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LETTER TO THE EDITOR

Decreased expression of platelet human scavenger receptor class B type I in patients with type 2 diabetes mellitus

Diabetes and prediabetic conditions are associated with derangement of platelets and coagulation. Previously, we have reported that human scavenger receptor class B type I (hSR-BI/CLA-1), a receptor for high-density lipoprotein (HDL), is expressed on the surface of and within human platelets[1]. The levels of hSR-BI/CLA-1 expression are inversely correlated with the cholesterol ester content and aggregation of platelets obtained from patients with atherosclerotic disease. A recent report showed that oxidatively modified HDL (OxHDL) exhibits potent antiplatelet activity through platelet-expressed hSR-BI/CLA-1[2].

To determine the expression of hSR-BI/CLA-1, platelets were incubated with anti-SR-B1/CLA-1 guinea pig antibody (5:100 dilution) and phycoerythrin (PE)-conjugated anti-CD41 antibody (Dako Japan, Tokyo, Japan), and then fluorescent cells were analyzed on a FACScan system (Becton Dickinson, San Jose, CA, USA) as previously described[1]. Platelet aggregation was examined by simultaneously measuring the maximum percent decrease in optical density (OD) and laser-light scattering intensity (LSI), using an aggregometer (PA-200; Kowa, Tokyo, Japan), as described previously[1].

The surface expression of hSR-BI/CLA-1 was significantly lower (approximately 40% decrease) in platelets derived from 22 patients with diabetes mellitus (glycated hemoglobin [HbA1c; National Glycohemoglobin Standardization Program (NGSP)] 7.9 ± 0.3%; no medication) than in those derived from age-matched healthy volunteers (HbA1c [NGSP] 5.6 ± 0.2%). In the absence of adenosine disphosphate (ADP), the degree of aggregation was similar in the patient-derived and control platelets. After stimulation with 100 nmol/L ADP, significantly more small aggregates were formed in the patient-derived platelets than in the control platelets ($P < 0.05$). In other words, the degree of aggregation was high in platelets expressing low levels of hSR-BI/CLA-1 (Table 1). The platelet aggregation was significantly correlated with HbA1c ($P < 0.05$). However, cholesterol ester accumulation and platelet aggregation were not significantly correlated with the plasma cholesterol, HDL, low-density lipoprotein (LDL) or triglyceride levels. These results suggest that the abundance of the hSR-BI/CLA-1 protein is inversely correlated with both the cholesterol ester content in and ADP-stimulated aggregation of platelets – two parameters that reflect platelet function.

Oxidative stress leads to the generation of at least two circulating products that affect platelet function – OxLDL and OxHDL. The OxLDL–CD36 axis triggers platelet activation and promotes aggregation, whereas OxHDL and its receptor, SR-BI/CLA-1, appear to provide a natural shield mechanism restricting excessive platelet stimulation and subsequent thrombotic events[2]. Recent reports showed that native HDL also inhibited platelet aggregation through SR-BI. The inhibitory effects of native HDL, moderately oxidized HDL and SR-BI ligands were abolished in SR-BI-deficient platelets, but not in CD36-deficient platelets[3]. Sagel *et al.*[4] reported that platelets are sensitive to aggregating agents (e.g., ADP and collagen), and this feature is most prominent in patients with frank diabetes, moderately prominent in those with latent diabetes and minimally prominent in those with prediabetes. These observations suggest that platelet aggregation might be increased in early diabetes, and might be involved in the development of diabetic microangiopathy[4]. Future studies should explore the regulatory mechanisms of hSR-BI/CLA-1 in diabetes mellitus.

Table 1 | Summary of the findings

	Control ($n = 22$)	DM patients ($n = 22$)	*P*
Age	54 ± 6.2	56 ± 8.2	NS
Male/female	12/10	13/9	
BMI	23.73 ± 3.7	24.32 ± 4.1	NS
TG (mg/mL)	125.2 ± 21.2	168.7 ± 41.2	<0.05
T-Chol (mg/mL)	177.2 ± 19.8	221.8 ± 28.6	<0.05
HDL (mg/mL)	51.5 ± 7.2	48.1 ± 11.5	NS
SR-BI/CLA-1 expression (%)	32.4 ± 8.23	19 ± 5.87	<0.05
PCE/PTC (%)	8.8 ± 1.2	15.0 ± 1.8	<0.05
Platelet aggregation (AUC × 10^6)	6.3 ± 3.2	22.6 ± 7.3	<0.05

DM, diabetes mellitus; HDL, high density lipoprotein; NS, no significant difference; PCE/PTC, platelet cholesterol ester / platelet total cholesterol; SR-BI/CLA-1, human scavenger receptor class B type I; TG, triglyceride; T-Chol, total cholesterol.

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In summary, the expression levels of hSR-BI/CLA-1 are negatively correlated with platelet aggregation in diabetes mellitus patients.

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