Review

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Regenerative Medicine

Stem cells for osteodegenerative diseases: current studies and future outlook

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As the worldwide population grows and life expectancies continue to increase, degenerative diseases of the bones, muscles, and connective tissue are a growing problem for society. Current therapies for osteodegenerative disorders such as hormone replacement therapies, calcium/vitamin D supplements and oral bisphosphonates are often inadequate to stop degeneration and/or have serious negative side effects. Thus, there is an urgent need in the medical community for more effective and safer treatments. Stem cell therapies for osteodegenerative disorders have been rigorously explored over the last decade and are yielding some promising results in animal models and clinical trials. Although much work still needs to be done to ensure the safety and efficacy of these therapies, stem cells represent a new frontier of exciting possibilities for bone and cartilage regeneration.

Keywords: adult stem cells • embryonic stem cells • induced pluripotent stem cells • osteoporosis • regeneration

Background & current treatments

Bone and cartilage-related diseases affect millions of people annually and, once injured, these tissues do not regenerate themselves as other organs do [1]. Osteoporosis and osteoarthritis are the most prolific afflictions, affecting more than 200 million and 151 million people worldwide, respectively. Both disorders are more common in women, the elderly and the obese. Moreover, because low bone density is such a rapidly growing problem, the US Surgeon General predicts that by 2020, over half of all Americans will have weak bones and/or osteoarthritis [2]. These disorders present as a degeneration of bone mass or cartilage over time, often resulting from faulty interaction between osteoclasts, osteoblasts and chondrocytes, making for weak, brittle bones. They compromise overall quality of life and can lead to further complications during or after the healing process [3]. For example, due to slower healing time and decreased mobility, an elderly patient sustaining a bone fracture is four times more likely to die within 3 months than a patient with healthy bones [4]. Furthermore, patients who experience fractures resulting from these diseases (very commonly hip fractures) must undergo surgery, and the implants used can often become infected, leading to additional surgeries and secondary infections [5]. This highlights the need for both research that could help identify preventative measures against osteodegenerative disorders and the need for improved treatment of injuries resulting from the onset of these afflictions.

Current treatment options for osteodegenerative disorders are limited, and none give a definitive solution to the problem. One promising treatment used prior to 2002 was hormone replacement therapy, in which postmenopausal women given estrogen showed great improvement in bone density. However, in 2002, Isaksson *et al.* published a landmark study revealing a correlation of hormone replacement therapy with an increased incidence of breast cancer and heart disease [6]. Following the cessation of this treatment, options have been limited

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to calcium/vitamin D supplementation and the use of oral bisphosphonates, which may increase risk of esophageal cancer, although there are insufficient studies to confirm this at present [7,8]. The advent of tissue engineering from stem cells has begun to provide possible solutions and therapies for formerly devastating diseases and injuries in a variety of organs, and they have shown promise as a potential remedy for osteodegenerative afflictions.

Different types of stem cells & therapies

Stem cells are a promising tool for the field of regenerative medicine because of their abilities to self renew and differentiate into multiple lineages. There are several different sources of stem cells and each subset has unique properties.

Adult stem cells

Adult stem cells are classified as multipotent, meaning that although they can differentiate into a range of progenitors, their fate is locked into a particular subset of lineages and they cannot make cells outside of those lineages. These cells are found in different stromal niches throughout the body and have been isolated from bone marrow and peripheral blood [9,10], muscle [11], adipose tissue [12,13], synovium [14], and periosteum [15] of the mesoderm, intestine [16], endoderm and skin [17], deciduous teeth [18], and nerve tissue of the ectoderm [19,20]. Adult stem cell populations are thought to originate during embryonic development, localize to niches within the tissue and remain there in a dormant state until they are needed to replace cells from their downstream lineages in the body. When they are needed, cues from the surrounding environment will bias them to differentiate into the necessary lineage [20,21]. This ability of stem cells to differentiate into a diverse array of phenotypes depending on the surrounding environment makes them an attractive tool for physicians and researchers searching for new treatments for degenerative disorders. Because stem cells can be harvested from a person's own body, cultured to adopt the preferred lineage and injected back into the injured area, they do not carry the risks of graft-versus-host disease or tissue rejection that are of concern with other transplant type technologies. Although various populations of adult stem cells exist in each germline of the body, the most appropriate populations for treating osteogenic disorders are those of mesodermal lineage: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). The latter may also be derived from neural crest tissue.

