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Adipose-derived Stem Cells: Current Findings and Future Perspectives

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Abstract: Adipose tissue is an abundant source of mesenchymal stem cells, which have shown promise in the field of regenerative medicine. Furthermore, these cells can be readily harvested in large numbers with low donor-site morbidity. During the past decade, numerous studies have provided preclinical data on the safety and efficacy of adipose-derived stem cells, supporting the use of these cells in future clinical applications. Various clinical trials have shown the regenerative capability of adipose-derived stem cells in subspecialties of medical fields such as plastic surgery, orthopedic surgery, oral and maxillofacial surgery, and cardiac surgery. In addition, a great deal of knowledge concerning the harvesting, characterization, and culture of adipose-derived stem cells has been reported. This review will summarize data from *in vitro* studies, pre-clinical animal models, and recent clinical trials concerning the use of adipose-derived stem cells in regenerative medicine.

Introduction

In the field of regenerative medicine, basic research and preclinical studies have been conducted to overcome clinical shortcomings with the use of mesenchymal stem cells

(MSCs). MSCs are present in adult tissues, including bone marrow and adipose tissue. For many years, bone marrow-derived stem cells (BSCs) were the primary source of stem cells for tissue engineering applications (Caplan, 1991; Pittenger et al., 1999; Caplan, 2007). However, recent studies have shown that subcutaneous adipose tissue provides a clear advantage over other stem cell sources due to the ease with which adipose tissue can be accessed as well as the ease of isolating stem cells from harvested tissue (Schäffler et al., 2007). Initial enzymatic digestion of adipose tissue yields a mixture of stromal and vascular cells referred to as the stromal-vascular fraction (SVF) (Traktuev et al., 2008). A putative stem cell population within this SVF was first identified by Zuk *et al*. and named processed lipoaspirate (PLA) cells (Zuk et al., 2001; Zuk et al., 2002).

There is no consensus when it comes to the nomenclature used to describe progenitor cells from adipose tissue-derived stroma, which can sometimes lead to confusion. The term PLA refers to adipose-derived stromal cells and adipose-derived stem cells (ASCs) and describes cells obtained immediately after collagenase digestion. Accordingly, the term ASC will be used throughout this review.

ASCs exhibit stable growth and proliferation kinetics and can differentiate toward osteogenic, chondrogenic, adipogenic, myogenic, or neurogenic lineages *in vitro* (Zuk et al., 2002; Izadpanah et al., 2006; Romanov et al., 2005). Furthermore, a group has recently described the isolation and culture of ASCs with multipotent differentiation capacity at the single-cell level (Rodriguez, et al., 2005).

Using these attractive cell populations, recent studies have explored the safety and efficacy of implanted/administrated ASCs in various animal models. Furthermore, clinical trials using ASCs have been initiated in some medical subspecialties. This review summarizes the current preclinical data and ongoing clinical trials and their outcomes in a variety of medical fields.

Characterization and Localization

ASCs express the mesenchymal stem cell markers CD10, CD13, CD29, CD34, CD44, CD54, CD71, CD90, CD105, CD106, CD117, and STRO-1. They are negative for the hematopoietic lineage markers CD45, CD14, CD16, CD56, CD61, CD62E, CD104, and CD106 and for the endothelial cell (EC) markers CD31, CD144, and von Willebrand factor (Zuk et al., 2002; Musina et al., 2005; Romanov et al., 2005). Morphologically, they are fibroblast-like and preserve their shape after expansion *in vitro* (Zuk et al., 2002; Arrigoni et al., 2009; Zannettino et al., 2008).

The similarities between ASCs and BSCs may indicate that ASCs are derived from circulating BSCs, which infiltrate into the adipose compartment through vessel walls (Zuk et al., 2002; Zannettino et al., 2008; Brighton et al., 1992; Canfield et al., 2000; Bianco et al., 2001). On the other hand, according to a recent theory, these stem cells are actually pericytes (Traktuev et al., 2008; Chen et al., 2009; Crisan et al., 2008; Zannettino et al., 2008; Tintut et al., 2003; Abedin et al., 2004; Amos et al., 2008). Pericytes around microvessels express alpha-smooth muscle actin (α-SMA) as well as certain MSC markers (CD44, CD73, CD90, CD105); however, they do not express endothelial or hematopoietic cell markers (Chen et al., 2009). Pericytes adhere, proliferate in culture, sustain their initial antigenic profile, and can differentiate into bone, cartilage and fat cells (Chen et al., 2009). Moreover, injected MSCs migrate to the blood vessels *in vivo* and become pericytes (Chen et al., 2009). Considering the above-mentioned data, it can be speculated that pericytes are the ancestors of MSCs, but this does not mean that all MSCs are descendants of pericytes (Chen et al., 2009) or that all pericytes are necessarily stem cells (Lin et al., 2008; Traktuev et al., 2008; da Silva et al., 2008; Abedin et al., 2004; Tintut et al., 2003; Zannettino et al., 2008; Amos et al., 2008).

Traktuev et al. (2008) defined a periendothelial pericyte-like subpopulation of ASCs. These cells were CD34+, CD31-, CD45-, and CD144- and expressed mesenchymal cell markers, smooth muscle antigens, and pericytic markers, including chondroitin sulfate proteoglycan (NG2), CD140a, and CD140b (PDGF receptor α and β, respectively) (Traktuev et al., 2008; Amos et al., 2008). However, Lin et al. (2008) could not co-localize CD34 and CD104b, and thus concluded that CD34+/CD31- cells of adipose vasculature are not pericytes.

The differences in the expression of surface markers in these studies may be explained by the stage of culture growth (Romanov et al., 2005). Similarly, the variability of CD34 positivity in several reports is likely a consequence of the down-regulation of expression of this marker within the first few days of *in vitro* expansion (Traktuev et al., 2008).

Paracrine Secretion

Adipose tissue actively participates in endocrine processes by secreting cytokines and growth factors (Kilroy et al., 2007). ASCs secrete high levels of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), and brain-derived neurotrophic factor (BDNF) (Chen et al., 2009; Kilroy et al., 2007; Rehman et al 2004; Cai et al., 2007; Ebrahimian et al., 2009; Kim et al., 2009; Kim et al., 2007; Wei et al., 2009). They also secrete cytokines such as Flt-3 ligand, granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-11 (IL-11), interleukin-12 (IL-12), leukemia inhibitory factor (LIF), and tumor necrosis factor-alpha (TNF-α) (Kilroy et al., 2007; Rehman et al 2004). This secretion of paracrine factors by the adipose tissue likely contributes to the elevated levels of these cytokines in cases of obesity (Kilroy et al., 2007; Hotamisligil et al., 1995).

