Scavenger Receptor A and CD36 Are Implicated in Mediating Platelet Activation Induced by Oxidized Low-Density Lipoproteins

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36, previously known as GPIIIb or GPIV, is an 88-kDa membrane glycoprotein that was isolated from blood platelets soon after being identified on monocytes by monoclonal antibody OKM5. Cloning the CD36 gene showed this cell adhesion molecule to be a member of the scavenger receptor class B family. Moreover, it was observed that CD36 has the capacity to bind oxidized low-density lipoproteins (oxLDL) but not acetylated lipoproteins. Scavenger receptor class A (SRA),1 also expressed on platelets and monocytes/macrophages, is a trimer of 77 kDa, that binds to acetylated and oxidized lipoproteins. SRA is closely associated to macrophage CD36 in initiating atherosclerotic lesions, in some studies but not all.2,3,4 Very little was known, up to now, on the role played by oxLDL in activating platelets via CD36 and SRA and promoting a prothrombotic phenotype.

The study, in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, by Suzanne Korporaal and coworkers,5 shows very elegantly that oxLDL, in tandem with CD36 and SRA, is activating platelets and potentially increasing the risk of thrombosis. This investigation brings some exciting data on a novel platelet-activating pathway triggered by partially oxidized (30% to 60%) LDL and mediated by the combined activity of CD36 and SRA. The authors observed a 2-fold increase, with no change in transient kinetics, in the phosphorylation of platelet p38MAPK induced by oxLDL compared with native LDL (nLDL). Such an increase was not attributable to stronger activation of the LDL receptor family member apolipoprotein E receptor-2 (apoER2’), also known as LRP8.6 Indeed, the authors had previously shown that apoER2’ mediates nLDL activation of p38MAPK, which subsequently induces platelet hypersensitivity to agonists.7 The authors used several different strategies in their quest to identify whether oxLDL triggers p38MAPK activation via apoER2’ or the lysosphosphatic acid (LPA) receptors. They initially saturated the apoER2’ receptors with nLDL and then added a further dose of nLDL or oxLDL. Results obtained show that addition of oxLDL, but not nLDL, increased p38MAPK activation to a level similar to that observed with oxLDL when added to platelets in the absence of nLDL. Alternatively, when using a receptor-associated protein (RAP) to block nLDL binding to apoER2’, they observed that RAP, while blocking nLDL phosphorylation of p38MAPK, had no effect on oxLDL. Finally, both chondroitinase ABC, which completely abolished phosphorylation of p38MAPK by nLDL, and L-NASPA (an inhibitor of lysosphosphatic acid receptors LPA1 and LPA3) had no effect on oxLDL activity. Moreover, the nLDL receptor could be desensitized by repeated prolonged treatment with nLDL but not oxLDL. All these observations presented robust evidence to Suzanne Korporaal and coworkers that oxLDL was signaling in platelets through a receptor that was independent of apoER2’ and LPA1/LPA3. This incited them to look at the possibility that scavenger receptors CD36 and SRA could be implicated in binding oxLDL and in platelet activation. Interestingly, they found that blocking together CD36 (using a functional monoclonal antibody [FA6.15] known to bind to CD36 on a binding site of oxLDL) and SRA (using fucoidan which inhibits oxLDL binding to SRA) showed p38MAPK phosphorylation levels to be similar to those obtained in the absence of nLDL. Surprisingly, joint, but not individual, blockage of CD36 and SRA completely shut down the p38MAPK phosphorylation induced by oxLDL but had no effect on nLDL signaling activities (see the Figure). These results, further confirmed by the authors using murine platelets that were deficient in either CD36 or SRA, clearly show that these 2 major scavenger receptors are required for oxLDL signaling in blood platelets. Activation of p38MAPK by oxLDL enhanced adhesion of platelets to immobilized fibrinogen. Blocking the 2 scavenger receptors, as previously described, or the use of an inhibitor of p38MAPK very significantly reduced the adhesion of platelets to immobilized fibrinogen. The presence of a P2Y12 blocker did not affect the enhanced adhesion of platelets to fibrinogen induced by oxLDL.

The observations by Suzanne Korporaal et al further amplify and buttress the role of oxLDL and platelet scavenger receptors after those published, a few weeks earlier, by Eugene Podrez and coworkers8 where they beautifully showed the role of CD36 in promoting platelet activation via endogenous oxidized phospholipids. Oxidation of LDL generates oxidized phospholipids such as oxidized choline glycerophospholipids (oxPCCHO) that are present in the plasma of humans with low HDL levels and in hyperlipidemic mice. Several lines of evidence were used by Podrez et al to implicate oxLDL and CD36 in a prothrombotic phenotype. They observed that occlusion of mesenteric arterioles after injury in ApoE−/− hyperlipidemic mice was considerably shortened in platelets of animals expressing CD36 compared with those who were CD36 deficient. Hyperaggregable platelets responding to threshold dose of ADP were observed in
ApoE<sup>−/−</sup> hyperlipidemic animals expressing CD36 but not in those that were CD36<sup>+/−</sup>. Moreover, and most significantly, fibrinogen bound to platelet α<sub>IIbβ<sub>3</sub> even in the absence of ADP, by hyperlipidemic plasma or by oxPC<sub>CD36</sub> in platelets expressing CD36 but not in those that were CD36 deficient. Finally, release of P-selectin by platelets activated by oxPC<sub>CD36</sub> or oxidized LDL, occurred only when CD36 was expressed by platelets.

Levels of oxLDL in circulation may be increased in patients with atherosclerotic diseases but are thought to be generally low. However, it is possible that diseased vessel walls release oxLDL in a microenvironment, after plaque fissuration or ulceration, which would sensitize platelets in the immediate vicinity and induce them to become more responsive to subthreshold concentrations of activating agonists. Alternatively, in patients with low HDL levels, oxidized phospholipids such as oxPCCD36 may equally induce a prothrombotic phenotype with severe clinical consequences. Antithrombotic therapy related to the role of oxLDL on platelets could involve treatment of patients by statins to downregulate platelet scavenger receptor expression.9

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