The osteogenic disorder that adult stem cells have shown the best promise of treating thus far is osteoarthritis. Adult stem cell therapies for osteoarthritis have been thoroughly researched for nearly 20 years and, recently, several clinical trials have attempted to improve symptoms of osteoarthritis using HSCs or MSCs [22–25]. Both of these cell types are of mesodermal lineage, and HSCs can be derived from peripheral blood, bone marrow, the thymus and the placenta. They express CD34 but are negative for CD38 and lineage markers [26], and are capable of producing all cells of the blood and immune system. MSCs are found in muscle, adipose, synovial and periostial tissues, and express the markers CD105, CD90 and CD73, but not CD45, CD34, CD14, CD11b, CD79α, CD19 or HLA-DR surface markers; they adhere to plastic in culture and produce nonhematopoietic mesodermal tissues, such as bone, cartilage and adipose tissue [27]. Although originally the proliferative capacity and chondrogenic activity of MSCs from osteoarthritic patients were called into question [28], more recent studies have shown that MSCs from osteoarthritic patients show no significant differences from healthy MSCs with regard to proliferative capacity or chondrogenic activity [29–31]. In addition, injection of MSCs into animal models of osteoarthritis have slowed progression of the disease and prevented the occurrence of post-traumatic arthritis [32,33]. Recently, a clinical trial attempted using injections of autologous fat pad stem cells into the knees of osteoarthritic individuals showed promising results; the condition of the patients was significantly improved and no major side effects were reported [34,35]. These results indicate that MSCs could represent a promising treatment for osteoarthritic conditions, but further tests are needed to assess whether the nature of the osteoarthritic environment into which the cells will be injected will support their viability and differentiation before conclusions can be made about the appropriateness of this treatment for individual patients. Currently, there are 20 different clinical trials underway testing various aspects of stem cell therapies for osteoarthritis [36]; hopefully, valuable information can be gained from these and other future studies that will bring us one step closer to developing a safe and effective stem cell treatment for osteoarthritis.

One concern about using MSCs to treat osteoarthritis is the large correlation between obesity and osteoarthritic conditions. According to the Center for Disease Control, obesity greatly increases the risk of developing osteoarthritis, and two out of three obese individuals will develop an osteoarthritic condition during their life [37]. In addition, obese individuals with osteoarthritis are almost twice as likely as individuals of a healthy weight to develop end-stage disease within 20 years [38]. Taken together, these statistics

demonstrate that there is a huge need for better treatments to combat osteoarthritis in the obese. When MSCs from obese patients were compared with MSCs from non-obese patients, they showed decreased proliferation, premature senescence and increased cytokine expression [39]. In addition, the capacity to differentiate into chondrogenic, osteogenic and adipogenic pathways was impeded by increased levels of free fatty acids and dysregulation of the Wnt, Notch and Hedgehog signaling pathways [39,40]. These results suggest that treatment with autologous MSCs may not be well suited for obese individuals and that new and better therapies are needed to address the specific issues of this rapidly growing, high-risk population.

