Perspective

Therapeutic potential of stem cells in orthopedics

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Introduction

There are a myriad of musculoskeletal disease conditions and injuries that presently have limited therapeutic options and could benefit from developing technologies in regenerative medicine. The goal of regenerative medicine is to functionally repair tissues and organs using cell-based techniques, thereby avoiding the need for artificial replacement therapies. Within this field, stem cells hold great potential as a method to either stimulate repair through systemic/local delivery or grow new organ systems *de novo* through tissue engineering technologies. Despite rapid progress, significant challenges remain in the translation of these stem cell therapies for clinical applications.

The purpose of this review is to first provide a working definition of stem cells and discuss the hierarchal potential of different cell populations. The remainder of the review will offer a perspective on the current state of stem cell research. Together, this information should be encouraging, yet cautionary, toward the potential application of stem cell therapy in orthopedic surgery and traumatology.

What Makes a Cell a "Stem Cell"?

The phrase "stem cell" has become so commonly used and misused that the rigor behind its scientific meaning has, in many cases, been lost. For a cell to be a stem cell, by definition, it must have the capacity to differentiate into multiple types of cells and the cell must be able to self-renew. The ability of a stem cell to simultaneously maintain the stem cell pool and generate daughter cells that can terminally differentiate into numerous tissues describes the unique capability of stem cells to undergo asymmetric cell division. This contrasts with somatic cells that divide symmetrically to create two identical daughter cells with the same potential. When activated during fetal development or in disease/repair states, stem cells can also undergo symmetrical cell division and rapid proliferation, but they typically remain relatively quiescent.

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The Niche Defines Stem Cell Activity

The stem cell niche is an extracellular microenvironment in which the cell resides. The niche is an important regulator of the biochemical and physical signals that a stem cell receives, thereby impacting key aspects of activity, such as cell survival, proliferation and differentiation.[1-3] Tissue mechanics, composition/structure of the extracellular matrix, and cell–cell interactions are defining attributes of a specific stem cell niche. For example, tissues such as bone, cartilage, and muscle naturally have distinct moduli,[4] and stem cells will preferentially differentiate toward certain cell types depending on the mechanical properties and nanostructure of the extracellular environment.[5-8] Similarly, the affinity of a stem cell for certain niches defines its localization within the body, as well as its ability to mobilize and engraft. These niche requirements impact the therapeutic potential of the stem cell as they will not engraft or function properly outside of their niche. the extracellular niche may also contribute to disease states in which stem cell differentiation or inherent tissue repair mechanisms are altered.[3] Consequently, when designing artificial systems to promote tissue regeneration, it is critical to engineer a niche environment conducive to the desired tissue response.[9-11]

Not All Stem Cells are The Same!

Totipotent stem cells

Even after meeting the scientific requirements necessary to be classified as a "stem cell," there is a highly variable capacity for differentiation. The number and types of progeny cells that an individual stem cell can produce define its "potency." Totipotent stem cells are the most potent stem cell type, and can differentiate to form all of the embryonic and extraembryonic cells (such as the placenta) in an organism. Totipotent stem cells are generally obtained

at, or before, the morula stage (an early, preimplantation stage of an embryo representing the 2–32 cell stage of development).

Pluripotent stem cells

As the embryo continues to divide, stem cell potency becomes more restricted. At the blastocyst stage, the cells divide into two "pluripotent" stem cell populations: embryonic and extraembryonic. The word pluripotent comes from the Latin "plurimus" (very many) and "potentia" or (powered) and refers to the ability of these cells to differentiate into a diverse set of progeny. Embryonic stem cells (ESCs) are found in the inner cell mass of a blastocyst and can generate all of the cells of the embryo. The trophoectoderm of the blastocyst contains the extraembryonic (trophoblast) stem cells, which can populate the placenta.[12]

