Editorial

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Possible Regulation of Platelets by Native and Modified Low Density Lipoprotein-Cholesterol Particles

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An excess number of low density lipoprotein-cholesterol (LDL-C) particles is an independent risk for a cardiovascular event in the future. LDL particles diffused into the developing atherosclerotic plaques bind to proteoglycans in the intima, become oxidized and phagocytosed to macrophages. This causes the generation of foam cells, which aggravate the generation of fatty streaks and induce platelet attachment.[1)]

It is highly probable that platelets may have contact with oxidized LDL (oxLDL).[2)3)] Several results describe that oxLDL can be exposed to circulating blood or can even be formed in plasma at sites of oxidative stress. Platelets express a series of receptors that specifically recognize oxLDL, such as CD36 and scavenger receptor A (SRA). oxLDL-bound CD36 and SRA induce phosphorylation of p38 MAP kinase (MAPK), which in turn triggers the production of thromboxane A2 through the activation of a cytoplasmic type of phospholipase A2.[4)] Thus, the stimulation with oxLDL enables platelets to induce aggregation independently or with other stimulatory signals such as adenosine diphosphate (ADP), collagen or thrombin in a synergistic manner.

Unlike oxLDL, native and non-oxLDL particles are functionally inert and little has been described regarding the activity of native LDL on any type of cells that may contribute to the development of atherosclerosis. Interestingly, platelets express the variant form of ApoB/E receptor (ApoB/E-R) and it contains specific amino acid sequences, which recognize and bind to apoB100 apoproteins. Platelet ApoE-R2' messenger ribonucleic acid encodes a 130 kDa protein with a single ligand-binding domain that comprises four complement repeats (eight in ApoE-R2 complementary deoxyribonucleic acid), an epidermal growth factor precursor homology domain with an YWTB domain for ligand disscociation, a β-propellor, an O-linked sugar domain, and a single transmembrane domain connected to a short cytoplasmic tail. LDL particles can activate the Thr/Tyr protein kinase p38MAPK in platelets, which is expected to trigger signals for the platelet aggregation, too.[5)] Recent result showed evidence that LDL particles may prime the aggregating activity of platelets in response to ADP and other agents, but the potency remains uncertain.[6)]

An article by Kang et al.[7)] published here described that there was no significant association between LDL particle size and on-treatment platelet reactivity (OPR) in patients undergoing percutaneous coronary intervention. All subjects had dual anti-platelet therapy with aspirin and clopidogrel and they measured the magnitude of platelet agglutination induced by either arachidonic acid in the aspirin assay and ADP, and prostagladin E1 in the P2Y12 assay. Platelet reactivity was reported as aspirin reaction units (ARU) and P2Y12 reaction units (PRU). A higher reaction unit, which reflected higher OPR was defined as an OPR greater than 454 ARU or 264 PRU, which could be regarded as resistant to antiplatelet agents.

There are several possibilities to show the negative relationship between platelet activity and the characteristics of LDL particles.

First, the dominance of small-dense LDL-C suggests a greater number of LDL particles at the same level of LDL-C, which may prime circulating platelets to show an exaggerated response upon the secondary stimulation with ADP etc. However, LDL-C levels for all subjects were very low (<100 mg/dL), which may minimize the functional relevance of LDL particle size on the platelet activities.

Second, small-dense LDL particles are relatively labile and vulnerable to oxidation. Although a group of subjects had small-dense LDL

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dominancy, most isolated platelets from the circulation may not have a chance to be exposed to the modified form of small-dense LDL.

Third, the small-dense LDL-dominant phenotype may reflect a population group that has a higher incidence of cardiovascular disease risks, suggesting that small-sense LDL is a marker as well as a direct mediator. Unfortunately, the subjects analyzed in this study did not show any significant difference of major clinical parameters between type A and B phenotypes and only one exception was the lower HDL-cholesterol levels in type B. It is notable that the medication with statin, for example, was not controlled in this study, which may have been medicated to most subjects. Such intensive lipid modification may diminish the deference of A and B phenotypes. Several reports describe the phenotypic change of A and B types after the statin medication especially atorvastatin.[8]

During the process of platelet aggregation, other signals also play an important role, too. For instance, lysophosphatidic acid (LPA) generated by lipid oxidation activates the Rho-A pathway in platelets through LPA-receptor activation. Guanosine triphosphage (GTP)-protein G13α and Rho kinase are known to be involved in the process and the resulted phosphorylation of myosin light chain (LC) drives the disc to sphere transition known as the shape change of platelets, which is one of the earliest responses induced by platelet agonists. Moreover, LPA at a higher dose activates the GTP-protein Gq inducing Ca^{2+} mobilization and mechanisms that control Ca^{2+} entry. The rise in Ca^{2+} activates calmodulin-mediated phosphorylation of myosin LC facilitating actin binding. The capacity to increase cytosolic Ca^{2+} makes mildly oxLDL an independent activator inducing aggregation and secretion in the stirred suspensions of platelets.[9] Therefore, intensive medical treatment with statins as well as with aspirin and clopidogrel may substantially suppress the activity of platelets at various levels and may precipitate the study result to show an insignificant cause-and-effect relationship in general.

Further studies about atherogenic and thrombogenic potential are anticipated in order to evaluate the impact of small-dense LDL particles on platelet activities.

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