Another hurdle that must be overcome if MSCs are going to be used to treat osteoarthritis is the susceptibility of these cells to high levels of endogenous cytokines. Several studies have shown that the high levels of inflammatory cytokines present in the joints of osteoarthritic patients can impair the differentiation of MSCs and even after long periods of *in vitro* culture, chondrocytes differentiated from MSCs are susceptible to IL-1β damage after injection [40–42]. Although the MSCs themselves have the ability to differentiate normally, it appears that the inflamed niche plays a huge role in their lineage commitment and final fate. Thus, just as cells released from the body itself are not adequate to control the pathology and symptoms of osteoarthritis, injected stem cells may also suffer defects in efficacy because of the dysregulated nature of the osteoarthritic environment. In the future, it may be necessary to pair stem cell therapies with other treatments, such as anti-inflammatory medications, to help stabilize the inflammation in the injured area in order to obtain the best possible results from MSC therapy.

Along with osteoarthritis, adult stem cell therapies have also been suggested for osteoporosis. Although there are fewer studies on stem cell remedies for osteoporosis than osteoarthritis, strides are being made in recent years towards developing stem cell remedies for this disorder. HSCs differentiated into osteoblasts were shown to home to the bone marrow and improve bone deposition, mineral density and microarchitecture in mice [43], and when senescent mesenchymal progenitor cells were replaced with younger ones in aged mice, skeletal aging associated with osteoporosis was significantly reduced [44]. MSCs with a ligand attached that caused them to preferentially home to bone caused increased osteogenic differentiation, bone mass and trabecular bone formation in mouse models, suggesting that researchers are starting to be able to overcome the decreased ability of MSCs to make osteoblasts in older age [45]. In human clinical trials, patients suffering from idiopathic osteoporosis, who were treated with cord blood HSCs, showed increased levels of insulin-like growth factor 1, which has been shown to promote bone mineral density [46]. Although these results are encouraging, there has yet to be a human study performed that demonstrates improved bone density after adult stem cell treatment. In order to evaluate the potential of adult stem cells to treat osteoporosis, more studies confirming the positive results in rodent models and human studies testing the best cells to use and way to administer them must be performed. Research on adult stem cell therapies for osteoporosis is in its infancy, as few studies can be found addressing the topic before 2012, and this field shows great potential for knowledge expansion in the near future.

Pluripotent stem cells

While adult stem cells present great therapeutic promise given their patient- and tissue-specific nature, they do possess a few limitations. They are difficult to locate and isolate, and are not found in all tissues in the body [47]. Their rarity coupled with an inefficient *in vitro* expansion potential, especially when isolated from older donors, makes it difficult to use them in therapy, as large numbers of cells are required for transplantation [48,49]. Consequently, pluripotent stem cells may represent a better option for treating osteogenic disorders. Pluripotency describes the capability of the cells to both self-renew and differentiate into any type of cell from any of the three germ layers [50,51]. Because of these characteristics, pluripotent stem cells are of immense interest for use in therapeutics and regenerative medicine in a variety of illnesses, from severe degenerative disorders such as multiple sclerosis to full or partial organ regeneration. They express some classical markers that maintain their characteristic abilities, including Oct-4, a homeodomain transcription factor involved in the formation of the inner cell mass in the blastocyst, Nanog, a transcription factor necessary for maintaining pluripotency via upregulation of downstream factors, and Sox-2, a transcription factor thought to be involved in pluripotency via control of Oct-4 [52]. Research has shown that the absence of these factors results in differentiation, loss of the ability to self-renew and failure of the blastocyst to develop properly [53]. There are two types of pluripotent cells being used in research: induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs).

Induced pluripotent stem cells

iPSCs are a type of pluripotent stem cell artificially derived from somatic cells, typically fibroblasts, by

ectopically expressing a defined set of factors to induce expression of a specific set of genes (Figure 1). The ectopic expression of these factors is achieved using viral vectors, including retroviruses, although newer alternatives are shying away from viral integration because of its associated risk of cancer. This was first achieved by Shinya Yamanaka and Kazutoshi Takahashi in mouse cells in 2006 [54], and human cells in 2007 [55]. Each time their studies demonstrated that cells derived by these methods were capable of chimera formation, teratoma formation and *in vitro* differentiation into all germ layers, all required capabilities in order to be classified as pluripotent. Also, they expressed characteristic endogenous factors of pluripotent cells, including Oct-4, Sox-2 and Nanog.

