Stem Cells for Bone Regeneration: Current State and Future Directions

Alexandra O. Luby, MS, Kavitha Ranganathan, MD, Jeremy V. Lynn, BS, Noah S. Nelson, MPH, Alexis Donneys, MD, and Steven R. Buchman, MD

Abstract: Mesenchymal stem cells (MSCs) are capable of differentiating into osteoblasts, chondrocytes, and adipocytes, each of which is important for musculoskeletal tissue regeneration and repair. Reconstruction and healing of bony defects remains a major clinical challenge. Even as surgical practices advance, some severe cases of bone loss do not yield optimal recovery results. New techniques involving implantation of stem cells and tissue-engineered scaffolds are being developed to help improve bone and cartilage repair. The invasiveness and low yield of harvesting MSCs from the bone marrow (BMSCs) has led to the investigation of alternatives, including adipose-derived mesenchymal stem cells (ASCs). A review of the literature yielded several studies concerning the use of BMSCs and ASCs for the treatment of bone defects in both in vitro and in vivo models. Although both ASCs and BMSCs have demonstrated bone regenerative capabilities, BMSCs have outperformed ASCs in vitro. Despite these in vitro study findings, in vivo study results remain variable. Analysis of the literature seems to conclude there is no significant difference between bone regeneration using ASCs or BMSCs in vivo. Improved study design and standardization may enhance the application of these studies to patient care in the clinical setting.

Key Words: adipose-derived stem cell, ASC, BMSC, bone defect, bone marrow stem cell, bone regeneration, osteogenesis, stem cell

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Although studies involving embryonic stem cells have been hindered because of ethical and legal concerns,[1] adult stem cells, which originate from differentiated postnatal tissues, have become a burgeoning focus of many fields of research. While stromal cells have already differentiated into a specific cell lineage, stem cells are undifferentiated progenitor cells that are capable of self-renewal and multi-lineage differentiation.[2] Although it was previously thought that adult stem cells were only capable of differentiation into lineages that are characteristic of their tissue or organ of origin, recent studies have demonstrated that adult stem cells have more differentiation capabilities than previously thought and are involved in regeneration and repair during soft tissue injury, bone injury, wound healing, and aging.[3,4] Adult stem cells have also demonstrated a more robust safety profile from a tumorigenesis perspective than pluripotent stem cells. From a clinical perspective, adult stem cells are also easier to harvest and use, and eliminate the need for immunosuppressive therapy when used in an autologous fashion.[5] Given these important advantages, adult stem cell therapy has become an attractive avenue of study for their therapeutic applications.

Because bone is a dynamic tissue in its capacity for renewal and regeneration, reconstruction of bone defects remains a major clinical challenge. Importantly, however, fractures of the long bones and craniofacial region are a significant contributor to health care costs nationally. Upon analysis of the 2008 Nationwide Inpatient Sample, facial fractures represented more than 21,000 hospitalizations out of an estimated 39 million.[6] These procedures required $1.06 billion in hospitalization costs and resulted in 93,000 hospitalization days. Large bone defects may be caused by trauma, tumor removal, or infection.[7] Based on the size of the bony defect, these cases often require surgical intervention.[7] Unfortunately, however, even the most valiant reconstruction efforts often result in disability, donor site morbidity, and inadequate bone stock for implants. Patients are left to live with persistent functional deficits given the inadequacies of current treatments and surgical options. Given these limitations, stem cells represent an important option to consider and develop. New techniques involving implantation of stem cells and tissue-engineered scaffolds may help improve the regenerative potential of bone and cartilage defects to decrease the morbidity of both injury and surgical repair.[13]

The extent of bone loss determines the treatment needed. For small defects less than 4 to 6 cm in length, bone grafts are the current standard of treatment. Autogenous grafts are attractive because they are harvested from the individual patient, which reduces the potential of an immune reaction upon implantation. However, this technique has important disadvantages including donor site morbidity, limited supply, and questionable long term graft survival.[9] Additionally, bone grafts are unable to restore form and function to larger defects including those greater than 6 cm. In these settings, free tissue transfer is necessary for reconstruction. Allografts are another option for use in the repair of bony defects. Although these grafts limit donor site morbidity, they are extremely expensive and may be associated with an inflammatory response and risk of disease transmission upon implantation. Given the limitations of autologous and allogenic methods of tissue reconstruction, bone tissue engineering has emerged as a more ideal, potentially revolutionary, yet currently experimental, method of reconstruction.[10]