It is important to note that these angiogenic and anti-apoptotic growth factors are secreted in bioactive levels by ASCs and that their secretion increases significantly under hypoxic conditions (Rehman et al., 2004; Cai et al., 2007; Lee et al., 2009). HGF is possibly the main angiogenic factor secreted by ASCs and it plays a central role in the paracrine effects on ASCs. Its suppression has been shown to impair the angiogenic and regenerative effects of ASCs in ischemic tissues. Silencing HGF reduces the ability of ASCs to promote EC proliferation and inhibits the pro-angiogenic effects of HGF *in vitro* (Cai et al., 2007).

Soft Tissue Regeneration and Wound Healing

The materials currently used in soft tissue regeneration, which include collagen, hyaluronic acid, silicon, and other filler materials, have several disadvantages such as high cost, immunogenicity/allergenicity, and the risk of transmitting infectious diseases. Meanwhile, autologous fat grafts are more widely available; however, one limitation of this technique is the poor long-term graft retention in current clinical practice (Min et al., 2010). The transplanted fat grafts can lose volume over time due to tissue resorption that can result in the loss of 20-90% of the original graft volume (Cherubino et al., 2009). The ideal solution for soft tissue regeneration would promote the regeneration of vascularized adipose tissue to completely fill the defect volume (Brayfield et al., 2010).

Recently, Frerich et al. (2005) reported an in vitro co-culture model using human adipose stromal cells and human umbilical vein ECs, where perfused tubes formed capillary-like networks that sprouted from the central lumen wall. Kang et al. (2009) developed an *in vitro* 3D model of tissue regeneration in which human vascularized adipose tissue, human ASCs, and human umbilical vein ECs were co-cultured on 3D aqueous silk scaffolds. After two weeks of co-culture, continuous endothelial lumens formed. Furthermore, Min et al. (2010) demonstrated in an *in vivo* murine model that the transplantation of fat tissue with non-cultured ASCs improved long-term graft retention. Compared with transplanted fat tissue alone, fat tissue transplanted with non-cultured ASCs had a higher density of capillaries six and nine months after transplantation. The reasons for these successful results might be the pro-angiogenic growth factors secreted by ASCs, as described previously.

Wound healing might be interrupted by a variety of pathological conditions, such as diabetes, radiation and immunosuppression, resulting in refractory chronic wounds (Lorens et al., 2006). Growth factors involved in wound healing have been individually applied to the wound to promote wound healing in unfavorable conditions. However, the theoretical promise of this approach was unfulfilled due to the complex nature of wound healing, which involves a number of different growth factors (Ebrahimian et al., 2009; Brem et al., 2009). To achieve optimal results, all these growth factors should be applied continuously, as opposed to the intermittent applications of individual growth factors

(Brem et al., 2009; Blanton et al., 2009).

ASCs secrete nearly all of the growth factors that take part in normal wound healing (Ebrahimian et al., 2009; Blanton et al., 2009; Kim et al., 2007; Rehman et al., 2004). After application, ASCs may remain viable at the wound site and secrete growth factors in a continuous and regulated manner in response to environmental cues, just as occurs in the natural wound healing process (Badillo et al., 2007). ASCs promote wound healing by increasing vessel density, granulation tissue thickness, and collagen deposition (Ebrahimian et al., 2009), and they also improve the cosmetic appearance of resultant scars (Blanton et al., 2009).

A ready blood supply is crucial for wound healing. VEGF secreted from ASCs induces the migration and proliferation of ECs, increasing the vascularity of the wound bed (Lorens et al., 2006; Rehman et al., 2004). It was both experimentally and clinically shown that the topical administration of ASCs to full-thickness radiated wounds increase the healing rate of the wound (Ebrahimian et al., 2009; Rigotti et al., 2007). Kim et al. (2007) demonstrated that ASCs stimulate fibroblast proliferation and migration and type I collagen secretion in an *in vitro* wound model. These findings suggest that ASCs may promote *in vivo* wound healing.

Musculoskeletal Regeneration

Current therapeutic approaches for muscle loss cannot restore muscle function effectively. ASCs can differentiate into chondrogenic, osteogenic, and myogenic cells *in vitro,* and thus could potentially be used to regenerate tissue in musculoskeletal system disorders (Zuk et al., 2001; Mizuno et al., 2002).

Muscle tissue contains muscle progenitor cells called satellite cells that lie underneath the basal lamina (Kim et al., 2006; Di Rocco et al., 2006; Mizuno et al., 2002). These cells can divide and fuse to repair or replace damaged fibers in response to acute muscle injury or in chronic degenerative myopathies (Kim et al., 2006; Mizuno et al., 2002). However, continuous muscle degeneration-regeneration cycles in chronic cases lead to a depletion of the satellite cell pool. Moreover, it is difficult to expand satellite cells *in vitro* and they rapidly undergo senescence (Di Rocco et al., 2006; Mizuno et al., 2002).

ASCs may provide an easily accessible and expandable alternative cell source for the cellular therapy of muscular disorders. ASCs were successfully differentiated into skeletal muscle cells and smooth muscle cells *in vitro* (Jeon et al., 2010; Mizuno et al., 2002; Di Rocco et al., 2006). Differentiated ASCs even exhibited a contractile function similar to that of smooth muscle cells *in vivo* (Rodríguez et al., 2006). ASCs have also shown a capacity for myogenic differentiation *in vivo*. Allogeneic ASCs injected intravenously or directly into the affected muscle could restore muscle function in a murine muscular dystrophy model without any signs of immune rejection (Di Rocco et al., 2006). In another study, poly lactic-co glycolic acid (PLGA) spheres attached to myogenically-induced ASCs were injected subcutaneously into athymic nude mice. Injected ASCs differentiated into muscle cells and regenerated into new muscular tissue (Kim et al., 2006). However, it is still unclear whether ASCs directly differentiate into myogenic lineage cells or whether they become incorporated into muscle fibers via cell fusion. It is likely that ASCs contain different subsets of cells capable of either function (Di Rocco et al., 2006).

ASCs can form osteoid *in vitro* and *in vivo* (Hattori et al., 2004). ASCs combined with biomaterials were successfully used to repair critical bone defects (Di Bella et al., 2008; Yoon et al., 2007). Moreover, ASCs secrete osteoinductive growth factors, which may potentially recruit host bone-forming cells and induce osteogenesis when implanted *in vivo* (Hao et al., 2010). ASCs genetically modified to secrete bone morphogenic protein-2 (BMP-2) may also be an effective method for enhancing bone healing (Peterson et al., 2005).