As previously stated, there are a variety of newer alternatives being tested to generate iPSCs that aim to make this therapy safer and more cost effective. For example, to combat the issue of random genomic integration of the factors into the genome, scientists are looking to use small molecules to mimic the effect of overexpressing the compounds [56,57]. Furthermore, as the use of retroviruses has been associated with increased tumorigenesis, researchers are looking into using alternative vectors such as adenoviruses [58] and plasmids such as PiggyBac and Sleeping Beauty [59,60], or even drug-like chemicals and miRNAs that increase iPSCs programming at the molecular level [61,62]. These alternatives have greatly advanced the field of iPSCs and brought them closer to being an ideal candidate for stem cell therapeutics.

One of the main advantages of iPSCs is the lack of ethical concern, since their derivation does not result in the destruction of an embryo. Combined with the patient-specific aspect of iPSC-derived cell lines, many researchers have shifted their work toward understanding how to differentiate iPSCs into various cells types for therapeutic use, mainly in early-onset neurological and metabolic disorders [63]. However, iPSCs currently present copious shortcomings that have thus far prevented them from being an ideal candidate for routine medical usage. Elevated rates of mutation and prohibitively high costs, which are concerns with any stem cell-based therapy, are especially problematic with iPSCs and will be discussed in more detail later on. In addition, studies have shown that iPSCs maintain epigenetic memories from their somatic origin [64–66], which often dictate their behavior, including their propensity to develop into specific cell types [67,68]. This introduces a new level of complexity because scientists must determine which iPSCs will work best for their particular disease model before they can begin to carry out meaningful research. In an attempt to address this issue, studies have been performed using bone marrow- and adipose tissue-derived MSCs to create iPSCs [69], and these cells were able to differentiate into all three germ layers. Although promising, this study is quite preliminary and does not address whether the osteogenic potential of these iPSCs is any better than that of iPSCs derived from nonmesenchymal tissues. Moreover, studies have been conducted that have demonstrated that fibroblast-derived iPSCs are capable of differentiating into a mesenchymal-like state, and later into osteoblasts [70], but these studies fail to address whether the process is efficient enough to be useful for clinical purposes. Furthermore, recent studies showed that the propensity of an iPSC to differentiate into cartilage or bone varies with clones [71], further complicating the use of iPSCs as an effective way to treat bone disorders. Most of the studies involving iPSCs currently focus on ways to improve mesenchymal- or osteo-specifc output from iPSCs, including scaffold engineering [72] and lineage selection [73]. While there is a consensus that iPSCs are progressing toward therapeutic applications [74–76], studies involving the use of iPSCs to treat a specific osteodegenerative disease are rare, if not nonexistent at this point in time, and it is clear that much work is needed in this field before human trials can begin.

Embryonic stem cells

ESCs are pluripotent cells derived from the inner cell mass of a preimplantation blastocyst, which, *in vivo*, will give rise to the embryo proper. Since their discovery in 1981 [77,78], these cells have shown immense promise as a tool for disease treatment and tissue regeneration. One of the most appealing characteristics of ESCs is their undefined nature that allows researchers, under the correct conditions, to produce high yields of specific cell types, at the desired stage of maturity. The derivation of differentiation techniques for ESCs has allowed researchers to study their therapeutic potential in the research setting, some of which have progressed to clinical trials [36]. One of the more well-known human ESC clinical trials was the Geron Spinal Cord Injury Clinical trial, in which patients with recent spinal cord injuries were injected with stem cells in the hope that it would stimulate nerve growth and repair the injury [79]. The trial was stopped early due to funding and inconclusive preliminary results [80], and the FDA received much criticism in its process of approving such controversial clinical trials [81]. Subsequent human clinical trials are now focused on treating vision problems, such as macular degeneration [82] and myopia [83].