Mesenchymal stem cells (MSCs) are an important class of stem cells that are capable of differentiating into osteoblasts, chondrocytes, and adipocytes.[11] Each of these cell types are critically important for musculoskeletal tissue regeneration and repair.[3,7,11,12] As MSCs were originally isolated from bone marrow,[9] this

From the Department of Plastic Surgery, Craniofacial Research Laboratory, University of Michigan Health Systems, Ann Arbor, MI.

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Address correspondence and reprint requests to Steven R. Buchman, MD, Associate Professor of Plastic and Reconstructive Surgery, Department of Surgery, Michigan Medicine 1540 E. Hospital Drive, SPC 4219, Ann Arbor, MI 48109; E-mail: sbuchman@med.umich.edu

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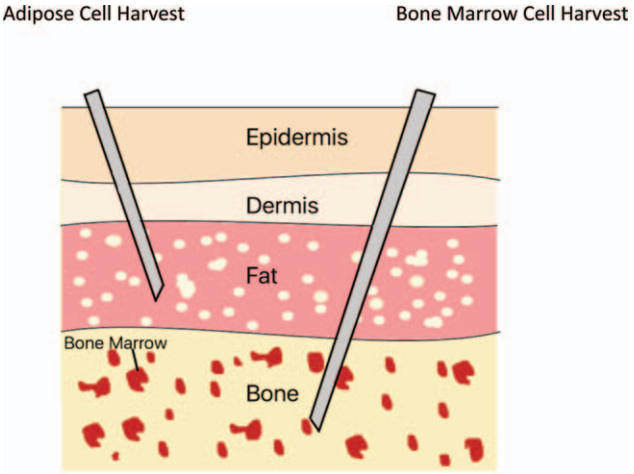

FIGURE 1. Relative ease of harvest for adipose-derived stem cells and bone marrow-derived stem cells.

particular site was thought to be the main source of MSCs.[11] In recent years, however, it has been established that MSCs can be isolated from many different types of adult and fetal tissues including adipose, dermis, periosteum, umbilical cord, blood, placenta, and amniotic and synovial fluid.[4] While all of these sources of MSCs are important to consider, adipose-derived stem cells (ASCs) are of particular relevance given their ease of harvest, minimal donor site morbidity, and relative abundance (Fig. 1). Although ASCs and BMSCs have been studied in great detail, there is no consensus regarding which of these cell types is better in animal or human studies focused on bone regeneration.[9]

BMSCs are commonly obtained from the iliac crest. Importantly, however, this is an invasive, painful procedure which often results in a low yield of MSCs that require extensive expansion in vitro before implantation in animal models. This leads to an additional limitation of BMSCs in that their proliferation and differentiation capabilities decline with increased culture passage and age.[14] Although bone marrow has been considered the main source of MSCs, these limitations have led to the investigation of alternatives, including ASCs.

ASCs, like BMSCs, have multilineage differentiation capabilities and promising therapeutic potential for their ability to repair damaged tissues after trauma. Unlike BMSCs, however, ASCs are plentiful in the body and can be isolated by minimally invasive methods including liposuction. Given the abundance of ASCs, there is much higher yield of ASCs during isolation. Zuk et al studied ASCs and found that one gram of adipose tissue yields approximately 500-fold greater number of cells than the number of MSCs isolated from bone marrow. A greater yield from harvest results in less time required for in vitro expansion, which is a valuable factor that can increase the translational application of this cell type.[15] Importantly, however, the efficacy of each of these cell types in comparison to one another remains unclear. Although many studies have been completed using in vitro models, the future of bone tissue engineering relies on the development of in vivo animal models that can be translated into controlled clinical trials in humans. Both ASCs and BMSCs have demonstrated the capacity for osteogenic differentiation,[19,31] but whether ASCs are "equivalent" to BMSCs remains unknown. Although most in vitro studies focused on defining osteogenic potential demonstrate the superiority of BMSCs over ASCs, in vivo studies produce conflicting results.

