Adipose-Derived Mesenchymal Stem Cells

Subjects: Medicine, General & Internal

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Adipose-derived mesenchymal stem cells (AMSCs) are more accessible and easier to collect from subcutaneous tissue, they can be collected in large quantities, with less morbidity of the patients, via lipoaspirates or adipose tissue biposy, they are easily isolated, and can simply be expanded in vitro. Moreover, AMSCs have been shown to be immunoprivileged, with low risk of rejection, and more genetically stable in long term culture, with a greater proliferative rate than BM-MSCs.

Keywords: adipose-derived mesenchymal stem cells ; musculoskeletal diseases

1. AMSCs in the Treatment of Muscular Disorders

Although muscle has some inherent regeneration capacity to repair damage resulting from physical or chemical trauma to muscle tissue, complete functional recovery of skeletal muscle after severe injury remains a challenge [1][2]. The return of muscular function is comprised by the incomplete recovery from muscle atrophy and fibrosis, which affects muscle fiber number, muscle cross-sectional area, and thus, muscle force [2].

While some in vitro works have shown direct formation of myotubes from AMSCs cultures [3][4][5], most investigations have shown that in vitro myogenic differentiation of AMSCs requires co-culture with myoblasts or satellite cells [1][6][7][8][9][10][11][12]. Even though the in vitro differentiation potential of AMSCs into myocytes has been demonstrated, there is little evidence about AMSCs transplantation after skeletal muscle injury. Bacou et al. were the first to test the potential of AMSCs in a nonphysiological cardiotoxin induced muscle damage model in rabbits. Fifteen days after the transplantation, the cells expressed skeletal muscle markers, suggesting myogenic differentiation. In addition, two months after the treatment, muscles were heavier, showed a significantly larger fiber section area, and developed a significantly higher maximal force compared with damaged control muscles [13].

AMSCs promote the proliferation of myoblasts, which could explain the regenerative capacity shown in vivo [14][12][15][16][17].

Muscular tears or lacerations are common lesions within athletes. Conventional therapies include medical management with non-steroideal anti-inflammatory drugs (NSAIDs), antioxidant therapy, and steroids; or surgical management such as myotenectomy or myectomy [18][19]. These therapies are unsuccessful and generally do not prevent the formation of fibrous tissue as well as do not promote muscle regeneration, leading to a limited function of the limb [18][20]. Therefore, regenerative therapies are gaining interest, particularly AMSCs, and some animal studies have been carried out in order to assess the in vivo efficacy of AMSCs in muscular tears. Peçanha et al. investigated how AMSCs contribute to skeletal muscle healing after a surgically performed laceration in the rat model. They conclude that AMSCs may accelerate the process of muscle repair, since the number of regenerating muscle fibers and muscle developed force significantly increased in the treated group [19]. Recently, Gorecka et al. have demonstrated that AMSCs transplantation into acute damaged skeletal muscle in a mice model, significantly improves functional muscle tissue regeneration without direct participation in muscle fiber formation [21].

RM is also gaining interest in the field of muscular dystrophies. Duchenne muscular dystrophy (DMD) is the most common and most severe form of muscular dystrophy. It is an X-linked genetic disorder caused by mutations in the dystrophin gene, which cause dystrophin deficiency. The loss of dystrophin leads to a breakdown of the structural integrity of myofibers, resulting in progressive myofibers necrosis, fibroblast proliferation, and growth of fibrous tissue and fat [22]. DMD is a progressive and lethal degenerating disease that affects both skeletal and cardiac muscle. Thus far, there is no effective treatment for DMD; however, several studies on cell therapy, including the application of MSCs have became a promising treatment to restore dystrophin in DMD patients. The use of AMSCs has also been proposed, but this therapy is still in preliminary testing and more experiments are required [2][12][16][17]. Animal models have become increasingly important for testing these regenerative therapies. Mdx mouse is the most widely used animal model for DMD, presenting the same molecular and protein defect as seen in humans with the disease [23].

It was firstly observed that AMSCs treatment increases the content of VEGF and anti-inflammatory cytokines in dystrophin-deficient skeletal muscle, which promotes angiogenesis and reduces the inflammation, respectively. Moreover, a decrease in the content of TNF-α and Interleukin 6 (IL-6) were also reported in the AMSCs treated group, suggesting a protective action of the AMSCs on inflammation-induced injury. The AMSCs treated group showed improved muscle strength and resistance to acute muscle fatigue, after one injection of AMSCs per week during four weeks. In addition, a histological analysis was performed and an increase in fiber cross-sectional area and an augment of myogenin content was observed in AMSCs treated group [16]. Similar results were obtained by Lee et al., who demonstrated that AMSCs up-regulated myogenin, mTOR and raptor proteins, which contribute to the formation of myofibres. Thus, leads to an increase in muscle size when compared to control group [17]. These results support the proposition that AMSCs transplantation is a promising treatment for muscular dystrophies. Nevertheless, there is no clinical trials supporting these results; hence, further investigation is needed to determine the long-term effects of AMSCs in dystrophin-deficient muscles, and to find an accurate therapy for this pathology.

