Stem cells in treatment of delayed and non-union of fractures

Essay

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Abstract

The complexity of the bone healing process and the multiple possible causes of atrophic nonunion, on the macroscopic and microscopic levels, have ignited massive research to find an alternative solutions. One area of this research is the use of stem cells' applications.

The use of adult stem cells offers an alternative method by turning the cells into a''small factory'' that can supply considerable amounts of osteogenic proteins in vivo.

Key word

- Delayed and nonunion
- Stem cells

Aim of the work

The aim of this study is to clarify the role of stem cells utilization in treatment of delayed and nonunion of bone fracture and to simplify their mechanisms of action, application, advantages and disadvantages.

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- **OP**: Osteogenic proteins.
- **BMP**: Bone Morphogenetic Proteins.
- **MSCs:** mesenchymal stem cells.
- **FGF:** Fibroblast growth factor.
- **TGFb:** transforming growth factor beta.
- **ILGF 1:** InsulinLike Growth Factor 1.
- **DBM:** demineralized bone matrix.
- **ESC:** Embryonic stem cells.
- **Non-ESC:** nonembryonic stem cells.
- **HBMS cells:** Human Bone marrow Mesenchymal Stem cells.
- **rhBMP:** recombinant Bone Morphogenic Protein.
- **LMP:** LIM Mineralization Protein-1.

Introduction

Some fractures heal slowly or fail to heal. It is difficult to set the time when a given fracture should be united, but when healing progresses more slowly than average; the slow progress is referred to as delayed union. This fracture healing may be related to the severity of the injury, poor blood supply, the age and nutritional status of the patient. Failure of bone healing or nonunion results from an arrest of the healing process.(1)

For the successful treatment of nonunion, the addition of bone autograft at the fracture site is recommended to promote healing. A cancellous autograft facilitates bone formation, through its osteogenesis, osteoconduction and osteoinduction. It can be utilized to treat patients with nonunion, poor osteogenic potential, highly comminuted fractures and osteomyelitis. Hence, a cancellous autograft is still considered the 'gold standard'. However, there are several disadvantages for autograft. These include a high risk of fracture, infection and pain at the donor site In addition, the amount of cancellous bone is limited and many other options were used also.Lately studies have focused on bone tissue engineering to overcome these disadvantages.(2)

Adult stem cells have received intense scrutiny over the past few years due to surprising discoveries regarding unknown abilities to form multiple cell and tissue types, as well as the discovery of such cells in an increasing number of tissues. The term "adult stem cell" is somewhat of a misnomer; because the cells are present even in infants and similar cells exist in umbilical cord and placenta. More accurate terms have been proposed, such as tissue stem cells, somatic stem cells, or post-natal stem cells.(3)

Stem cells are basic human cells that have the potential to give rise to many different cell types in the body. They are simple or undifferentiated cells.Stem cells help to create new cells in existing healthy tissues and may help to repair tissues in those structures that are injured or damaged. They are the basis for the specific cell types that makes up each organ in the body.[4]

The signaling proteins that direct the stem cells into differentiation into a specific bone tissue are called Osteogenic proteins (OP), which are a class of natural growth factors called Bone Morphogenetic Proteins (BMP). The isolation of the genes coding these proteins from human DNA has identified a family of proteins,that induces bone formation by causing the differentiation of mesenchymal cells into chondroblasts and osteoblasts.[5]

Regional gene therapy usingmesenchymalstem cells(MSCs) as a vehicle for localized expression of osteoinductive proteins has shown promising results in animal models. Human bone marrow stromal cells transfected with BMP leads to more robust trabecular bone formation that have same histological characteristics as conventional autogenous bone healing.[6]

The standard procedure of aspiration of bone marrow from the posterior iliac blade ,uses a 16-gauge bone marrow aspiration needle and about 100-150 ml of autogenous MSCs are aspirated and are directly injected, percutaneously at fracture site.[7]

Studies have shown that autologous marrow grafting is a simple and effective method of providing cellular reactivation of osteogenesisyet, although

clinicalresults with bone morphogenetic proteins have been satisfactory,they have not been as impressive as those reported in animalstudies. So further understanding of the biology of fracture repairmay lead to improved treatment modalities.[8]