Use of ASCs in intervertebral disc regeneration has also been reported (Hoogendoorn et al., 2008). Other applications of ASCs in musculoskeletal system are periodontal tissue regeneration and tendon regeneration. Tobita et al. (2008) reported that implanted ASCs were differentiated into the periodontal tissues including alveolar bone, cementum, and periodontal ligament in a rat model. In addition, topical administration of ASCs to tendon repair sites in rabbits accelerated tendon repair and significantly increased tensile strength (Uysal et al., 2011).

Cardiovascular Regeneration

Acute and chronic ischemic heart diseases are among the leading causes of mortality worldwide (Bai et al., 2010; Psaltis et al., 2008). Conventional management generally does not replace lost cardiomyocyte mass or myocardial fibrotic tissue (Psaltis et al., 2008). The injection of both cultured and freshly-isolated ASCs has the potential to improve cardiac function in experimentally-induced myocardial injury (Danoviz et al., 2010; Cai et al., 2009; Miyahara et al., 2006; Schenke-Layland et al., 2009; Valina et al., 2007; van der Bogt et al., 2009; van der Bogt et al., 2008; Wang et al., 2009; Van't Hof et al., 2007; Léobon et al., 2009). Bai et al. (2010) injected human ASCs into the peri-infarct region of the hearts of mice. Cardiac function was preserved; moreover, left ventricular end-systolic volume was significantly lower in the mice that received injections of ASCs. Valina et al. (2007) reported similar results in a porcine model.

Human ASCs spontaneously differentiate into cardiomyocytes *in vitro*, express the cardiac-specific markers troponin-I and myosin light chain 2 (Song et al., 2007; Choi et al., 2010), and even contract rhythmically (Planat-Bénard et al., 2004). However, as with smooth muscle differentiation, the *in vivo* differentiation of ASCs into cardiomyocytes is still controversial. Strem et al. (2005) reported that ASCs expressed cardiac markers *in vivo* two weeks after injection, but Cai et al. (2009) found that intramyocardially-injected human ASCs differentiated into smooth muscle cells but not into cardiomyocytes in rats. Intramyocardially-injected ASCs can promote angiogenesis and inhibit apoptosis of cells in injured hearts via the secretion of pro-angiogenic growth factors (Bai et al., 2010). Moreover, ASCs may also directly stimulate nerve sprouting in ischemic myocardium, thereby increasing cardiac contractile performance (Bai et al., 2007; Cai et al., 2010).

The conventional method of delivery of ASCs is needle-based intramyocardial injection. However, significant cell death or cell washout may occur, which can decrease the efficacy of treatment (Shimizu et al., 2009). An alternative method is epicardial delivery via scaffold-free cell sheets that are prepared on temperature-responsive dishes. The advantages of these cell sheets are the absence of any foreign material, the preservation of cell cohesiveness, and the possibility of incorporating different cell populations (Bel et al., 2010; Shimizu et al., 2009). Several types of cell sheet-based patches have improved damaged heart function in rat, canine, and porcine models (Shimizu et al., 2009).

Nervous System Regeneration

A variety of growth factors, such as nerve growth factor (NGF), ciliary neurotrophic factor (CNF), IGF, and FGF, are secreted from nerve stumps following injury (Bixby et al., 1988; Longo et al., 1983). These growth factors stimulate axonal growth in close contact with Schwann cells, which are the primary support cells of the peripheral nervous system (Shimizu et al., 2007; Sofroniew et al., 2001). Since the above-mentioned regeneration sequence is known to fail in long nerve defects, cellular treatments, such as stem cell therapy, might be useful (Lundborg et al., 1982) as a means to introduce growth factors into the gap and thereby promote nerve regeneration. ASCs can secrete some nerve growth factors, including IGF and FGF (Rehman et al., 2004; Zavan et al., 2010), so these cells might have the capacity to promote nerve healing. In addition, a number of recent studies reported the successful differentiation of ASCs into neural lineage cells and Schwann cells *in vitro* (Safford et al., 2002; Fujimura et al., 2005; Xu et al., 2008; Kingham et al., 2007; Oh et al., 2010). When compared to BSCs, ASCs express a significantly higher proportion of nestin, which is commonly used to identify proliferating adult neural progenitor cells (Safford et al., 2002). Several results suggest that the differentiation of ASCs into Schwann cells, the mechanism of which has been described in detail (Deng et al., 2001; Cohen et al., 1999; Shah et al., 1999; di Summa et al., 2010), is not an incomplete, reversible process resulting from the disruption of the cytoskeleton (Safford et al., 2002; Fujimura et al., 2005; Kingham et al., 2007).

A study testing the effects of ASCs, which were differentiated into a Schwann cell-like phenotype, on peripheral nerve healing has been reported by di Summa et al. (2010). However, more experimental data must be gathered using larger animal models before these methods can be safely tested in the clinic.

ASCs can be used not only in peripheral nerve injuries but also in central nervous system injuries (Chi et al., 2010; Zhang et al., 2009; Ohta et al., 2008; Kang et al., 2006; Ryu et al., 2009). Ryu et al. (2009) used ASCs to treat acute spinal injuries in a canine model and reported an improvement in neurological function. They also could document the *in vivo* differentiation of ASCs into astrocytes, oligodendrocytes and neuronal cells. In another study, ASCs were used for spinal cord injury in rats after *in vitro* differentiation into Schwann cells (Ohta et al., 2008). But in this study, the authors stated that functional improvement was not observed despite the significant histological improvement achieved at the primary injury site by the transplantation of Schwann cells. Therefore, it was speculated that a full recovery of spinal cord function requires a much more complex treatment combining different modalities rather than an injection of a single type of cell or cytokine.

It has been well established that ASCs can survive in the nervous system after injection and promote nerve healing either by direct differentiation or through the secretion of a number of paracrine factors. ASCs thus show promise for the future of the treatment of central nervous system injuries, as well as peripheral nerve injuries.

Cancer Metastasis and Invasion

Because stromal cells contribute to the development of a variety of tumors, it is important to consider the effect of implanted/administrated mesenchymal stromal/stem cells on cancer development before these cells can be used clinically in regenerative medicine. Stromal cell compartments contain a variety of cell types such as fibroblasts, pericytes, myofibroblasts, vasculature, and macrophages, which together form a microenvironment that tightly controls the proliferation and differentiation of epithelial cells (Bissell et al., 2002). During the initiation and progression of breast cancer, the tumor cells reorganize the tissue microenvironment to support their proliferation and invasion into the surrounding tissue (Pupa et al., 2002). Tumors recruit stromal fibroblasts in a process referred to as a desmoplasmic reaction. These tumor-associated fibroblasts are reprogrammed to produce growth factors, cytokines, and extracellular matrix-remodeling proteins (Orimo et al., 2005).

Recent studies have demonstrated that BSCs recruited by breast carcinomas promote breast cancer metastasis and invasion (Karnoub et al., 2007). BSCs produce chemokine ligand 5 (CCL5), which promotes breast tumor progression in direct co-cultures.

