

Regulation of Platelet Function by Class B Scavenger Receptors in Hyperlipidemia

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Abstract—Platelets constitutively express class B scavenger receptors CD36 and SR-BI, 2 closely related pattern recognition receptors best known for their roles in lipoprotein and lipid metabolism. The biological role of scavenger receptors in platelets is poorly understood. However, in vitro and in vivo data suggest that class B scavenger receptors modulate platelet function and contribute significantly to thrombosis by sensing pathological or physiological ligands, inducing prothrombotic signaling, and increasing platelet reactivity. Platelet CD36 recognizes a novel family of endogenous oxidized choline phospholipids that accumulate in plasma of hyperlipidemic mice and in plasma of subjects with low high-density lipoprotein levels. This interaction leads to the activation of specific signaling pathways and promotes platelet activation and thrombosis. Platelet SR-BI, on the other hand, plays a critical role in the induction of platelet hyperreactivity and accelerated thrombosis under conditions associated with increased platelet cholesterol content. Intriguingly, oxidized high-density lipoprotein, an SR-BI ligand, can suppress platelet function. These recent findings demonstrate that platelet class B scavenger receptors play roles in thrombosis in dyslipidemia and may contribute to acute cardiovascular events in vivo in hypercholesterolemia. (*Arterioscler Thromb Vasc Biol.* 2010;30:2350-2356.)

Key Words: lipids ■ lipoproteins ■ oxidized lipids ■ platelets ■ signal transduction

Scavenger receptors (SR) are a group of structurally heterogeneous cell surface receptors that share an ability to recognize chemically modified or oxidized forms of low-density lipoprotein (LDL). SR belong to a wider family of pattern recognition receptors that mediate the innate immune host response which includes Toll-like receptors. Platelets express several SR including class B SR CD36 and SR-BI, 2 closely related multiligand receptors, best known for their roles in lipoprotein and lipid metabolism.¹ Other platelet SR include LOX-1 and CD68.¹ Expression of class B SR in platelets is mainly constitutive, whereas other receptors are rapidly exposed on platelet activation. Ligands for these receptors can be roughly divided into 3 groups: physiological ligands, pathological endogenous (changed self) ligands, and pathological exogenous ligands. Pathological endogenous ligands for platelet SR may be present in circulation in a number of pathophysiological states related to dyslipidemia and oxidative stress. Pathological exogenous ligands may be present in cases of infections. The biological role of SR in platelets is not understood yet. However, evidence is accumulating that SR contribute significantly to thrombosis by sensing pathological or physiological ligands, inducing prothrombotic signaling, and increasing platelet reactivity. This in turn may lead to thrombosis in the presence of threshold concentrations of agonists. Platelet hyperreactivity or increased platelet response to agonists is associated with

augmented platelet adhesion, integrin activation, and aggregation.²⁻⁴ Subjects with increased measures of platelet reactivity are at increased prospective risk for coronary events and death.³⁻⁷ The pathophysiological significance of prothrombotic effects of platelet hyperreactivity may be very large.⁸ The mechanisms responsible for enhancing platelet reactivity in vivo during dyslipidemia are gradually emerging, particularly because of the availability of novel murine knockout models, but these mechanisms are still poorly understood. The data demonstrating that class B SR modulate platelet reactivity under conditions of hyperlipidemia and oxidative stress and contribute to cardiovascular events are reviewed below.

Platelet CD36, Oxidized Phospholipids, and Thrombosis

CD36 is a multifunctional cellular receptor with broad ligand specificity that is expressed on macrophages, platelets, microvascular endothelial cells, and other cells.⁹ It is structurally composed of 2 transmembrane and 2 cytoplasmic domains, as well as a large heavily glycosylated extracellular domain. CD36 regulates cellular adhesion and angiogenesis, serving as a receptor for thrombospondin. It serves as an SR in macrophages, mediating uptake of apoptotic cells and modified lipoproteins, and participates in carbohydrate and lipid metabolism, modulating insulin resistance and long-

Received on: September 16, 2010; final version accepted on: September 30, 2010.