Beyond their future promise in the clinic, ESCs also serve as an ideal model for osteodegenerative

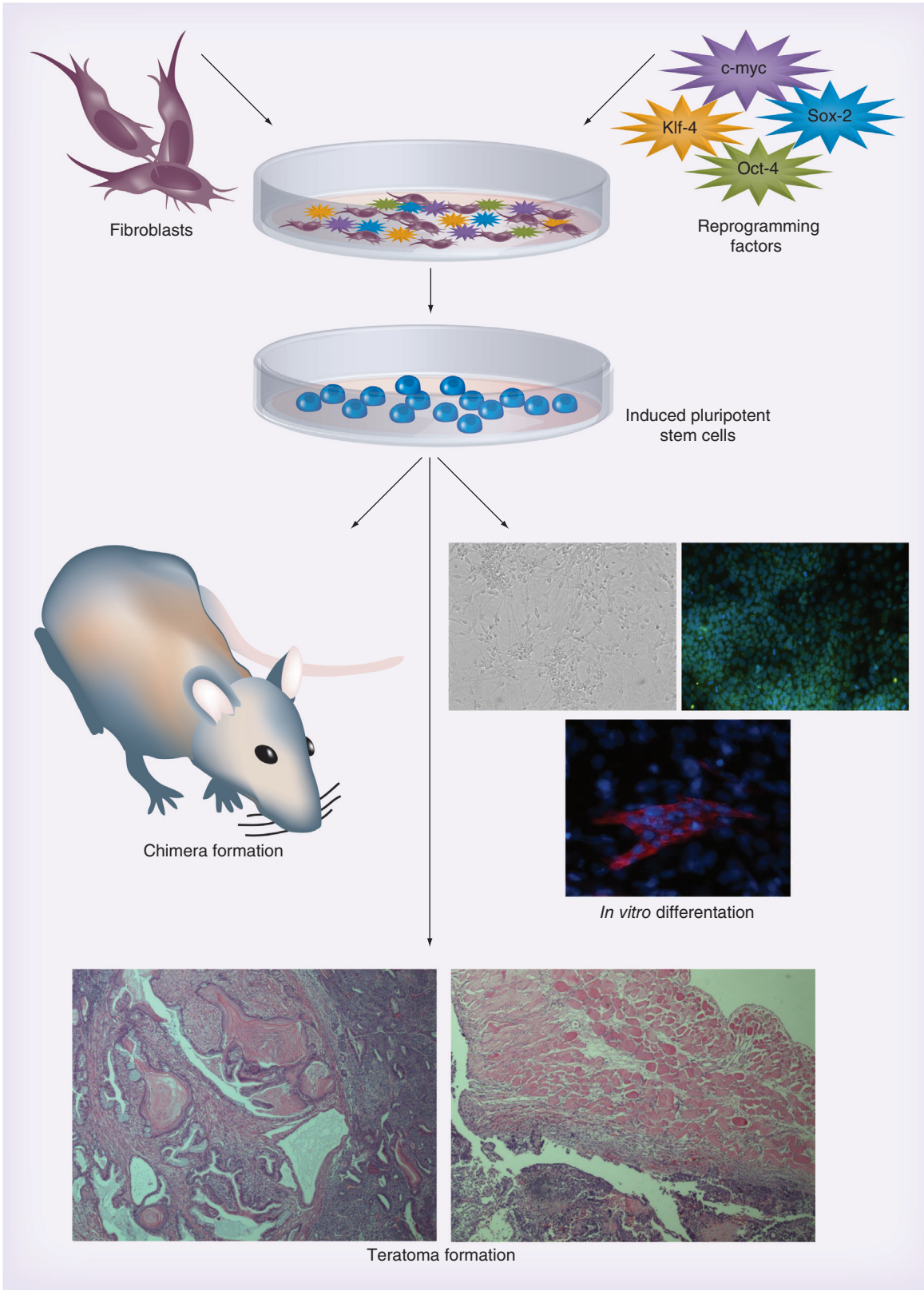

Figure 1. Schematic of induced pluripotent stem cell induction. Fibroblasts are harvested from the skin and reprogrammed by inducing expression of Oct-3/4, c-myc, Klf-4 and Sox-2 within the cells, typically by viral integration. Pluripotency of resulting cells is verified by standard assays, including their ability to make chimeric mice, form teratomas and differentiate *in vitro* into cells of all three germ layers.