Compared with BSCs, ASCs are tissue-resident stem cells that occur locally adjacent to breast cancer cells, and interactions between adipocytes and breast cancer cells have been described previously (Iyengar et al., 2003; Manabe et al., 2003). Recent studies have linked white adipose-derived cells to cancer development. An *in vivo* murine model demonstrated that ASCs home to tumor sites when injected intravenously, and the stromal-derived growth factor-1 (SDF-1)/CXC receptor 4 (CXCR4) axis plays an important role in mediating the tumor-promoting effect of ASCs (Muehlberg et al., 2009). Walter et al. (2009) reported that IL-6 secreted by ASCs is related to the migration and invasion of breast tumor cells. IL-6 is a critical growth factor for several types of cancer such as multiple myeloma (MM) and prostate cancer (Smith et al., 2001). Furthermore, an *in vivo* study showed that SDF-1 secreted by ASCs promoted the invasion and metastasis of breast cancer (Muehlberg et al., 2009). Another study reported that human ASCs produce CCL5. Significant amounts of CCL5 were detected in conditioned medium from human ASCs after co-culture with MDA-MB-231 breast cancer cells (Pinilla et al., 2009).

However, the effect of ASCs against cancer tumor cells is controversial. Several studies have reported that implanted ASCs inhibited breast cancer metastasis and growth in a murine model (Sun et al., 2009).

Reciprocal interactions between breast tumor cells and stromal cells are mediated by inflammatory cytokines and chemokines, and may affect tumor development and progression. Therefore, the molecular basis of the effects of adipose tissue on the behavior of tumor cells should be carefully examined before the future clinical application of stem cell therapies.

Current Clinical Trials

Cell therapies using ASCs are widely promising in various clinical fields based on *in vitro* and *in vivo* research results. Currently, clinical trials for the regeneration of soft tissue, craniofacial tissue, and cardiovascular tissue enrolled a number of patients.

Breast reconstruction and augmentation trials have been reported by Yoshimura and colleagues (Yoshimura et al., 2008; Yoshimura et al., 2010). The stromal vascular fraction (SVF) was isolated from half of the aspirated fat tissue, recombined with the remaining half, and then used in combination with lipoinjection in over fifty patients. These results showed no evidence of fibrosis or adhesions and improved fat grafting by the SVF cells with retention of volume for over twelve months. Furthermore, a clinical trial was conducted for facial lipoatrophy using the same technique (Yoshimura et al., 2008). The authors note improved facial contour, although there was no statistically significant difference in clinical improvement score compared to the conventional lipoinjection.

Regarding craniofacial defects, ASCs were first used to stimulate bone repair in calvarial defects (Lendeckel et al., 2004). This surgical team used fibrin glue and autologous adipose-derived stromal cells including stem cells in a 7-year-old female, and new bone formation was evident three months after reconstruction. Meanwhile, a Finnish team reported clinical outcomes with autologous ASCs (Mesimäki et al., 2009). The authors harvested autologous fat tissue from a 65-year-old male who had undergone a hemimaxillectomy twenty-eight months earlier due to a large recurrent keratocyst, expanded the cells in culture, mixed them with BMP-2, and seeded them onto a β-tricalcium phosphate scaffold formed into the shape of the defect. Eight months after this construct was implanted into the patient's rectus abdominis muscle, the construct was resected and transplanted into the maxillofacial defect. The patient regained full oral function for at least twelve months.

ASCs hold great promise for the treatment of cardiovascular diseases and no cardiac side effects (e.g., electrical instability) have been reported to date (Bai et al., 2010). Currently, an ongoing clinical trial using ASCs for cardiovascular treatment has been reported. The clinical trial is being carried out in patients with acute myocardial infarction (AMI) (Sanz-Ruiz et al., 2009), and it is a prospective, double-blind, randomized, placebo-controlled, sequential dose-escalation trial including up to forty-eight patients. Freshly-isolated ASCs are delivered through intracoronary infusion in patients with AMI and left ventricular (LV) ejection fraction impairment. For chronic myocardial ischemia, a clinical trial is also being carried out in up to thirty-six patients (Sanz-Ruiz et al., 2009). The freshly-isolated ASCs are delivered via transendocardial injections in patients with coronary artery disease. However, clinical trials of cardiac cell therapy have yielded inconsistent results (Bel et al., 2010). A number of issues such as appropriate type and number of cells, timing and route of cell delivery, and the detailed mechanism of action should be optimized for more consistent clinical results (Danoviz et al., 2010).

ASCs were also used to heal chronic fistulas in Crohn's disease (Garcia-Olmo et al., 2005; Garcia-Olmo et al., 2008). This disease is an inflammatory bowel disorder characterized by bloody stools, diarrhea, weight loss, and autoimmune-related symptoms. In a phase I trial with patients with fistulas unresponsive to standard treatment, cultured ASCs were directly injected into the rectal mucosa, and 75% of cases healed completely. In a phase IIb trial, the proportion of patients who achieved fistula healing was significantly higher with ASCs than with fibrin glue. Rigotti et al. (2007) reported successful results after injection of lipoaspirates containing ASCs to wounds caused by post-mastectomy irradiation. According to ultrastructural analysis, the early stages of tissue mesenchymalization were observed after application of lipoaspirates and a tissue resembling normal mature adipose tissue was formed at the site of application. The authors commented that this effect of lipoaspirate on wound healing was largely due to the angiogenic growth factors secreted by ASCs (Rigotti et al., 2007). These results were valuable in terms of showing the safety and feasibility of ASCs for clinical wound management (Hanson et al., 2010; Garcia-Olmo et al., 2005).

Conclusions

ASCs are under investigation for a variety of therapeutic applications. These cells are known to home to some tissues such as injured tissue. Although the mechanisms underlying the migration of ASCs remain to be determined, clarification of the roles of chemokine receptors and adhesion molecules on ASCs may lead to the development of therapeutic strategies to enhance the recruitment of cultured ASCs to injured or damaged tissue.

Because human adipose tissue is a promising alternative source of stem cells, autologous ASCs will lead to novel clinical applications in various medical fields. However, a greater understanding of the mechanisms of interactions among ASCs, growth factors, and biomaterials on tissue regeneration is needed to advance the clinical utility of this therapy. Because chemokines derived from ASCs may also affect cancer metastasis or invasion, additional findings are necessary to address the safety of ASCs in the field of clinical tissue regeneration.

Disclosure

The authors report no conflicts of interest.

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References

Abedin M, Tintut Y, Demer LL. Mesenchymal stem cells and the artery wall. *Circ Res* 95(7):671-676, 2004.