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Arterioscler Thromb Vasc Biol is available at <http://atvb.ahajournals.org>

DOI: 10.1161/ATVBAHA.110.207498

chain fatty acid transport.^{10–15} CD36 has been implicated in a variety of pathological conditions, including atherosclerosis, diabetes, and cardiomyopathy.^{10,13,16,17}

Even though multiple lines of evidence suggest that CD36 may play a role in platelet activation, earlier studies of platelet function isolated from CD36 deficient patients did not demonstrate a significant role for platelet CD36 in physiological conditions.^{18–22} Since then, a number of various physiological and pathological ligands for CD36 have been identified raising a possibility that CD36 may play a role in platelet activation by pathological ligands. The incomplete list of CD36 ligands includes ghrelin, diacylated bacterial lipopeptide, lipoteichoic acid, phosphatidylserine, β -amyloid, serum amyloid A, and specific oxidized phospholipids (ox-PC_{CD36}).^{23–29} oxPC_{CD36} is generated when LDL or cellular phospholipids containing polyunsaturated fatty acids at the *sn*-2 position undergo oxidative attack. In general, oxidized phospholipids that are generated via mild physiologically relevant oxidative processes have been shown to possess multiple biological activities and are associated with an increased risk of cardiovascular events.^{30–33} oxPC_{CD36} represent a small fraction of total oxidized phospholipids that possess high affinity for CD36.^{29,34} Increased concentrations of oxPC_{CD36} were detected at sites of oxidative stress, such as human and animal atherosclerotic lesions.^{34,35} oxPC_{CD36} also accumulates in significant concentrations in plasma of hyperlipidemic apolipoprotein E (apoE)–deficient and LDL receptor–deficient mice.³⁶ In humans, a subset of patients with low high-density lipoprotein (HDL) levels have plasma oxPC_{CD36} levels comparable to that of hyperlipidemic animals.³⁶ In macrophages, oxPC_{CD36} mediate uptake of oxidized LDL (oxLDL) via CD36 and, subsequently, foam cell formation. The roles of oxPC_{CD36} and CD36 in atherosclerosis have recently been extensively reviewed.^{9,31} Because oxPC_{CD36} is present in plasma, a hypothesis has been proposed that the interaction of oxPC_{CD36} with platelet CD36 could modulate platelet function, potentially inducing prothrombotic signals associated with hyperlipidemia.³⁶

A defining feature of oxPC_{CD36} is an *sn*-2 acyl group that incorporates a terminal γ -hydroxy (or oxo)- α,β unsaturated carbonyl²⁹ (Figure 1a). Recent studies of the conformation of oxPC_{CD36} in the membrane have revealed that because of its polarity, the oxidized *sn*-2 fatty acid moiety of oxPC_{CD36}, instead of being buried within the membrane, protrudes into the aqueous phase, rendering it accessible for the receptors (Figure 1b).³⁷ Studies using a series of model oxidized phospholipids demonstrated that a terminal negatively charged carboxylate at the *sn*-2 position of oxPC suffices to generate high binding affinity to both class B SR, CD36 and SR-BI.³⁸ The minimal binding domain of CD36 for oxPC_{CD36}, has been identified recently.³⁹ It contains 2 conserved lysine residues that are indispensable for the binding activity. Subsequently, interaction via an electrostatic mechanism of negatively charged *sn*-2 moiety of oxidized phosphatidylcholine, exposed on the phospholipid surface, with positively charged residues in CD36 has been shown to play a key role in high-affinity binding.³⁹ It should be mentioned that to be a ligand for CD36, oxidized *sn*-2 residues should be part of the otherwise intact PC, containing the *sn*-1 hydrophobic

