World Journal of Stem Cells

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DOI: 10.4252/wjsc.v6.i3.288

World J Stem Cells 2014 July 26; 6(3): 288-295
ISSN 1948-0210 (online)

TOPIC HIGHLIGHT

WJSC 6th Anniversary Special Issues (2): Mesenchymal stem cells

Osteogenic potential: Comparison between bone marrow and adipose-derived mesenchymal stem cells

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Supported by Chang Gung Memorial Hospital, No. CMRPG381331-3, No. CMPRG381321-3 and No. CMRPG381311-3
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Received: October 26, 2013 Revised: January 17, 2014
Accepted: April 25, 2014
Published online: July 26, 2014

Abstract

Bone tissue engineering (BTE) is now a promising research issue to improve the drawbacks from traditional bone grafting procedure such as limited donor sources and possible complications. Stem cells are one of the major factors in BTE due to the capability of self renewal and multi-lineage differentiation. Unlike embryonic stem cells, which are more controversial in ethical problem, adult mesenchymal stem cells are considered to be a more appropriate cell source for BTE. Bone marrow mesenchymal stem cells (BMSCs) are the earliest-discovered and well-known stem cell source using in BTE. However, the low stem cell yield requiring long expansion time *in vitro*, pain and possible morbidities during bone marrow aspiration and poor proliferation and osteogenic ability at old age impede its' clinical application. Afterwards, a new stem cell source coming from adipose tissue, so-called adipose-derived stem cells (ASCs), is found to be more suitable in clinical application because of high stem cells yield from lipoaspirates, faster cell proliferation and less discomfort and morbidities during harvesting procedure. However, the osteogenic capacity of ASCs is now still debated because most papers described the inferior osteogenesis of ASCs than BMSCs. A better understanding of the osteogenic differences between ASCs and BMSCs is crucial for future selection of cells in clinical application for BTE. In this review, we describe the commonality and difference between BMSCs and ASCs by cell yield, cell surface markers and multiple-differentiation potential. Then we compare the osteogenic capacity in vitro and bone regeneration ability *in vivo* between BMSCs and ASCs based on the literatures which utilized both BMSCs and ASCs simultaneously in their articles. The outcome indicated both BMSCs and ASCs exhibited the osteogenic ability to a certain extent both *in-vitro* and *in-vivo*. However, most *in-vitro* study papers verified the inferior osteogenesis of ASCs; conversely, *in-vivo* research reviews revealed more controversies in this issue. We expect the new researchers can have a quick understanding of the progress in this filed and design a more comprehensive research based on this review.

Key words: Bone marrow mesenchymal stem cell; Adipose-derived stem cell; Osteogenesis

Core tip: Both bone marrow stem cells (BMSC) and adipose-derived stem cells (ASC) have been reported to have the osteogenic capacity *in vitro* and *in vivo*. ASCs possess some attractive characters for clinical application compared to BMSCs, such as abundant stem cells from lipoaspirates, faster growth and less discomfort and morbidity during surgery. Nevertheless, the arising question is that "Is the osteogenic capacity of ASCs the same or far better than BMSCs?". The purpose of this review paper is to compare the osteogenic capacity between BMSCs and ASCs based on the literatures

which using both BMSCs and ASCs simultaneously in their articles.

Liao HT, Chen CT. Osteogenic potential: Comparison between bone marrow and adipose-derived mesenchymal stem cells. *World J Stem Cells* 2014; 6(3): 288-295 Available from: URL: http://www.wjgnet.com/1948-0210/full/v6/i3/288.htm DOI: http://dx.doi.org/10.4252/wjsc.v6.i3.288

INTRODUCTION

Bone defect reconstruction after tumor ablation, trauma injury and infection is still a challenge issue for orthopedic surgeon and cranio-facial surgeon. Traditionally, autogenous bone grafting is the first choice for bridging the bone defect. The merits are free of immunogenic problem and absolutely biocompatible because it comes from patient himself. The disadvantages are limited donor source, donor site morbidities and variable bone graft survival[1,2]. Xenograft and Allograft are alternative choices for the treatment. However, immunogenic reaction and inadequate bone regeneration due to incomplete resorption sometimes result in non-union or pathologic fracture, respectively. Recently, bone tissue engineering (BTE) becomes a promising issue to improve bone defect repair.

