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Comparison of osteogenic differentiation ability between bone marrow-derived mesenchymal stem cells and adipose tissue-derived mesenchymal stem cells

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Abstract

An important clinical problem is the fast restoration of large bone defects caused by trauma, tumour resection, infections, or skeletal anomaly. Autografts and allografts are commonly known approaches to bone repair, however, they have a lot of limitations. Bone tissue engineering has been considered as the alternative solution to bone rebuilding when natural grafts cannot be used. The primary model of bone tissue engineering comprises three elements: scaffold, growth factors, and stem or progenitor cells. The role of cells is to differentiate into osteoblasts and to form a bone extracellular matrix. Mesenchymal stem cells (MSCs) possess the mentioned features which make them a promising tool in supporting bone restoration process. MSCs are present in multiple tissues, including bone marrow and adipose tissue. This study presents the similarities and differences between bone marrow-derived mesenchymal stem cells (BMDSCs) and adipose tissue-derived mesenchymal stem cells (ADSCs). The study also compares the osteogenic potential of these cells, based on available literature. The presented comparison showed that both BMDSCs and ADSCs possess osteogenic ability under *in vitro* and *in vivo* conditions. However, most of the *in vitro* research confirmed the inferior osteogenic potential of ADSCs, compared to BMDSCs. Contrariwise, the *in vivo* studies revealed more controversies on this point in the scientific community; namely, some research studies considered the ADSCs as the promising alternative for BMDSCs which have been successfully used to-date for bone tissue engineering applications.

Key words

bone formation, stromal cells, tissue engineering, bone tissue

INTRODUCTION AND OBJECTIVE

Restoration of large bone defects is still a challenge for regenerative medicine. The bone defects may be caused by trauma, tumour resection, infections, skeletal anomaly, or by impaired regenerative process. Due to the increase in life expectancy, the reduction or treatment of bone healing complications is becoming more important. Regeneration by means of autograft or allograft provides great effects, but it has a number of limitations. Autografts are limited by morbidity due to surgical harvesting procedures and the potential risk of infection, chronic pain, and haematoma at the site of donation. However, autografts are still considered as the gold standard because they are non-immunogenic and histocompatible. The use of allografts also has constraints, e.g. by tissue matching, the risk of infection or disease transmitting. The limited use of auto- and allografts has driven the development of research on a broad diversity of biomaterials to be applied as scaffolds. Bone tissue engineering has been considered as the alternative solution to bone rebuilding. One of the crucial purposes of this approach is to seed patient osteoprogenitor cells onto biomaterial and to enhance osteogenic differentiation of stem cells within the scaffold in *in vitro* conditions in order to obtain a clinically applicable bone construct [1–2].

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The primary model of bone tissue engineering comprises three elements: scaffold, growth factors, and stem or progenitor cells. The three-dimensional porous scaffold promotes a new tissue formation by providing a surface, void volume, and mechanical stability that supports osteoblastic cells' attachment, proliferation, migration, and desired differentiation. Growth factors stimulate cellular growth, proliferation, and differentiation at the site of implantation, whereas the role of osteoprogenitor/stem cells is to accelerate the bone regeneration process by their differentiation into osteoblasts capable of forming a bone extracellular matrix (ECM). The production of clinically applicable bone scaffold *in vitro* needs a great number of cells [1, 3, 4]. Embryonic stem cells (ESCs) and adult stem cells possess some appropriate features for bone tissue engineering applications. Among the potential candidate cells, ESCs are desirable in view of their pluripotency, but their application is limited due to the ethical issue. Additionally, scientists have found that transplantation of ESCs led to teratoma formation in the animal model [5–6].