Ethical and political controversy over the origin and use of ESCs motivated researchers to engineer a system that would create functionally equivalent cell populations. In 2007, the laboratories of James Thomson[13] and Shinya Yamanaka[14] simultaneously published methods to create embryonic-like human stem cells from mature fibroblasts. Hailed as the "Nature Method of the Year" in 2009,[15-17] the formation of these so-called "induced pluripotent stem cells" (iPS) was achieved by transfecting non-pluripotent cells with characteristic sets of four genes that could infer pluripotency. The genes used to generate the original iPS cells were slightly different: Yamanaka used retroviral transfection to deliver Oct3/4, Sox2, Klf4, and c-Myc, while Thomas transfected Oct 4, Sox2, Nanog, and Lin28 using a lentiviral system. Subsequent work has sought to refine the mechanisms and efficiency with which iPS cells are made, enhance techniques to expand the cell population, and characterize their differentiation potential.[18]

Adult stem cells

Adult stem cells are part of a "multipotent" cell population that is maintained and accessible in stem cell niches. These cells typically only generate progenitor cells along a specific cell lineage, and are therefore significantly more restricted in potential than the pluripotent stem cells. Hematopoetic stem cells found in the bone marrow, epidermal stem cells found in the bulge of the hair follicle, and intestinal stem cells found in the intestinal villus crypt are examples of adult stem cells and their associated niches.[1,19]

Mesenchymal stem cells

Of the adult stem cells, mesenchymal stem cells (MSCs) are probably the most interesting for orthopedic applications because of their potential to differentiate to both bone and cartilage. This population of progenitor cells was first identified by Friedenstein *et al.* as a population of mononuclear, fibroblast-like tissue culture adherent cells capable of colony formation.[20,21] Subsequently, it has been repeatedly demonstrated that these cells are multipotent and the classic definition now includes a minimal ability to differentiate toward adipose, bone, and cartilage tissues *in vitro*.[22,23] Differentiation toward other skeletal or mesenchymal cell types including tendon/ligament,[24] muscle,[25] and stromal tissue[26] has been demonstrated, but not rigorously vetted. Similarly, the ability of MSCs to regenerate non-mesenchymal lineages, such as cardiac,[27] neuronal,[28] and skin[29] tissues, has been reported. However, more recent research on this phenomenon demonstrates that engraftment and direct differentiation of MSCs into these cell types is minimal, suggesting their effect is likely due to a stimulation of the innate repair responses within these tissues.[30-32]

MSCs have been isolated from a number of tissue sources including bone marrow,[33,34] adipose tissue,[35] periosteum,[36,37] and the synovial lining.[38,39] Interestingly, pericytes (also called adventitial reticular cells) appear to have the same defining characteristics as MSCs,[40] bringing into question whether the perivasculature is another MSC niche or if these cells represent some precursor population.[41,42] Presently, it is not clear whether MSCs from these different niches are identical or share the same differentiation potential.[43-45] Within any tissue, the population of MSCs is small and decreases with age. For example, the adherent population of cells represents at the most 1/10,000–1/2,000,000 of the initial mononuclear cells of bone marrow[46] and this population is heterogeneous. Consequently, the clinical application of MSCs will likely require *in vitro* expansion prior to therapeutic use. The capacity for *in vitro* expansion of MSCs offers a clear therapeutic advantage of these cells over both pluripotent stem cells, which are difficult to expand, and their fully differentiated counterparts, such as chondrocytes, which become phenotypically modulated when cultured in monolayer.[47-50]

Where are We Now and Where are We Going with Stem Cell Research?

Embryonic and induced pluripotent stem cells

The inherent potency and differentiation potential of the various stem cell populations define both the clinical utility and associated risk in therapeutic applications. For example, ESCs or the embryonic-like iPS cells have the potential to differentiate into all types of tissues, and therefore offer tremendous therapeutic promise. However, despite significant progress in this field, it remains highly difficult to achieve tight control over the lineage-specific differentiation of these cells.[51] The consequence of this problematic control has been demonstrated in experiments showing the formation of

teratomas following the injection of undifferentiated ESCs into the knee joint[52-54] and heart.[55]

