

MASTER'S THESIS

Therapeutic potential of nucleic acid aptamers against sclerostin in the treatment of osteoporosis

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Abstract

Osteoporosis is a skeletal disease characterized with poor bone quality and low bone mineral density. The pathogenesis of osteoporosis is the imbalance of bone resorption and bone formation. Two strategies can be employed to cure osteoporosis. One is to inhibit bone resorption and the other is to stimulate bone formation. Currently, therapeutic drugs approved by FDA are mainly antiresorptive agents. Till now, there is only one bone anabolic agent approved. Obviously, more efforts should be poured into the development of bone anabolic agents.

Sclerostin is a key negative regulator of osteoblast Wnt signaling making it a promising therapeutic target for bone anabolic therapy. Anti-sclerostin humanized monoclonal antibody romosozumab, which could effectively promote bone formation, has been accepted by the FDA for the review of biologic license application in 2017. However, there are several concerns about the humanized anti-sclerostin antibody, including immunogenicity, high cost of production and relative low stability.

Nucleic acid aptamers are short single stranded oligonucleotides. They can bind to their targets with similar high affinity as antibodies. Moreover, aptamers have some superior advantages compared to antibodies, such as no immunogenicity, easily synthesized, and high stability. Aptamers against sclerostin could be a promising alternative to antibodies in terms of promotion of bone formation and reversal of osteoporosis.

In this thesis, 20 rounds of SELEX were performed to select aptamers with high binding affinity and specificity to sclerostin. The inhibition potency of aptamer candidates to the antagonistic effect of sclerostin on Wnt signaling was also evaluated. Low K_D and EC_{50} values of aptamer candidates against sclerostin implied a great potential of sclerostin aptamer being the novel agents to promote bone formation. The study establishes the foundation for the next stage of preclinical studies and it will benefit the development of novel bone anabolic agents to reverse osteoporosis.

Key words: osteoporosis; bone anabolic agents; sclerostin; Wnt signaling; romosozumab; aptamer; affinity; specificity; inhibition potency.

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