the main mode of action of MSC, including ADSC, is through secretion of a plethora of paracrine factors. These trophic factors include mitogens such as hepatocyte growth factor (HGF), insulin growth factor (IGF), and fibroblasts growth factors (FGF), but also immunological factors such interleukin 6 (IL-6) and tumor growth factor beta (TGF-beta) as well as matrix remodeling enzymes such as matrix metalloproteases (MMPs). All of these factors are constitutively produced by in vitro cultured ADSC. This fact alone shows that ADSC are genuine culture artifacts, because it would seem highly unlikely for any tissue cell to produce such a complex mixture of factors. This also complicates the investigation of the role of
single factors produced by ADSC. Moreover, most if not all, of the ADSC-secreted factors are pleiotropic by nature (73, 74). The ‘secretome’ of ADSC, in terms of composition and concentration, dictates their therapeutic capacity. However, the redundant nature of the secretome of ADSC might warrant a balanced response in the post-infarction microenvironment. Ever since the discovery of the proangiogenic capacity of vascular endothelial growth factor (VEGF), cardiovascular therapy has strongly focused on the improvement of perfusion, i.e. the upregulation of vascularization, in cardiovascular disease. This quest was continued with the revolutionary discovery of Asahara and coworkers that part of the hematopoietic stem cells in bone marrow were vasculogenic as well as proangiogenic (75). This set the stage for the use of stem cells in provasculogenic therapies after myocardial infarction. Also ADSC are strongly proangiogenic through secretion of e.g. VEGF, FGFs, and angiopoietins. Importantly, ADSC can promote vessel formation in vitro through juxtacrine interaction with endothelial cells as well (76, 77). Part of this juxtacrine interaction that promotes stable vessels, is governed by secretion of extracellular matrix components by ADSC (78). The ‘pericytic’ ADSC fraction from adipose tissue, could stabilize vascular structures in vitro, which depended on cell-cell contacts and on mutual signaling with paracrine factors (79). This suggests that in vivo ADSC not only promote angiogenesis through paracrine signaling, but also through juxtacrine signaling i.e. by acquiring a pericyte function.

An exciting feature of MSC that is shared by ADSC is their immunosuppressive behavior. Earlier we referred to the POSEIDON trial, in which allogeneic ADSC were administered after MI without noticeable side effects (51). In fact, human ADSC could by transplanted not only allogeneically, but also over a xeno barrier i.e. in rats, dogs and rabbits (68, 80–82). These were different disease models, but in all cases the human ADSC exerted an immunomodulatory effect, primarily through secretion of prostaglandin E2 (PGE-2) (83). In general, the immunomodulatory effect of MSC and ADSC comprises of suppression of T lymphocyte function (84). Immunosuppression is exerted through secretion of 2.3-dioxygenase (IDO), PGE-2, or nitric oxide (NO), some of which reprogram the microphages into the anti-inflammatory phenotype and upregulate production of the anti-inflammatory cytokine interleukin 10 (IL-10) (85). In vitro, ADSC reduced proliferation of T and B lymphocytes as well as Natural Killer cells but also by directed macrophages to alternatively activated i.e. type 2 macrophages, shifting the acute remodeling phase into the genuine tissue repair (86).

### Stem cell responses to the host microenvironment

The secretion profile and the fate of stem cells change in response to microenvironmental cues (87). Strong cues in the post-infarction myocardium are hypoxia and pro-inflammatory mediators that might negatively influence the regenerative properties of therapeutic cells. Surprisingly, hypoxia and stimulation with proinflammatory cytokines such as interleukin 1 beta (IL-1beta) augmented the regenerative capacity and secretome of ADSC In particular. Under hypoxia or in the presence of IL-1beta, tumor necrosis factor alpha (TNF alpha) or IL-6, neither ADSC survival nor their proliferation were significantly reduced (88, 89). Similarly, aged ADSC were not negatively affected by hypoxia or proinflammatory factors (90). Moreover, hypoxia promoted the capacity of ADSC to augment in vitro sprouting of endothelial networks on matrigel. This increased therapeutic capacity was associated with increased levels of proangiogenic factors. Similarly, ADSC promoted vascularization of matrigel plugs in vivo (91). Older ADSC did, however, show a reduction on proangiogenic
proteases such as MMPs, which suggests that aging might influence the therapeutic behavior of these stem cells. Others confirm that ADSC acquire a ‘stronger’ therapeutic capacity under hypoxia, although this response mounts slower than in hypoxic BM-MSC (92). Thus hypoxia and inflammation render ADSC more angiogenic. As mentioned earlier, ADSC can acquire a pericytic phenotype in co-cultures with endothelial cells. This suggests that ADSC make a fate choice, because pericytes are vessel-stabilizing mural cells, more than pro-angiogenic cells. In rats with chemically-induced mesenteric damage which is a model for hypoxia and inflammatory induced damage, injected ADSC showed to promote healing angiogenesis, while part of the ADSC acquired a perivascular position (93). This suggests that also in vivo ADSC might serve a bifunctional role. It remains to be investigated whether in clinical trials such as APOLLO or POSEIDON, ADSC also end up as pericytes.