Chapter 1

Histology of bone

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Bone is a dynamic tissue that can rapidly adapt to the structural and metabolic demands placed upon it, achieved by an intricate balance between the formation and resorption of bone tissue. The most interesting aspect of bone is its capacity to remodel, adapt, and repair itself. At the gross level, each bone has distinct morphology comprising both cortical bone in the outer shell, and cancellous bone in epiphysis and metaphysical regions of long bones. At the microscopic level, two types of bone are identified: the disorganized hyper cellular woven bone and the highly organized hypo cellular lamellar bone. All bone tissue can be described by either of these two morphologies whether mature, growing, pathologic or healing. (9)

Normal bone is lamellar and can be cortical or cancellous. Immature bone and pathologic bone are woven and in comparison to lamellar bone,are more random with more osteocytes ،have increased turnover ، and are weaker and more flexible. Woven bone is a product of rapid bone formation ,which is characterized by an irregular, disorganized pattern of collagen orientation and osteocyte distribution. Cortical bone (compact bone)makes up 80 % of the skeleton and is composed of tightly packed osteons or haversian systems that are connected by haversian (or Volkmann's)canals.These canal contain arterioles,venules,capillaries ، nerves and possibly lymphatic channels .Interstitial lamellae lie between the osteons. (10)

Lamellar bone is stress oriented ؛woven bone is not stress oriented. The birefringent pattern of both circumferential lamellae and single osteons is believed to be produced by the altering of direction of collagen bundles from one layer to the next, therefore maximizing strength in a number of different planes. Although the collagen bundles within each of these lamellar plates are highly oriented, individual fibers will often traverse interlamellar spaces. Such a composite integration will increase both the individual osteons resistance to external loads and the effective strength of the bone structure fig (1-1). [10]

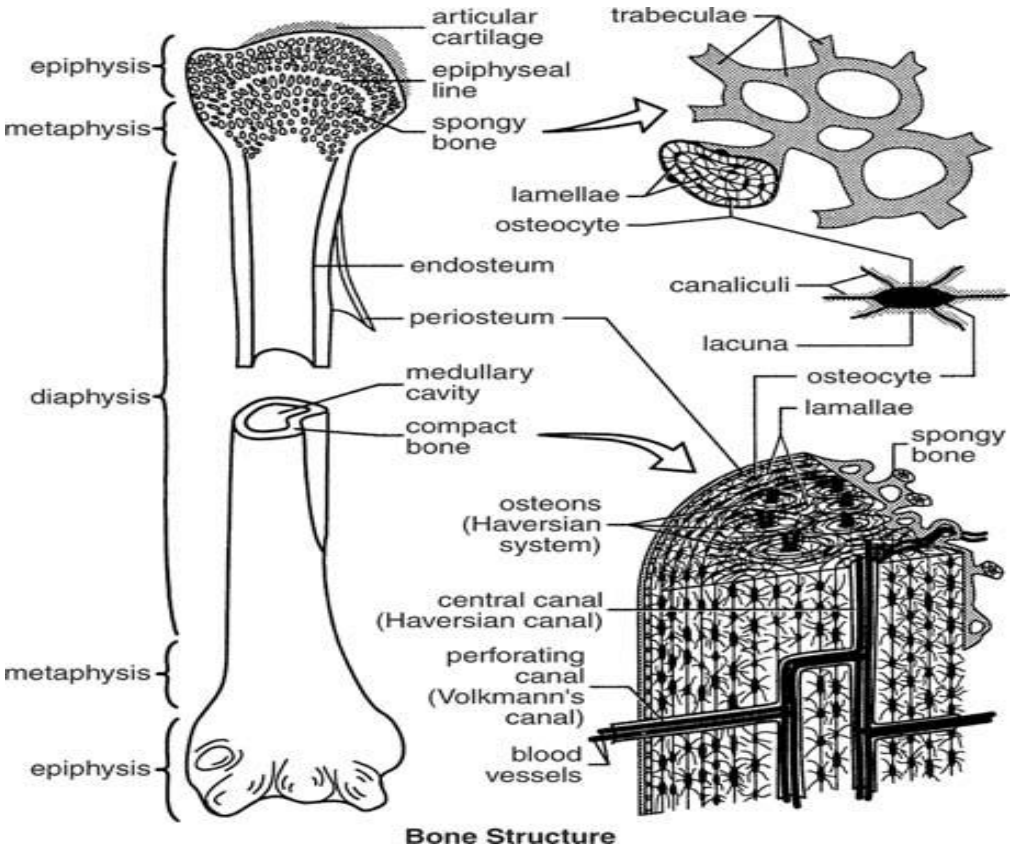

Fig (1-1): Main features of a long bone [10].

