Scavenger receptor-targeted plaque delivery of microRNA-coated nanoparticles for alleviating atherosclerosis

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Atherosclerosis treatments by gene regulation are garnering attention, yet delivery of gene cargoes to atherosclerotic plaques remains inefficient. Here, we demonstrate that assembly of therapeutic oligonucleotides into a three-dimensional spherical nucleic acid nanostructure improves their systemic delivery to the plaque and the treatment of atherosclerosis. This noncationic nanoparticle contains a shell of microRNA-146a oligonucleotides, which regulate the NF-κB pathway, for achieving transfection-free cellular entry. Upon an intravenous injection into apolipoprotein E knockout mice fed with a high-cholesterol diet, this nanoparticle naturally targets class A scavenger receptor on plaque macrophages and endothelial cells, contributing to elevated delivery to the plaques (~1.2% of the injected dose). Repeated injections of the nanoparticle modulate genes related to immune response and vascular inflammation, leading to reduced and stabilized plaques but without inducing severe toxicity. Our nanoparticle offers a safe and effective treatment of atherosclerosis and reveals the promise of nucleic acid nanotechnology for cardiovascular diseases.[1]

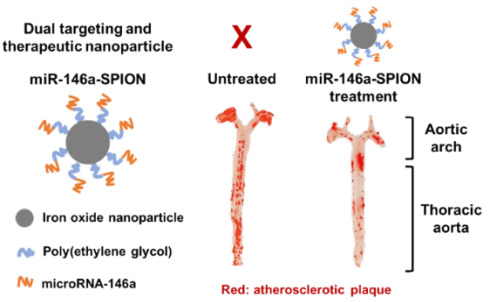

Figure 1: We present a noncationic nucleic acid-based nanostructure to overcome these gene delivery obstacles to atherosclerotic plaques, with nucleic acid serving as a dual targeting agent for engaging plaque-related receptors and gene regulation agent for blocking biological pathways linked to atherogenesis.

[1] Bai, Q; Xiao, Y; Hong, H; Cao, X; Zhang, L; Han, R; Lee, LKC; Xue, EY; Tian, XY; Choi, CHJ. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, 39, e2201443119.