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Review

Mediating bone regeneration by means of drug eluting implants: From passive to smart strategies

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ABSTRACT

In addition to excellent biocompatibility and mechanical performance, the new generation of bone and craniofacial implants are expected to proactively contribute to the regeneration process and dynamically interact with the host tissue. To this end, integration and sustained delivery of therapeutic agents has become a rapidly expanding area. The incorporated active molecules can offer supplementary features including promoting oteoconduction and angiogenesis, impeding bacterial infection and modulating host body reaction. Major limitations of the current practices consist of low drug stability overtime, poor control of release profile and kinetics as well as complexity of finding clinically appropriate drug dosage. In consideration of the multifaceted cascade of bone regeneration process, this research is moving towards dual/multiple drug delivery, where precise control on simultaneous or sequential delivery, considering the possible synergetic interaction of the incorporated bioactive factors is of utmost importance.

Herein, recent advancements in fabrication of synthetic load bearing implants equipped with various drug delivery systems are reviewed. Smart drug delivery solutions, newly developed to provide higher tempo-spatial control on the delivery of the pharmaceutical agents for targeted and stimuli responsive delivery are highlighted. The future trend of implants with bone drug delivery mechanisms and the most common challenges hindering commercialization and the bench to bedside progress of the developed technologies are covered.

Contents

1. Introduction

Bone functions in human body range from shielding and supporting other vital organs to producing blood, storing minerals, housing several progenitor cells, and many others. Treatments of many bone complications including osteogenesis imperfecta, osteomalacia, osteoporosis, osteosarcoma and traumatic injuries may require bone sectioning inducing cavities, imperfections and non-unions. Considering that the natural healing capability of bone tissue is reduced by age and injuries, the gold standard in such cases has been autogenous bone grafting. It

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consists in removing bone segments from other parts of the same patient's body to fill the gap in the damaged area. Bone grafting can lead to donor site morbidity, excessive inflammation, disease transmission, extensive hospitalization and rehabilitation, infection and limited availability besides patient pain and suffering [1]. In order to address the high rate of the complications associated with cancellous bone grafting, scientists developed various synthetic materials as bone implants and scaffolds. Therefore, synthetic orthopedic implants, including prosthetic joints and fixation plates, became a routine practice with worldwide growing number of procedures annually. However, scientists and clinicians are still dealing with many challenging issues of the currently used synthetic strategies imposed by the bioinert nature of commonly used materials, inadequate mechanical strength, stress shielding, fibrous encapsulation around the implant and insufficient expression of extrinsic factors required for the regeneration process. One possible strategy to address these challenges is to functionalize the synthetic material. So far, a wide variety of surface modifying approaches ranging from mechanical and physical to biological and chemical functionalization have been applied to provide material surface with specific microstructure, topography, porosity as well as chemical and biological characteristics to optimize mechanical functionality and modulate the implant-tissue interaction [2–4]. Surface nanocrystallization, multiscale surface roughening, surface patterning through lithography, photoetching, anodization, *etc*., and various coating techniques have been employed to modulate protein absorption, guiding cellular contact and growth, enhancing extracellular matrix deposition, as well as limiting bacterial adhesion and proliferation [5]. Rapid development of such approaches have led to advanced and refined solutions that provide mechanically stable and reliable implant solutions. However, still considerable re-operation rates are reported at later follow-ups involving persistent symptoms, progression of degenerative changes, non-healing damages, implant loosening, infection and antimicrobial resistance associated problems; the latter has been recognized among the top three issues affecting human health [6–8]. Moreover, current bone fracture treatments largely fail to address open fractures and critical size bone defects when the natural healing process is impaired and external intervention is required for large defect healing and union.

The aforementioned challenges and complications have pushed new trend of solutions towards developing multifunctional and bioactive bone scaffolds acting as local drug delivery platforms, which are intended to dynamically contribute to the regeneration process interfering with the host body response, promoting integration, oteoconduction and angiogenesis, impeding bacterial infection and/or offering many other desired functions to promote faster and secure healing. Controlled and regulated administration of a series of biologically active molecules inducing signals to direct bone regeneration are found to effectively increase bone healing and regeneration process [8, 9], avoiding systematic toxicity that is commonly caused by traditional drug administration methods and promoting their effectivity due to higher concentration of drug in the implantation site [10,11]. Locally delivered molecules can range from therapeutic agents including antibiotic and anti-inflammatory substances to various growth factors, proteins, enzymes, and non-viral genes (DNAs, RNAs) that can be used to address musculoskeletal syndromes in different ways.