Amos PJ, Shang H, Bailey AM, Taylor A, Katz AJ, Peirce SM. IFATS collection: The role of human adipose-derived stromal cells in inflammatory microvascular remodeling and evidence of a perivascular phenotype. *Stem Cells* 26(10):2682-2690, 2008.

Arrigoni E, Lopa S, de Girolamo L, Stanco D, Brini AT. Isolation, characterization and osteogenic differentiation of adipose-derived stem cells: from small to large animal models. *Cell Tissue Res* 338(3):401-411, 2009.

Badillo AT, Redden RA, Zhang L, Doolin EJ, Liechty KW. Treatment of diabetic wounds with fetal murine mesenchymal stromal cells enhances wound closure. *Cell Tissue Res* 329(2):301-311, 2007.

Bai X, Alt E. Myocardial regeneration potential of adipose tissue-derived stem cells. *Biochem Biophys Res Commun* 401(3):321-326, 2010.

Bai X, Ma J, Pan Z, Song YH, Freyberg S, Yan Y, Vykoukal D, Alt E. Electrophysiological properties of human adipose tissue-derived stem cells. *Am J Physiol Cell Physiol* 293(5):C1539-C1550, 2007.

Bel A, Planat-Bernard V, Saito A, Bonnevie L, Bellamy V, Sabbah L, Bellabas L, Brinon B, Vanneaux V, Pradeau P, Peyrard S, Larghero J, Pouly J, Binder P, Garcia S, Shimizu T, Sawa Y, Okano T, Bruneval P, Desnos M, et al. Composite cell sheets: a further step toward safe and effective myocardial regeneration by cardiac progenitors derived from embryonic stem cells. *Circulation* 122(Suppl 11):S118-S123, 2010.

Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. *Stem Cells* 19(3):180-192, 2001.

Bissell MJ, Radisky DC, Rizki A, Weaver VM, Petersen OW. The organizing principle: microenvironmental influences in the normal and malignant breast. *Differentiation* 70(9-10):537-546, 2002.

Bixby JL, Lilien J, Reichardt LF. Identification of the major proteins that promote neuronal process outgrowth on Schwann cells in vitro. *J Cell Biol* 107(1):353-361, 1988.

Blanton MW, Hadad I, Johnstone BH, Mund JA, Rogers PI, Eppley BL, March KL. Adipose stromal cells and platelet-rich plasma therapies synergistically increase revascularization during wound healing. *Plast Reconstr Surg* 123(Suppl 2):56S-64S, 2009.

Brayfield C, Marra K, Rubin JP. Adipose stem cells for soft tissue regeneration. *Handchir Mikrochir Plast Chir* 42(2):124-128, 2010.

Brem H, Kodra A, Golinko MS, Entero H, Stojadinovic O, Wang VM, Sheahan CM, Weinberg AD, Woo SL, Ehrlich HP, Tomic-Canic M. Mechanism of sustained release of vascular endothelial growth factor in accelerating experimental diabetic healing. *J Invest Dermatol* 129(9):2275-2287, 2009.

Brighton CT, Lorich DG, Kupcha R, Reilly TM, Jones AR, Woodbury RA 2nd. The pericyte as a possible osteoblast progenitor cell. *Clin Orthop Relat Res* 275:287-299, 1992.

Cai L, Johnstone BH, Cook TG, Liang Z, Traktuev D, Cornetta K, Ingram DA, Rosen ED, March KL. Suppression of hepatocyte growth factor production impairs the ability of adipose-derived stem cells to promote ischemic tissue revascularization. *Stem Cells* 25(12):3234-3243, 2007.

Cai L, Johnstone BH, Cook TG, Tan J, Fishbein MC, Chen PS, March KL. IFATS collection: human adipose tissue-derived stem cells induce angiogenesis and nerve sprouting following myocardial infarction, in conjunction with potent preservation of cardiac function. *Stem Cells* 27(1):230-237, 2009.

Canfield AE, Doherty MJ, Wood AC, Farrington C, Ashton B, Begum N, Harvey B, Poole A, Grant ME, Boot-Handford RP. Role of pericytes in vascular calcification: a review. *Z Kardiol* 89(Suppl 2):II20-II27, 2000.

Caplan AI. Mesenchymal stem cells. *J Orthop Res* 9(5):641-650, 1991.

Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol* 213(2):341-347, 2007.

Chen CW, Montelatici E, Crisan M, Corselli M, Huard J, Lazzari L, Péault B. Perivascular multi-lineage progenitor cells in human organs: regenerative units, cytokine sources or both? *Cytokine Growth Factor Rev* 20(5-6):429-434, 2009.

Cherubino M, Marra KG. Adipose-derived stem cells for soft tissue reconstruction. *Regen Med* 4(1):109-117, 2009.

Chi GF, Kim MR, Kim DW, Jiang MH, Son Y. Schwann cells differentiated from spheroid-forming cells of rat subcutaneous fat tissue myelinate axons in the spinal cord injury. *Exp Neurol* 222(2):304-317, 2010.

Choi YS, Dusting GJ, Stubbs S, Arunothayaraj S, Han XL, Collas P, Morrison WA, Dilley RJ. Differentiation of human adipose-derived stem cells into beating cardiomyocytes. *J Cell Mol Med* 14(4):878-889, 2010.

Cohen RI, McKay R, Almazan G. Cyclic AMP regulates PDGF-stimulated signal transduction and differentiation of an immortalized optic-nerve-derived cell line. *J Exp Biol* 202(Pt 4):461-473, 1999.

Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L, Norotte C, Teng PN, Traas J, Schugar R, Deasy BM, Badylak S, Buhring HJ, Giacobino JP, Lazzari L, Huard J, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell* 3(3):301-313, 2008.

Danoviz ME, Nakamuta JS, Marques FL, dos Santos L, Alvarenga EC, dos Santos AA, Antonio EL, Schettert IT, Tucci PJ, Krieger JE. Rat adipose tissue-derived stem cells transplantation attenuates cardiac dysfunction post infarction and biopolymers enhance cell retention. *PLoS One* 5(8):e12077, 2010.

da Silva Meirelles L, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. *Stem Cells* 26(9):2287-2299, 2008.

Deng W, Obrocka M, Fischer I, Prockop DJ. In vitro differentiation of human marrow stromal cells into early progenitors of neural cells by conditions that increase intracellular cyclic AMP. *Biochem Biophys Res Commun* 282(1):148-152, 2001.

Di Bella C, Farlie P, Penington AJ. Bone regeneration in a rabbit critical-sized skull defect using autologous adipose derived cells. *Tissue Eng Part A* 14(4):483-490, 2008.

Di Rocco G, Iachininoto MG, Tritarelli A, Straino S, Zacheo A, Germani A, Crea F, Capogrossi MC. Myogenic potential of adipose-tissue-derived cells. *J Cell Sci* 119(Pt 14):2945-2952, 2006.