The best current applications for ESCs/iPS likely remain in the realm of basic research.[56,57] Addressing the significant challenges associated with the *in vitro* culture, expansion, homogeneity, and maintenance of pluripotency are all essential to the future success of any clinical application. Current research efforts include a number of diverse approaches focused on optimizing the biochemical composition of the media or designing engineering controls to replicate the physical and/or structural microenvironment of the stem cell niche.[58-61] Significantly more research is needed in order to produce a more reliable set of guidelines to reproducibly direct differentiation toward a specific cell or tissue lineage. Culture with defining growth factors, such as transforming growth factor (TGF)-β and bone morphogenic protein (BMP), may help direct differentiation toward orthopedically relevant tissues, but this approach has still been shown to produce heterotypic tissues following differentiation.[62-64] More recently, the concept of utilizing a step-wise differentiation protocol, in which ESCs are first induced to MSCs, may enhance homogeneity and/or control over the resultant phenotype.[65-67]

One area of translational research that iPS cells specifically hold great potential is the ability to replicate diseased states *in vitro*. Since iPS cells can be generated from adult somatic cells, it is possible to establish iPS cells that reflect disease conditions where the underlying cause is either unknown or cannot be easily replicated *in vivo* or *in vitro*. Within orthopedics, a variety of genetic disease conditions, such as fibrodysplasia ossificans progressiva and fibrous dysplasia, could benefit from mechanistic studies with iPS cells.

Mesenchymal stem cells

Significantly more research has been conducted on the therapeutic potential of MSCs. One treatment option with these cells capitalizes on their ability to differentiate into bone and cartilage, using them for the repair of damaged or diseased tissues. A number of tissue engineering systems are being developed with a focus on treating articular cartilage[68-70] and segmental bone[71-73] defects. These systems generally combine stem cells and bioactive factors with a three-dimensional scaffold to support the development of a tissue-specific extracellular matrix. Significant challenges still exist in obtaining the appropriate biomechanical characteristics from the engineered tissue, facilitating integration of the graft and host and controlling the tissue-specific differentiation of stem cells *in vivo*. Translation of these potential therapies will require research move from the bench into clinically relevant animal models. This progression will be best accomplished through collaborations between basic scientists, engineers, and clinicians.

In addition to the capacity of MSCs for multipotent differentiation, they also function to create a supportive microenvironment in the bone marrow that facilitates survival and differentiation of hematopoietic stem cells.[74] Recently, this characteristic has been more generally appreciated as a stimulatory or "tropic" influence of MSCs on other cells.[31] Some research has been done to determine the secretory molecules produced by MSCs, identifying measurable levels of TGF-β, stem cell factor (SCF), insulin-like growth factor (IGF), epidermal growth factor (EGF), and granulocyte and macrophage colony stimulating factors (G/M-CSF).[75,76] Current evidence suggests that these paracrine trophic effects, rather than MSC engraftment/differentiation,[31,32,77-79] are responsible for observed repairs following MSC therapy in disease conditions such as stroke,[80,81] osteogenesis imperfecta,[82] and myocardial infarction.[30]

Therapeutically, MSCs also appear to be immunoprivileged and immunosuppressive. MSCs do not display major histocompatibility complex (MHC) class II cell surface markers, but only MHC class I markers without the co-stimulator molecules, indicating that they will not illicit an immune response during allogeneic use.[83] Additionally, MSCs secrete immunosuppressive and anti-inflammatory cytokines, such as interleukin-10,[84] nitric oxide[85] and prostaglandins,[86] that can prevent host versus graft rejection through the modulation of T-cells.[87,88] MSC regulation of T-cells appears to occur in an antigen independent manner[89] through the suppression of the primary and secondary T-cell responses by inhibiting cell proliferation.[75,90,91]

Conclusions

Despite significant progress in the field of stem cell biology and regenerative medicine, there are a number of outstanding issues that should be appropriately addressed prior to the generalized adoption of clinical therapies. For example, most basic studies are conducted in healthy systems, and it remains unclear how disease states, such as arthritis, would influence any applied regenerative therapy. More serious concerns related to the long-term safety and efficacy of any stem cell treatment must also be addressed. For these studies, the issues of donor-to-donor variation, immunogenicity, and tumorgenic capacity of both pluripotent and adult stem cell populations must be rigorously examined. Establishing delivery mechanisms (scaffold versus injection), dosage, and timing of stem cell therapies for maximum efficacy are also needed to promote clinical success.

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