The Cells of Bone

Bone is a living tissue, thanks to the osteocytes buried within the intrinsic system of canaliculi and lacunae and the cell population lining

the periosteal and endosteal surface as well as the walls of the intracortical canals. The bone cells control and maintain the quality of bone matrix,participate in the regulation of the calcium level in the tissue fluids and are responsible for the repair of microdamage and fractures. Active cell population derived from two distinct cellular lineages. Multipotential primitive mesenchymal cells form the pool from which osteoblasts, bone lining cells and osteocytes arise. Osteoclasts originate in the hematopoietic monocyte-macrophage series. These cells despite separate origins are coupled to provide bone modeling and remodeling fracture healing and mineral homeostasis fig (1-2). [11]

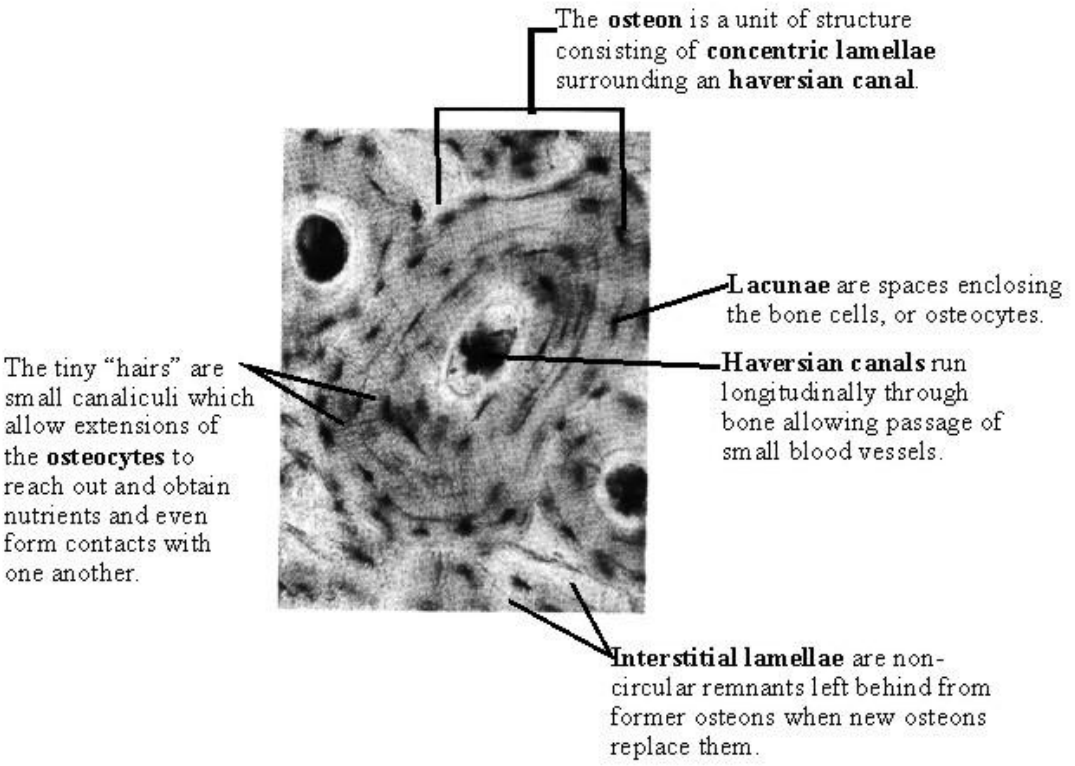

Fig (1-2): Cortical bone is composed of haversian systems (osteons). Each osteon has a central haversian canal and peripheral. [11]

Osteoblasts

The role of osteoblasts is to synthesize osteoid, the non-mineralized portion of the bone matrix. Differentiation of mesenchymal progenitor cells into preosteoblasts and osteoblasts marks the first stage of formation