Di Summa PG, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. *J Plast Reconstr Aesthet Surg* 63(9):1544-1552, 2010.

Ebrahimian TG, Pouzoulet F, Squiban C, Buard V, André M, Cousin B, Gourmelon P, Benderitter M, Casteilla L, Tamarat R. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing. *Arterioscler Thromb Vasc Biol* 29(4):503-510, 2009.

Frerich B, Kurtz-Hoffmann J, Lindemann N. Influence of growth hormone on maintenance of capillary-like structures in an in vitro model of stromal vascular tissue — results from morphometric analysis. *Artif Organs* 29(4):338-341, 2005.

Fujimura J, Ogawa R, Mizuno H, Fukunaga Y, Suzuki H. Neural differentiation of adipose-derived stem cells isolated from GFP transgenic mice. *Biochem Biophys Res Commun* 333(1):116-121, 2005.

Garcia-Olmo D, Garcia-Arranz M, Herreros D. Expanded adipose-derived stem cells for the treatment of complex perianal fistula including Crohn's disease. *Expert Opin Biol Ther* 8(9):1417-1423, 2008.

García-Olmo D, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum* 48(7):1416-1423, 2005.

Hanson SE, Bentz ML, Hematti P. Mesenchymal stem cell therapy for nonhealing cutaneous wounds. *Plast Reconstr Surg* 125(2):510-516, 2010.

Hao W, Pang L, Jiang M, Lv R, Xiong Z, Hu YY. Skeletal repair in rabbits using a novel biomimetic composite based on adipose-derived stem cells encapsulated in collagen I gel with PLGA-beta-TCP scaffold. *J Orthop Res* 28(2):252-257, 2010.

Hattori H, Sato M, Masuoka K, Ishihara M, Kikuchi T, Matsui T, Takase B, Ishizuka T, Kikuchi M, Fujikawa K, Ishihara M. Osteogenic potential of human adipose tissue-derived stromal cells as an alternative stem cell source. *Cells Tissues Organs* 178(1):2-12, 2004.

Hoogendoorn RJ, Lu ZF, Kroeze RJ, Bank RA, Wuisman PI, Helder MN. Adipose stem cells for intervertebral disc regeneration: current status and concepts for the future. *J Cell Mol Med* 12(6A):2205-2216, 2008.

Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 95(5):2409-2415, 1995.

Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, Flanagan L, Tenniswood MP, Guha C, Lisanti MP, Pestell RG, Scherer PE. Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization. *Oncogene* 22(41):6408-6423, 2003.

Izadpanah R, Trygg C, Patel B, Kriedt C, Dufour J, Gimble JM, Bunnell BA. Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. *J Cell Biochem* 99(5):1285-1297, 2006.

Jeon ES, Moon HJ, Lee MJ, Song HY, Kim YM, Bae YC, Jung JS, Kim JH. Sphingosylphosphorylcholine induces differentiation of human mesenchymal stem cells into smooth-muscle-like cells through a TGF-beta-dependent mechanism. *J Cell Sci* 119(Pt23):4994-5005, 2006.

Kang JH, Gimble JM, Kaplan DL. In vitro 3D model for human vascularized adipose tissue. *Tissue Eng Part A* 15(8):2227-2236, 2009.

Kang SK, Shin MJ, Jung JS, Kim YG, Kim CH. Autologous adipose tissue-derived stromal cells for treatment of spinal cord injury. *Stem Cells Dev* 15(4):583-594, 2006.

Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 449(7162):557-563, 2007.

Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. *J Cell Physiol* 212(3):702-709, 2007.

Kim M, Choi YS, Yang SH, Hong HN, Cho SW, Cha SM, Pak JH, Kim CW, Kwon SW, Park CJ. Muscle regeneration by adipose tissue-derived adult stem cells attached to injectable PLGA spheres. *Biochem Biophys Res Commun* 348(2):386-392, 2006.

Kim WS, Park BS, Park SH, Kim HK, Sung JH. Antiwrinkle effect of adipose-derived stem cell: activation of dermal fibroblast by secretory factors. *J Dermatol Sci* 53(2):96-102, 2009.

Kim WS, Park BS, Sung JH. The wound-healing and antioxidant effects of adipose-derived stem cells. *Expert Opin Biol Ther* 9(7):879-887, 2009.

Kim WS, Park BS, Sung JH, Yang JM, Park SB, Kwak SJ, Park JS. Wound healing effect of adipose-derived stem cells: a critical role of secretory factors on human dermal fibroblasts. *J Dermatol Sci* 48(1):15-24, 2007.

Kingham PJ, Kalbermatten DF, Mahay D, Armstrong SJ, Wiberg M, Terenghi G. Adipose-derived stem cells differentiate into a Schwann cell phenotype and promote neurite outgrowth in vitro. *Exp Neurol* 207(2):267-274, 2007.

Lee EY, Xia Y, Kim WS, Kim MH, Kim TH, Kim KJ, Park BS, Sung JH. Hypoxia-enhanced wound-healing function of adipose-derived stem cells: increase in stem cell proliferation and up-regulation of VEGF and bFGF. *Wound Repair Regen* 17(4):540-547, 2009.

Lendeckel S, Jödicke A, Christophis P, Heidinger K, Wolff J, Fraser JK, Hedrick MH, Berthold L, Howaldt HP. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report. *J Craniomaxillofac Surg* 32(6):370-373, 2004.

Lin G, Garcia M, Ning H, Banie L, Guo YL, Lue TF, Lin CS. Defining stem and progenitor cells within adipose tissue. *Stem Cells Dev* 17(6):1053-1063, 2008.

Longo FM, Manthorpe M, Skaper SD, Lundborg G, Varon S. Neuronotrophic activities accumulate in vivo within silicone nerve regeneration chambers. *Brain Res* 261(1):109-116, 1983.

Lorens HP, Longaker MT. Wound healing: repair biology and wound and scar treatment. In: *Plastic Surgery, 2nd ed*. Mathes SJ (ed.). pp209-232. Saunders Elsevier, Philadelphia, Pennsylvania, USA, 2006.

Lundborg G, Dahlin LB, Danielsen N, Gelberman RH, Longo FM, Powell HC, Varon S. Nerve regeneration in silicone chambers: influence of gap length and of distal stump components. *Exp Neurol* 76(2):361-375, 1982.

Léobon B, Roncalli J, Joffre C, Mazo M, Boisson M, Barreau C, Calise D, Arnaud E, André M, Pucéat M, Pénicaud L, Prosper F, Planat-Bénard V, Casteilla L. Adipose-derived cardiomyogenic cells: in vitro expansion and functional improvement in a mouse model of myocardial infarction. *Cardiovasc Res* 83(4):757-767, 2009.

