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Editorial

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A Novel Indicator for HDL Functionality

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Although several epidemiological studies have revealed that high-density lipoprotein (HDL) cholesterol (HDL-C) is a negative risk factor for coronary artery disease (CAD), clinal trials on increased HDL-C levels have failed to show the beneficial effects of HDL-C as an anti-atherosclerotic factor[1]. These results prompt us to determine whether the anti-atherosclerotic effects of HDL depend on its quality.

While the anti-atherosclerotic action of HDL is principally attributable to the reverse cholesterol transport (RCT) from peripheral cells to the liver, HDL has multiple anti-inflammatory and anti-oxidative actions. Therefore, functional assays for determining its role have garnered interest[2]. Several metrics have been developed for the assessment of specific functions of HDL[3] (**Table 1**). Among them, assessment of cholesterol efflux capacity (CEC), which is related to the initiation of RCT, is a common method to examine the anti-atherosclerotic effects of HDL. In fact, Rohatgi *et al.*[4] have reported in a large cohort study that CEC is an inverse predictor of CAD, independent of HDL-C levels. However, the quantification of CEC is not yet suitable in clinical settings because the procedure not only requires cultured cells but also is time-consuming. This problem has been much overcome recently by the establishment of a cell-free assay system for cholesterol uptake capacity (CUC) of HDL, which can allow a high-throughput and automated characterization of HDL function[5, 6].

The anti-oxidative activity of HDL is one of its functions besides RCT. Myeloperoxidase (MPO) and paraoxonase 1(PON1) are the binding proteins of HDL and are associated with oxidant stress and atherosclerosis. MPO, PON1, and HDL form a ternary complex wherein PON1 partially inhibits MPO activity, whereas MPO inactivates PON1[7]. It is of interest to examine whether MPO and PON1 activities are associated with HDL functions. A recent study has suggested that serum MPO/PON1 ratio is a potential indicator of dysfunctional HDL and risk stratification in patients with CAD[8]. Thus, evaluation of MPO and PON1 activities provides an alternative way of measuring the anti-atherosclerotic effects of HDL. In addition, Navab *et al.*[9] have developed a cell-free assay to assess the anti-oxidative activity of HDL, which helps prevent the formation of oxidized phospholipids. Moreover, nuclear magnetic resonance (NMR) spectroscopy enables determining the size and number of HDL particles based on its physical properties[10]. NMR analysis is a simple assay, which does not require sample preparation but requires expensive and specialized equipment.

In an issue of Journal of Atherosclerosis and Thrombosis, Kakino *et al.*[11] have reported developing a new system that determines the functional activity of HDL depending on its binding affinity to low-density lipoprotein receptor-1 (LOX-1). They have defined the LOX-1 ligand containing ApoA-1 (LAA) as an indicator of HDL function and reported that LAA is associated with HDL oxidation, leading to a decrease in the CEC and PON1 activities in HDL. Because of the heterogeneity of HDL subpopulations, there is a need for evaluating the whole dysfunctional activity of HDL. In this regard, and in addition to a high reproducibility, the LAA methodology may be superior to other conventional methods. Even if LAA is a surrogate marker of HDL functionality, the findings reported by Kakino *et al.*[11] have expanded our understanding and repertory of the HDL functional-

Key words: **High-density lipoprotein, Low-density lipoprotein receptor-1, HDL functionality**

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Table 1. HDL functional assay

Method	Advantages	Limitations
Cholesterol efflux capacity	Gold standard Inversely associated with CAD	Low throughput Require culture cells
Cholesterol uptake capacity	Rapid, reproducible and automated	Lack evidence in a large clinical trial to predict CAD events
MPO and PON1 assay	Rapid and reproducible	Lack evidence in a large clinical trial to predict CAD events
Anti-oxidant capacity assay	Cell-free assay	Lack validation in large-scale clinical samples
NMR spectroscopy	No sample preparation Directly estimate particle size and number	Require specialized equipment

MPO: myeloperoxidase; PON1: paraoxonase 1; NMR: nuclear magnetic resonance

ity assays. Molecular mechanisms through which the binding affinity of HDL to LOX-1 modulates HDL functions, as well as the precise HDL function related directly to LAA, need to be determined in the near future. Because this paper implies the relationship between HDL function and the binding affinity of HDL to proteins such as LOX-1, proteome study for exploring binding proteins with impaired HDL can help find a clue to the understanding of physiological and pathological activities of dysfunctional HDL.

With the recent emergence of new methodologies such as CUC and LAA assays, HDL function assays have gained greater potential to be applied into clinical practice. The significance of HDL functionality should be further validated in large-scale clinical trials to determine its utility to predict CAD, which could eventually replace HDL-C as a routine cardiovascular risk biomarker.

Conflict of Interest

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