Advanced Drug Delivery Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Biomimetic approaches in bone tissue engineering: Integrating biological and physicomechanical strategies☆

Marc A. Fernandez-Yague [a], Sunny Akogwu Abbah [a], Laoise McNamara [b], Dimitrios I. Zeugolis [a], Abhay Pandit [a], Manus J. Biggs [a,*]

[a] Network of Excellence for Functional Biomaterials (NFB), National University of Ireland Galway (NUI Galway), Galway, Ireland
[b] Biomedical Engineering, College of Engineering and Informatics, National University of Ireland Galway (NUI Galway), Galway, Ireland

ARTICLE INFO

Available online xxxx

Keywords:
Bone regeneration
Tissue engineering
Biomimetic scaffolds
Osteoconductive
Osteoinductive
Drug delivery
Ion delivery
Growth factors
Gene delivery
Cell delivery

ABSTRACT

The development of responsive biomaterials capable of demonstrating modulated function in response to dynamic physiological and mechanical changes in vivo remains an important challenge in bone tissue engineering. To achieve long-term repair and good clinical outcomes, biologically responsive approaches that focus on repair and reconstitution of tissue structure and function through drug release, receptor recognition, environmental responsiveness and tuned biodegradability are required.

Traditional orthopedic materials lack biomimicry, and mismatches in tissue morphology, or chemical and mechanical properties ultimately accelerate device failure. Multiple stimuli have been proposed as principal contributors or mediators of cell activity and bone tissue formation, including physical (substrate topography, stiffness, shear stress and electrical forces) and biochemical factors (growth factors, genes or proteins). However optimal solutions to bone regeneration remain elusive. This review will focus on biological and physicomechanical considerations currently being explored in bone tissue engineering.

Contents

Abbreviations: HA, hydroxyapatite; GAG, glycosaminoglycan; PG, proteoglycan; ECM, extracellular matrix; VEGF, vascular endotelial growth factor; HIF-1α, hypoxia-inducible factor-1 alpha; PDGF, platelet-derived growth factor; IL-1, interleukin 1; TNF, tumor necrosis factor; TGF-β, transforming growth factor beta; IGF, insulin-like growth factor; ROS, reactive oxygen species; COX-2, cyclooxygenase 2; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; RUNX2, runt-related transcription factor 2; MSC, mesenchymal stem cells, non-steroidal anti-inflammatory drug, NSAID; LPS, lipopolysaccharides, macrophage colony-stimulating factor, M-CSF; PGE2, prostaglandin E2; BMSCs, bone marrow stromal cells; CaP, calcium phosphate; CVD, chemical vapor deposition; BMP-2, bone morphogenetic protein-2; MRSA, methicillin-resistant straphylococus aureus; SDF-1, stromal derived growth factor-1; c-di-GMP, Bis-(3′–5′)-cyclic dimeric guanosine monophosphate; RGD, arg-gly-asp; FN, fibronectin, OCN, osteocalcin; PGF, placenta growth factor.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Scaffolds, Cells, Biologics: At the Crossroads of Musculoskeletal Repair".

* Corresponding author at: Network of Excellence for Functional Biomaterials, National University of Ireland, Galway, Biosciences, Corrib Village, Dangan, Galway, Ireland.
E-mail address: manus.biggs@nuigalway.ie (M.J. Biggs).

http://dx.doi.org/10.1016/j.addr.2014.09.005
0169-409X/

1. Introduction

Bone tissue regeneration remains an important challenge in the field of orthopedic and craniofacial surgery. Traumatic injuries and various pathological diseases, including osteoporosis, osteoarthritis, osteogenesis imperfecta and Paget's disease, can impair normal bone functions and lead to bone fractures non-unions, immobility, severe pain and deformity. As such the demand for bone grafts is considerable, and represents the second most common tissue transplantation procedure after blood, with over 2.2 million bone graft procedures conducted worldwide annually in orthopedics and dentistry [1]. Current clinical treatments for large defects are challenging, and despite the natural capacity of bone for healing, if an injury is beyond a critical limit (critical size defect), it cannot heal by regeneration. (See Tables 1–3.)