In this review, we will synthesize and define the variability present between studies focused on in vivo and in vitro models of bony defects that use either ASCs or BMSCs to regenerate bone. Although the advancements in our scientific knowledge of these methods have been in many ways, invaluable, the adoption of these tissue engineering techniques in the clinic has not been implemented in a commensurate fashion. By defining the current state of evidence, additional studies in the future may design more targeted methodologies and hypothesis to further this field. By comparing the applications of ASCs and BMSCs and identifying their potential effect on bone regeneration, we hope to identify gaps in our current knowledge, improve future study design, and define the current state of knowledge regarding stem cell use for bone regeneration.

Marker	Description
Alkaline Phosphatase (ALP)	Enzyme in the osteoblast membrane, associated with early osteogenesis and precedes new bone mineralization. One of the most common markers used to evaluate in vitro osteogenic differentiation.
Osterix	Transcription factor necessary to trigger the formation of mature osteoblasts from pre-osteoblasts.
Bone Sialoprotein (BSP)	Late stage osteogenic marker that indicates the progression into the final phases of osteogenic differentiation and the beginning of matrix mineralization.
Osteopontin	A extracellular structural protein and late stage osteogenic marker.
Osteocalcin (OC)	Highly specific marker of differentiation, secreted by late stage osteoblasts. Glycoprotein for bone, expression indicates the presence of mature osteoblasts.
RUNX-2	Early osteogenic marker in ASCs, late marker in BMSCs.
Collagen Type 1a (COL1A)	An early marker of osteogenic differentiation. The main constituent of organic bone matrix, representing 90% of the matrix.

FIGURE 2. Common osteogenic gene markers.

EFFECT OF STEM CELLS ON BONE REGENERATION: IN VITRO RESULTS

Although cell culture techniques and methods of analysis vary between studies, in vitro studies have consistently demonstrated that BMSCs have a greater osteogenic potential than ASCs. Upon addition of osteogenic differentiation medium (ODM), BMSCs consistently produced higher alkaline phosphate (ALP) enzymatic activity, more mineral, and greater expression of osteogenic gene markers. Commonly measured osteogenic markers are summarized in Figure 2. Importantly, however, although unable to differentiate to the same degree as BMSCs in vitro, ASCs are capable of undergoing some degree of osteogenic differentiation. When induced in vitro using ODM, ASCs consistently upregulate ALP activity, produce osteogenic proteins, and deposit mineralized extracellular matrix. Elkhenay et al[14] investigated the differentiation of bone marrow and adipose stem cells isolated from goats. Low-passage BMSCs (P2-P3) demonstrated the best osteogenic potential in vitro, when compared to low passage ASCs (P2-P3), high passage BMSCs (P12-P14), and high passage ASCs (P12-P14). Interestingly, although high-passage BMSCs and ASCs could be induced and differentiate into osteocytes, they did not produce mineralized calcium deposits. These results along with the poor staining when assessed with alizarin red indicate reduced differentiation potential of high passage MSCs in general. Thus, based on the results of this study, ASCs are optimal for osteogenic differentiation within 3 to 4 passages, whereas this capacity of BMSCs is preserved through passage 6. Additionally, low-passage BMSCs appear to be the best option for bone tissue engineering. Interestingly, although OPN and p38 proteins were highly expressed in BMSCs differentiating into osteocytes, bone morphogenic protein 7 (BMP-7) was more highly expressed in ASCs undergoing differentiation. This finding suggests that BMP-7 may facilitate osteogenic differentiation in ASCs but not in BMSCs.