The basic concepts of BTE comprise of three components: scaffold, cytokines and cells. Scaffold provides support for cell attachment, void space for cell proliferation and guides the surrounding tissue to grow into. Usually the scaffold using in BTE should have three-dimensional porous structure with interconnected tunnel between pores and good mechanical strength to replace the loading bearing function before new bone regeneration. Cytokines can enhance cell proliferation, the homing of circulating or regional mesenchymal stem cells and differentiation of cells into osteoblast lineage. The function of cells in BTE is to be differentiated into osteoblasts which can produce the extracellular matrix, secret bone-specific proteins and cytokines to enhancing new bone formation, angiogenesis, *etc.*

Stem cells are the first choice in BTE due to the ability of selfrenewal and multi-lineage differentiation. Although the use of embryonic stem cells is attractive due to their pluripotency, their clinical applications are limited owing to ethic issues and difficulties in controlling single-lineage differentiation, which usually result in teratoma formation. Alternatively, scientists find out the mesenchymal stem cells from adult residing in wide range of tissue, which own the function to repair damage or diseased tissue. The adult stem cells possess the multipotent ability of differentiation at least into osteoblasts, chondrocytes and adipocytes. Bone marrow mesenchymal stromal/stem cells (BMSCs) are the most well-known and-characterized source of adult stem cells. It was first described by Friedenstein *et al*[3] that the stem cell could be isolated from bone marrow with the character of adherence to plastic surface and fibroblast-like appearance in culture. Since then, papers based on BMSCs were published in application of BTE both *in-vitro* and *in-vivo* study. The disadvantages of BMSCs are the low stem cell yield from bone marrow aspirates, painful procedure, potential complications derived from the procedure and poor mutlipotent ability after extensive passage or at aged people. Therefore, scientists are urged to search a better alternative cell source for BTE.

In 2001, Zuk *et al*[4] described a new mesenchymal stromal/stem cell isolated from adipose tissue after liposuction procedure. Briefly, the lipoaspirate tissue is digested with collagenase first, followed by centrifugation to obtain a cell pellet at the bottom of tube. The cell pellet is so-called stromal vascular fraction.(SVF) Actually, the SVF is a heterogeneous cell population of red blood cells, fibroblasts, endothelial cells, smooth muscle cells, pericytes and adipose tissue-derived stromal/stem cells (ASCs) which have the plastic-adherent character. After culturing SVF *in vitro* overtime, the cell population becomes homogenous to primarily plastic-adherent ASCs. The ASCs also display the ability of multilineage differentiation into adipocytes, osteoblasts, chondrocytes and myocytes. In addition, the liposuction procedure is simple, easy and repeatable with less discomfort and complications. The cell yield of ASCs from adipose tissue is higher than BMSCs from bone marrow aspirates. Hence, the ASCs have been suggested as a better cell sources in BTE than BMSCs. Since then, many researches demonstrated the osteogenic potential of ASCs both *in vitro* and *in vivo*.

Although the ASCs are considered to have the opportunity to replace the role of BMSCs in BTE, the arising question is that "Is the osteogenic capacity of ASCs the same or far better than BMSCs?". The issue is still controversial now because the majorities of papers describe the osteogenic potential or bone regeneration capacity only by either BMSCs or ASCs. A lot of variations in culturing and analytic methods, selection of scaffolds and animal models result in difficulties to make a convinced conclusion to prove the best stem cells for BTE by comparing these papers. The purpose of this review paper is first to describe the commonality and difference between BMSCs and ASCs, followed by comparing the osteogenic capacity *in vitro* and bone regeneration ability *in vivo* between BMSCs and ASCs based on the literature which utilized both BMSCs and ASCs simultaneously in their articles.