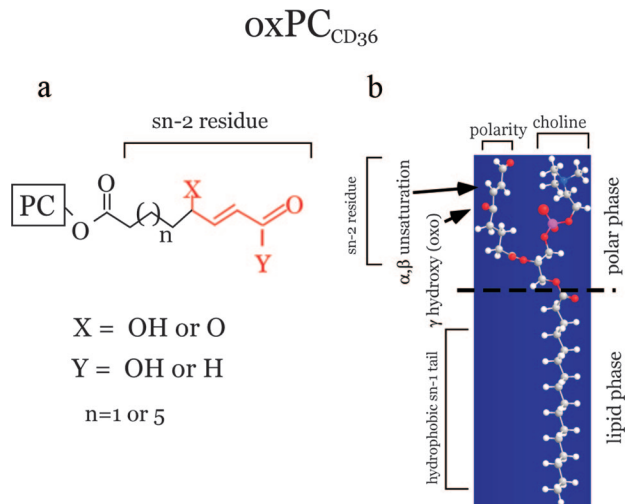


Figure 1. a, Structure and conformation of oxidized phospholipid-specific ligands for CD36 (oxPC_{CD36}). Truncated oxidized fatty acid esterified to the *sn*-2 position of oxidized phosphatidylcholine (PC) is shown. It contains a terminal aldehyde or carboxylic acid, a double bond in the β position, and a ketone or alcohol in the γ position. The core structural motif conserved among the various oxidized PC species that are high-affinity ligands for CD36 is shown in red. b, Unusual conformation of oxPC_{CD36} in the phospholipid membrane. The truncated polar *sn*-2 fatty acid moiety of oxPC_{CD36} protrudes into the aqueous phase, rendering it accessible for receptors such as class B SR.

chain and the *sn*-3 hydrophilic phosphocholine or phosphatidic acid group.³⁸ Additional factors, such as polarity, rigidity, optimal chain length of *sn*-2 and *sn*-3 positions, and a negative charge at the *sn*-3 position of phospholipids, further modulate the binding affinity.³⁸ Studies with model oxPC suggest that in addition to oxPC_{CD36}, other oxidized phospholipids observed in vivo, possessing some but not all features of oxPC_{CD36}, represent weak ligands for class B SR.³⁸

In vitro studies have shown that oxPC_{CD36} bind to platelets via CD36, activate platelets, and sensitize platelets to other agonists at pathophysiological concentrations.³⁶ In vivo relevance of these observations came from experiments with hyperlipidemic mice. A number of groups using several thrombosis models have demonstrated that hyperlipidemic apoE-deficient mice or LDL receptor-deficient mice do have a prothrombotic phenotype.^{36,40,41} The platelet contribution to this phenotype has been established only recently. In vitro studies demonstrate that platelets of hyperlipidemic apoE-deficient mice are hyperreactive to physiological agonists,³⁶ similar to platelets from hypercholesterolemic patients and other species of hypercholesterolemic animals.^{2,42–44} It has been demonstrated that a factor conferring hyperreactivity resides in hyperlipidemic plasma and identified as oxPC_{CD36}.³⁶ Genetic deletion of CD36 protected mice from hyperlipidemia-associated enhanced platelet reactivity and the prothrombotic phenotype. Moreover, studies in vitro have demonstrated that endogenous oxPC_{CD36} in human plasma modulate the platelet response to agonists via CD36.³⁶ oxPC_{CD36} binding peptides significantly inhibited thrombosis in vivo in hyperlipidemic apoE^{-/-} mice and had only a weak effect in normolipidemic mice (S. Panigrahi and E. Podrez, unpublished data, 2010). Similar results were obtained using

apoA-I mimetic peptide L-4F, capable of removing oxidized phospholipids from the plasma through direct binding.⁴⁵ Interestingly, recent findings have demonstrated that amyloids appearing as a result of protein misfolding induce platelet aggregation via an activation pathway mediated by CD36, p38 mitogen-activated protein kinase, and thromboxane A2.⁴⁶ It has been established that oxLDL contains amyloid-like structures, suggesting that this may be another CD36-dependent pathway activated by oxLDL in platelets.⁴⁷