The conclusion that BMSCs are more osteogenic than ASCs, however, is somewhat dependent on the time point studied and the

animal model used. Numerous studies have compared the osteogenic potential of ASCs and BMSCs harvested from canine models. Some studies have demonstrated that ASCs have greater osteogenic potential than BMSCs based on greater ALP activity, mineralization, and osteogenic gene expression of Osterix, RUNX2, and OCN.[18,19] In a more recent study, however, Alves et al[20] found that ASCs had higher ALP activity, greater collagen synthesis, and increased expression of osterix during the early phases of osteogenic differentiation (day 7). Later, however, ALP activity, collagen synthesis, and osterix expression were all higher in BMSCs by day 14. These results demonstrate that the time point studied and the nature of the genes evaluated can dramatically affect the conclusion of which cell type is more osteogenic.

Studies performed using ASCs and BMSCs harvested from human tissues have more consistently demonstrated that BMSCs are more osteogenic than ASCs. Im et al studied human ASCs and BMSCs in vitro using ALP and Von Kossa staining, and found that BMSCs had greater osteogenic potential than ASCs.[7] In another study, Wen et al[21] compared proliferation between human ASCs and BMSCs in vitro. In this 7-day proliferation study, it was found that ASCs and BMSCs had similar growth rates until day 3, after which time ASCs had a significantly higher proliferation than BMSCs. When evaluating osteogenic differentiation directly, however, BMSCs were found to have greater ALP staining and activity compared to ASCs. Other human studies have compared how ASCs and BMSCs are affected by various disease processes including osteoporosis and arthritis. One such study by Wyles et al[22] isolated ASCs and BMSCs from patients with osteonecrosis of the femoral head. ASCs were isolated from the periarticular adipose tissue, while BMSCs were harvested from the femoral bone marrow. This study evaluated cell proliferation between the 2 cell types during a period of 20 days. Similar to previous studies, ASCs proliferated more than BMSCs; cell number was higher at every time point for ASCs and was found to be 4-fold greater than BMSCs at day 20. Other metrics evaluated in the proliferation study, including generation time and cumulative population doubling, were also significantly higher in ASCs than BMSCs. This study also compared the osteogenic differentiation between the 2 stem cell lineages. After 14 days of osteogenic differentiation, the differentiation was measured using ALP quantification. Optical density was 2.25-fold greater in ASCs compared to BMSCs. Transcriptome profiling was also used in this study to evaluate expression profiles between ASCs and BMSCs, and significant differences were found between gene expression in the 2 lineages as well.

One of the biggest obstacles is translating in vitro studies into successful and significant in vivo studies. To help bridge this gap, some in vitro studies have incorporated more physiological factors into their models. These studies aim to integrate dynamic culture conditions into the experimental design. Although static cell culture is the foundation for cell studies, it is rudimentary and often fails to translate into significant in vivo findings. Although most in vitro studies use a 2-dimensional system, such models are not representative of the physiological 3-dimensional environment of bone cells in vivo. For this reason, studies have developed 3D cell culture methods to better incorporate the physiological environment of bone cells and evaluate the osteogenic potential between cells. Zhang et al[23] found BMSCs demonstrated greater osteogenic potential than ASCs when loaded into a 3D bio-mimetic scaffold made of polycaprolactone and tricalcium phosphate and cultured using ODM. BMSCs demonstrated higher calcium deposition and greater expression of osteogenic genes, specifically RUNX2, ALP, ON, and COL-1. This study also evaluated these 3D scaffolds using scanning electron microscopy, which showed networks of mineral deposits, resembling trabeculae of in vivo bone, within the BMSC scaffold; these networks were not present in ASC scaffolds.

Additionally, bones are under constant mechanical stress and stimulation. Therefore, native osteoblasts and their progenitor cells within bony networks are under continuous interstitial pressure and shear stress. Given this aspect of the natural bone microenvironment, studies have tried to examine the effect of mechanical stimulation and fluid flow on stem cells. Both BMSCs and ASCs are mechanosensitive and osteogenically responsive to fluid flow in a way that enhances their osteogenic differentiation potential.[10,24,25] Therefore, in vitro models have incorporated mechanical stimulation and shear stress into their systems to better mimic the physiological conditions these cells experience in vivo. Osteogenesis of human BMSCs and ASCs was evaluated under mechanical stimulation in a study by Park et al.[26] Dynamic hydraulic compression was shown to increase osteogenic matrix components, specifically BSP, OPN, and COL-1, in both ASCs and BMSCs. Osteogenic genes, including BSP, OPN, RUNX2, were also upregulated in both cell lines. Stains for ALP and calcium were significantly increased in BMSCs but not in ASCs. Taken together, these studies suggest that BMSCs are more sensitive to mechanical stimulation and more likely to undergo osteogenic differentiation under such conditions than ASCs.[10,24–27]

