Brief communication

Carbohydrate composition of amphiphilic macromolecules influences physicochemical properties and binding to atherogenic scavenger receptor A

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1. Introduction

Atherosclerosis, the occlusive artery disease, is triggered by the build-up of oxidized low density lipoprotein (oxLDL) in blood vessel walls [1]. The oxLDL accumulation generates an inflammatory response which results in the recruitment of circulating monocytes followed by their differentiation to macrophages and upregulation of macrophage membrane-based scavenger receptors [2]. The major scavenger receptors, namely scavenger receptor A (SR-A) and CD36, mediate the uptake of oxLDL [3–5], leading to unregulated cholesterol accumulation and foam cell formation, a key characteristic of the onset of atherogenesis [6,7].

Aside from lifestyle changes, cholesterol lowering therapies (i.e. statins) are the most common methods for atherosclerosis treatment. Such drugs, however, indirectly mediate atherosclerosis by decreasing cholesterol synthesis, which ultimately results in decreased oxLDL in the blood vessel walls. A more direct and promising approach in the treatment and prevention of atherosclerosis involves designing functional inhibitors against scavenger receptors to abrogate uncontrolled oxLDL uptake [8–11]. Our research group has previously presented carbohydrate-based, nanoscale amphiphilic macromolecules (AMs) that competitively inhibit scavenger receptor-mediated oxLDL uptake [12,13]. Comprising a hydrophobic domain based on the sugar, mucic acid, acylated with four aliphatic chains, and a hydrophilic poly(ethylene glycol) (PEG) tail, the AMs exhibit high biocompatibility and stability [14]. Further, the AMs self-assemble into micelles in aqueous media at relatively low (10−7 M) concentrations, enabling drug encapsulation within the micellar core. To understand the key structural features relevant to oxLDL inhibition, systematic variations to the AM structure were performed, including the PEG chain length, PEG architecture and aliphatic chain length as well as type, charge, number, and rotational motion of anionic charges. These studies also tested whether amphiphilicity was a significant attribute in preventing oxLDL internalization [15,16]. The structure–function studies demonstrated that while amphiphilicity was necessary, it alone was insufficient; charge and hydrophobicity better contributed to the polymer’s ability to inhibit oxLDL uptake. Overall, anionic charge and a rigid, hydrophobic carboxylic acid presentation significantly enhanced the inhibitory activity of AMs.

The AM hydrophobic domain compositions have not been optimized to date, however, and the impact of carbohydrate stereochemistry and conformation remain to be elucidated. Minute changes in carbohydrate stereochemistry and conformation can...