MASTER'S THESIS

A delivery system specifically approaching bone resorption surfaces to facilitate therapeutic modulation of MicroRans in osteoclasts

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Abstract

Dysregulated microRNAs in osteoclasts could cause many skeletal diseases. The therapeutic manipulation of these pathogenic microRNAs necessitates novel, efficient delivery systems to facilitate microRNAs modulators targeting osteoclasts with minimal off-target effects. Bone resorption surfaces characterized by highly crystallized hydroxyapatite are dominantly occupied by osteoclasts. Considering that the eight repeating sequences of aspartate (D-Asp_8) could preferably bind to highly crystallized hydroxyapatite, we developed a targeting system by conjugating D-Asp_8 peptide with liposome for delivering microRNA modulators specifically to bone resorption surfaces and subsequently encapsulated antagomir-148a (a microRNA modulator suppressing the osteoclastogenic miR-148a), *i.e*. (D-Asp_8)-liposome-antagomir-148a. Our results demonstrated that D-Asp_8 could facilitate the enrichment of antagomir-148a and the subsequent down-regulation of miR-148a in osteoclasts *in vivo*, resulting in reduced bone resorption and attenuated deterioration of trabecular architecture in osteoporotic mice. Mechanistically, the osteoclast-targeting delivery depended on the interaction between bone resorption surfaces and D-Asp_8. No detectable liver and kidney toxicity was found in mice after single/multiple dose(s) treatment of (D-Asp_8)-liposome-antagomir-148a. These results indicated that (D-Asp_8)-liposome as a promising osteoclast-targeting delivery system could facilitate clinical translation of microRNA modulators in treating those osteoclast-dysfunction-induced skeletal diseases.

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