EFFECT OF STEM CELLS ON BONE REGENERATION: IN VIVO RESULTS

The development of robust in vivo models for bone tissue engineering is crucial for the translation of this regenerative therapy. The use of in vivo models allows for a more generalizable, translational approach to compare the efficacy of ASCs and BMSCs in their ability to heal bony defects. Furthermore, it allows for more detailed evaluations of the local niche at the site of injury, which can have important effects on cell-based therapies in general. Both ASCs and BMSCs have demonstrated the capacity for bone formation in vivo. Although many studies have compared the osteogenic potential of ASCs and BMSCs in vitro, very few have performed comparative analyses in vivo. Furthermore, even among those studies that evaluated one specific type of cell-based therapy, important limitations exist. Variability between models and lack of standardization in experimental design limit the ability to build on and translate the findings of these studies further. Although cell preparation, culture conditions, and timing of osteogenic induction can increase variability between in vitro studies, in vivo studies are confounded by variations in the size of bony defects, location of the defects, cell delivery method, and scaffold type. Although many studies attempt to increase generalizability by evaluating standard outcome measures including micro-CT, histology, bone mineral density, and biomechanical strength, important variations in experimental design must be taken into consideration.

Calvarial defect and long bone fracture models are most commonly used to compare the osteogenic potential of ASCs and BMSCs in vivo. For calvarial defect models, many studies have used bicortical, full-thickness critical size defect within the frontal or parietal bones to evaluate the regenerative potential of ASCs and BMSCs. Models evaluating bone regeneration within the long bones often use tibial or femoral defects.

Interestingly, most studies have not found significant differences between the extent of regeneration and defect closure induced by ASCs and BMSCs. Stockman et al harvested ASCs and BMSCs and implanted these 2 cell types into a porcine calvarial defect model.[28] In this study, ASCs or BMSCs were loaded onto collagen scaffolds and cultured in ODM to osteoinduce the cells before implantation. The scaffolds were surgically implanted into 1-mm calvarial defects. Using light microscopy, this study tracked matrix deposition and bone formation at the defect site. After 60 days, woven bone had filled the entire defect after implantation of ASCs

or BMSCs. Additionally, there was no difference in bone maturation based on whether ASCs or BMSCs were implanted. After 90 days, defects reinforced with stem cell-enriched scaffolds demonstrated complete bone regeneration in both groups according to micro-CT and histological analysis. This study concluded there was no significant difference in bone formation and healing rate between ASCs and BMSCs. Similarly, Kang et al compared bone healing using ASCs or BMSCs in a 1.5-cm radial bone defect in canines, and did not find a significant difference in bone regeneration between the 2 groups.[18]

Importantly, however, variability does exist in that some studies have demonstrated one cell type to be superior to the other. Niemeyer et al[29] studied critical size defects in the tibia of sheep. ASCs and BMSCs were loaded onto a collagen sponge and implanted into a 3-cm tibial defect. This study had a third experimental group wherein ASCs were seeded with platelet-rich plasma (PRP) and loaded into the collagen sponge. This study found superior bone regeneration in defects treated with BMSCs rather than ASCs alone. The defects treated with ASCs and PRP performed better than the ASCs alone and were found to have no significant difference from the bone regeneration by BMSCs. Similar results were found in a study by Xie et al,[30] which concluded that bone regeneration was greater for BMSCs than ASCs in a rabbit model.

The addition of growth factors to in vivo models is another active area of study.[28] Although growth factors are an integral part of osteogenesis, the addition of growth factors has failed to demonstrate an enhancement of bone formation in vivo.[27] After creating bicortical full-thickness 1.5-mm calvarial defects in a rabbit model, ASCs and BMSCs were implanted on scaffolds and seeded with and without bone morphogenic protein-2 (BMP-2), bone morphogenic protein-7 (BMP-7), or VEGF. Although the addition of BMP-2, BMP-7, or VEGF was expected to increase bone formation, there was no significant effect on bone formation both in vitro and in vivo.