In resting platelets, membrane CD36 is palmitoylated and localized in caveolin-negative, cholesterol-enriched lipid rafts, which also contain several Src family tyrosine kinases.^{48,49} There are also data indicating that in these lipid rafts, CD36 exists as a multiprotein complex containing, in addition to Src-family kinases, tetraspanin protein CD9 and fibrinogen receptor integrin $\alpha_{IIb}\beta_3$ or laminin receptor integrin $\alpha_6\beta_1$.^{48,50,51} The CD36 enriched fraction of platelet membranes is also enriched in GPIb, another major platelet glycoprotein essential for normal platelet adhesion and clot formation at sites of vascular injury.⁴⁹ The functional significance of the association of CD36 with platelet glycoproteins is not clear, even though it has been shown that signaling events induced via CD36 may lead to activation of $\alpha_{IIb}\beta_3$.³⁶ Src-family kinases associated with CD36 in platelets include Fyn, Lyn, and c-Yes.⁴⁸ Lyn and CD36 do not interact directly but do so through a lipid mediator,⁵² further pointing to the importance of raft-associated lipids in CD36-mediated signal transduction. It has been proposed that in resting platelets CD36-anchored Lyn is negatively regulated by Csk homologous kinase.⁵³ On platelet activation, CD36-anchored Lyn is released from suppression through the rapid translocation of Csk homologous kinase and subsequent dephosphorylation of its C-terminal negative regulatory tyrosine residue.⁵³

It has long been established that oxLDL induces platelet activation and adhesion and enhances platelet aggregation.^{54,55} Signaling pathways induced by oxLDL in platelets include activation of Rho/Rho kinase⁵⁶ and Src-family and Syk tyrosine kinases.^{57,58} A number of recent studies provide evidence of the signaling events initiated by oxLDL in platelets and mediated by CD36. One of the earlier events in this activation is the recruitment and activation of Lyn and Fyn to CD36.⁵⁹ This is followed by the downstream activation of mitogen-activated protein kinase kinase 4 and c-Jun N-terminal kinase 2 (Figure 2). The significance of this pathway is supported by the observation that pharmacological inhibition of JNK prolonged thrombosis times in wild-type mice but not in CD36-deficient mice.⁵⁹ The downstream targets of Lyn and Fyn include the Vav family of proteins. Vavs are rapidly phosphorylated in platelets in a CD36-dependent manner.⁵⁹ Silverstein et al reported that genetic deletion of Vav family members rescues the high-fat diet-induced prothrombotic phenotype in mice in a way similar to the rescue by CD36 knockout.⁵⁹ Downstream of CD36 is also p38 mitogen-activated protein kinase, which, according to a recent report, requires the SR class A for maximal activation by oxLDL.⁶¹ Mechanisms described in other cell types may be relevant to platelet activation by oxLDL but require further study. In macrophages, the generation of reactive oxygen

