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Original Contribution

Mature proprotein convertase subtilisin/kexin type 9, coronary atheroma burden, and vessel remodeling in heterozygous familial hypercholesterolemia

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BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9), an important contributor to low-density lipoprotein metabolism in heterozygous familial hypercholesterolemia (HeFH), exhibits direct proatherogenic effects. PCSK9 circulates as mature and furin-cleaved forms, which differ in its biological activity. However, it remains to be elucidated whether each PCSK9 subtype has different atherogenic properties.

OBJECTIVE: To investigate the association of each PCSK9 subtype with coronary atherosclerosis in HeFH.

METHODS: About 204 nonculprit segments in 138 HeFH subjects with coronary artery disease were evaluated by using intravascular ultrasound. Mature, furin-cleaved PCSK9 and total concentration of PCSK9 subtypes were measured by using enzyme-linked immunosorbent assay (BML Inc., Tokyo, Japan). The relationship of these PCSK9 values with intravascular ultrasound measures was investigated.

RESULTS: Mature PCSK9 level was positively associated with percent atheroma volume (PAV: $r = 0.78$, $P = .003$). Despite extensive atheroma under a higher mature PCSK9 level, vessel volume did not change across any mature PCSK9 levels ($r = 0.05$, $P = .78$). These responses resulted in smaller lumen volume, which was negatively correlated to mature PCSK9 level ($r = 0.65$, $P = .009$). By contrast, there were no significant relationships of PAV with furin-cleaved ($r = 0.12$,

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P = .45) and total PCSK9 (r = 0.37, P = .25) levels. On multivariate analysis, mature PCSK9 level independently contributed to PAV (odds ratio: 1.45, 95% confidence interval: 1.11–1.67, P = .01). Even in subjects with low-density lipoprotein cholesterol level <2.6 mmol/L, greater PAV was still observed in association with an elevated mature PCSK9 level (P = .003).

CONCLUSIONS: Mature PCSK9 associated with atheroma volume and impaired vessel remodeling in HeFH patients with coronary artery disease. These findings suggest the potential role of mature PCSK9 in propagation of coronary atherosclerosis in HeFH.

Introduction

Considerable attentions have focused on proprotein convertase subtilisin/kexin type 9 (PCSK9) as a novel therapeutic target to further lower low-density lipoprotein cholesterol (LDL-C) in patients with heterozygous familial hypercholesterolemia (HeFH). PCSK9 elevates LDL-C level via degrading low-density lipoprotein receptor (LDLR).[1–3] In addition to its role in LDL metabolism, PCSK9 has been shown to directly promote inflammatory activities, oxidative stress, and atheroma formation.[4–8] These findings suggest a critical role of PCSK9 in a marked elevation of LDL-C level and atherosclerotic cardiovascular disease in HeFH subjects.

Despite these proatherogenic properties of PCSK9, inconsistent relationship between circulating PCSK9 level and atherosclerotic cardiovascular diseases has been reported in recent cohort studies.[9,10] This observation may be possibly due to the notion that measurement of circulating PCSK9 does not necessarily reflect its biological activity. PCSK9 circulates as mature and furin-cleaved forms (Fig 1).[11,12] Although mature PCSK9 has the ability to degrade LDLR, furin-cleaved form has been shown to have no activity modulating LDLR.[13] These distinct features suggest mature PCSK9 as a major contributor to atherosclerosis in HeFH subjects rather than furin-cleaved form. Our group has recently developed a novel sandwich enzyme-linked immunosorbent assay (ELISA), which enables to measure mature, furin-cleaved forms and total PCSK9 concentrations, quantitatively and respectively.[14] Therefore, the present study sought to determine the association of total PCSK9 and its subtypes with coronary atherosclerosis in HeFH subjects with coronary artery disease (CAD) by using intravascular ultrasound, which visualizes coronary atheroma burden in vivo.[15–18]

Material and methods

Study population

The present study enrolled 153 HeFH subjects with CAD who underwent intravascular ultrasound (IVUS) imaging before percutaneous coronary intervention (PCI) from January, 2010, to December, 2015. The diagnosis of HeFH in Japan was conducted according to the presence of the following 2 or more factors: LDL-C≥ 4.6 mmol/L, tendon/skin xanthomas, and a family history of FH or premature CAD within the second degree of kinship.[19] Of these, 15 patients were excluded due to suboptimal quality of IVUS images (n = 11) and bypass graft imaging (n = 4). The remaining 138 patients were included in the current analysis. The study was approved by the Institutional Review Board committee of the National Cerebral Cardiovascular Centre, and all patients provided written informed consent.

Acquisition of IVUS images

IVUS imaging of the entire target vessel for PCI was performed as previously described.[15–18] In brief, an IVUS catheter (30–40 MHz) was advanced to the distal site of the target artery for PCI after intracoronary administration of nitroglycerin (100–300 μg). Continuous ultrasonic imaging was acquired at a constant rate of 0.5 mm/s. When patients had multiple target vessels requiring PCI, all these vessels were imaged and included into the analysis. Images

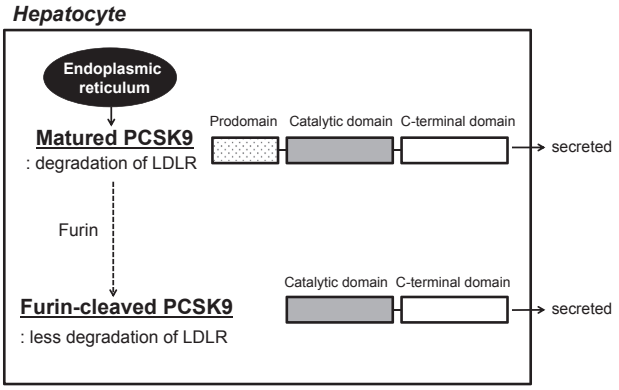

Figure 1 Schematic diagram of the structure of mature and furin-cleaved PCSK9. Mature PCSK9 is synthesized by endoplasmic reticulum. It consists of prodomain, catalytic domain, and C-terminal domain. Following cleavage of mature PCSK9 by furin, furin-cleaved PCSK9 is formulated. Hepatocytes secrete both PCSK9 subtypes into the circulation. LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.