Mesenchymal stem cells (MSCs) are adult stem cells having the ability of self-renewal and multi-lineage differentiation, including osteogenic capacity [4]. Moreover, MSCs possess lack of immunogenicity [1]. About 50 years ago, Friedenstein et al. discovered MSCs in bone marrow tissue with adherence phenotype and fibroblast-like shape in culture conditions [7]. Since then, it has been proved that MSCs are also present in multiple tissues, including trabecular bone [8], synovium [9], skeletal muscle [10], periosteum [11], among others. Bone marrow and adipose tissue are the well-known and studied

origin of MSCs, which are able to form *inter alia* bone and cartilage.

The prsented study describes the similarities and differences between BMDSCs and ADSCs, and compares the osteogenic potential of these cells, based on available literature.

ACTUAL STATE OF KNOWLEDGE

Characterization and isolation of mesenchymal stem cells. To define human MSCs, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy suggests three major requirements for this population of cells. Firstly, MSCs must be adherent to plastic when cultivated under standard culture condition. The second criteria is expression of CD73, CD90, CD105, and lack of expression of CD45, CD34, CD11b or CD14, CD19 or CD79alpha and HLA-DR surface markers. Finally, MSCs must be capable of differentiation into osteoblasts, adipocytes, and chondroblasts under *in vitro* conditions [12]. These features are important for all MSCs, although slight discrepancies may occur in MSCs isolated from different tissue sources; thus, BMDSCs and ADSCs may show minor differences in the expression of surface markers, e.g. unlike BMDSCs, ADSCs express CD49d marker, whereas BMDSCs express CD106 marker, which is absent from the surface of ADSCs [13].

At present, bone marrow is a very common source of MSCs, which were successfully isolated from different species, e.g. mouse, rat, pig, dog, and human [14–17]. A variety methodologies have been used for the isolation and expansion of BMDSCs, including low- and high-density culture systems [17], frequent culture medium changes [19] or enzymatic digestion approach [20]. It is worth noting that the type of isolation method used, as well as the origin and age of the donor, can significantly affect the proliferation potential of the isolated BMDSCs. Moreover, researchers have observed differences in the proliferation rates of stem cells isolated from various bone areas [21].

Bone marrow aspirates contain some haematopoietic cells, which are also adherent to the plastic dishes; however, during the sub-culturing step these cells are removed, and the remaining culture contains only adherent BMDSCs revealing a spindle-shape appearance. On average, there are 6 x 10^6 nucleated cells in 1 milliliter of bone marrow aspirate, and stem cells constitute about 0.001% – 0.01% of all nucleated cells [17, 22]. The low yield of stem cells' isolation from bone marrow aspirates, as well as painful bone marrow biopsy and aspiration, are the main drawbacks to the use of BMDSCs in bone tissue engineering applications. Therefore, researchers have been recently sought an alternative source of stem cells.

Adipose tissue is considered as an attractive alternative source of MSCs due to its easy availability in large quantities in the living organism. ADSCs can be obtained from adipose tissue collected by lipectomy and liposuction. These methods of cells' harvesting are simple, repeatable and carry low risk of possible complications. The adipose tissue is enzymatically digested followed by centrifugation to obtain a cell pellet called stromal vascular fraction (SVF) [23]. Adipose tissue-derived SVF is a heterogeneous cells' population that contains stromal cells, endothelial cells and their progenitors, vascular smooth muscle cells, leukocytes, haematopoietic progenitors, pericytes, preadipocytes, and ADSCs. MSCs occurring in SVF have the plastic adherent character under standard culture condition. Washing procedure, immunomagnetic separation or flow cytometric sorting may be used for purification of ADSCs from SVF. However, specific cell surface markers can be modified by the cell culturing procedure and by the number of passages [2]. ADSCs may differentiate not only into adipocytes, osteoblasts, and chondrocytes but also into myocytes, hepatocytes, endothelial cells and neuronal cells [13]. The cells' isolation yield from lipoaspirate tissue is 2 x 10^6 cells per 1 gram of adipose tissue, and stem cells constitute about 10% of all nucleated cells [24]. Stem cells derived from bone marrow and adipose tissue initially appear as adherent, single colony clusters known as fibroblast colony-forming units (CFU-F). Importantly clonogenic assays indicated that there are 5000 CFU-F in 1 gram of adipose tissue, whereas 1 milliliter of bone marrow contains only 100–1000 CFU-F. Therefore, the stem cells' isolation yield from adipose tissue is higher than from bone marrow [25].