research in the laboratory because defined protocols exist that allow researchers to differentiate each of the three cell types involved in these disorders so that scientists are able to easily study their interaction *in vitro* [84–86]. Many osteogenic disorders result in decreased bone density resulting from the imbalance between bone resorption and formation, meaning that treating these disorders may require more than one type of cell. Osteoporosis, for example, results from a combination of excessive bone resorption and inadequate bone formation, impairing the ability of the bone to reach peak bone mass [87]. Similarly, osteoarthritis is characterized by a loss in articular cartilage in the joints, resulting from a molecular imbalance that causes chondrocyte degradation instead of cartilage differentiation [88]. ESCs give scientists the ability to study the molecular mechanisms of both osteoclasts, which resorb bone, and osteoblasts, which reform the bone, in one dish specified from a very early common precursor [89,90]. Understanding bone formation at the molecular level will allow scientists to characterize osteodegenerative diseases more specifically, which may open the door for better drug development to treat patients with the disease. It will also enhance the prevention of these afflictions by enabling researchers and doctors to collaborate in designing better screening processes and common markers to identify patients whose genetic makeup or lifestyle behaviors render them more susceptible to these diseases prior to their onset. If individuals with a predisposition for an osteogenic disorder can be identified early enough in life before onset of symptoms, it could be possible to design proactive therapies and dietary supplements to prevent them from ever developing an osteogenic disorder.

In addition to their use as a model, ESCs, like their adult stem cell counterparts, have the capacity to regenerate tissues. Because they are grown *in vitro* rather than developing in the body, ESCs must be cultured to obtain a desired progenitor state before they are useful as a regenerative agent. To address this concern, several research groups have focused on developing standard protocols for growing transplantation-quality cells in culture and efficiently differentiating them into a desired lineage. Specific differentiation of ESCs can be directed by manipulating culture conditions and the microenvironment to mimic conditions found during *in vivo* embryogenesis [91–93]. During *in vivo* embryogenesis, the cells of the inner cell mass initiate early differentiation into three primary germ layers, ectoderm, mesoderm and endoderm, through gastrulation [94], and the osteogenic lineage is derived from the mesoderm or mesenchymal cells of the ectodermal neural crest [95]. Differentiation of ESCs *in vitro* by removing the feeder cell layer or soluble differentiation-inhibiting agents that are typically added to undifferentiated ESCs and allowing the cells to aggregate on low-adhesion plates [96] or form embryoid bodies (EBs) [97] have become standard methods in most stem cell laboratories. More recently, several groups have identified specific factors, such as β-glycerophosphate, ascorbic acid, dexamethasone, retinoic acid and 1,25-hydroxy vitamin D3, that can be applied to preferentially induce *in vitro* osteogenic, chondrogenic or osteoclastic lineage differentiation from spontaneously derived cells within the EB [98–104]. Because pure cell populations are a necessary prerequisite to any study that would utilize ESC derivatives in human patients, studies such as these are a necessary first step to harnessing the power of ESCs for future clinical use.

Along with pure populations, large numbers of cells are also needed for clinical treatments. To meet this need, several research groups have focused on the enhancement of mesenchymal progenitors, either from the mesoderm or ectoderm, in order to obtain a greater number of osteoblasts per culture. This has been accomplished by coculture with hepatic cells or the use of conditioned medium from hepatic cells or hepatocarcinoma cell lines [105–107], as these cells are part of the visceral endoderm, which plays an important role in inducing mesoderm formation *in vivo* [94]. Further studies have drawn upon the knowledge that craniofacial bone is derived from the neural crest during development and investigated the propensity of neural crest stem cells to differentiate into bone [108], an advancement that could prove very useful in the treatment of calvarial defects and head trauma injuries. As the ability to culture large numbers of cells in a short period of time becomes a reality, ESCs are an increasingly viable option for tissue regeneration.