Manabe Y, Toda S, Miyazaki K, Sugihara H. Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. *J Pathol* 201(2):221-228, 2003.

Mesimäki K, Lindroos B, Törnwall J, Mauno J, Lindqvist C, Kontio R, Miettinen S, Suuronen R. Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. *Int J Oral Maxillofac Surg* 38(3):201-209, 2009.

Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, Ishino K, Ishida H, Shimizu T, Kangawa K, Sano S, Okano T, Kitamura S, Mori H. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. *Nat Med* 12(4):459-465, 2006.

Mizuno H, Zuk PA, Zhu M, Lorenz, HP. Benhaim P, Hedrick MH. Myogenic differentiation by human processed lipoaspirate cells. *Plast Reconstr Surg* 109(1):199-209, 2002.

Muehlberg FL, Song YH, Krohn A, Pinilla SP, Droll LH, Leng X, Seidensticker M, Ricke J, Altman AM, Devarajan E, Liu W, Arlinghaus RB, Alt EU. Tissue-resident stem cells promote breast cancer growth and metastasis. *Carcinogenesis* 30(4):589-597, 2009.

Musina RA, Bekchanova ES, Sukhikh GT. Comparison of mesenchymal stem cells obtained from different human tissues. *Bull Exp Biol Med* 139(4):504-509, 2005.

Oh JS, Ha Y, An SS, Khan M, Pennant WA, Kim HJ, Yoon do H, Lee M, Kim KN. Hypoxia-preconditioned adipose tissue-derived mesenchymal stem cell increase the survival and gene expression of engineered neural stem cells in a spinal cord injury model. *Neurosci Lett* 472(3):215-219, 2010.

Ohta Y, Takenaga M, Tokura Y, Hamaguchi A, Matsumoto T, Kano K, Mugishima H, Okano H, Igarashi R. Mature adipocyte-derived cells, dedifferentiated fat cells (DFAT), promoted functional recovery from spinal cord injury-induced motor dysfunction in rats. *Cell Transplant* 17(8):877-886, 2008.

Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell* 121(3):335-348, 2005.

Peterson B, Zhang J, Iglesias R, Kabo M, Hedrick M, Benhaim P, Lieberman JR. Healing of critically sized femoral defects, using genetically modified mesenchymal stem cells from human adipose tissue. *Tissue Eng* 11(1-2):120-129, 2005.

Pinilla S, Alt E, Abdul Khalek FJ, Jotzu C, Muehlberg F, Beckmann C, Song YH. Tissue resident stem cells produce CCL5 under the influence of cancer cells and thereby promote breast cancer cell invasion. *Cancer Lett* 284(1):80-85, 2009.

Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. *Science* 284(5411):143-147, 1999.

Planat-Bénard V, Menard C, André M, Puceat M, Perez A, Garcia-Verdugo JM, Pénicaud L, Casteilla L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. *Circ Res* 94(2):223-229, 2004.

Psaltis PJ, Zannettino AC, Worthley SG, Gronthos S. Concise review: mesenchymal stromal cells: potential for cardiovascular repair. *Stem Cells* 26(9):2201-2210, 2008.

Pupa SM, Menard S, Forti S, Tagliabue E. New insights into the role of extracellular matrix during tumor onset and progression. *J Cell Physiol* 192(3):259-267, 2002.

Rehman J, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, Pell CL, Johnstone BH, Considine RV, March KL. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation* 109(10):1292-1298, 2004.

Rigotti G, Marchi A, Galiè M, Baroni G, Benati D, Krampera M, Pasini A, Sbarbati A. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg* 119(5):1409-1422, 2007.

Rodriguez AM, Elabd C, Amri EZ, Ailhaud G, Dani C. The human adipose tissue is a source of multipotent stem cells. *Biochimie* 87(1):125-128, 2005.

Rodríguez LV, Alfonso Z, Zhang R, Leung J, Wu B, Ignarro LJ. Clonogenic multipotent stem cells in human adipose tissue differentiate into functional smooth muscle cells. *Proc Natl Acad Sci U S A* 103(32):12167-12172, 2006.

Romanov YA, Darevskaya AN, Merzlikina NV, Buravkova LB. Mesenchymal stem cells from human bone marrow and adipose tissue: isolation, characterization, and differentiation potentialities. *Bull Exp Biol Med* 140(1):138-143, 2005.

Rubina K, Kalinina N, Efimenko A, Lopatina T, Melikhova V, Tsokolaeva Z, Sysoeva V, Tkachuk V, Parfyonova Y. Adipose stromal cells stimulate angiogenesis via

promoting progenitor cell differentiation, secretion of angiogenic factors, and enhancing vessel maturation. *Tissue Eng Part A* 15(8):2039-2050, 2009.

Ryu HH, Lim JH, Byeon YE, Park JR, Seo MS, Lee YW, Kim WH, Kang KS, Kweon OK. Functional recovery and neural differentiation after transplantation of allogeneic adipose-derived stem cells in a canine model of acute spinal cord injury. *J Vet Sci* 10(4):273-284, 2009.

Safford KM, Hicok KC, Safford SD, Halvorsen YD, Wilkison WO, Gimble JM, Rice HE. Neurogenic differentiation of murine and human adipose-derived stromal cells. *Biochem Biophys Res Commun* 294(2):371-379, 2002.

Sanz-Ruiz R, Fernández-Santos E, Domínguez-Muñoa M, Parma R, Villa A, Fernández L, Sánchez PL, Fernández-Avilés F. Early translation of adipose-derived cell therapy for cardiovascular disease. *Cell Transplant* 18(3):245-254, 2009.

Schenke-Layland K, Strem BM, Jordan MC, Deemedio MT, Hedrick MH, Roos KP, Fraser JK, Maclellan WR. Adipose tissue-derived cells improve cardiac function following myocardial infarction. *J Surg Res* 153(2):217-223, 2009.

Schäffler A, Büchler C. Concise review: adipose tissue-derived stromal cells–basic and clinical implications for novel cell-based therapies. *Stem Cells* 25(4):818-827, 2007.

Shah NM, Groves AK, Anderson D.J. Alternative neural crest cell fates are instructively promoted by TGF beta superfamily members. *Cell* 85(3):331-343, 1996.

Shimizu S, Kitada M, Ishikawa H, Itokazu Y, Wakao S, Dezawa M. Peripheral nerve regeneration by the in vitro differentiated-human bone marrow stromal cells with Schwann cell property. *Biochem Biophys Res Commun* 359(4):915-920, 2007.

Shimizu T, Sekine H, Yamato M, Okano T. Cell sheet-based myocardial tissue engineering: new hope for damaged heart rescue. *Curr Pharm Des* 15(24):2807-2814, 2009.