COMMONALITY AND DIFFERENCE OF BMSCS AND ASCS

Before the comparison of osteogenesis between BMSCs and ASCs, we should clarify whether both BMSCs and ASCs fit the criteria of mesenchymal stromal/stem cell and realize the commonality and differences between them. The Mesenchymal and Tissue Stem Cell committee

of the International Society for Cellular Therapy provided the minimal criteria for defining the human mesenchymal stem cells (MSCs): (1) Plastic-adherence when maintained under standard culture conditions; (2) Multilineage differentiation into osteogenic, adipogenic and chondrogenic cells; (3) Expressing stromal surface markers of CD73, CD90 and CD105; and (4) Not expressing hematopoietic lineage markers c-kit, CD14, CD11b, CD34, CD45, CD19, CD79-α and human leukocyte antigen-DR[5].

As we know, both MSCS are plastic-adherent under standard culture conditions with the fibroblastic, spindle-shape appearance. Both cells also are clonogenic, formed colonies in culture conditions. However, ASCs have been found that they can be maintained *in vitro* for extended periods with stable population doubling, higher proliferative capacity and low levels of senescence compared with BMSCs[6,7]. Furthermore, the osteogenic potential and cell proliferation of BMSCs seems to be reduced by age. In contrast, the decline in osteogenic potential of ASCs is not so prominent by aging[8-10]. Chen *et al*[9] compared the osteogenic differentiation of ASCs and BMSCs between young group (36.4 ± 11.8 years old) and elderly patients (71.4 ± 3.6 years old). They found the level of matrix mineralization of ADSCs from aged patient was comparable to that of ADSCs from young patient, whereas BMSCs from aged patient produced least amount of mineral deposits and had a lower expression level of osteogenic genes[9]. Wu *et al*[10] described the effect of age on human adipose stem cells by comparing the osteogenic potential among infant (< 1 year), adult (22-54 years) and old (> 55 years). They concluded the infant adipose-derived stem cells exhibited elongated spindle morphology and increased telomere length compared with older cells. Angiogenic factors were more highly expressed by infant cells, whereas osteogenic expression was similar among all ages[10]. Except the minimal criteria of trilineage differentiation into bone, cartilage, and adipose tissues *in vitro*, both stem cells are able to differentiate into other mesodermal tissues such as skeletal muscle, tendon, and myocardium[11,12]. Furthermore, both stem cells have also been demonstrated to cross germinal boundaries and differentiate into ectodermic origin and endodermic origin[11,12].

Although there is no single specific surface maker that is unique to stem cells, some known surface markers are found on them. Both stem cells have the stromal cell markers such as CD13, CD73 and CD90. Both stem cells have negative expression of hemopoietic markers CD11b and CD45. However, the CD34 is generally expressed on ASCs during the early phase of culture with decreasing after extensive passage[13]. In contrast, BMSCs do not express CD34. The alternative surface markers to distinguish ASCs from BMSCs are CD36 and CD106 because the ASC, in contrast to BMSC, is positive for CD36 and negative for CD106[13].

Another difference between BMSCs and ASCs is the cell yield from the bone marrow- and lipo-aspirates, respectively. The bone marrow aspirates yield 6×10^6 nucleated cells per mL in average, only 0.001% to 0.01% are stem cells[12]. In contrast, 2×10^6 cells can be isolated from 1 gm adipose tissue, and 10% are thought to be stem cells[14,15]. The feature makes the ASCs to be a good cell source for clinical application. For example, if we draw 100 mL bone marrow aspirates from an adult patient, in which there are only 6×10^3 to 6×10^4 stem cells. The cell population is usually insufficient for clinical applications. However, we can usually draw 1000-2000 cc lipoaspirates from patient without any discomfort or complication; there may be 2×10^8 to 4×10^8 stem cells, which are already enough for repairing a small bone defect. Namely, extensive *in-vitro* passaging to obtain adequate cell numbers usually is required in BMSCs, not in ASCs. The disadvantages of long-term *in-vitro* passaging are the possible contamination, time-consuming, labor-dependent and possible gene mutation during passaging.