Because treatments for bone disorders must stabilize the injured area while allowing for regeneration of dead or damaged cells, a scaffolding mechanism is a necessary component of any viable treatment for a disorder such as osteoporosis. Several recent studies have attempted to develop viable scaffolds for implantation with ESCs. Expression of osteogenic markers such as alkaline phosphatase and osteocalcin were greatly enhanced in human ESC cultures on 3D polylactic co-glycolic acid scaffolds in comparison with the same cells cultured in a 2D environment [109]. Furthermore, self-assembling peptide structures made of commercially available peptides such as RAD16-I peptide or Peptide Hydrogel (BD Biosciences, CA, USA) were used to encapsulate ESC-derived EBs, and the entrapped cells within these hydrogels differentiated into osteoblast-like

cells [110]. Moreover, successful bone tissue formation by ESC-derived osteoblasts was achieved in studies involving the subcutaneous implantation into immunodeficient mice of BMP-inoculated 3D scaffolds composed of polylactic co-glycolic acid and hydroxyapatite as a delivery vehicle for generating bone-like tissue *in vivo* [111].

Although ESCs are currently far behind their adult stem cell counterparts with regard to usefulness in the clinic, huge strides have been made in the last decade toward making these cells a viable option for regenerative medicine. Considering that human ESC therapies were only conceived within the last two decades and that public funding for research using them has been restricted for considerable portions of their existence, the field has made remarkable progress in a short period of time. Publications utilizing ESCs for research have grown at an exponential rate over the last decade, and with so many people studying their possible clinical use, it is only a matter of time before ESC treatments for osteodegenerative and other degenerative disorders are successful in animal models and make their way into the clinic. Currently, ESC treatments for osteodegenerative disorders are in their infancy and, within the next few years, this field will experience tremendous growth and could possibly overtake adult stem cells as the best clinical option for treating patients. There are, however, large obstacles to widespread clinical use of ESCs that must be overcome, and these will be expanded upon below (Table 1).

Conclusion & future perspective

Although ESCs may, in the future, lead to new therapies for osteodegenerative disorders, there are still many issues to be worked out concerning these technologies. Ethical concerns over the origin of these cells must be appeased so that governments will be more open to providing research funds for ESC studies, and the public will need to have a more favorable opinion of these technologies. In the USA, the federal government currently regulates funding for research involving ESCs, with state legislatures also having another measure of control. Outside of the USA, countries vary widely in their acceptance of ESCs. The EU has no official stance on the issue, and European countries tend to take one of four positions: permissive, permissive with restrictions, restrictive or no position because of ambiguity in government rulings [112]. Likewise, Asian countries also differ considerably in their policies, with China having the most permissive stance in the world [113]. As society evolves and people live longer, it will become more important to examine moral beliefs that prohibit scientific advances leading to cures for degenerative conditions.

Culturing of ESCs must also become more cost effective as, presently, many of the sera and growth factors used in culture and differentiation are so expensive that cost prohibits use in the clinic [114]. In addition, because therapies of this nature are still considered experimental, most insurance companies do not cover the costs [115], meaning that, for the average patient, this kind of treatment is out of reach.

Table 1. Comparison of embryonic, induced pluripotent and adult stem cells.

