Summary

Growth Hormone (GH) is a peptide hormone that stimulates growth and cell reproduction in humans and other animals. It is a 191-amino acid, single chain polypeptide hormone which is synthesized, stored, and secreted by the anterior pituitary gland, which is under control of hypothalamus.

Growth hormone directly activates cells expressing growth hormone receptors on their surface. These receptors bind growth hormone after being released from the Anterior Pituitary into the blood stream. The binding of growth hormone to the receptor activates the cell. While, The majority of growth hormone's effects are mediated by Insulin-like Growth Factor 1(IGF-1) which is produced by the liver when stimulated by growth hormone.

The physiological actions of GH involve multiple organs and physiological systems, GH exerts many metabolic effects that persist throughout life. GH is essentially an anabolic hormone, inducing positive nitrogen balance and protein synthesis in muscle . Muscle size is increased in GH-deficient individuals undergoing replacement therapy with recombinant human GH (rhGH) at all ages .

During the process of longitudinal bone growth, prechondrocytes in the germinal cell layer differentiate and thereafter undergo limited clonal expansion in individual chondrocyte columns in the growth plate. Subsequently, cells in the hypertrophic zone mature and degenerate and are eventually incorporated into bone , it has been demonstrated that GH stimulates growth of cartilage and other tissues by increasing the number of cells rather than by increasing cell size .

GH exerts direct actions on osteoblasts. Not only does GH stimulate the proliferation of osteoblasts, but, in some studies, it also stimulates differentiated functions of these cells. Thus, typical phenotypic functions of osteoblasts such as osteocalcin and type I collagen are stimulated by GH .

Considering the pharmacological GH dose levels administered to the adult tibial fracture population , the results demonstrate that in the overall group of open and closed tibial fractures, no significant effect of GH on time to healing was identified, whereas in closed tibial fractures comprising the vast majority of tibial fractures, GH accelerated healing significantly during the 12-month study period. The GH-induced enhancement of healing may be of potential benefit in patients with closed tibial fractures .

Growth factors (GFs): According to current knowledge, no comprehensive taxonomy has been developed for the factors that regulate cells. General terms such as hormone, cytokine, and growth factor are principally of historical interest. Specific terms, such as insulin-like growth factor, fibroblast growth factor, and platelet-derived growth factor, were derived from early descriptions of a factor's action or source, and the names given to these substances are best viewed not as meaningful descriptors of their function but rather as identifiers accepted by tradition. Some of the principal regulators of the skeleton are transforming growth factor-b (TGF-β), bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), the insulin-like growth factors (IGFs), plateletderived growth factor (PDGF) and nerve growth factors (NGF).

Transforming Growth Factors-β (TGFs-β) was originally characterized as a protein (secreted from a tumor cell line) that was capable of inducing a transformed phenotype in non-neoplastic cells in culture. This effect was reversible, as demonstrated by the reversion of the cells to a normal phenotype following removal of the TGF-β, the Transforming growth factor beta (TGFβ) signaling pathway is involved in many cellular processes in both the adult organism and the developing embryo including cell growth, cell

differentiation, apoptosis, cellular homeostasis and other cellular functions.

Growth factors in the transforming growth factor-β (TGF-β) superfamily, including bone morphogenetic proteins (BMPs), are the most intensively studied group of peptides involved in embryogenesis and in adult bone repair and are the most promising group of growth factors for use in the enhancement of bone repair, only a subset of BMPs has the unique property of inducing de novo bone formation, or osteoinduction, by themselves. BMP-2 through 7 and BMP-9 have been shown to have this property, meaning that these osteoinductive BMPs have the capacity to provide the primordial signal for the differentiation of mesenchymal stem cells into osteoblasts.

The fibroblast growth factors (FGFs) are a family of structurally related polypeptides that are characterized by their affinity for the glycosaminoglycan heparin-binding sites on cells and are known to play a critical role in angiogenesis and mesenchymal cell mitogenesis. The most abundant FGFs in normal adult tissue are acidic fibroblast growth factor (FGF-1 or a-FGF) and basic fibroblast growth factor (FGF-2 or ß-FGF). Both FGF-1 and FGF-2 promote growth and differentiation of a variety of cells, including epithelial cells, myocytes, osteoblasts, and chondrocytes.

The mitogenic effects of FGF-1 have been associated with chondrocyte proliferation, while FGF-2 is expressed by osteoblasts and is generally more potent than FGF-1.

