Advanced Drug Delivery Reviews 64 (2012) 1257–1276

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Biomaterial delivery of morphogens to mimic the natural healing cascade in bone ☆

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ARTICLE INFO

Article history:
Received 19 October 2011
Accepted 3 May 2012
Available online 22 May 2012

Keywords:
Growth factor delivery
Bone regeneration
Biomaterials
Tissue engineering
Spatial regulation
Temporal regulation
Bio-inspired

ABSTRACT

Complications in treatment of large bone defects using bone grafting still remain. Our understanding of the endogenous bone regeneration cascade has inspired the exploration of a wide variety of growth factors (GFs) in an effort to mimic the natural signaling that controls bone healing. Biomaterial-based delivery of single exogenous GFs has shown therapeutic efficacy, and this likely relates to its ability to recruit and promote replication of cells involved in tissue development and the healing process. However, as the natural bone healing cascade involves the action of multiple factors, each acting in a specific spatiotemporal pattern, strategies aiming to mimic the critical aspects of this process will likely benefit from the usage of multiple therapeutic agents. This article reviews the current status of approaches to deliver single GFs, as well as ongoing efforts to develop sophisticated delivery platforms to deliver multiple lineage-directing morphogens (multiple GFs) during bone healing.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Targeted delivery of therapeutics to bone and connective tissues".

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doi:10.1016/j.addr.2012.05.006

1. Introduction

1.1. Relevance of the topic

Bone transplantation is one of the most common clinical procedures worldwide. Bone loss from trauma injury, tissue resection of tumors, revision surgery, osteonecrosis, spinal deformities, trabecular void, and infection can lead to significant bone loss with poor healing capacities or non-unions that pose a major clinical and socioeconomic problem. It is estimated that there are approximately 6.3 million fractures each year in the United States, with roughly 1 million who have skeletal defects [1] and over 500,000 requiring bone grafting procedures, costing approximately $2.5 billion [2]. These costs are estimated on fractures that heal on a first time successful surgical outcome. However, there is only an 85% success rate on a first procedure using bone grafting, and costs associated with complications and revision surgeries are estimated at 3 times this cost and more. A recent forecast of population development from the Federal Statistics Office predicts that in the year 2050, half of the population in Germany will be older than 48 and one-third will be at least 60 years old. The proportion of people over the age of 80 will triple [3]. The aging population will lead to an increase in the demand for surgery for joint replacement and fracture treatment. The need for effective and scalable osteosynthesis strategies will take center stage in the coming decade.

1.2. Classical treatment approaches for large bone defects and their limitations

Although bone repair in fracture healing is usually an efficient process, there is a subset of cases that have been reported as complications, most often during the treatment of large bone defects and resulting non-unions. While there is no universally accepted definition of non-union resulting from segmental or large bone defects, it can be considered the failure of a bony union within 6–8 months [4] without any signs of further progression towards healing. The diagnosis for such cases in humans is based on a combination of clinical symptoms and physical findings, including radiographic evidence of a failure in osseous union. For non-union or critical-sized defect scenarios, a temporary material must be used to fill the bone defect. Historically, management of posttraumatic large bone defects and the resultant poor outcomes was done by amputation. In the past decades, massive cancellous bone autografts, free vascularized grafts, bone transport with distraction osteogenesis, often in combination with metal implants have been the alternatives to amputation for large bone defects, but still often involve delayed union, prolonged treatment time, and revision surgeries.

The current gold standard treatment of critical-sized bone defects is autogenous bone grafting. In this treatment, the host bone is removed from another site (typically from the pelvis or iliac crest) and used to fill the bone defect [5,6]. However, the complication rate in autogenous bone grafting is high and may include donor site morbidity, pain, paresthesia, prolonged hospitalization and rehabilitation, increased risk of deep infection, inflammation, and restricted availability. Another option for patients and surgeons is the use of bone allografts (typically derived from human cadavers). Many orthopedic allograft procedures have been FDA-approved and utilized for years. Success in both autograft and allograft procedures is attributed to the physical and biological similarity in donor (site or patient) and host tissue. However, orthopedic allografts carry risks of donor to recipient infection and disease transmission, and host immune responses. As a last resort, patients requiring bone repair or replacement may also consider a xenograft, or tissue grafting from a non-human. Early success in xeno-transplantation of a variety of cells, tissues, and organs created optimism towards this approach. However, after decades of research investigation as well as global clinical trials, bone xenografts are now considered to be unsuitable for transplantation due to risk of disease or virus transmission, infection, toxicity associated with sterilization, immunogenicity, and finally host rejection [7]. Synthetic bone graft substitutes have evolved, as a result of the limitations of bone grafts, and continue to be developed, but not yet reached clinical efficacy for the treatment of posttraumatic segmental bone defects. The limited bone regeneration potential of allograft, xenograft and synthetic replacements has prompted the pursuit of tissue engineering approaches for the regeneration of functional bone tissue [8–10].

1.3. New strategies in the treatment of segmental bone defects

Although, the classical approaches have not been entirely successful in restoration of functional bone tissue, they still serve as motivation and a gold standard for newer tissue engineering approaches. The ability of bone grafts, or devitalized, de-mineralized bone to release osteoinductive signals and induce a response in adult stem-like cells, and osteogenic cells has unveiled promising strategies in bone tissue engineering, based on delivery of cells, matrix and bioactive molecules. Numerous growth factor (GF) proteins with an important role in this autoinductive process have been investigated for their therapeutic potential in regeneration of segmental bone defects, including bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor (IGF), vascular growth factor (VEGF), platelet derived growth factor (PDGF), and stromal derived growth factor (SDF1) [11,12]. However, these strategies still remain inferior, costlier and more complicated compared to the gold standard treatment of bone grafting. These inferior results may be due to the mode and timing of their delivery, poor control over the subsequent distribution of the factors locally and systemically, rapid degradation of the factors, undesirable systemic effects and toxicity, and an insufficient local concentration for the required time frame during regeneration. Consequently, the need to orchestrate the spatiotemporal delivery of single or multiple cues (simultaneously or sequentially) capable of instructing both cells resident in the tissue and transplanted cells will likely be key to the ultimate success of the regenerative process during bone healing [13]. The aim of this article is to review recent progress in delivering lineage-directing morphogens in the treatment of bone healing, with a specific focus in segmental or large bone defects. The article will cover:

(i) An overview of biological mechanisms in bone healing,
(ii) A brief review of current tissue engineering and regeneration strategies for bone,
(ii) Growth factors and delivery methods in treatment of bone defects,
(iii) Approaches that could provide greater control over bone regeneration driven by delivered GFs,
(iv) Future outlook in bone tissue regeneration strategies.

This review does not attempt systematic comparisons of different morphogens and their outcomes in bone healing, or cover recent