2. AMSCs in the Treatment of Tendon Injuries

The high incidence of tendon injuries is mainly associated with sport practice and aging, and they range from acute traumatic ruptures to chronic tendinopathy [24][25]. Tendon injuries represent a clinical challenge because their natural repair process is slow, complex, and inefficient, as well as a financial challenge. Tendon has limited inherent healing capacity, as it is a slightly cellular and poorly vascularized tissue, and often responds inadequately to treatments; hence, prolonged recovery times are needed [24][25][26]. After injuries, the structural composition and organization of tendons, which are responsible of the specific mechanical tendon properties, are not completely restored. Following the repair process, a fibrous scar is formed, causing significant dysfunction and joint movement inability, leading to a biomechanically weakened tendon, making it more vulnerable to re-rupture [25][27]. Tendinopathies and tendon tears have been treated with conservative approaches for managing symptoms, including rest, anti-inflammatory drugs, corticosteroids, and physiotherapy. On the other hand, the gold standard to treat tendon rupture is surgical suture, combined or not with allo- or auto-grafts [24][28]. Despite the improvements made in surgical techniques, none of the therapeutic options have provided successful long-term solutions [25][26]. New treatments are needed with the objective of improving tendon regeneration, and AMSCs have been adopted to repair tendon and ligament tears. It has been demonstrated that AMSCs can differentiate in vitro towards tenocytes. It is widely known that the control of stem cell activity is influenced by several environmental factors, including GF such as insulin like growth factor (IGF), TGF-β and growth differentiation factor 5 (GDF-5), which have been successfully used in a co-culture wit primary tenocytes, to promote AMSCs differentiation towards tenocytes in vitro [25][29][30].

AMSCs are also gaining interest among veterinarians. Race horses often suffer from superficial flexor digitorium longus tendon (SFDLT) lesions. There is clinical evidence that the injection of AMSCs after SFDLT spontaneous lesion significantly improves healing [31]. AMSCs were administered under ultrasonographic guidance in four horses suffering from SFDLT lesions. Treated horses showed shorter periods of lameness and better organization of collagen fibers assessed by ultrasound examination [31]. These results concur with those obtained by Carvalho et al., in a horse's collagenase-induced SFDLT lesion controlled trial [32]. The histological evaluation demonstrated that AMSCs combined with a platelet concentrate therapy resulted in a better organization of collagen fibers and a decrease of the inflammatory infiltrate. In addition, the ultrasound evaluation showed a lack of lesion progression in the treated group [32] (**Table 1**).

Table 1. Clinical application of AMSCs in tendon injuries.

Authors	Patients	Injury	Treatment	AMSCs Origin	Outcomes
Lee et al., 2015 [28]	**Human**	**Lateral epicondylosis**	**Locally injected AMSCs + fibrin glue**	**Allogenic subcutaneous fat**	**VAS score improvement. Tendon's defect size decreased**
Skutella, 2016 [31]	**Race horses**	**SFDLT tear**	**Local injection of AMSCs**	**Autologous subcutaneous fat**	**Improvements in gait and lameness assessment. Sonographyc improvement of the defect size and organization of collagen bundles**
Kim et al., 2017 [33]	**Human**	**Rotator cuff tear**	**Arthroscopy + local AMSCs + fibrin glue**	**Autologous buttock fat pad**	**Lower retear rate with almost complete healing of the defect by 12 months follow-up**

Authors	Patients	Injury	Treatment	AMSCs Origin	Outcomes
Usuelli et al., 2018 [34]	Human	Non-insertional Achilles tendinopathy	Intratendinous adipose-derived SVF	Autologous abdominal subcutaneous fat	Pain relif and function restoration during at least 6 months

AMSCS: Adipose-derived Mesenchymal Stem Cells, SFDLT: Superficial flexor digitorium longus tendon, SVF: Stromal Vascular Fraction, VAS: Visual Analogue Scale.

The efficacy of SVF injection in the treatment of Achilles tendinopathy has also been studied by Usuelli et al. [34]. The clinical controlled trial aimed to compare the effectiveness of the injection of PRP, with the injection of adipose-derived SVF for the treatment of chronic Achilles tendinopathy. Fifty-six patients affected by non-insertional Achilles tendinopathy were randomly divided into PRP or SVF treatment group. Either PRP or SVF was locally injected and a clinical exam was carried out at 15, 30, 60, 120, and 180 days after treatment. Moreover, ultrasound and MRI examination were conducted 4 and 6 months after treatment.

AMSCs transplantation is a good alternative for the treatment or tendinopathies and tendon ruptures.