Harvesting bone from autologous or allograft donor sites is an expensive and painful procedure, which is linked with added health risks associated with additional surgical procedures in elderly patients, increased risk of infection or disease transmission or rejection from donors [2,3]. Novel solutions are required to overcome the limitations of current bone grafting approaches and in vitro strategies, through tissue engineering or regenerative medicine approaches, which are promising strategies for treating bone diseases and reconstructing bone defects.

Tissue engineering approaches involve the combination of cells, biomaterial scaffolds and specialized culture conditions incorporating biochemical and physical stimuli to encourage in vitro bone formation. The development of responsive biomaterials capable of producing modulated function in response to the dynamic physiological and mechanical environments in vivo remains an important challenge in bone tissue engineering to achieve long-term repair and good clinical outcomes [4]. Despite considerable progress in the understanding of the biological and physicomechanical properties of organs and tissues, relatively few orthopedic biomaterials designed with biomimetic and bioresponsive characteristics have been translated into clinical solutions to date [5]. Nevertheless, according to the EU-Report on Nanotechnology, the global market for 'smart biomaterials' reached $47 billion in 2009 and will rise to $113 billion by 2025 [6].

Most current orthopedic technologies draw on simple or composite building blocks, yet next-generation tissue-engineering strategies in bone regeneration must combine multiple functions such as drug release, receptor recognition, environmental responsiveness and tuned biodegradability [7]. Furthermore, traditional medical devices lack biomimicry, and mismatches in tissue morphology, or chemical and mechanical properties ultimately accelerate implant failure [8,9]. In particular, current scaffold and implant designs are not biochemically, or physically specific to a particular patent, and long-term or permanent implants are not ideal for many applications, due to risks of stress shielding [10,11] and implant loosening [12]. Biomimetic approaches to biomaterial design enable molecular, structural and biological compatibility similar to that of the tissue being replaced to facilitate the regeneration of complex tissues [13–15]. Multiple stimuli have been proposed as principal contributors or mediators of cell activity and bone tissue formation, including physical (substrate topography, stiffness, shear stress and electrical forces) and biochemical factors (such as growth factors, genes or proteins). However, next-generation scaffolds and tissue engineered constructs need to be driven by a personal medicine approach and must integrate a range of biological and physical properties for optimal bone regeneration.

2. Structural and functional elements of bone tissue

Bone tissues can be understood as a nanocomposite 3D scaffold of nano-HA and type-I collagen and can be principally defined as either cortical or cancellous bone, dependent on the structural organization, porosity and mechanical properties. Cortical bone (<20% porosity) consists of close packets of osteons, cylindrical (Haversian) systems with a central channel that consists of a blood vessel surrounded by concentric rings (lamellae) of bone matrix. The mechanical properties of this system are anisotropic, being a function of the direction of applied force ($E = 20$ GPa along the Haversian system and $E = 8$ GPa along the transverse axis) [16,17]. In contrast, cancellous bone is less dense (>90% porosity) and is structured in plates (trabeculae) offering a larger surface area to mass ratio, making it an effective structure for ion exchange (homeostasis), hematopoiesis, and imparting flexibility in load-bearing bones ($E = 100$ MPa) [18]. Within the osteon and cancellous bone matrices are complex networks of canalilculi, which connect bone cells (osteocytes) and are believed to play an important role in traducing mechanical stresses, arising from every day from physical loading, into a cellular biochemical process to regulate bone remodeling a process known as mechanostransduction [19,20].

Bone tissue is a highly specialized and hierarchical connective tissue with structural, cellular organization and component material properties that direct bone function. The bone architecture is under continuous

Please cite this article as: M.A. Fernandez-Yague, et al., Biomimetic approaches in bone tissue engineering: Integrating biological and physicomechanical strategies, Adv. Drug Deliv. Rev. (2014), http://dx.doi.org/10.1016/j.addr.2014.09.005