Calcium Phosphate Nanoparticles in Bone

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Bone injuries and diseases constitute a burden both socially and economically, as the consequences of a lack of effective treatments affect both the patients' quality of life and the costs on the health systems. This impended need has led to a recent focus on the development of efficacious bone tissue engineering solutions. Here, the use of biomaterial-based nanoparticles for the delivery of therapeutic factors is summrised. Among the biomaterials being considered to date, calcium phosphates have emerged as one of the most promising materials for bone repair applications due to their osteoconductivity, osteoinductivity and their ability to be resorbed in the body. Calcium phosphate nanoparticles have received particular attention as non-viral vectors for gene therapy, as factors such as plasmid DNAs, microRNAs (miRNA) and silencing RNA (siRNAs) can be easily incorporated on their surface. Calcium phosphate nanoparticles loaded with therapeutic factors have also been delivered to the site of bone injury using scaffolds and hydrogels. Here an overview of the use of calcium phosphate nanoparticles as carriers for therapeutic factors for application in bone tissue engineering is provided.

Keywords: Bone tissue engineering ; calcium phosphates ; drug delivery ; gene therapy ; nanoparticle ; non-viral vectors ; therapeutic delivery

1. Introduction

Bone defects or loss of bone, whether caused by trauma, congenital disorders or diseases, represent a significant burden for the population and the health system. The ability of bones to self-heal depends mainly on three factors: (1) The size of gap to bridge, (2) the stability of the fracture site and (3) the patient's bone quality. Many common diseases can affect the quality and self-healing potential of bones, above all osteoporosis. [1] Other factors playing a significant role in bone quality include older age and diabetes. When considering that an average of 10 million people are affected by osteoporosis and/or diabetes in the US, and the ageing population, the challenges relating to bone regeneration are expected to continue to rise in the future.[2] Therefore, there is an increasing need for the development of effective therapies for bone regeneration.

In order to address this clinical challenge, there has been an increased interest in the development and administration of therapeutic factors to promote bone tissue regeneration. Generally, these therapies are delivered systemically which has numerous disadvantages including the requirement for larger doses and the potential for off-target effects. Therefore, research has focussed on the development of biomaterials that can act as carriers for the localised targeted delivery of drugs, therapeutic factors and genetic cargoes that can treat diseases and promote bone healing and thus overcome some of the limitations associated with systemic delivery. Among the biomaterials being considered to date, calcium phosphates, such as hydroxyapatite (HA), have been extensively investigated for use in bone repair applications due to their similarity to the mineral phase of natural bones, which confers them an excellent biocompatibility.[3] Many calcium phosphates are also osteoinductive as the high levels of calcium and phosphate ions effectively enhance the osteogenic differentiation of pluripotent cells into osteoblasts,[4][5] and most are considered bioresorbable.[6] The family of calcium phosphates is therefore regarded as a safe and efficient class of material for use in bone repair applications.

2. Calcium Phosphate Nanoparticles for Therapeutic Applications in Bone Regeneration

Different approaches have been proposed over the years to tailor the application of calcium phosphate-based materials to the bone healing process. The current trend is focussed on the design and development of calcium phosphates in nanoparticulate form as it has been reported that hydroxyapatite nanoparticles best replicate the form of calcium phosphate found in natural healthy bones.[5] Nanoparticles employed for therapeutic applications are generally between 10 to 100 nm in size, as smaller particles are easily excreted by the kidneys, and particles of a large size are usually removed by the spleen after being phagocytosed.[7] Such nanoparticles have been found to offer a number of advantages in relation to their therapeutic applications in vivo: They are generally well-accepted by the body and have a large surface-to-volume ratio that allows for a higher driving force for diffusion and increased particle solubility.[8] This high surface-to-volume ratio can influence the adhesion of specific proteins, making them particularly suited for the delivery of therapeutic factors.[8] Calcium phosphate nanoparticles have been successfully used for the delivery of a range of therapeutic factors for bone repair (Figure 1), some of which include antibiotics,[9] anti-inflammatory agents and growth factors, such as bone morphogenetic factors (BMPs) and cytokines in order to enhance osteogenesis.[10] They have also shown promise for use in conjunction with gene therapy to deliver therapeutic cues for bone repair purposes, whereby the nanoparticles interact with the host tissue, producing a complex that can further enhance bone tissue repair and regeneration.[10][11]

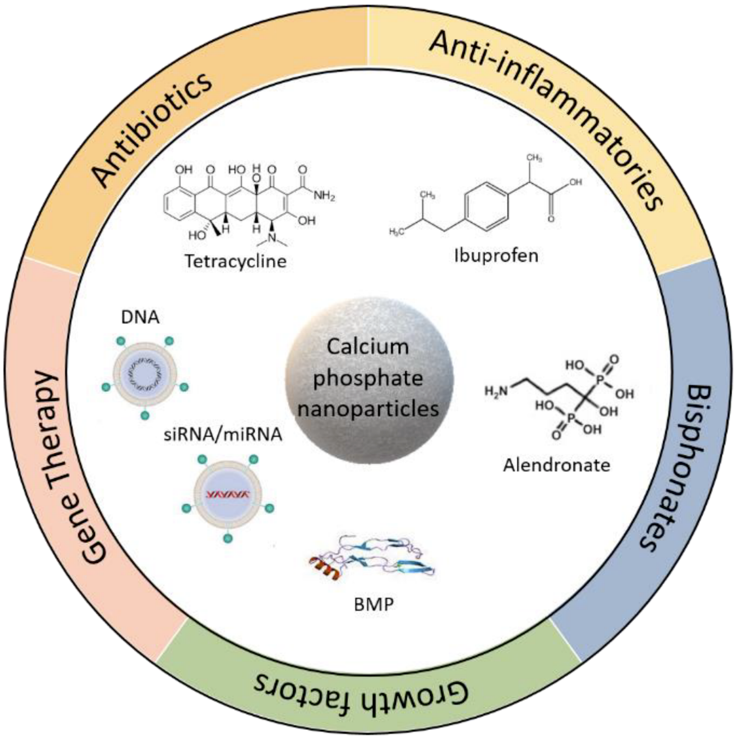

Figure 1. Application of calcium phosphate nanoparticles for the delivery of therapeutic factors for bone repair.

Gene therapy is regarded as a more effective way to deliver osteogenic key factors. The approach makes use of small circular DNA molecules, known as plasmid DNA (pDNA), to deliver specific genes encoding particular proteins. These DNA molecules are then loaded on a delivery vector designed to enhance cellular uptake.[10] Numerous studies have proven the feasibility of using calcium phosphate nanoparticles as delivery vectors for gene therapy, for example using pDNA encoding bone morphogenetic protein-2 (BMP-2).[12] MicroRNAs[13] and silencing RNA (siRNAs)[14] have also been successfully delivered using calcium phosphate nanoparticles.[15] Furthermore, calcium phosphate nanoparticles loaded with therapeutic factors have been combined with scaffolds and hydrogels in order to deliver them to the site of bone injury within the body.[16][17]

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