RESEARCH ARTICLE

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Osteophilic and Dual-Regulated Alendronate-Gene Lipoplexes for Reversing Bone Loss

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The pathogenesis of postmenopausal osteoporosis (PMOP) is mainly determined by the adhesion of osteoclasts to the bone matrix and the involvement of various molecules in bone resorption. The dual regulation strategy of the physical barriers of bone matrix and intracellular gene regulation generated by advanced biomaterials is a decent alternative for the treatment of PMOP. Herein, for the first time, it is identified that hsa-miR-378i/mmu-miR-378a-3p are closely associated with PMOP. Then, an osteophilic and dual-regulated alendronate-gene lipoplex (antagomir@Aln-Lipo), composed of medicative alendronate-functionalized liposomal vehicle and encapsulated specific microRNAs is engineered, for bone-targeting delivery of genes to achieve combined mitigation of bone loss. Alendronate targets hydroxyapatite in the bone matrix and occupies the adhesion site of osteoclasts, thus providing the "physical barriers". Antagomir is coupled precisely to specific endogenous microRNAs, thus providing the "genetic signals". These functionalized lipoplexes exhibited long-term stability and good transfection efficiency. It is proven that antagomir@Aln-Lipo could synergistically regulate osteoclastogenesis and bone resorption in vitro and in vivo. Furthermore, intravenous injection of antagomir@Aln-Lipo efficiently reverses bone loss through a dual mechanism driven by alendronate and antagomir-378a-3p. In conclusion, the osteophilic and dual-regulated antagomir@Aln-Lipo offers a brand-new bifunctional strategy for the precise treatment of PMOP.

1. Introduction

Bones are composed of a mineralized bone matrix and a highly active basic multicellular unit.[1] Along with a dynamic imbalance between osteoblasts and osteoclasts, osteoporosis pathological alterations are also manifested as a decrease in the bone matrix.[2] In recent decades, anti-osteoporosis drugs have made significant progress in the prevention and treatment of osteoporosis and osteoporotic fractures by reestablishing the equilibrium of the bone microenvironment, effectively increasing bone mass and reducing fracture risk.[3] However, current osteoporosis medicines, including bone resorption inhibitors and bone formation promoters, primarily focus on the biological behavior of cells, while neglecting the extracellular matrix. As a result, these drug design flaws inevitably cause numerous clinical adverse effects, such as osteonecrosis of the jaw, atypical femur fractures, and rapid bone loss after drug discontinuation.[4] Inspired by this, it is expected that the development of biomaterials with a dual-driven mechanism as a synergistic

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