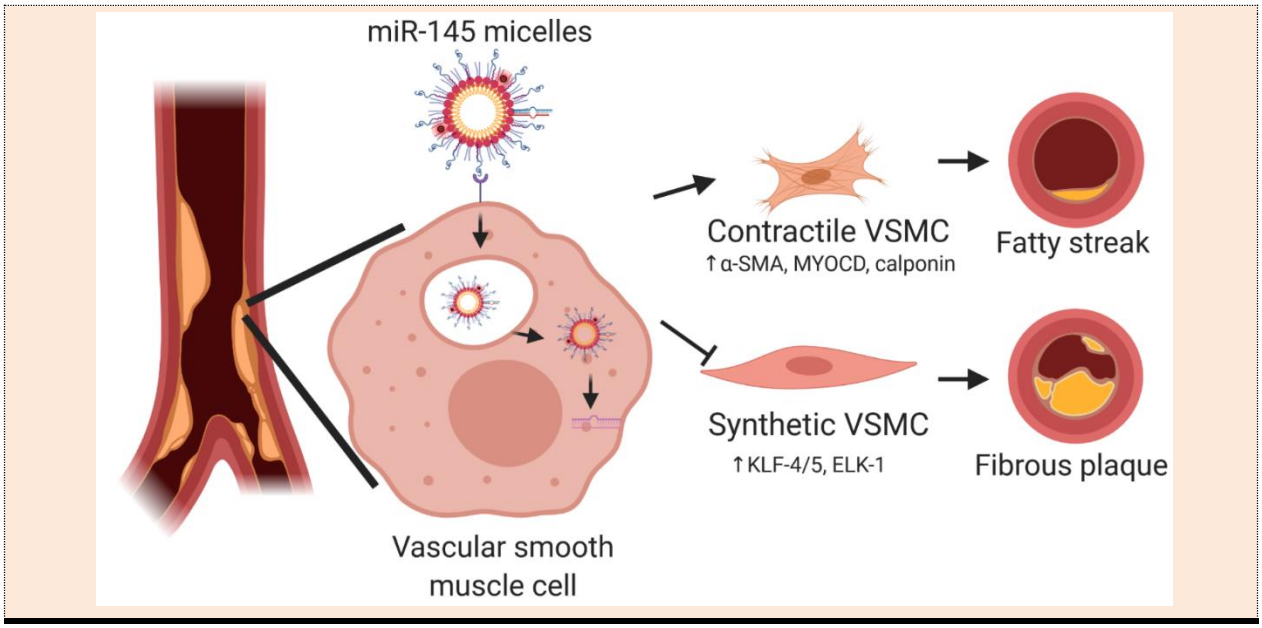

MicroRNA-145 Delivery by Targeted Peptide Micelles for Atherosclerosis Therapy

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Atherosclerosis is characterized by the buildup of plaques in the arteries that can severely exacerbate blood flow. These plaques consist of lipids, calcium, and a heterogenous population of cells including macrophages, foam cells, osteogenic cells, and vascular smooth muscle cells (VSMCs). However, more recent studies have identified that up to 70% of the cells found in atherosclerotic plaques are derived from dedifferentiated and transdifferentiated VSMCs [1]. Notably, microRNA-145 (miR-145), a short, non-coding RNA that is the most abundant in the vasculature, is a key regulator of the dedifferentiation of healthy, contractile VSMCs into the synthetic and disease-propagating phenotypes [2]. Specifically, miR-145 maintains healthy contractile VSMC phenotypes by downregulating synthetic genes: KLF4/5, and ELK-1. Thus, we hypothesize that miR-145 therapy can mitigate atherosclerotic plaque growth by promoting healthy VSMC maintenance.

To facilitate miR-145 delivery to atherosclerotic plaques, we utilize monocyte chemoattractant peptide-1 (MCP-1) that binds to C-C chemokine receptor 2 (CCR2) expressed on synthetic VSMCs. These peptides are incorporated into micelles that contain covalently attached miR-145 (miR-145 micelles) for the targeted delivery to plaques. In atherosclerotic mice, miR-145 micelles demonstrate accumulation in plaques and upregulation of contractile VSMC phenotypes through miR-145 therapy. Subsequently, plaque size was reduced in the aorta by up to 49% compared to non-treated controls and stability improved due to enhanced extracellular collagen production. Overall, we demonstrate the potential of miR-145 micelles as a therapy for atherosclerosis.

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[2] Lovren, Fina et al. “MicroRNA-145 targeted therapy reduces atherosclerosis.” Circulation vol. 126,11 Suppl 1 (2012): S81-90. doi:10.1161/CIRCULATIONAHA.111.084186