IN-VITRO OSTEOGENESIS POTENTIAL BETWEEN HUMAN BMSCS AND ASCS

Although the ASCs possess so many better features than BMSCs for future clinical application in BTE, the determinant factor relies on "do ASCs have equal or far better osteogenic ability than BMSCs". If the answer is yes, then the ASCs can replace the role of BMSCs in BTE without any doubt. In this section, we search in the literatures to find the articles that comparing the osteogenic potential between BMSCs and ASCs *in vitro* simultaneously to avoid the bias from different culturing and analytic methods among different papers. Zuk *et al*[4] was first describing the isolation of ASCs from adipose tissue and executed some experiments to characterize their phenotype and multipotency. In their study, they found the alkaline phosphatase (AP) activity was significantly higher in osteo-induced human ASCs than in BMSCs at 3 wk induction. However, the matrix calcification was 35-fold and 68-fold increase in induction of ASCs and BMSCs over the 6 wk induction period, respectively. Although they performed the gene expression of specific osteogenic gene such as osteocalcin (OCN), core-binding factor subunit alpha-1 (Cbfα-1) also known as Runt-related transcription factor 2 (Runx Ⅱ), AP, osteonectin (ON), osteopontin (OPN), and bone morphogenic protein-2 (BMP-2) on both osteo-induced ASCs and BMSCs, no quantitative data (qPCR) was shown to compare the relative expression between two cells. No conclusions were made from their results to prove which cells had superior osteogenic potential. Afterwards, more and more papers began to compare the osteogenic potential by quantitative methods such as biochemical analysis (AP activity, calcium assay), qPCR of osteogenic gene expression and microarray (Table 1).

De Ugarte *et al*[16] in 2003 showed no significant difference of osteogenesis between human ASCs and BMSCs by AP activity and calcium content assay. The AP activity was 0.10 ± 0.12 and 0.08 ± 0.07 nmol p-nitrophenol produced/min per μg protein; and total calcium

Table 1 ***In-vitro*** **osteogenesis potential between human bone marrow mesenchymal stem cells and adipose-derived stem cells**

Ref.	Osteogenic medium	Culturing condition	Analytic methods	Outcome of osteogenic ability
Park *et al*[22]	0.1 mmol/L nonessential ammino acids, 50 μg/mL ascorbic acid-2-phosphate, 100 nmol/L dexamethasone and 10 mmol/L β-glycerolphosphate	Mechanical stimulation by dynamic hydraulic compression	AP, Alizarin red stian, qPCR, immunofluorescence	BMSC > ASC under mechanical stimulation
Vishnubalaji *et al*[20]	10 nmol/L calcitriol, 10 nmol/L β-glycerophosphate, 50 μg/mL L-ascorbic acid, 10 nmol/L dexamethasone	2-D static cuture	AP, Alizarin red, Von Kossa stain, Calcium concentration, qPCR	BMSC > ASC
De Ugarte *et al*[16]	50 μg/mL ascorbic acid-2-phosphate, 100 nmol/L dexamethasone and 10 mmol/L β-glycerolphosphate	2-D static culture	AP activity, calcium assay	BMSC = ASC
Im *et al*[17]	100 nmol/L dexamethasone, 50 μmol/L ascorbate-2- phosphate, 10 mmol/L dexamethasone β-glycerophosphate	2D static culture	AP activity, Von Kossa staining	BMSC > ASC
Shafiee *et al*[19]	10 nmol/L dexamethason, 0.2 mmol/L ascorbic acid-2-phosphate, 10 mmol/L β-glycerophosphate	2D cell culture	AP activity, Alizarin red staining, qPCR	BMSC > ASC
Liu *et al*[18]	0.1 μmol/L dexamethasone, 50 μmol/L ascorbic acid-2-phosphate and 10 mmol/L β-glycerophosphate	2D cell culture	Alizarin red stain and microarray	BMSC > ASC
Zhang *et al*[21]	10 mmol/L β-glycerophosphate, 10^{-8} mol/L dexamethasone, and 0.2 mmol/L ascorbic acid	2D cell culture 3D cell culture	Calcium assay, qPCR, SEM	BMSC > ASC

AP: Alkaline phosphatase; BMSC: Bone marrow mesenchymal stem cell; ASC: Adipose-derived stem cell; 2D: Two dimensional; SEM: Scanning electronic microscope.