These findings imply that a potentially hostile microenvironment is of no concern to administered ADSC. Moreover, hypoxic or proinflammatory preconditioning might even augment the ADSC’s capacity to promote tissue revascularization and repair (94). MSC preconditioned with TGF-beta or a combination of TGF-beta and IL-6 showed a stronger cardioprotective effect than untreated MSC (95, 96). This is both remarkable and exciting, because TGF beta and IL-6 are the culprit factors in the onset and progression of cardiac fibrosis and subsequent heart failure. It again emphasizes that cardiac therapy should not be judged on the effect of single factors alone. Pretreatment of MSC with TGF-beta and IL-1beta prior the injection also synergistically improved vascularization of the ischemic cardiac tissue through augmented production of vascular endothelial growth factor (97).

Thus, cardiac stem cell therapy with ADSC still needs to be further fine-tuned in terms of preconditioning with oxygen concentration and preconditioning with distinct inflammatory mediators.

**The conditioned medium in cardiovascular regeneration**

We have come a long way from the discovery of the peculiar phenomenon that plastic adherent cells from the stromal vascular fraction of adipose tissue secrete a plethora of therapeutic factors to the fact that these paracrine factors secreted by cultured ADSC are their major mode of action in cell and tissue regeneration. Yet, the interdonor variation of ADSC can be significant (Przybyt et al, unpublished data). Therefore, the question rises whether it would be possible to replace ADSC with their secreted factors i.e. conditioned culture media. The advantages are that a clonal ADSC line or an immortalized ADSC line could be selected with an optimal therapeutic spectrum. It would also allow for an off-the-shelf product which is available at all times for cardiac intervention. Recent data indicate the use of the conditioned medium from human ADSC improved cardiac regeneration and function in a pig model for MI (98, 99).

**Potential of ADSC in attenuation of cardiac fibrosis**

As mentioned, one of the major findings in the APOLLO clinical trial with use of therapeutic ADSC in the treatment of MI is the significant reduction in the scar size and improved perfusion of the myocardium. The juxtacrine and paracrine interactions exerted by ADSC in the post-MI microenvironment, strongly reduce the acute ventricular remodeling which results in reduced long term fibrotic remodeling too (100). Beside the secretion of pro-angiogenic and anti-fibrotic growth factors and cytokines, ADSC produce and remodel extracellular matrix resulting in the formation of a repaired cardiac niche with adequate
perfusion and stiffness (101,102). The concept of improved post-MI cardiac stiffness is also currently a new approach that employs nature-inspired biomaterials for the treatment of MI (103). ADSC have been proven beneficial in skin regeneration by accelerated wound healing and the reduction of dermal fibrosis (104-107). According to Spiekmann et al. ADSC suppress fibrotic remodeling through inhibition of TGF-beta driven cellular hypertrophy and myofibroblast differentiation. Furthermore, ADSC have shown antifibrotic properties after transplantation to the various organs such as liver or lungs (108,109). Thus, current data suggest that ADSC might carry limited risk in appearance of cardiac fibrosis after the administration to the post-MI microenvironment.

Conclusions

The therapeutic benefit of cardiac stem cell therapy is at best similar to conventional therapeutics such as ACE inhibitors or beta blockers. This raises continues concern and debate on the use of stem cells in regenerative medicine. Nevertheless, costly clinical trials with therapeutic stem cells are ongoing and are engaged on a continuous basis. In this review we have shown that after the initial hype of cardiac stem cell therapy, we started to understand that mesenchymal stem or stromal cells might be more potent than hematopoietic stem cells or other blood-born therapeutic cells. In contrast to the traditional view on stem cells, which is to differentiate parenchymal cells from stem cells, cardiac stem cell therapy relies primarily on the secretion of trophic factors by mesenchymal stem cells. The understanding of the working mechanism of MSC has greatly increased and led to the discovery that these cells can be primed to a higher level a therapeutic capacity by potentially deleterious stimuli such as hypoxia and inflammation. As ADSC are of perivascular origin, this raises the question why cardiac perivascular cells apparently do not respond to the stimuli in a ‘therapeutic fashion’. This is likely due to the fact that only upon culturing on plastic and in simple growth media, MSC and ADSC acquire their highly active and diverse secretome.

Future experiments will further dissect the paracrine functioning of ADSC as well as their juxtacrine function as pericytes in neovasculature.


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