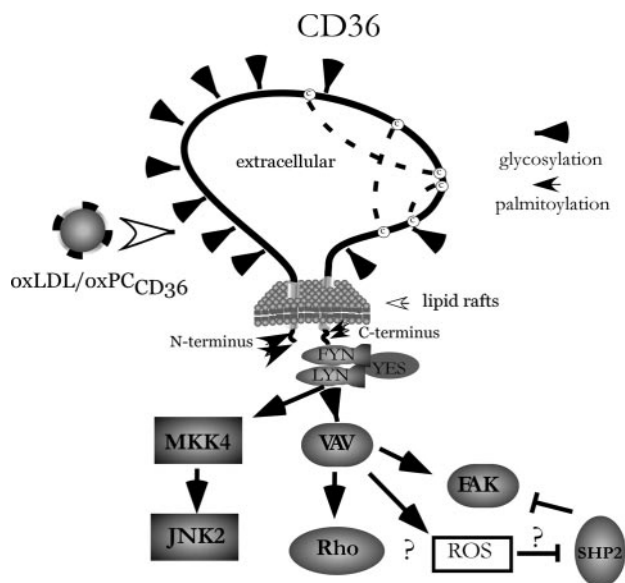


Figure 2. Signal transduction pathways induced by oxLDL and mediated by CD36 in platelets. oxPC_{CD36} in oxLDL induces specific signaling cascades after binding to the scavenger receptor CD36. Initially, Src-family kinases Fyn, Lyn, and Yes associate to CD36. Downstream events include the activation of mitogen-activated protein kinase kinase 4 (MKK4), c-Jun N-terminal kinase 2 (JNK2), Vav family proteins (VAV), Rho/Rho kinase (Rho), and focal adhesion kinase (FAK). CD36 also mediates the production of reactive oxygen species (ROS) that lead to the inactivation of the phosphatase SHP2. Question mark (?) indicates pathways identified in macrophages only.

species by oxLDL takes place through the formation of a complex between CD36 and a heterodimer of toll-like receptors (toll-like receptor 4 and toll-like receptor 6).⁶² Also in macrophages, oxLDL induces the phosphorylation of focal adhesion kinase and the inactivation of the protein-tyrosine phosphatase SHP2, which are responsible for cytoskeletal changes.⁶³ Even though oxPC_{CD36} is only one biologically active component in oxLDL, we have observed that oxLDL and oxPC_{CD36} share activation pathways. Platelet activation induced by both oxLDL⁶⁰ and oxPC_{CD36} can be prevented by Src-kinase inhibitors (A. Zimman and E. Podrez, unpublished data, 2010). Also, both oxLDL and oxPC_{CD36} activate protein kinase C and induce the phosphorylation of Syk⁵⁷ (A. Zimman and E. Podrez, unpublished data). However, it should be mentioned that a complex ligand such as oxLDL contains multiple biologically active components that can affect platelet function in a CD36-independent manner. Examples include oxidized lipids that increase intracellular Ca^{2+} through the PAF receptor,⁶⁴ lysophosphatidylcholine,⁶⁵ oxysterols and TBARS,⁵⁸ lysophosphatidic acid,⁶⁶ and amyloid-like structures.⁴⁶

SR-BI, Dyslipidemia, Oxidative Stress, and Platelet Function

SR-BI shares 30% sequence homology with CD36, has similar structural organization, and shares with CD36 several common ligands, including oxidized lipoproteins and oxidized phospholipids.^{67–69} Recently, the presence of this receptor has been demonstrated on the surface of human and murine platelets.^{70,71} The major physiological function of SR-BI is to serve as a receptor for HDL and to promote