In contrast to ADSCs, there is a necessity to perform a lot of *in vitro* passages of BMDSCs in order to obtain a sufficient amount of osteoprogenitor cells for small bone defect repair. Furthermore, long-term *in vitro* culture of BMDSCs is time-consuming and may increase the risk of contamination and gene mutation [26].

Osteogenic differentiation potential of MSCs *in vitro*. Osteogenic differentiation is a multi-stage process which involves the proliferation, ECM maturation, and ECM mineralization phase. The universal protocol for *in vitro* osteogenic differentiation of MSCs requires long-term culture (2–3 weeks) of cells in the presence of a growth medium containing dexamethasone, beta-glycerol phosphate and ascorbic acid. These reagents are used in appropriate concentrations, so as to create the physiological state under *in vitro* conditions [27]. Since the discovery of BMDSCs and ADSCs osteogenic differentiation *in vitro*, considerable development has been made in the direction of the use of these cells as an optimal source for bone regeneration. One of the approaches of modern regenerative medicine involves the direct administration of stem cells into scaffolds in order to generate bone graft *in vitro* [2]. In this subsection, the osteogenic capacity *in vitro* is compared between BMDSCs and ADSCs, based on the literature (Tab. 1).

Zuk et al. found that ADSCs isolated from adipose tissue by suction-assisted lipectomy and maintained *in vitro* for the extended time, had lower levels of senescence and more stable population doubling in comparison to BMDSCs. In the presence of lineage-specific induction factors, ADSCs could differentiate into adipogenic, myogenic, chondrogenic, and osteogenic cells [28]. De Ugarte et al. demonstrated that there were no significant differences between BMDSCs and ADSCs concerning their osteogenic potential, cell senescence, adhesion capacity, growth kinetics, and gene transduction efficiency. Osteogenic differentiation was detected by evaluation of alkaline phosphatase (ALP) activity and calcium content. De Ugarte et al. showed that ALP activity was equal to 0.08 ± 0.07 and 0.10 ± 0.12 nmol p-nitrophenol produced/min per 1 μg protein, and total calcium content was 42 ± 55 and 33 ± 38 mM Ca per 1 μg protein in BMDSCs and ADSCs, respectively [29]. Likewise, Kern et al. observed no distinct differences between BMDSCs and ADSCs in the osteogenic differentiation capacity [26]. Interestingly, Przekora et al. demonstrated by using the

Table 1. Comparison of *in vitro* osteogenic ability between bone marrow-derived mesenchymal stem cells and adipose tissue-derived mesenchymal stem cells