	ESCs	iPSCs	Adult stem cells
Ethical concerns	High, generation of ESCs involves the destruction of an embryo	None, derived from reprogrammed adult tissues	None, derived from adult tissues
Therapeutic capacity	Promising, ESCs have the most potential in differentiating into cell types of all three germ layers	Promising, but limited. iPSCs tend to maintain a 'memory' from their original tissue and have a propensity to differentiate into cells of that lineage	Promising, but limited. Adult stem cells are limited throughout the body and are difficult to isolate and purify
Limitations	Teratoma formation, differentiation efficiency, possibility of immune rejection	Teratoma formation, differentiation efficiency, the use of c-myc to reprogram cells	Numbers of cells are limited, difficult to culture *ex vivo*, limited differentiation capacity, not all tissues have adult stem cells
Clinical trials	Just beginning	Not yet approved in the USA, approved abroad	Widespread

ESC: Embryonic stem cell; iPSC: Induced pluripotent stem cell.

Furthermore, many of these cells are still cultured in serum or matrices derived from nonhuman mammals, which presents another challenge because of the introduction of animal by-products into the human body that must be overcome before clinical use. In addition, new methods must be developed that will improve the purity of populations of cells derived from stem cells, so that patients can be assured that they are receiving only the cells they need and not undifferentiated cells that may lead to cancer later in life. In 2009, a boy treated for a neurodegenerative disorder with fetal stem cells developed tumors in his brain and spinal cord that were found to have originated from the transplanted cells [116]. Although the safety practices in the clinic where the treatment was performed have been called into question, this study highlights the potential dangers of stem cell therapies. Indeed, ESCs mutate at a very high rate [117,118], and unless these mutations can be controlled, the risk of cancer may outweigh the potential benefits of these cells in regenerative medicine. Whereas adult stem cells have been used to treat various disorders since 1959 [119], the potential value of ESCs was not realized until the 1980s and it is only within the last 15–20 years that stem cell therapies have been seriously considered as treatment options.

Because the field is so new and many characteristics of ESCs remain poorly understood, more preliminary studies in animal models addressing safety concerns are needed to perfect the science of stem cell differentiation before clinical use is truly feasible. These cells hold tremendous potential for treating osteodegenerative disorders, but foundational basic research leading to near-complete understanding of their characteristics and differentiation potential must be completed before moving into the clinical phase of research. The breadth of knowledge concerning stem cell properties and abilities is constantly increasing at a very high rate. Already, researchers are experimenting with completely animal-free culture conditions for stem cell expansion [120], a necessary prerequisite to widespread clinical use. These obstacles should be completely overcome in the near future. Within the next decade, it is completely feasible that scientists will have mapped the cellular and transcriptional pathways controlling the self-renewal and differentiation of these very special cells. Armed with this newfound knowledge, researchers will be able to carefully control the renewal function of stem cells so that they can be transplanted into patients without the concern of causing a tumor. In addition, studies will better define the optimal microenvironment for stem cell differentiation so that mesenchymal cells can be more robustly differentiated from pluripotent stem cells and patients can be pretreated with supplements that will ensure survival and proper integration of stem cells into the surrounding tissue. Finally, stem cell culture will become more refined so that mass production at low cost is possible, so that these treatments are accessible to all patients in need, and not just those who are extremely wealthy.

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Executive summary

Need for stem cell therapies

- Current therapies for osteodegenerative disorders, which are rapidly increasing in incidence as people live longer and become more obese, are inadequate and prone to devastating side effects; therefore, new treatments for these disorders are urgently needed. Stem cell therapies are an attractive option as a possible remedy for osteodegenerative disorders.

Adult stem cells

- Over the last decade, many promising advances have been made concerning adult stem cells for the treatment of osteogenic disorders, but the inflammatory microenvironment of niches in the most at-risk populations must be controlled if these remedies are to be used widely in the clinic.

Pluripotent stem cells

- Although induced pluripotent stem cell therapies are attractive because of their patient specificity and lack of ethical concern, these technologies are in their infancy and must be further developed in order to be realistic options for medical applications.

Embryonic stem cells

- Embryonic stem cells may, in the future, be the ideal treatment for osteogenic disorders, but problems related to tumor formation, animal contamination and high cost must be worked out before they will become common in the clinical setting.

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