was 33 ± 38 *vs* 42 ± 55 mmol/L Ca/μg per protein in osteo-induced ASCs and BMSCs, respectively. Im *et al*[17] demonstrated the ASCs may have an inferior potential for osteogenesis compared with BMSCs due to the much less AP staining and amount of matrix mineralization by Von Kossa staining in osteo-induced ASCs. In addition to alizarin red staining, Liu *et al*[18] in 2007 further used microarray to screen the different gene expressions in multilineage differentiation between BMSCs and ASCs, followed by qPCR assay to confirm the differences. The outcome in osteogenesis showed the BMSCs had more calcium depositions than ASCs under 14-d osteogenic induction; and the extracellular matrix genes [osteomodulin (*OMD*) and tissue inhibitor of metalloproteinase-4 (*TIMP4*)] were progressively increasing expressions in BMSCs, in contrast, no changes or decreasing in ASCs. Their conclusion suggested that BMSCs differentiate more efficiently into bone and cartilage, whereas ASCs differentiate better into adipocytes. Shafiee *et al*[19] demonstrated ASCs had lower AP activity and mineralization than BMSCs during osteogenic differentiation on days 7 and 14. Although ASCs expressed higher levels of collagen type Ⅰ, ON and BMP-2 in undifferentiated state, these were expressed higher in BMSCs during osteogenic differentiation. BMSCs also expressed higher levels of AP, OCN and Runx Ⅱ during induction. Their conclusions supported the BMSCs had the best capacity for osteogenic differentiation and hold promising potential for BTE. Vishnubalaji *et al*[20] also verified the superior osteogenic capacity of BMSCs than ASCs by cytochemical qualitative analysis, calcium mineralization and qPCR of AP, osteocalcin and osteopontin.

Generally speaking, the osteoblasts and osteocytes are living in a three-dimensional (3D) bone tissue environment, which is different from *in-vitro* 2D culture dish. Thus, the outcome of comparing the osteogenic ability between BMSC and ASC on bio-mimetic 3D scaffold seems to be more convincing than in 2D dish. Zhang *et al*[21] seeded both stem cells on the three-dimensional Polycaprolactone/tricalcium phosphate (PCL/TCP) scaffold and cultured them under osteo-induced medium to distinguish which cells had superior osteogenic capacity on 3D environment. They found human BMSC exhibited superior osteogenic potential by more calcium production per scaffold, higher expression of osteogenic gene (Runx Ⅱ, AP, ON, collagen type Ⅰ) compared to human ASC. In addition, SEM demonstrated trabecular-like networks with minerals (calcium/phosphate) deposits within the scaffold construct only on BMSC group, in contrast, none on ASC group.

Cells, especially the osteocytes, are apt to sense, adapt and respond to mechanical stimuli for maintaining the physiological and mechanical properties of mature bone. Mechanical stimuli also were known to regulate the osteogenesis of stem cells. Park *et al*[22] compared the osteogenesis between ASCs and BMSCs under the mechanical stimulus of dynamic hydraulic compression (1 Hz, 1 psi) by a micro cell chip. They found the dynamic hydraulic compression increased production of extracellular matrix [bone sialosprotein (BSP), OPN, collagen type Ⅰ]. In addition, the osteogenic specific genes (BSP, OPN and Runx Ⅱ) were also upregulated on both cells. However,

the AP and alizarin red staining showed significant increases in BMSCs, whereas no significant in ASCs under the mechanical stimulus. They concluded the BMSCs were more sensitive to mechanical stimulation and more effective towards osteogenic differentiation than ASCs under dynamic hydraulic compression. Taken together, most evidences support human BMSCs have superior osteogenic potential than human ASCs under static or dynamic compression culture.