References	Osteogenic potential	Growth substrate	Technique of markers' detection	Osteogenic medium composition
De Ugarte et al. [29]	BMDSC=ADSC	tissue culture polystyrene dish	ALP activity (colorimetric assay) calcium content (colorimetric assay)	50 µM ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 0,1 µM dexamethasone
Kern et al. [26]	BMDSC=ADSC	tissue culture polystyrene dish	ALP activity (histochemical staining) bone mineral content (von Kossa staining)	0.2 mM ascorbate-2-phosphate 10 mM β-glycerolphosphate 100 nM dexamethasone
Przekora et al. [30]	BMDSC>ADSC	chitosan/ β-1,3-glucan/ hydroxyapatite	Col I and OC synthesis (immunofluorescence staining)	50 µg/mL ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 10 nM dexamethasone
	BMDSC=ADSC	tissue culture glass coverslip		
Im et al. [32]	BMDSC>ADSC	tissue culture polystyrene dish	ALP activity (histochemical staining) bone mineral content (von Kossa staining)	50 µM ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 0.1 µM dexamethasone
Liu et al. [33]	BMDSC>ADSC	tissue culture polystyrene dish	bone mineral content (alizarin red staining)	50 µM ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 0.1 µM dexamethasone
Shafiee et al. [34]	BMDSC>ADSC	tissue culture polystyrene dish	ALP activity (colorimetric assay) calcium content (colorimetric assay) ALP, Col I, Runx2, ON, OC, BMP-2 (RT-PCR)	0.2 mM ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 10 nM dexamethasone
Vishnubalaji et al. [35]	BMDSC>ADSC	tissue culture polystyrene dish	ALP activity (histochemical staining) bone mineral content (von Kossa staining, alizarin red staining) calcium content (colorimetric assay) ALP, Col I, Runx2, ON, OC, BMP-2 (RT-PCR)	50 µg/mL ascorbic acid-2-phosphate 10 mM β-glycerolphosphate 10 nM dexamethasone 10 nM calcitriol

immunofluorescent technique that ADSCs aspirated under low negative pressure (-200 mmHg) during a liposuction procedure, produced greater amounts of type I collagen (Col I), compared to ADSCs which were aspirated under high negative pressure (-700 mmHg), but a similar quantity of Col I, compared to BMDSCs [30].

Furthermore, Izadpanah et al. evaluated the differentiation potential of BMDSCs and ADSCs, derived from humans and rhesus monkeys. Early populations of human and rhesus monkey MSCs presented similar osteogenic differentiation capability, where the percent of colonies which were liable to osteogenic differentiation extended between 50% – 65% of the total colonies in all MSC types. Nevertheless, the percent of MSC colonies revealing osteogenic differentiation ability was reduced to 20%-25% in rhesus monkey ADSCs and human BMDSCs at passage 20, and to 30%-35% in human ADSCs and rhesus monkey BMDSCs at passage 30 [31]. Im et al. also showed, using ALP staining and bone mineral staining by von Kossa, that ADSCs had lower osteogenic potential compared with BMDSCs [32]. Liu et al. proved that recruitment of different late differentiation factors affected BMDSCs which differentiated more successfully into bone and cartilage, whereas ADSCs differentiated preferably into adipocytes [33]. Similarly, Shafiee et al. demonstrated that during osteogenic differentiation, BMDSCs had higher ALP activity and mineralization capacity than ADSCs. Although ADSCs produced higher amounts of Col I, osteonectin (ON) and bone morphogenic protein-2 (BMP-2) in the undifferentiated state, these proteins were higher expressed in BMDSCs during osteogenic differentiation. Moreover, during induction of the differentiation process, BMDSCs showed higher levels of ALP, osteocalcin (OC), and Runt-related transcription factor 2 (Runx2), compared to ADSCs [34]. The superior osteogenic potential of BMDSCs compared to ADSCS was also proved by Vishnubalaji et al., who showed, using Real-Time PCR technique, that relative genes' expression for ALP, OC, and osteopontin (OP) was lower in ADSCs compared with BMDSCs [35].