3. Application of AMSCs in the Treatment of Osseous Diseases

AMSCs can differentiate into different cell types, including osteocytes, and the lineage-specific differentiation is associated with the expression of explicit phenotypic markers and mature tissue genes. In vitro, osteogenic differentiation of AMSCs can be obtained using medium supplemented with ascorbic acid, b-glyc-erophosphate, dexamethasone, 1.25 vitamin D_3 or bone morphogenic protein 2 [35][36][37][38][39]. Osteogenic induction was thought to be a necessary step for AMSCs to have osteogenic ability, but it has been demonstrated that AMSCs undergoing, or not, osteogenic induction are able to adhere to scaffolds, migrate, proliferate, and differentiate when transplanted in bone tissue in vivo [40][41].

Bone fractures, segmental bone defects and critical size defects (CSDs) are important causes of patient morbidity and place an incredible economic burden on the healthcare system. They are usually secondary to trauma, post-resection of tumors, or post-debridement of infection [42]. Around 5 billion dollars are annually spend in treating bone defects in the US, mainly on bone grafts and implants for bone injuries and other pathologies associated with defective fracture healing, such as non-union [43]. Conventional treatments, including autologous bone grafts, and distraction osteogenesis (DO) have some limitations, such as long immobilization periods, donor site morbidity, muscular atrophy and surgical complications such as infection, pain, or hemorrhage [42][44][45]. Tissue engineering and cell-based therapies have been adopted as alternatives therapies to promote bone repair, and AMSCs have been proposed to treat CSDs [45][46][47][48][49] [50][51] and delayed fracture healing and the resulting segmental bone defects [44][52][53][54][55]. Furthermore, the implication of AMSCs in DO in animal models has been investigated [56][57].

Levi et al. introduced PLGA scaffolds alone or PLGA scaffolds with AMSCs in critical size calvarial defects in mice, and near complete healing was observed among AMSCs engrafted calvarial defects in comparison to control group, that showed little healing [47]. Liu et al. [45], who previously demonstrated that autologous AMSCs loaded onto natural coral scaffolds could repair cranial CSDs in a canine model [51], were the first to show that allogenic AMSCs combined with coral scaffolds are suitable to regenerate the same kind of defects without using immunosuppressive therapy [45]. Critical tibial defects treated with hydroxyapatide scaffolds combined with AMSCs showed an improved healing process when compared to that occurred when only the scaffold was used [50]. Moreover, the defects treated with AMSCs showed greater mechanical properties, suggesting an enhanced ability to bear mechanical loading [50]. Du et al. combined the osteogenesis and angiogenesis advantages of AMSCs with modified mesoporous bioactive glass scaffolds to optimize the restoration of CSDs, and the results demonstrated that the combination of different induction of AMSCs into osteogenic cells and endothelial cells is practical and beneficial for CSDs [49].

Concerning the application of AMSCs in the treatment of bone fractures, in a case report by Saxer et al., autologous adipose SVF was loaded onto ceramic granules within fibrin gel and used to treat humeral fractures in eight patients along with standard open reduction and internal fixation [54]. Biopsies of the repair tissue 12 months after the transplantation of AMSCs, demonstrated formation of bone ossicles, structurally disconnected and morphologicaly distinct from osteoconducted bone, suggesting the osteogenic and angiogenic nature of implanted SVF cells [54]. Anti-inflammatory effects of AMSCs have also been demonstrated in an equine bone fracture case report [55]. Lee et al. analyzed synovial fluid of racehorses suffering bone fractures before and after the intra-articular (IA) injection of AMSCs, and the level of pro-inflammatory factors was significantly decreased in synovial fluids of AMSCs treated horses [55].

Age-related skeletal changes, such as osteoporosis, are closely related to imbalanced bone remodeling characterized by elevated osteocyte apoptosis and osteoclast activation [58]. Recently, a study has demonstrated for the first time that AMSCs exosomes inhibits induced osteocyte apoptosis and osteocyte-mediated osteoclastogenesis [59]. The use of AMSCs as a regenerative therapy for osteoporosis is a topic of current interest, as it could potentially reduce the susceptibility of fractures and increase lost mineral density [60]. Mirsaidi et al. evaluated the use of AMSCs as a treatment strategy for age-related osteoporosis, both in vitro and in vivo [61].

Avascular necrosis (AVN), also known as osteonecrosis, of the femoral head, is a debilitating disorder that causes necrosis, bone structure collapses, bone destruction, and consequently, pain and joint dysfunction [62]. Despite that BM-MSCs have been used as a cellular therapeutic option for treatment of AVN of the femoral head, limited success has been achieved. Wyles et al. demonstrated that AMSCs outperformed BM-MSCs in growth rate and bone differentiation potential in the setting of AVN, suggesting they could provide a more-potent regenerative therapeutic strategy [63].

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