In summary, significant variability in study design has limited the ability to draw consistent conclusions from in vivo models. Consequently, it still remains unclear whether ASCs or BMSCs are superior in their capacity to heal bony defects. Studies that use both in vivo and in vitro models and mirror bone-related pathologies in humans must be the focus of research in this field moving forward.

STEM CELLS AND BONE REGENERATION: CHALLENGES AND FUTURE DIRECTIONS

ASCs and BMSCs have the potential to completely transform the standard of clinical care and treatment of bone defects and fractures due to trauma or disease. Despite promising experimental results, further studies are required before translating such results into clinical practice. The main question that must be answered is whether or not these stem cells are actually incorporated into the bony regenerate to directly impact osteogenesis. The answer to this question is critical to understand the potential implications of stem cell treatment as it relates to bone regeneration during the process of Food and Drug Administration (FDA) approval.

There are several studies that have tried to address this issue. Initially, MSCs were thought to differentiate directly into cells of the osteoblast lineage along the defect site. Importantly, however, this hypothesis has been challenged, and there is also consideration of the importance of paracrine effects on tissues as a result of stem cell implantation. In this hypothesis, MSCs secrete biologically active molecules that exert beneficial effects on injured tissues by promoting angiogenesis and tissue regeneration, while inhibiting fibrosis, apoptosis, and inflammation.[3] A growing number of in vitro and in vivo studies have investigated this hypothesis and shown that many cell types respond to paracrine signaling from MSCs and affect many cellular responses like proliferation, migration, and gene expression. There is growing support for the paracrine mechanism based on the successful outcomes of a number of studies simply using stem cell conditioned medium to activate local stem cells for regenerative purposes.[32,33] If in fact the secreted factors are what is responsible for the regenerative capabilities of stem cells, future therapies may potentially be cell-free and solely secretome-based. This could circumvent the risks associated with stem cell based therapies, including immune rejection, accumulation of genomic alterations, senescence-induced genetic instability, and the risk involved with stem cell harvest. Understanding the mechanisms responsible for these effects improves our ability to translate the relationship between cell-mediated interactions, the microenvironment at the site of implantation, and the local wound niche into clinically meaningful advances in patient care.

Challenge	Method for Adressing Challenge	Benefits
Heterogeity Between Studies	Implementing a standard protocol for donor matched ASCs and BMSCs for comparison.	Avoids a number of confounding variables that are present in existing literature.
Clinical Translation	Further research into stem cell niches and use of dynamic culture conditions for in vitro trials.	Findings in vitro will be more directly comparable to in vivo stem cell activity.
FDA Regulation	Use of new FDA regulatory shortcuts. Designing studies that use minimally manipulated stem cells.	Expedited clinical translation.

FIGURE 3. Challenges to stem cell therapy advancement.

Although ASCs and BMSCs offer important advantages over current bone repair practices, there are a few challenges that must be addressed (Fig. 3). One current challenge is heterogeneity between studies (Fig. 4). Although MSCs can be isolated from different sources, this can create differences in their biological properties. This interpopulation heterogeneity of ASCs and BMSCs isolated from various donors and tissues is one of the main sources of variability within experimental results.[34] Variations in source, isolation, and culture technique, preparation, scaffold use, animal models, and analytic methods make it difficult to conclude which source of stem cells has greater osteogenic properties based on the literature. Standardization of these processes must be a focus of future studies. Some studies are beginning to address the issue of heterogeneity by using donor matched ASCs and BMSCs in their intrastudy comparisons. Confounding variables are unaccounted for in previous studies using different donors for ASCs and BMSCs, as age, general health, hormone levels, and even sex can affect outcomes. Studying ASCs and BMSCs harvested from the same individual can alleviate some of these confounding effects by minimizing inter-subject variability.[10] Despite these efforts, however, heterogeneity within the field of stem cell research continues to be a problem.

Translating these stem cell-based therapies from the laboratory benchtop into successful human models is another major challenge.