Osteogenic differentiation potential of MSCs *in vivo*. To adequately confirm the osteogenic potential of the MSCs in the area of clinical applications, there is need to verify results obtained with *in vitro* studies by performing reliable *in vivo* experiments. There are many research papers describing studies on animal models in the available literature (Tab. 2). Hayashi et al. compared new bone formation in rats by subcutaneous implantation of hydroxyapatite biomaterials seeded with rat stem cells (ADSCs and BMDSCs). Six weeks after implantation, composites were harvested and subjected to micro-computed tomography (µCT) and histological analyses. The experiment demonstrated that composites seeded with BMDSCs to a greater extent promoted formation of new bone than composites seeded with ADSCs [36]. Niemeyer et al. presented a comparison of osteogenic potential of ovine BMDSCs and ADSCs which were cultured on mineralized collagen sponges. In addition, they evaluated the influence of platelet-rich plasma (PRP) on the osteogenic ability of ADSCs. Scaffolds seeded with the stem cells were implanted into the sheep tibia. Twenty-six weeks after implantation, a radiographic evaluation was performed which showed a superior new bone formation process within the scaffold seeded with BMDSCs, compared to the scaffold seeded with ADSCs. However, the ADSC-loaded scaffold applied in combination with PRP revealed a similar ability to new bone formation as the scaffold seeded with BMDSCs [37]. Wen et al. compared bone regeneration process within cranial defects of rats using BMDSCs and ADSCs cultured on collagen gel. They revealed, by means of histological and X-ray analysis, similar new bone formation process within collagen gel, regardless of the type of MSCs seeded (BMDSCs and ADSCs) [38]. Kang et al. used in their experiments BMDSCs or ADSCs combined with β-tricalcium

Table 2. Comparison of *in vivo* osteogenic ability between bone marrow-derived mesenchymal stem cells and adipose tissue-derived mesenchymal stem cells.

References	Osteogenic potential	Analytical method	Animal model and type of scaffold
Hayashi et al. [36]	BMDSC>ADSC	µCT histological analysis	rat (subcutaneous) hydroxyapatite
Niemeyer et al. [37]	BMDSC>ADSC BMDSC=ADSC+PRP	radiographic analysis histological analysis	sheep (tibial defect) collagen sponge
Wen et al. [38]	BMDSC=ADSC	X-ray histological analysis	rat (calvarial bone defect) collagen gel
Kang et al. [39]	BMDSC=ADSC	radiographic analysis histological analysis histomorphometric analysis	dog (radial bone defect) tricalcium phosphate
Stockmann et al. [40]	BMDSC=ADSC	microradiography histomorphometric analysis	pig (calvarial bone defect) bovine type I collagen
Brennan et al. [41]	BMDSC>ADSC	histological analysis histomorphometric analysis	nude mouse (subcutaneous) biphasic calcium phosphate
Fennema et al. [2]	BMDSC>ADSC	histological analysis	nude mouse (subcutaneous) calcium phosphate ceramic scaffolds and a platelet-rich plasma gel

phosphate materials, which were implanted into segmental bone defects in dogs for twenty weeks. Unlike the above-mentioned researchers, they reported similar osteogenic capacities of BMDSCs and ADSCs, indicating that ADSCs can potentially be used instead of BMDSCs for bone tissue engineering [39]. Similarly, Stockmann et al., who studied the regeneration of pig monocortical calvarial bone defect using collagen scaffolds seeded with stem cells, demonstrated that the new bone formation and the healing rate were not significantly different between BMDSCs and ADSCs [40].

Brennan et al. compared the osteogenic potential of human xenofree-expanded ADSCs and BMDSCs in a nude mouse model of ectopic bone formation. MSCs were seeded onto biphasic calcium phosphate biomaterials and subcutaneously implanted for eight weeks. The results showed that ADSCs failed to form ectopic bone, but revealed enhanced *in vivo* neovascularization compared with BMDSCs [41]. Fennema et al. investigated whether aggregation of BMDSCs, ADSCs, and SVF cells could improve ectopic bone formation. The ectopic bone formation was estimated after implantation of tissue engineered constructs (spheroids of MSCs combined with calcium phosphate ceramic scaffolds and a platelet rich plasma gel) in immunodeficient mice for six weeks. The following variants were implanted: constructs with ADSCs, constructs with BMDSCs, constructs with SVF cells (with and without rhBMP-2 – morphogenetic growth factors). *In vivo* study showed that ADSCs and SVF cells both formed ectopic bone in the absence of rhBMP-2. BMDSCs formed a new bone in the highest amount, followed by SVF + rhBMP-2, ADSCs and SVF. Moreover, ADSCs showed inferior spheroid formation compared to BMDSCs. Researchers discovered that aggregation of ADSCs induced a meaningful positive regulation of osteogenic markers' gene expression, such as ALP and Col I, in comparison to non-aggregated ASDCs. Aggregation can boost ectopic bone tissue formation by ADSCs, but is less effective than rhBMP-2 [42].

