Multifunctional nanoparticles for prevention and treatment of atherosclerosis

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Technology description

PAGE SUMMARY

Atherosclerosis is a chronic inflammatory disease of the artery wall and a major cause of cardiovascular disease, the leading cause of death in the US and many developed economies. The inflamed cells release free radicals that produce a strong local oxidative environment where low density lipoproteins (LDLs) are oxidized. The oxidized LDL (oxLDL) particles are endocytosed by macrophages via scavenger receptors. As a result, the macrophages develop into lipid-laden foam cells. Foam cells play a pivotal role in the occurrence and development of atherosclerosis by contributing to lipid accumulation, necrotic core expansion and further inflammatory amplification at the plaque sites. They eventually die and form part of the atherosclerotic plaque. In addition, high blood level of LDL cholesterol has been associated with high risk of atherosclerosis, heart attack, and stroke. Currently, there is no effective pharmacologic therapy to treat atherosclerosis.

To address this problem Drexel’ s researcher have developed specialized nanoparticles (NPs) that can effectively: 1) reduce LDL cholesterol level in the serum through binding to LDL cholesterol, 2) inhibit oxLDL uptake by macrophages, and 3) promote cholesterol efflux from foam cells in vitro (intracellular cholesterol was restored to normal level in 24 hours, most lipid was removed in 5 hours). The particles consist of Dextran sulfate (DS), a biocompatible and biodegradable polysaccharide that is highly negatively charged and can selectively bind to the positively charged apolipoprotein B molecule in LDL. DS has been used in LDL apheresis, a procedure that runs a patient’ s blood through a machine with DS-filled column to remove LDL cholesterol. In addition, DS can bind to scavenger receptor A (SR-A), which can be used to inhibit oxLDL uptake by macrophages. However, DS cannot be removed from blood circulation after it binds to LDL, which is why direct injection of DS into the bloodstream cannot be used to reduce blood LDL cholesterol. Additionally, DS by itself cannot induce cholesterol efflux. However, the DS-based NPs, developed at Drexel, can upregulate the expression of apoA-1 gene by 112-fold. ApoA-1 is the major component of high density lipoprotein (HDL) that is considered to be the “good cholesterol” that transports cholesterol from foam cells to the liver and protects against atherosclerosis.

The Drexel NP’ s consist of polyelectrolyte complexes (PIC) of dextran sulfate and chitosan (CH). CH is a natural biocompatible polysaccharide with abundant amine groups that can form strong electrostatic interactions with the sulfate groups on DS. The strong electrostatic interactions between the two

polymers enables the formation stable insoluble PIC of various sizes. To prolong the retention time of NPs in blood circulation to increase their chance to reach the target tissue, the size of NPs should be in the range of 100 to 200 nm to avoid clearance of NPs by liver and spleen. Drexel researchers have developed specific formulations, fabrication method, and collection method to obtain NPs in the desired size range (120-200 nm) with high yield. In addition, it was found that DS can be replaced by some other negatively charged polymers such as heparin (Hep) in order to inhibit oxLDL uptake by macrophages and promote cholesterol efflux from foam cells.
Addition of FDA approved drugs such as minocycline and curcumin into the NPs enhances their effect. Minocycline is an anti-inflammatory and antioxidant drug that can reduce local inflammation and oxidation of LDL leading to a direct effect on reducing the toxic environment present in a plaque. Curcumin has been shown to reduce oxLDL uptake and increase cholesterol efflux. It was found that pre-treating macrophages with DS-CH NPs loaded with curcumin followed by treating the cells with oxLDL without NPs can effectively inhibit foam cell formation. This suggests that NPs can have long-lasting effect on inhibiting foam cell formation even after the NPs are cleared from blood circulation.

Application area

Preventing and reversing atherosclerosis
Reducing the risk of acute MI, stroke and development of cardiovascular disease

Advantages

Injectable alternative to apheresis
Has the potential to actually reverse atherosclerosis by pharmaceutical means

Institution

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