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REVIEW

Cell therapy for disorders of bone

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Bone marrow transplantation (BMT) has changed the course of treatment for an array of diseases, including disorders of bone. Hematopoietic stem cells (HSC) within the marrow are known to be the precursors of osteoclastic bone cells, and trials of BMT in osteopetrosis, a disorder characterized by a deficiency of osteoclasts, have resulted in significant clinical improvement in patients. The origin of the other major bone cell, the osteoblast, remains uncertain, although studies have identified osteoprogenitor cells within the marrow, leading to further investigation of both mesenchymal stromal cells (MSC) and HSC as candidates for this role. A better understanding of the source of osteoblasts and normal bone metabolism is crucial to efforts to develop effective cell therapy for bone disorders characterized by deficient or abnormal osteoblast function. This review focuses on systemic and local cell therapy in the treatment of several genetic bone disorders and osteoporosis, an acquired disorder caused by abnormal bone metabolism, with the intent of presenting both the progress and challenges associated with this emerging form of therapy. Although the risks of systemic transplantation must be carefully considered, cell therapy for disorders of bone carries the potential for long-term and potentially curative benefits, justifying further intensive research on this important treatment option.

Keywords

Bone disease, cell therapy, stem cell.

Introduction

Bone marrow transplantation (BMT) is a well-accepted treatment modality for a variety of non-malignant disorders, including hematopoietic failure, autoimmune disease, osteopetrosis and metabolic disorders. The topic of this review, cell therapy for bone disorders, has been an active area of research, leading to clinical trials of BMT for several genetic and acquired disorders of bone. There is evidence of an osteoprogenitor in the bone marrow (BM) cell population and the knowledge base for the complex regulatory interactions between marrow stromal cells and bone cells is continually growing. The clinical improvements observed in some bone diseases, including osteopetrosis [1], osteogenesis imperfecta (OI) [2] and infantile hypophosphatasia (HPP) [3], have encouraged investigations into how BM stromal cells may lead to development of normal osteogenesis in recipients. Thus far, the treatment options for many disorders of bone metabolism have been supportive in nature, including mainly non-curative approaches associated with persistent morbidity.

Therapy with multipotent stem cells, which can self-renew and differentiate into a desired cell population *in vivo*, has the potential to cure or greatly improve the quality of life of patients with bone disorders. The well-known risks of systemic transplantation, such as graft-versus-host (GvH) reactions, must always be considered, but the possibility of long-term benefits should be the overriding impetus that drives research efforts forward. Advances have been made in both systemic and local forms of cell therapy for both genetic and acquired disorders of bone metabolism. Of particular interest are the genetic disorders of osteopetrosis, OI and infantile HPP, as recent work on these diseases is highly illustrative of both the progress and challenges associated with cell therapy in patients. Clinical and translational studies with BMT have demonstrated biochemical, biomechanical and functional effects in animal models and humans, while laboratory efforts are contributing to the identity of stem cells giving rise to the various bone cells.

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While it is generally accepted that osteoclasts are derived from the monocyte–macrophage lineage of hematopoietic stem cells (HSC) [4], the source of osteoblasts (the osteoprogenitor) has remained elusive. It is widely accepted that an osteoprogenitor may exist in the endosteum or periosteum of bone, but currently there is no compelling support for such a cell. Candidate cells in the BM include both mesenchymal stromal cells (MSC) and HSC. Here we summarize bone and BM biology; describe the MSC and HSC niches and the various marrow osteoprogenitor candidates; and update the clinical trials that illustrate both the successes and challenges in reconstituting normal bone metabolism in affected patients.

Bone and BM environment

Bone contributes to the structure, movement and protection of the body. It is a porous mineralized tissue with vascular and cellular connections throughout. Compact bone provides strength, whereas a smaller fraction of bone is trabecular, with less dense and more elastic qualities. Bone consists of collagen fibrils, mineral deposits, several non-collagenous proteins and various cells at different stages of development, including osteoblasts, osteocytes and osteoclasts. Collagen is particularly important for bone elasticity and matrix organization, allowing for mechanical integrity in the face of stress [5]. Osteoblasts synthesize extracellular matrix on bone-forming surfaces, becoming lining cells that protect bone from the extracellular fluid space. Osteocytes are mature differentiated osteoblasts that have become enveloped by bone and help support bone structure. Osteoclasts are of HSC origin and are multinucleated cells whose main function is resorption of bone. Although bone is a solid tissue, it is continually remodeled by the combined functions of osteoblasts and osteoclasts responding to endogenous and external factors [6].

The BM cavity is encased by a shell of bone and contains several different types of stromal cells, including fibroblasts, macrophages, endothelial cells, adipocytes and MSC as well as HSC, the precursors of all blood cell types [7]. MSC are believed to be the potential source of most marrow stromal cells [8,9] and do not appear to contribute to hematopoietic reconstitution [9,10] (Figure 1).

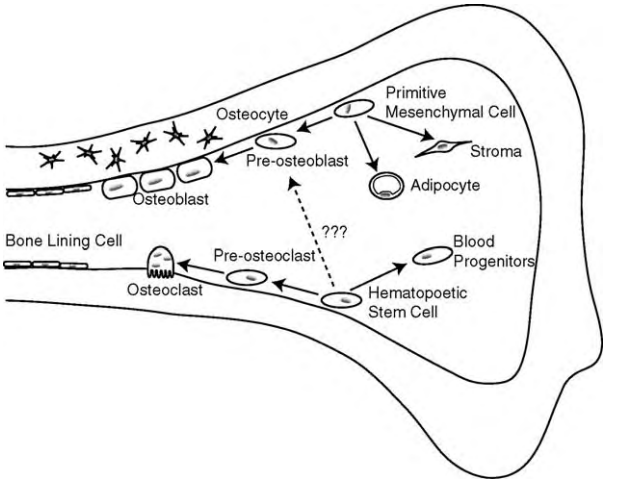

Figure 1. *Schematic representation of bone depicting mature bone cells and precursors. HSC within BM are the precursors for all blood progenitors. In addition, the osteoclast, a bone resorbing cell, is derived from the monocyte–macrophage lineage. Osteoblasts, marrow stromal cells and adipocytes are mesenchymal cells thought to be derived from a primitive mesenchymal cell, possibly a mesenchymal stem cell. The osteoblast, which synthesizes bone matrix, progresses in stages from pre-osteoblast to osteoblast to either bone lining cells or osteocytes. Some osteoblasts may also arise from the HSC under certain conditions.*

Bone and BM regulatory mechanisms

The HSC niche

Stem cell niches are sites in tissues where cellular quiescence and self-renewal are carefully regulated. The HSC niche supports stem cells that give rise to blood cell precursors. It consists of various stromal cell types, including osteoblasts, endothelial cells, fibroblasts and adipocytes, each of which affects stem cell development and proliferation in different ways via chemotactic factors, cell adhesion molecules and growth factors [11–13]. Many BM stromal cells may be derived from MSC, which can differentiate into chondrocytes, osteoblasts, fibroblasts and adipocytes under supportive *in vitro* growth conditions [8]. Despite this evidence, the *in vivo* characterization of MSC lineages remains an ongoing effort.

Osteoclasts arise from hematopoietic precursors, specifically sharing a progenitor with the monocyte–macrophage lineage. The development of osteoclasts from these precursors is affected by products of osteoblasts and BM stromal cells. Osteoblast-derived macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa B ligand (RANKL) play significant