IN-VITRO OSTEOGENESIS POTENTIAL BETWEEN ANIMAL BMSCS AND ASCS

Before the BTE can be translated from bench study to clinical application, pre-clinical animal studies are required. Hence, there are some papers discussing about the *in-vitro* osteogenic differentiation between ASCS and BMSCs in other species in order to set up the *in-vivo* animal model. Kang *et al*[23] found the osteogenesis ability of canine ASCs was better than BMSCS due to the higher AP activity and mineralization in osteo-induced ASCs. They concluded the canine ASC can potentially be used in place of BMSCs for clinical BTE. Chung *et al*[24] showed similar osteogenic potential between canine ASCs and BMSCs with the similar alizarin red stain and pattern of gene expression (Osterix, Runx Ⅱ, and OCN). They also found the hypoxia environment would inhibit the osteogenesis on both cells, which should be considered when using ASCs or BMSCs in clinically hypoxic environment (*e.g.*, fracture or infection). Vidal *et al*[25] showed the better osteogenesis of equine BMSCs than ASCs due to early formation of positive Alizarin red nodule and macroscopic AP staining in BMSC group. Toupadakis *et al*[26] detailed the osteogenic gene expression between osteo-induced equine BMSCs and ASCs and revealed that BMSCs had the highest overall expression of the osteogenic genes *Cbfα1*, *Osteorix*, and *OMD*. Hayashi *et al*[27] found the rat BMSCs appeared superior osteogenic ability than rat ASCs by mineralization, AP activity and osteocalcin secretion. Monaco *et al*[28] conducted an interesting functional analysis by transcriptomics which might indicate the differences in therapeutic application between osteogenic porcine BMSC and ASC. They found ASC appeared to be more myogenic and BMSC appeared to be more prone to migration, induce to bone and neurons prior differentiation. Both cells expressed in large amount of collagen formation, immune suppression and angiogenesis prior differentiation. During early osteogenic differentiation, ASC seemed to have higher lipid metabolism, migration, immunomodulation, while the BMSC had larger induction of inflammation, cell growth and steroid biosynthesis. During late osteogenic differentiation, the ASCs have better angiogenesis capacity than BMSCs. Although they did not make a conclusion of which cells have superior osteogenic ability, the gene expression characters prior or during differentiation gave the scientists a basis to select or design the suitable cells for their BTE component. For example, the angiogenesis is a crucial factor for successful bone tissue engineering. The early vascularization can enhance the survival of stem cells within the scaffolds. Although the ASCs and BMSCs both showed good angiogenesis prior differentiation, the ASCs were reported to exhibit higher angiogenic efficacy than BMSCs by either the ability of differentiation into endothelial cells or angiogenic factors secretion[29]. The endothelial cells induced by angiogenic factors secreted by MSCs could further produce BMP-2 to enhance the osteogenesis of MSCs[30]. In addition, the expression and activity of the early osteoblastic marker, AP, was found to be elevated when the MSCs were co-cultured with human umbilical vein endothelium cells[31]. In summary, the angiogenesis not only enhance the survival of stem cells but also the osteogenesis.

OSTEOGENESIS POTENTIAL BETWEEN BMSCS AND ASCS IN ANIMAL MODEL

Although both BMSCs and ASCs have been reported to have the capacity of orthotopic and ectopic bone formation *in vivo*, direct comparison between both cells are scarce in human study and few in animal study (Table 2). Hayashi *et al*[27] implanted the composite of rat stem cells/hydroxyappetite in the rat subcutaneous pocket. After 6 wk implantation, they found more new bone formation in BMSC groups than ASC groups by micro-CT and histological analysis. Niemeyer *et al*[32] created a critical size defect in sheep tibia as the animal model. They implanted the collagen sponge/BMSCs or ASCs into the defect and collagen sponge/ASCs mixed with platelet rich plasma (PRP) as another group. After 26 wk implantation, radiographic evaluation revealed a higher new bone formation in BMSC group than ASC group. However, surprisingly the PRP-plus ASC group showed similar bone formation as the BMSC group. Their conclusion addressed the inferior osteogenic ability of ASCs compared to BMSCs but it can partially be compensated by addition of PRP. Kang *et al*[23] used the canine radius defect as animal model. They implanted the β-tricalcium phosphate/BMSCs or ASCs into the defect. After 20 wk implantation, they found the similar healing rate and new bone formation area between BMSCs and ASCs. They considered the ASCs can replace the role of BMSC in future clinical bone reconstruction. Stockmann *et al*[33] studied the pig monocortical calvarial bone defect model. They filled the defect with a collagen scaffold seeded either by ASCs or BMSCs. They found the healing rate and new bone formation were not significantly different between ASCs and BMSCs group. Wen *et al*[34] compared the bone regeneration capacity on 5 mm cranial defect of SD rat between human ASCs and BMSCs which combined with collagen gel. They found no significant difference of new bone regeneration between two groups by X-ray and histology analysis. They also transfected the human mesenchymal stem cell with *GFP* gene by lentivirus to further confirm the cell sources in the regenerated bone tissue. The expression of GFP *via* immunohistochemistry

