

Piperazine-Structured Lipid Nanoparticles Enable Enhanced Targeted Delivery of SHP-1 siRNA to Macrophages for Treatment of Atherosclerotic Vulnerable Plaques

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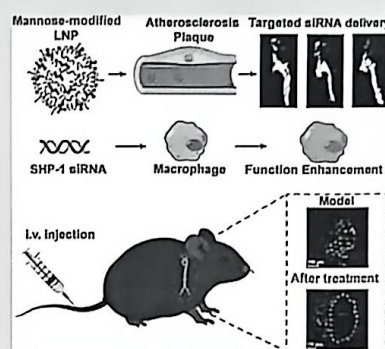
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ABSTRACT: Atherosclerotic vulnerable plaques pose a risk for acute coronary syndrome and sudden cardiac death due to plaque rupture and thrombosis. While nanomedicines modulating macrophage functions have attracted intensive interest, efficient delivery to plaque macrophages remains challenging. Here, mannose-modified lipid nanoparticles (LNPs) are developed for targeted delivery of a novel SHP-1 (Src Homology 2 Domain-containing Phosphatase-1) siRNA to macrophages within atherosclerotic vulnerable plaques, aiming to enhance macrophage function and stabilize plaques. In ApoE^{-/-} mice with vulnerable plaques, both MIC5 and SM-102 LNPs demonstrated robust plaque targeting capabilities (Cy5 fluorescence reaching $\sim 10^{10}$ p/sec/cm²/sr) and significantly reduced plaque area following SHP-1 siRNA delivery. Importantly, the piperazine-based MIC5 LNPs exhibited enhanced plaque targeting efficiency with M2 macrophage uptake efficiency reaching 46.32% as well as superior therapeutic effects. Collectively, these SHP-1 siRNA-loaded LNPs offer a promising targeted therapeutic strategy for atherosclerotic vulnerable plaques and establish a novel nanoplatform for RNA-based macrophage-modulation in various inflammatory diseases.

KEYWORDS: vulnerable plaques, lipid nanoparticles, plaque-targeted delivery, SHP-1 siRNA, macrophages



Atherosclerosis (AS) is a common cardiovascular disease whose complications, such as vulnerable plaque rupture, thrombosis, and stroke, significantly impact human health, making it one of the leading causes of mortality worldwide.¹ Current treatments for AS primarily include surgical interventions and pharmacological therapy. However, they are limited by potential surgical risks and drug-related side effects, prompting researchers to explore novel treatment strategies.

One significant feature of AS is the formation of plaques within the arterial walls. Advances in the understanding of AS plaque pathogenesis have highlighted the important role of macrophages in both the development and progression of atherosclerotic lesions.² Notably, different macrophage phenotypes exert distinct effects during this process. Pro-inflammatory M1 macrophages promote atherosclerotic development and plaque destabilization,^{3,4} whereas M2 macrophages secrete anti-inflammatory cytokines that alleviate oxidative stress and promote inflammation resolution, leading to fibrous cap thickening and enhanced plaque stability.^{5,6} Given the pivotal role of macrophages, researchers worldwide are turning to macrophage-targeted therapies for AS.^{7,8} For example, Zhang and co-workers successfully delivered mRNA encoding IL-10 to macrophages within atherosclerotic plaques through an inflammation-targeting strategy, achieving significant therapeutic efficacy against advanced atherosclerosis.⁹ Tao and co-

workers have systematically investigated the therapeutic potential of CaMKII γ inhibition for enhancing macrophage efferocytosis, as well as nanomedicines based on black phosphorus nanomaterials with antioxidant capabilities, for the treatment of atherosclerosis.^{10,11} In addition, Song and co-workers utilized various nanocarrier systems, including black phosphorus nanosheets, lipid-polymer hybrid nanoparticles, and ROS-responsive siRNA carriers, to achieve efficient targeting of lesional macrophages and demonstrated their therapeutic efficacy in atherosclerotic animal models.^{12–17}

With the advancement of RNA interference (RNAi) technology, methods to modulate macrophage function have evolved from traditional small-molecule inhibitors to nucleic acid-based approaches. Discovered over 25 years ago,^{18,19} RNAi has revolutionized drug development, as evidenced by FDA-approved siRNA therapeutics such as patisiran,²⁰ givosiran,²¹ and inclisiran.^{22–25} SHP-1 (Src Homology 2 Domain-containing Phosphatase-1) is a protein tyrosine

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