The insulin-like growth factors (IGFs) are polypeptides with high sequence similarity to insulin. IGFs are part of a complex system that cells use to communicate with their physiologic environment, Insulin-like growth factor-I (IGF-I) is the primary protein involved in responses of cells to growth hormone (GH): that is, IGF-I is produced in response to GH and then induces subsequent cellular activities, particularly on bone growth. Insulin-like growth factor-II (IGF-II) is almost exclusively expressed in embryonic and neonatal tissues. Following birth, the level of detectable IGF-II protein falls significantly. For this reason IGF-II is thought to be a fetal growth factor.

Platelet-derived growth factor (PDGF) is one of the numerous growth factors, or proteins that regulate cell growth and division. It plays a role in embryonic development, cell proliferation, cell migration, and angiogenesis. and has also been linked to several diseases such as atherosclerosis, fibrosis and malignant diseases, PDGF is a required element in cellular division for fibroblast, a type of connective tissue cell. In essence, the PDGFs allow a cell to skip the G1 checkpoints in order to divide.

PDGF is also known to maintain proliferation of oligodendrocyte progenitor cells.

Nerve growth factor (NGF) is a small secreted protein which induces the differentiation and survival of particular target neurons (nerve cells). Nerve growth factor (NGF), the prototypical growth factor, is a protein secreted by a neuron's target.

NGF play an important role in promoting neuronal survival, differentiation, function, and repair. It is well established that they regulate axonal growth in sensory neurons, both regenerative growth in response to injury and collateral sprouting of uninjured nerve terminals . In diabetes, it is thought that a reduction in neurotrophin production and support contributes, in part, to the failure in axonal regeneration and pathogenesis of diabetic neuropathy . Levels of nerve growth factor (NGF) are reduced in peripheral target tissue in experimental and clinical diabetes , and retrograde axonal transport is also impaired .

There is a great deal of interest in the development of clinical applications for growth factors in the enhancement of bone repair, including (1) acceleration of fracture-healing (particularly in patients who are at high risk for nonunion), (2) treatment of established nonunions, (3) enhancement of primary spinal fusion,

(4) treatment of established pseudarthrosis of the spine, (5) as one component of a comprehensive tissue-engineering strategy that could include gene therapy to treat large bone-loss problems, and (6) articular cartilage repair.

Three biologically based strategies have shown promise as new technologies to enhance fracture repair: use of exogenous growth factors, mesenchymal stem cell therapy, and gene therapy.

Certain conditions must be considered when selecting an appropriate carrier or delivery system: (1) the ability of the system to deliver the growth factor at the appropriate time and in the proper dose, (2) the presence of a substratum that will enhance cell recruitment and attachment and will potentiate chemotaxis, (3) the presence of a void space to allow for cell migration and to promote angiogenesis, and (4) the ability of the delivery system to biodegrade without generating an immune or inflammatory response and without producing toxic waste products that would inhibit the repair process, a number of carrier and delivery systems, including type-I collagen, synthetic polymers, and hyaluronic acid gels, have been used to deliver recombinant proteins in experimental and clinical models. A variety of so-called bone-graft substitutes, including demineralized bone matrix, calcium phosphate-containing preparations (such as hydroxyapatite,

coralline hydroxyapatite, and α-BSM [Bone Substitute Material]), and Bioglass , are also potential carriers for recombinant proteins.

It was found that a mixture of osteoinductive growth factors leads to increased formation of new bone and soft tissue in a tendon-bone gap, resulting in a stronger attachment between the tendon and bone at six and twelve weeks after repair. Because clinical studies of rotator cuff repair have demonstrated a relatively high prevalence of failure of complete healing of rotator cuff repairs, the use of extracellular matrix scaffolds and growth factors to augment healing may provide a clinically important improvement in rotator cuff repair. The use of biologic agents to improve healing is likely to be especially valuable in patients with diminished biologic healing potential due to rotator cuff tendinosis and associated osteoporosis of the greater tuberosity.

Using a well-established model of fracture repair in the rat, we showed that a single percutaneous injection of rhBMP-2 accelerates healing. If these findings can be translated into clinical applications, the impact of such an advance could be substantial. Not only might this technology obviate the need for harvesting autologous bone in certain settings in which bone graft is now needed, but the availability and ease of administration of an

injectable bone-inductive compound could be used to shorten the time to healing and restore skeletal function in patients in whom normal fracture-healing is anticipated .