Growth Factors in Bone Regeneration

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Contents

List of abbreviations:

Abreviation	Definition
BTE	Bone tissue engineering
GF(s)	Growth factor(s)
HGH(s)	Human growth hormone(s)
BMP(s)	Bone morphogenic protein(s)
TGF(s)	Transforming growth factor(s)
IGF(s)	Insulin growth factors(s)
PDGF(s)	Platelet derived growth factor(s)
FGF(s)	Fibroblast growth factor(s)
TNF(s)	Tumor necrosis factor(s)
IL	Interleukin
VEGF(s)	Vascular endothelial growth factor(s)
ECM	Extracellular matrix
GAG	Glycosaminoglycan
MSC(s)	Mesenchymal stem cell(s)
rhBMP(s)	Recombinant human bone morphogenetic protein(s)
RANK-L	Receptor activator of nuclear factor kappa beta

Abstract

An upcoming strategy for treating bone abnormalities is BTE. Given that GFs are essential for tissue regeneration, there has been a lot of interest in the development of relevant delivery systems. However, it is suggested that GFs should not be studied independently but with the application of scaffolds. This is because scaffolds increase the effectiveness of GFs in the redevelopment of bone. Multiple GFs are activated throughout various stages of bone regeneration. GFs are incorporated into polymer carriers i.e., scaffolds. Drug delivery systems should also be recognized. They control where and when signalling molecules are released which are vital for the stimulation of GFs. This study focuses on GFs integrated into polymer-based scaffolds for efficient bone healing. The use of artificial drug delivery systems for controlling GFs will also be introduced.

Introduction

There are many advancements in the industry of prosthetics and bone grafting. These involve the use of composite materials in replacing the actual, damaged bone. Challenges with this include fit and comfort for the patient – each prosthetic must be manufactured specifically for the patient; the process is also very costly. The reactivity of the materials used must be considered as well, since there's always a potential risk of infection. Moreover, each patient is different, they may react differently with the materials. Generally, they're made of titanium and zinc alloys, as well as other polymers and ceramics [1]. While the concept is beneficial, it still lacks efficiency, as such BTE was introduced.

BTE is an upcoming field that aims to create new bone tissue to replace damaged bone. It aspires to overcome the limitations of common methods of treatment utilising a combination of biomaterials, cells and growth factors [2]. In this, bone repair is done using the patient's own tissue therefore eliminating risk of infections due to foreign cells. One of the greatest qualities of BTE is that it's able to create tissue that strongly resembles natural bone. Unfortunately, BTE is currently unavailable clinically due to the lack of knowledge in the field.

GFs play a major role in BTE. GFs are a type of glycoprotein that aid in cell growth, differentiation, inflammation and tissue repair [3]. They're produced by all animal cells. HGHs are secreted by the pituitary gland and aid in bone, muscle and organ growth. Some of the GFs involved in natural bone healing are BMPs, TGFs, IGFs, FGFs and PDGFs [4]. In BTE, GFs can stimulate the growth of new bone tissue. In addition, stem cells can differentiate into various types of bone and cartilage cells which supports the regeneration of bone. In this report, the importance of GFs for BTE will be looked at in much detail.

Bone Regeneration

There are a few main stages of bone regrowth. In the first few days, hematoma forms around the fracture site [5]. In this, BMPs, TNF-α and IRs are secreted which cause the accumulation of white blood cells that remove damaged tissue and initiate bone healing by releasing VEGF. Between weeks 1-2, VEGF stimulates

angiogenesis in which MSCs differentiate to form fibroblasts, chondroblasts and osteoblasts. Chondrogenesis begins where collagen-rich fibres are released at the fracture ends, surrounded by hyaline.

Endochondral ossification begins between weeks 2-4; this is the conversion of cartilage to bone. RANK-L stimulates further differentiation of chondroblasts, chondroclasts, osteoblasts, and osteoclasts. The newly formed blood vessels continue proliferation allowing further migration of MSCs. The result of this stage is a calcified immature bone.

Past 18 days, bone remodelling occurs. This involves the ongoing migration of osteoblasts and osteoclasts causing the remodelling of hard callus. The callus' centre is replaced by compact bone and its edges are replaced by lamellar bone. After several months of bone remodelling, the natural bone structure regenerates. This phase could take up to several years for repair.

Growth Factors

As mentioned, GFs are essential for bone restoration. A GF is defined as a biologically active molecule that aids in cell growth [6]. A further definition of GFs is a secreted molecule that promotes or inhibits mitosis thus affecting cellular division. Enzymes also play a role in this, regarding the transmission of growth signals. The GFs can be subcategorised as inflammatory, angiogenic and pro-osteogenic GFs [6].

The first response to bone fracture is inflammation. Inflammatory cells are recruited to the site and a blood clot forms. Some inflammatory cytokines involved in this are TNF-α (increases osteoclast activity), FGF-2 (activates FGF receptors to regulate cell proliferation and angiogenesis [7]), IL-1 and IL-6 (regulates differentiation and apoptosis in pre-osteoblasts [8]).

Ischemia is a lack of blood vessels. It is a big risk factor in bone healing. Blood vessels act as a pathway for osteoblasts and promote signalling for cell differentiation, they're also vital for endochondral processes in bone restoration. Angiogenesis is the process in which blood vessels form from pre-existing vascular network. It does this by providing nutritional support for new tissue. FGFs, VEGF, TGF-β, PDGF and BMPs are the main angiogenic GFs. In this, FGFs and VEGFs promote proliferation of osteoblast and endothelial cells. It should be noted that VEGF's delivery must be controlled as there're risks of vascular permeability.

In osteogenesis, cells differentiate into osteoblasts. They deposit ECM components namely GAG which interact with GFs for morphogenetic processes. Pro-osteogenic GFs include TGF-β, PDGF, FGF, IGF and BMPs. BMPs are the most researched GF for osteogenesis. They trigger osteogenic differentiation of osteoprogenitors resulting in the accumulation of MSCs to the injury site. The processes of endochondral and intramembranous ossification reform bone which is then remodelled by osteoclasts.

Effects and Uses of Growth Factors on Bone Tissue Engineering

Using GFs for BTE shouldn't be done alone but by integrating bone scaffolds along with it [9]. Bone scaffolds are 3D matrices that allow the attachment and growth of osteoinductive cells on their surface. They're typically biocompatible and biodegradable and allow for the formation of new bone. Their mechanical properties should be adequate for load bearing and stress, with suitable porosity for cell infiltration. They normally consist of gelatine, chitosan, alginate, collagen and hyaluronic acid.

The scaffolds carry GFs, typically BMP-7, BMP-9 and rhBMP-2. There have been developments of artificial GFs that match the characteristics of angiogenic (e.g., VEGF) and osteogenic (e.g., BMP) GFs. This would mean that patients won't have to rely on their natural healing processes as much hence decreasing the healing time. Notably, scientists are finding methods of drug delivery systems to replicate signalling molecules released in natural healing which will stimulate the release of GFs.

Conclusion

To sum up, bone tissue engineering has enormous potential for treating bone fractures and disorders. Growth factors are essential for stimulating bone regeneration and fixing bone abnormalities but delivering them effectively is still difficult. A potential solution to this issue is the application of biomimetic drug delivery systems that can imitate the signalling molecules generated by natural healing processes. These devices are more effective at promoting bone regeneration because they can control the localisation, timing, and kinetics of growth factor release. Additionally, combining angiogenic and osteogenic GFs with bioscaffolds have demonstrated reassuring outcomes in bone healing. Overall, bone tissue engineering research and development must continue.

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