RNA nanoparticle as novel agent for atherosclerosis treatment

11 JAN 2023

KANAS CHAN

Researchers from the Chinese University of Hong Kong (CUHK) have developed a novel RNA nanoparticle that can target and treat atherosclerotic plaques without inducing severe toxicity, paving the way for the use of RNA nanotechnology in cardiovascular disease (CVD) management.

Conventional interventions for atherosclerosis involve balloon angioplasty or endarterectomy, which are invasive and insufficient for reducing multiple plaque sites. Meanwhile, statins only delay disease progression. Although gene regulation is recently garnering attention in atherosclerosis treatment, current technology for gene delivery to plaques remains inefficient. [*PNAS* 2022;doi:10.1073/pnas.2201443119]

"Existing atherosclerosis nanomedicines mostly employ cationic carriers to complex gene cargoes through electrostatic interactions for gene delivery into plaque cells," said the researchers. "Yet, these nanomedicines are often bulky [>100 nm], meaning they can be rapidly filtered by the liver and spleen following an intravenous [IV] injection before they reach the plaque. Also, their cationic properties may induce cytotoxicity."

To overcome these limitations, the researchers assembled a non-cationic and smaller (70 nm) RNA-based nanoparticle for promoting plaque delivery. "[It] includes a biocompatible iron oxide nanoparticle core and about 300 therapeutic microRNA-146a strands attached to the core's surface. It can naturally enter plaque cells without the aid of cationic transfection agents, thereby facilitating intracellular delivery of microRNA-146a," explained the researchers.

From left: Dr Shirley Bai, Prof Jonathan Choi, Prof Xiao-Yu Tian

Notably, RNA serves as a dual targeting agent for engaging plaque-related receptors (ie, class A scavenger receptor) and as a gene regulation agent for blocking biological pathways linked to atherogenesis.

Upon an IV injection into mice fed with a high-cholesterol diet (plaque-bearing mouse models), the RNA nanoparticle accumulated in atherosclerotic plaques and entered macrophages and endothelial cells inside the plaques, resulting in elevated delivery to the plaques 2 hours after injection. "The unique receptor-targeting property of the RNA nanoparticles contributes to their elevated accumulation of up to 1.2 percent of the injected dose in plaques, one of the highest in the field of nanomedicine," highlighted Dr Shirley Bai of the Department of Biomedical Engineering, CUHK.

Moreover, repeated injections of the RNA nanoparticle modulated genes, and led to reduced and stabilized plaques as well as downregulation of genes related to immune response and vascular inflammation. After 4 weeks of full treatment, there was no pronounced accumulation of RNA nanoparticles inside major internal organs, nor was severe toxicity observed. "The findings suggest that this RNA nanoparticle is a safe and effective agent for treatment of atherosclerosis, and it is now possible to design nucleic acid nanomedicines that are dual plaque-targeting and therapeutic agents," said Professor Tian of the Department of Biomedical Science, CUHK.

"This study highlights the promise of nucleic acid nanotechnology in CVD treatment. We hope to continue our collaboration with the CUHK Faculty of Medicine in validating the safety and efficacy of this RNA nanostructure in large animals," added Professor Jonathan Choi of the Department of Biomedical Engineering, CUHK. "Ultimately, we hope to offer a safe and effective nanomedicine for patients with CVD."