selective uptake of HDL cholesteryl esters in steroidogenic tissues and liver.⁷² In addition, SR-BI stimulates the bidirectional flux of free cholesterol between cells and lipoproteins, modifies membrane cholesterol distribution, and induces signaling events.⁷³ Because the antithrombotic function of HDL is well established, it seems logical that HDL interaction with platelet SR-BI may inhibit platelet function. However, previous reports on the effect of HDL on platelets have been contradictory.^{74–78} One explanation for the inconsistency may be the inadvertent oxidation of HDL during the isolation procedure. When extreme care was taken to prevent HDL oxidation during isolation, HDL or HDL subfractions HDL2 and HDL3 had no significant effect on the activation and aggregation responses of isolated platelets.⁷¹ This result looks particularly surprising, because HDL induces cholesterol efflux from cells, and in turn, the removal of cholesterol from platelets using cholesterol chelator M β CD is associated with a strong inhibition of platelet activation.⁷⁹ Recently, Calkin et al showed that reconstituted HDL, but not HDL, does inhibit platelet activation *in vivo*.⁸⁰ These authors suggested the reason for the difference is that reconstituted HDL has a higher capacity for cholesterol efflux than native HDL. Intriguingly, HDL oxidized by various pathways potently inhibits platelet activation and aggregation induced by physiological agonists.⁷¹ Studies using murine CD36^{-/-} or SR-BI^{-/-} platelets have demonstrated that the antithrombotic activity of oxHDL requires binding to platelet SR-BI but not to CD36 and that oxidized phospholipids in oxHDL are likely to play a role in this activity.⁷¹ Studies involving SR-BI in platelets are very limited for now. In endothelial cells, one of the most important downstream targets of SR-BI is the activation of endothelial nitric oxide synthase on HDL binding to this receptor.⁸¹ c-Src and PDZK1 form a complex with SR-BI in this cell type. Our preliminary studies have shown the association of SR-BI to c-Src in platelets (Podrez E., unpublished data, 2009). However, the effect of oxHDL on platelets is mediated by a pathway different from the endothelial nitric oxide synthase/Akt pathway operating in endothelial cells.⁷¹ A global survey of changes in protein phosphorylation by mass spectrometry⁸² revealed that oxHDL induces multiple changes in the phosphorylation of platelet proteins, including a group of proteins associated with focal adhesion and tight junctions (A. Zimman and E. Podrez, unpublished data). Taken together, this surprising finding suggests that lipid oxidation and oxidative stress appear not only to trigger prothrombotic effects mediated by CD36 but also to produce a previously unrecognized defense mechanism against thrombosis mediated by SR-BI.

The role of SR-BI deficiency and, specifically, platelet SR-BI deficiency in platelet function and thrombosis *in vivo* has been studied directly using SR-BI^{-/-} mice. It should be taken into account that complete SR-BI deficiency is characterized by severe dyslipoproteinemia associated with platelet abnormalities, including high unesterified cholesterol content, morphological changes, and thrombocytopenia. Platelets of SR-BI^{-/-} mice display either reduced or normal responses to selected physiological agonists.⁸³ This phenotype is particularly surprising taking into account that platelet enrichment in unesterified cholesterol has previously been directly

linked to increased platelet reactivity.^{42,84–86} To separate the effects of SR-BI-dependent dyslipidemia and platelet-specific SR-BI deficiency in platelet function, a bone marrow transplantation approach has been used. SR-BI^{-/-} platelets isolated from normolipidemic wild-type mice chimeras have normal platelet cholesterol content and normal morphology and show mild reduction in response to physiological agonists that was mostly evident at high concentrations of agonists.⁸⁷ *In vivo* studies have demonstrated that wild-type recipient mice with SR-BI-deficient bone marrow have delayed thrombosis in ferric chloride-induced carotid artery thrombosis assay, demonstrating that this seemingly mild defect still contributes significantly to thrombosis.⁸⁷ Wild-type platelets isolated from dyslipidemic SR-BI^{-/-} chimeric mice had cholesterol content increased by 60% and exhibited augmentation of activation responses to physiological agonists, in agreement with the published data on the impact of cholesterol on platelets.⁸⁵ Results from this study suggest that the unusual platelet phenotype observed in SR-BI-deficient mice is a reflection of the opposite effects of platelet SR-BI deficiency and platelet cholesterol overload on platelet reactivity. Most interestingly, *in vitro* studies revealed that SR-BI-deficient platelets are remarkably resistant to hyperreactivity induced by cholesterol overload, suggesting that platelet SR-BI may play a particularly prominent role in thrombosis under conditions of hypercholesterolemia. Indeed, *in vivo* studies confirmed that platelet SR-BI expression is prothrombotic *in vivo* in dyslipidemia associated with either apoE or SR-BI deficiency. These data strongly suggest that platelet SR-BI plays an important role in the widely known induction of platelet hyperreactivity by high platelet cholesterol content.^{42,84–86} It should be mentioned that the relevance of these studies to humans is not clear yet. No SR-BI-deficient patients have been reported so far. However, a single nucleotide polymorphism of the SCARB1 gene was associated with changes in SR-BI protein levels, which in turn were inversely associated with HDL cholesterol levels and HDL particle size,⁸⁸ resembling HDL changes in SR-BI^{-/-} mice. SCARB1 genetic polymorphisms in humans are associated with variations in plasma lipoproteins and coronary artery disease.^{89–91} It is not known whether or not platelet reactivity contributes to variations in coronary artery disease. However, SCARB1 polymorphisms show associations with the risk of peripheral artery disease, a condition in which platelet-dependent thrombosis plays a prominent role.⁹²

