Hydrophilic nanoparticles for active targeting atherosclerosis

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1. Introduction

Atherosclerosis, characterized by the build-up of lipid-rich plaques within the artery wall, is one of leading causes of cardiovascular disease such as myocardial infarction, stroke, and chronic angina [1–3]. The size and composition of the atherosclerotic plaque are responsible for its pathophysiological behavior [4,5]. In general, vulnerable plaques susceptible to rupture, which are associated with acute syndromes and death, contain a large number of inflammatory cells, large lipid cores, and thin fibrous caps [1,6]. The currently available drugs for atherosclerosis have the functions to alleviate hypertension and hyperlipidemia or to control hemostasis for prevention of thrombotic complications. However, they do not directly suppress the inflammatory mechanisms driving progression of atherosclerosis. Although there are emerging therapeutics such as high-density lipoprotein mimetics and IL-1 receptor antagonist [7–9], their targeted delivery to the atherosclerotic lesion by the passive targeting mechanism. Overall, it was evident that HA-NPs could effectively reach the atherosclerotic lesion via the active targeting mechanism after systemic administration, implying their high potential as the carrier for diagnosis and therapy of atherosclerosis.

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artery wall, and the plaque volume. However, they are often too invasive and do not impart information on functional changes in arterial walls. Therefore, there is an urgent need to develop the improved techniques by using the imaging probe which can specifically accumulate in the atherosclerotic lesion.

Over the last two decades, significant efforts have been made to develop nanoparticles for diagnosis and therapy of atherosclerosis [10]. For high diagnostic and therapeutic efficacy, they should have the ability to identify the targets at the atherosclerotic lesion such as integrins, adhesion molecules, and receptors [2,4]. Therefore, the surfaces of nanoparticles have often been decorated with the targeting moieties including antibodies, proteins, peptide, or other ligands [10–15]. Recently, our group has demonstrated that stabilin-2 (also called HARE), a receptor for hyaluronic acid (HA), is highly expressed in atherosclerotic plaques than in normal vessels [12]. In particular, stabilin-2 was abundant on macrophages, smooth muscle cells, and endothelial cells of atherosclerotic plaques. When polymeric nanoparticles bearing stabilin-2-specific peptide ligand were systemically administered into the low-density lipoprotein receptor-deficient (Ldlr−/−) mice, they were selectively accumulated into the atherosclerotic lesion. These results imply that stabilin-2 can be a primary target of atherosclerosis to make the nanoparticles for imaging and therapy.

Owing to its high biocompatibility and biodegradability, hyaluronic acid (HA) has attracted much attention for biomedical applications such as tissue engineering and drug delivery systems [16–18]. In particular, HA-based nanoparticles or nanoconjugates have shown promising potential as the drug carrier for cancer therapy, since HA can specifically bind to CD44 which is overexpressed on various cancer cells [19–23]. Interestingly, CD44 is

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**Fig. 1.** Development of hyaluronic acid nanoparticle (HA-NPs) for targeting atherosclerosis. (A) Chemical structure and (B) Illustration of HA-NPs. (C) Schematic illustration of active targeting atherosclerosis by HA-NPs.