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THERAPY

Targeted delivery of packaged siRNA promotes osteogenesis

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Therapeutic agents for metabolic skeletal disorders based on RNA interference have a risk of off-target effects and need shielding from scavenging mechanisms. In a new report by Liang *et al.* published in *Nature Medicine*, targeted delivery of an osteogenic small interfering RNA (siRNA) encapsulated within an aptamer-functionalized nanoparticle reduced target gene expression specifically in osteoblasts and improved multiple parameters of bone health *in vivo*.

"One of the major limitations in the use of nanoparticles lies [in] the necessity to escape the reticuloendothelial system and phagocytic cells before reaching the target tissue," says Constantino Pitzalis of Queen Mary University of London, UK, who was not involved in the study. To improve the selectivity of nanoparticle delivery systems for osteoblasts, Liang *et al.* used cell-based systematic evolution of ligands by exponential enrichment (cell-SELEX) to select aptamers that specifically bind to osteoblasts. One of the aptamer candidates (CH6) was used to functionalize lipid nanoparticles (LNPs) loaded with siRNA for the gene *Plekho1*, a negative regulator of bone formation, to develop a protected, osteoblast-specific osteogenic agent (CH6–LNP–siRNA).

Uptake of CH6–LNP–siRNA by rat osteoblasts *in vitro* by macropinocytosis and clathrin-mediated endocytosis led to significantly lower expression of *Plekho1* compared with other siRNA formulations ($P<0.05$). CH6–LNP–siRNA showed higher accumulation in bone tissue and lower accumulation in the liver and kidney *in vivo* when compared with nonfunctionalized LNP or LNPs functionalized with a random-sequence aptamer (Rd–LNP–siRNA). *Plekho1* siRNA colocalized with the osteoblast markers alkaline phosphatase and osteocalcin but not with the osteoclast markers osteoclast-associated receptor and cathepsin K, asserting the specificity of the CH6–LNP–siRNA formulation.

Importantly, ovariectomized rats treated with CH6–LNP–siRNA (1.0 mg/kg per week for 6 weeks) had improved bone mineral density, relative bone volume, trabecular thickness and structural model index in microCT assessments, and showed enhanced mineral apposition rate, bone formation rate, osteoblast surface and osteoblast numbers, when compared with those treated with Rd–LNP–siRNA ($P<0.05$); no adverse effects were observed in rats treated with CH6–LNP–siRNA.

Ge Zhang, one of the researchers involved in the study, says this strategy "provides a promising approach to fulfill a more accurate and safe delivery of osteogenic siRNAs" and "may facilitate the treatment of metabolic skeletal disorders associated with impaired bone formation". According to Pitzalis, this study represents "an outstanding effort to overcome the limitations of nanoparticle drug delivery and may open the gate for a new era of therapeutic intervention in conditions such as osteoporosis and arthritis".

João H. Duarte

Original article Liang, C. *et al.* Aptamer-functionalized lipid nanoparticles targeting osteoblasts as a novel RNA interference-based bone anabolic strategy. *Nat. Med.* doi:10.1038/nm.3791