SUMMARY

This study presented the comparison of osteogenic potential between BMDSCs and ADSCs, based on available literature. Most of the *in vitro* research confirmed the inferior bone formation capacity of ADSCs; however, several reports describing long-term studies on osteogenic differentiation of BMDSCs and ADSCs using *in vivo* models, revealed more divergent opinions on this matter. Namely, a number of researchers considered the ADSCs as the potential substitute of BMDSCs for bone tissue engineering applications. Moreover, they indicated that the osteogenic potential of ADSCs, to some extent, may be enhanced by the combination of ADSC-loaded scaffold with PRP. The opportunity to use ADSCs as an alternative to BMDSCs for bone restoration is of great interest due to easy accessibility and the abundance of adipose tissue, high stem cells' isolation yield, and rapid rate of ADSC proliferation *in vitro*. Nevertheless, further studies are necessary to investigate the clinical applications of ADSCs. This can lead to the development of new cellular therapies that may be used in the clinical treatments of various bone defects.

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Porównanie zdolności różnicowania osteogennego między mezenchymalnymi komórkami macierzystymi ze szpiku kostnego a mezenchymalnymi komórkami macierzystymi z tkanki tłuszczowej

Streszczenie

Istotnym problemem klinicznym jest szybka rekonstrukcja dużych wad kostnych spowodowanych przez uraz, wycięcie guza, infekcje lub anomalię szkieletu. Autoprzeszczepy oraz alloprzeszczepy to jedne z najbardziej znanych podejść do odbudowy kości, posiadają jednak wiele ograniczeń. Inżynieria tkanki kostnej została uznana za alternatywne rozwiązanie dla odbudowy kości w przypadku, kiedy nie jest możliwe zastosowanie wszczepów naturalnych. Podstawowy model inżynierii tkankowej kości składa się z trzech elementów: rusztowania, czynników wzrostu oraz komórek macierzystych lub prekursorowych. Rola tych komórek polega na różnicowaniu ich w osteoblasty oraz tworzeniu macierzy pozakomórkowej kości. Mezenchymalne komórki macierzyste (MSCs) posiadają wymienione cechy, które czynią je obiecującym narzędziem do wspomagania odbudowy kości. MSCs są obecne w wielu tkankach, m.in. w szpiku kostnym i tkance tłuszczowej. W niniejszym artykule przedstawiamy podobieństwa i różnice pomiędzy mezenchymalnymi komórkami macierzystymi pochodzącymi ze szpiku kostnego (BMDSCs) a mezenchymalnymi komórkami macierzystymi pochodzącymi z tkanki tłuszczowej (ADSCs). Ponadto prezentujemy porównanie potencjału osteogennego tych komórek na podstawie dostępnego piśmiennictwa. Otrzymane zestawienie wykazało, że zarówno BMDSCs, jak i ADSCs posiadają zdolność osteogenną w warunkach *in vitro* oraz *in vivo*. Jednakże większość badań *in vitro* wskazała słabszy potencjał osteogenny ADSCs w porównaniu do BMDSCs. W przeciwieństwie do tego, badania *in vivo* ujawniły w środowisku naukowym więcej rozbieżnych opinii w tej kwestii. Mianowicie w niektórych pracach badawczych uznano komórki ADSCs za obiecującą alternatywę dla komórek BMDSCs stosowanych dotychczas w inżynierii tkankowej kości.

Słowa kluczowe

kościotworzenie, komórki zrębu, inżynieria tkankowa, tkanka kostna