Nanoparticle Delivery of Antioxidant-Response Activating Drug to Atherosclerotic Plaque

Sarah Torzone

Atherosclerosis is a leading cause of death worldwide, as it precedes acute coronary syndromes, myocardial infarction, and strokes[4]. This disease is driven by synergistic effects of low-density lipoprotein (LDL) accumulation in the arteries and chronic inflammation that modulate the formation of fibrous lesions/plaque in the arterial wall[4]. Macrophages are recruited to sites of inflammation in the blood vessel where they ingest oxidized LDL particles to form foam cells in the vascular wall. Foam cell death and necrosis then results in hardening of the blood vessel that characterizes atherosclerosis.

Reactive oxygen species (ROS), are prominent activators of inflammatory response in the vascular wall[2]. Under normal conditions, ROS are cleared by cellular antioxidant mechanisms, however, redox imbalances can advance the progression of atherosclerosis. The canonical Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is responsible for the cell's response to oxidative stress[3]. At basal levels of oxidative stress, Nrf2 is bound to Kelch-like ECH-associated protein 1 (Keap1) where it is ubiquitinated for proteasomal degradation. Under increased oxidative stress, Keap1 dissociates from Nrf2, promoting nuclear translocation of Nrf2 which initiates transcription of antioxidant enzymes.

In an effort to halt the progression of atherosclerosis, an antioxidant response can be potentiated by the Nrf2-activating drug, CDDO-Methyl, to restore redox balance to the vascular endothelium and smooth muscle[3]. We employ a novel technique for drug delivery of CDDO-Me by flash nanoprecipitation to synthesize nanoparticle polymers that encapsulate the antioxidant-response-activating drug. These Antioxidant Response Activating nanoParticles (ARAPas) localize to atherosclerotic plaque and activate Nrf2 in the vasculature, serving as a potential therapeutic for atherosclerosis[3]. We seek to explore the efficacy of CDDO-Me ARAPas in treatment of atherosclerosis using both traditional histological analysis of mouse aortic roots and three-dimensional analysis of whole mouse aortas by light sheet fluorescent microscopy.