Table 2 Osteogenesis potential between bone marrow mesenchymal stem cells and adipose-derived stem cells in animal model

Ref.	Animal model	Scaffold	Analytic methods	Outcome of osteogenic ability
Hayashi *et al*[27]	Subcutaneous implantation in rat	Hydroxyapatite	Micro-CT	New bone volume BMSC (6.85 ± 1.89 mm^3) > ASC (0.05 ± 0.05 mm^3)
Niemeyer *et al*[32]	3-cm tibial defect in sheep	Collagen sponge	Radiographic and histologic analysis	BMSC > ASC BMSC = ASC + PRP No original data for bone volume
Kang *et al*[23]	1.5-cm radial bone defect in dog	Tricalcium phosphate	Radiographic, histological and histomorphometric analysis	New bone percentage: BMSC (33.56%) = ASC (33.9%)
Stockmann *et al*[33]	1-cm calvarial bone defect in pig	Bovine collagen type I	Microradiography, histomorphometric evaluation	BMSC = ASC No original data for bone volume
Wen *et al*[34]	5-mm calvarial defect in SD rat	Collagen gel	X-ray and histology	BMSC = ASC No original data for bone volume
Zhang *et al*[21]	Subcutaneous pocket of nude mice	PCL/TCP	Micro-CT	New bone volume: BMSC (16.6 ± 3.0 mm^3) > ASC (9.1 ± 1.1 mm^3)

BMSC: Bone marrow mesenchymal stem cell; ASC: Adipose-derived stem cell; PRP: Platelet rich plasma; PCL/TCP: Polycaprolactone/tricalcium phosphate; CT: Computed tomography.

addressed the implanted human mesenchymal stem cells participated in new bone formation on the defect. Zhang *et al*[21] implanted the composites of stem cells and PCL/TCP scaffold under the subcutaneous pocket of nude mice. They found the human BMSC had more ectopic bone regeneration than ASC by micro-computed tomography analysis and Von Kossa stain. Taken together, it is still controversial to conclude which cells had better osteogenic potential by animal study.

FUTURE DIRECTION AND SUMMARY

Although most papers support the inferior osteogenic capacity of ASCs than BMSCs, many issues remain to be elucidated in comparing the osteogenic potential between BMSCs and ASCs. For example, most papers only compare the two stem cells in the normal, healthy environment. However, in clinical situation there are many scenes that may be encountered in bone defect reconstruction such as fracture location and tissue condition around the bone defect such as non-union, osteomyelitis and osteoradionecrosis. In these circumstances, the surrounding tissue of the bone defect is relative non-vascularized with scarring tissue and inflammation or infection. In addition, the systemic illness or healthy conditions such as diabetes mellitus, heavy smoking, old age, osteoporosis, bone marrow disease, obesity and so on also influence the selection of stem cells for osteogenesis by clinical physicians.

Besides, most papers in the literature only use the same osteogenic medium containing dexamethasone, β-glycerophosphate and ascorbic acid to compare the osteogenic potential between BMSC and ASC. However, some chemical additives or growth factors such as 1,25-dihydroxyvitamin D3, BMP-2 and retinoic acid, tumor necrosis factor-α, and histone deacetylase inhibitor valproic acid were reported to be an osteogenic enhancer[35-37]. Mechanical stimulation and electric stimulation were proved to enhance bone regeneration[38-40]. Combining different strategies to enhance ASCs' osteogenic capacity to or above the level of BMSCs may be one of future directions to improve their future clinical application.

In summary, this review provides readers the current progress in comparison the osteogenesis between BMSCs and ASCs both *in vitro* and *in vivo* study. We expect the new researchers can have a quick understanding of the progress in this filed and design a more comprehensive research based on this review.

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