Factor	Examples
Cell Harvest	Donor source, age, gender, health, hormone levels
Cell Culture	Culture Pass Used
Osteogenic Differentiation	Day of Induction, Osteogenic media
Cell Delivery Method	Number of implanted cells, Scaffold type
Bony Defect	Size, Location (Long bone, Calvarial)
Methods of Analysis	Gene Expression, Imaging, Biomechanics, Histology, Mineral Density

FIGURE 4. Factors contributing to the heterogeneity of study design.

Although in vitro studies lay the foundation for these therapies, they are rudimentary and fail to address many challenging aspects encountered in vivo. Results from 2D static culture are not always representative of in vivo conditions and results, which the current literature well demonstrates. Therefore, one should be cautious to equate the osteogenic potential determined in vitro with superior bone regeneration in vivo, as excellent, long-lasting bone healing requires much more than the ability to form bone. In fact, it is possible that stimulation and maintenance of osteogenesis in vivo is more dependent on increasing other important factors, like vascularity, as existing approaches to bone healing have demonstrated that the deposition of bone at the pathologic site does not guarantee healing. Bone healing, like wound healing, is a complex process that requires synchronous, step-wise events to render efficacious results. This represents an important consideration for future bone tissue engineering initiatives. Additionally, in vitro models neglect important physiological factors of the bone microenvironment that impact bone formation, including mechanical loading, shear stress, fluid flow, and blood supply. Stem cell niches are dynamic microenvironments that modulate stem cell activity and involvements in homeostasis and repair throughout an organism's lifespan. The stem cell niche hypothesis was first introduced in 1978 by Schofield. It allows for the investigation of the nature of the niche in delicate balance and how disruption of this balance can contribute to aging and disease. Studying specific elements of these niches will help the development of stem-cell based interventions and translation to clinical medicine.[35]

Regulation and oversight of the FDA is a large hurdle for the advancement of stem cell utilization for bone tissue engineering in humans. There are multiple tiers of regulation these therapies must progress through according to law. Once they are cleared from preclinical studies with an Investigational New Drug application, these products must undergo a multiphase pipeline approval process, proceeding to Phase 1 trials. FDA regulations and trials are grueling, and many products either face delays or unsuccessfully clear these proceedings. To address this major impediment to stem cell therapies and clinical translation, researchers are turning to the development of autologous, ''minimally manipulated'' or chose a ''homologous use'' way to minimize FDA oversight and the associated inertia to scientific discovery.[5] Despite the challenges posed by FDA regulation, adult stem cells are the focus of a growing number of clinical trials for the treatment of very diverse clinical issues. There are several ongoing clinical trials involving ASCs for the treatment of various disease states, including osteoarthritis, cartilage and soft tissue defects, craniofacial bone injuries, Crohn disease, and multiple sclerosis.[22] With the many hurdles and difficulties in establishing a clinical trial, perhaps the most difficult task for biomedical researchers has become translating innovative laboratory results into feasible clinical applications to advance patient care and outcomes. By identifying specific areas for improvement in this review, the translational potential for using ASCs and BMSCs to enhance bone regeneration may be studied using more focused, standardized approaches. In this manner, findings from the realm of the scientific bench can be implemented in routine clinical practice to enhance bone healing and tissue regeneration in patients for whom limited options currently exist.

SUMMARY AND CONCLUSIONS

Despite some challenges facing the field of stem cell therapy, the future of this field is bright. Understanding of the cellular and local interactions involved in the complex processes of bone regeneration is critical for the advancement of bone tissue engineering. The regenerative properties of stem cells are being exploited to answer a number of clinical problems in addition to bone regeneration, including cardiac health, stroke recovery, and kidney disease. ASCs and BMSCs in particular have come to the forefront in many studies focused on bone healing using stem cell regenerative therapies. Although both ASCs and BMSCs have demonstrated bone regenerative capabilities, BMSCs have outperformed ASCs in vitro. Despite these in vitro study findings, in vivo study results remain variable. Understanding and minimizing variations in future study designs will allow for greater generalizability of results, and the ultimate translation of these findings into the clinic.

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