Sustained local delivery of therapeutic agents *via* functionalized implant material has the potential to address the common intrinsic challenges of systematic drug delivery such as inadequate physiological stability. High doses of drug administered to achieve sufficient therapeutic effects, due to the lack of targeting specificity and solubility of some common drugs, can regularly lead to adverse drug reactions including increased antibiotic resistance, as well as renal and liver complications [12]. Local delivery can also reduce the risk of potential toxicity and increase cost and time efficacy.

The bone scaffold used as potential drug career can contain the active substance on its surface or within the bulk structure [13–15], either through physical incorporation or chemical bonds and immobilization; it should preserve the stability of the active molecules over time and ensure precise control over the substance's release rate [16]. The drug loaded in the bulk material can be released in the physiological environment through diffusion, matrix degradation over time or drug discharge by osmotic pressure [17]. Surface grafting approach can be either dipping and soaking, chemical bonding or incorporation of the drug in surface coatings. Most surface grafting approaches are prone to burst release and provide less control on the release kinetics. Many parameters including size, composition and the microstructure of the drug career as well as its molecular weight, drug solubility, drug loading method and its efficiency can directly affect the release kinetics over time [18]. For example, in case of porous templates, the drug loading step is commonly based on capillary system through immersion in concentrated aqueous drug solution or fluid impregnation of the surface material. In these cases, delivery is mainly through diffusion and thus controlled by the pore size, particularly in nanoporous scaffolds/coatings where the pore size becomes comparable with the drug molecule size [19].

Surface coatings to add desired functions through incorporating specific drugs to facilitate local drug delivery have been widely exercised to functionalize the surface of biomedical implants. FDA approved biodegradable polymer films have been broadly used to deliver active therapeutic cargo to modulate the tissue response and healing rate [20]. Among polymer materials, poly(lactic acid-*co*-glycolic acid) (PLGA) is unquestionably the most widely used drug career in bone tissue engineering [21]. Nevertheless, the inadequate mechanical strength of polymer materials has limited the clinical application and has motivated the fabrication of polymer based composite materials [166,167]. On the other hand, deposited polymeric coating are reported to cause complications including detachment, compromised chemical stability in biological environment and probable adverse reactions from the side products; thus studies have focused on application of inorganic coatings as drug career [11]. Calcium phosphates (CaPs) are among the most common choices in hard tissue engineering thanks to the high similarity of their composition to bone mineral, outstanding bioactivity and cost effectiveness. Their physical and chemical characteristics have made them a suitable drug career and thus they have been widely studied as cements/bone scaffolds/coatings on implants as delivery vehicles for various growth factors and drugs for bone regeneration [22]. However, CaP based coatings, although offering additional biomimetic and osteogenic characteristics, have limited mechanical strength due to their intrinsic brittleness. This problem can also be resolved by adopting composite coatings as enhanced compressive strength and elastic modulus are reported for hydroxyapatite (HaP)-poly(epsilon-caprolactone) and HaP-chitosan-gelatin composite coatings/scaffolds [23,24].

More recently, bioactive glasses particularly, silica-based mesoporous materials have attracted more attention for drug delivery purposes in bone tissue engineering thanks to the high surface area and large pore volume, which facilitate incorporation of larger amounts of drug [25, 26]. Besides efficient drug loading and release characteristics, such ordered macro/meso porous platforms have high potential for promoting cell penetration, bone ingrowth as well as vascularization and bone oxygenation thanks to their biomimetic hierarchical and interconnected porous architecture [27]. Drug loading and sustained release can be also precisely modulated through chemical modification of pore walls *via* electrostatic interactions, controlling hydrophilic characteristics *via* hydrophilic-hydrophobic forces or electronic interactions [26,28]. Another widely used approach to obtain more control on the release kinetics is to use nano/micron size drug careers which have been dispersed in the homogeneous or composite scaffolds and coatings [8].

Despite all the advancements, there are still challenges to be addressed in the field of local bone drug delivery including effective and sustained release control, prolonged drug stability and activity, toxicity issues as well as immune inflammatory response [29]. In this review paper, multiple recent concepts of implantable devices for sustained bone drug delivery and their limitations are discussed. The choices to