490d Nanoscale Macromolecules for Modulating Cell-Ldl Interactions

Nicole M. Plourde, Nicole Iverson, Evangelia Chnari, Jinzhong Wang, Kathryn Urich, and Prabhas Moghe

Atherosclerosis, the single most prevalent form of vascular disease, is triggered by interactions between macrophages and smooth muscle cells and their extracellular matrix molecules, following the pathologic build-up of low density lipoproteins (LDL) within the vascular intima. Low-density lipoproteins (LDL) travel through the injured endothelium into the intima, where they are retained by extracellular matrix components called ptroteoglycans. Subsequent interaction of LDL with macrophages leads to uncontrolled uptake through scavenger receptors and foam cell formation, which results in increased cytokine formation and release that causes an inflammatory response in both endothelial cells and smooth muscle cells. LDL matrix retention within the intima is one of the key steps in the pathobiological cascade of atherogenesis. Many therapeutic approaches focus on inhibiting the synthesis of lipoproteins and do not target the management of lipoproteins sequestered within the intima. The objective is to develop nanoscale polymeric macromolecules, which can complex with LDL by mimicking the interactions between proteoglycans and LDL and control its cellular uptake. A second key feature of these nanocarriers is the ability to block surface scavenger receptors that play a role in LDL binding on macrophages and smooth muscle cells. A third mechanism to regulate LDL is to encapsulate a drug or vitamin within the micelles and biofunctionalize the nanocarriers to preferentially bind to inflamed cells and deliver the drug directly to the point of distress. The proposed nanocarriers consist of a hydrophobic part (alkyl chains), a hydrophilic part (methoxy-poly(ethylene glycol) chains) and a mucic acid. When functionalized with anionic groups, these nanocarriers can form micelles in aqueous solutions, which can project GAG-mimetic sites for electrostatically governed capture of LDL. Using dynamic light scattering it was shown that the nanocarriers were able to retain native and mildly oxidized LDL, whereas they did not sequester highly oxidized LDL. Nonetheless, uptake experiments showed that the nanocarriers prevented the uptake of all levels of oxidized LDL. Nanocarriers with such characteristics could sequester LDL at a mild oxidation state and present it to the cells in a controlled way to prevent damage, block the receptors responsible for the binding of highly oxidized LDL, and deliver drugs directly to the already inflamed cells.