The molecular mechanism of SR-BI involvement in the regulation of platelet function is currently unknown. The function of SR-BI demonstrated in platelets is related to platelet unesterified cholesterol content. Thus, it is of particular interest that the C-terminal transmembrane domain of SR-BI directly binds cholesterol.⁹³ This cholesterol binding property is unique to SR-BI among 3 class B SR family members. It has been proposed recently that SR-BI senses alterations in the cholesterol environment in the plasma,⁹³ leading to changes in association of SR-BI with partner protein(s) critical to downstream signaling. We observed that the sensitivity of platelets to physiological agonists is upregulated with increasing platelet cholesterol content if platelets express SR-BI. In the absence of SR-BI expression, responses to ADP and convulxin are oblivious to platelet cholesterol

content, and the increase in response to thrombin is significantly blunted.⁸⁷ One possibility is that enrichment in plasma membrane cholesterol leads to conformational changes in SR-BI and upregulates SR-BI-dependent signaling pathways in platelets. On the other hand, membrane depletion of cholesterol inhibits the SR-BI-dependent component of platelet signaling, leaving only a “basal” level of signaling. It should be noted, however, that SR-BI expression in other cell types is associated with significant changes in the organization of cholesterol in cell membranes.^{94,95} Cell membrane cholesterol, particularly cholesterol in specialized membrane microdomains, is important in the assembly of signaling complexes and plays an important role in signaling events in platelets.⁹⁶ SR-BI is highly enriched in caveolae in several cell types.⁹⁷ Thus, it may affect signaling events in platelets in a less specific way, by changing membrane structure. In our unpublished studies, we observed that cholesterol flux to HDL is reduced by $\approx 50\%$ in SR-BI-deficient platelets compared with wild-type platelets, potentially reflecting changes in cholesterol organization.

Conclusion

In the context of dyslipidemia and enhanced oxidative stress, platelet CD36 interaction with a small subset of endogenous oxidized phospholipids leads to prothrombotic signaling and accelerated thrombosis. The effects of other CD36 ligands on platelet function and thrombosis need further investigation. The role of SR-BI in platelet function is more complex. Liver deficiency of SR-BI leads to platelet hyperreactivity and accelerated thrombosis because of high cholesterol content in platelets. Platelet SR-BI plays a critical role in the induction of platelet reactivity by high platelet cholesterol content. On the other hand, specific ligands that are generated in oxidative stress and interact with platelet SR-BI may induce suppression of platelet function. It is tempting to speculate that platelet class B SR might be a specific target for antiplatelet therapies specifically aimed at platelet hyperreactivity in dyslipidemia.

Acknowledgments

We thank Detao Gao for technical assistance.

Sources of Funding

This work was supported in part by National Institutes of Health Grants HL077213, HL077213-05S1, 5P01HL073311-06, and HL053315.

Disclosures

None.

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Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Regulation of Platelet Function by Class B Scavenger Receptors in Hyperlipidemia Alejandro Zimman and Eugene A. Podrez

Arterioscler Thromb Vasc Biol. 2010;30:2350-2356; originally published online November 11, 2010;

doi: 10.1161/ATVBAHA.110.207498

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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