Smith PC, Hobisch A, Lin DL, Culig Z, Keller ET. Interleukin-6 and prostate cancer progression. *Cytokine Growth Factor Rev* 12(1):33-40, 2001.

Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. *Annu Rev Neurosci* 24:1217-1281, 2001.

Song YH, Gehmert S, Sadat S, Pinkernell K, Bai X, Matthias N, Alt E. VEGF is critical for spontaneous differentiation of stem cells into cardiomyocytes. *Biochem Biophys Res Commun* 354(4):999-1003, 2007.

Strem BM., Zhu M, Alfonso Z, Daniels EJ, Schreiber R, Beygui R, MacLellan WR, Hedrick MH, Fraser JK. Expression of cardiomyocytic markers on adipose tissue-derived cells in a murine model of acute myocardial injury. *Cytotherapy* 7(3):282-291, 2005.

Sun B, Roh KH, Park JR, Lee SR, Park SB, Jung JW, Kang SK, Lee YS, Kang KS. Therapeutic potential of mesenchymal stromal cells in a mouse breast cancer metastasis model. *Cytotherapy* 11(3):289-298, 2009.

Tintut Y, Alfonso Z, Saini T, Radcliff K, Watson K, Boström K, Demer LL. Multilineage potential of cells from the artery wall. *Circulation* 108(20):2505-2510, 2003.

Tobita M, Uysal AC, Ogawa R, Hyakusoku H, Mizuno H. Periodontal tissue regeneration with adipose-derived stem cells. *Tissue Eng Part A* 14(6):945-953, 2008.

Traktuev DO, Merfeld-Clauss S, Li J, Kolonin M, Arap W, Pasqualini R, Johnstone BH, March KL. A population of multipotent CD34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks. *Circ Res* 102(1):77-85, 2008.

Uysal AC, Mizuno H. Differentiation of adipose-derived stem cells for tendon repair. *Methods Mol Biol* 702:443-451, 2011.

Valina C, Pinkernell K, Song YH, Bai X, Sadat S, Campeau RJ, Le Jemtel TH, Alt E. Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction. *Eur Heart J* 28(21):2667-2677, 2007.

van der Bogt KE, Schrepfer S, Yu J, Sheikh AY, Hoyt G, Govaert JA, Velotta JB, Contag CH, Robbins RC, Wu JC. Comparison of transplantation of adipose tissue- and bone marrow-derived mesenchymal stem cells in the infarcted heart. *Transplantation* 87(5):642-652, 2009.

van der Bogt KE, Sheikh AY, Schrepfer S, Hoyt G, Cao F, Ransohoff KJ, Swijnenburg RJ, Pearl J, Lee A, Fischbein M, Contag CH, Robbins RC, Wu JC. Comparison of different adult stem cell types for treatment of myocardial ischemia. *Circulation* 118(Suppl 14):S121-S129, 2008.

Van't Hof W, Mal N, Huang Y, Zhang M, Popovic Z, Forudi F, Deans R, Penn MS. Direct delivery of syngeneic and allogeneic large-scale expanded multipotent adult progenitor cells improves cardiac function after myocardial infarct. *Cytotherapy* 9(5):477-487, 2007.

Walter M, Liang S, Ghosh S, Hornsby PJ, Li R. Interleukin 6 secreted from adipose stromal cells promotes migration and invasion of breast cancer cells. *Oncogene* 28(30):2745-2755, 2009.

Wang L, Deng J, Tian W, Xiang B, Yang T, Li G, Wang J, Gruwel M, Kashour T, Rendell J, Glogowski M, Tomanek B, Freed D, Deslauriers R, Arora RC, Tian G. Adipose-derived stem cells are an effective cell candidate for treatment of heart failure: an MR imaging study of rat hearts. *Am J Physiol Heart Circ Physiol* 297(3):H1020-H1031, 2009.

Wei X, Du Z, Zhao L, Feng D, Wei G, He Y, Tan J, Lee WH, Hampel H, Dodel R, Johnstone BH, March KL, Farlow MR, Du Y. IFATS collection: The conditioned media of adipose stromal cells protect against hypoxia-ischemia-induced brain damage in neonatal rats. *Stem Cells* 27(2):478-488, 2009.

Xu Y, Liu Z, Liu L, Zhao C, Xiong F, Zhou C, Li Y, Shan Y, Peng F, Zhang C. Neurospheres from rat adipose-derived stem cells could be induced into functional Schwann cell-like cells in vitro. *BMC Neurosci* 9:21, 2008.

Yoon E, Dhar S, Chun DE, Gharibjanian NA, Evans GR. In vivo osteogenic potential of human adipose-derived stem cells/polylactide-co-glycolic acid constructs for bone regeneration in a rat critical-sized calvarial defect model. *Tissue Eng* 13(3):619-627, 2007.

Yoshimura K, Asano Y, Aoi N, Kurita M, Oshima Y, Sato K, Inoue K, Suga H, Eto H, Kato H, Harii K. Progenitor-enriched adipose tissue transplantation as rescue for breast implant complications. *Breast J* 16(2):169-175, 2010.

Yoshimura K, Sato K, Aoi N, Kurita M, Hirohi T, Harii K. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg* 32(1):48-55, 2008.

Yoshimura K, Sato K, Aoi N, Kurita M, Inoue K, Suga H, Eto H, Kato H, Hirohi T, Harii K. Cell-assisted lipotransfer for facial lipoatrophy: efficacy of clinical use of adipose-

derived stem cells. *Dermatol Surg* 34(9):1178-1185, 2008.

Zannettino AC, Paton S, Arthur A, Khor F, Itescu S, Gimble JM, Gronthos S. Multipotential human adipose-derived stromal stem cells exhibit a perivascular phenotype in vitro and in vivo. *J Cell Physiol* 214(2):413-421, 2008.

Zavan B, Vindigni V, Gardin C, D'Avella D, Della Puppa A, Abatangelo G, Cortivo R. Neural potential of adipose stem cells. *Discov Med* 10(50):37-43, 2010.

Zhang HT, Cheng HY, Cai YQ, Ma X, Liu WP, Yan ZJ, Jiang XD, Xu RX. Comparison of adult neurospheres derived from different origins for treatment of rat spinal cord injury. *Neurosci Lett* 458(3):116-121, 2009.

Zhu M, Zhou Z, Chen Y, Schreiber R, Ransom JT, Fraser JK, Hedrick MH, Pinkernell K, Kuo HC. Supplementation of fat grafts with adipose-derived regenerative cells improves long-term graft retention. *Ann Plast Surg* 64(2):222-228, 2010.

Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 13(12):4279-4295, 2002.

Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 7(2):211-228, 2001.

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