There’s a saying that goes: “everything old is new again,” and I am reminded of this by the article by Luangrath et al. in this issue of *Arteriosclerosis, Thrombosis and Vascular Biology*. Not that this article shows old data, but that what was old, now cast in a different light, leads to new ideas and hypotheses. Just about 10 years ago, Calvo et al. showed that human CD36 bound native LDL, HDL, and VLDL. Later, Connelly et al. found that CD36 could mediate selective cholesterol ester uptake from LDL. These were both intriguing findings, but without in vivo data there was a question of relevance. Since then, most studies have focused on CD36 recognition of aberrant lipoproteins, and a role for CD36 in native lipoprotein biology has been overshadowed. With this article, and several others recently published, the spotlight has begun to shift to potential functional roles of CD36 in native lipoprotein biology.

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CD36 was first identified as a platelet glycoprotein (GP) and originally primarily thought of as a receptor for thrombospondin-1, and involved in adhesion. As the oxidation theory of lipoprotein modification gained traction as an underlying mechanism for atherogenesis, interest in receptors for oxidized LDL (oxLDL) increased. The observation that CD36 was an oxLDL receptor was the catalyst for many to probe the role of CD36 in atherosclerosis. Further work to define the ligand on oxLDL that was recognized by CD36 implicated the lipid of the lipoprotein, and later work identified specific truncated fatty acid moieties as the recognition motif for CD36. The spectrum of ligands was broadened by demonstrating that the polar head group need not be phosphatidyl choline, and provided explanation for CD36 recognition of apoptotic cell membranes and effete retinal rod outer segments. Recent elegant structural studies have given rise to the “whisker model” to explain how CD36 is able to recognize these specific fatty acids in a lipoprotein or exposed on an apoptotic cell or rod outer segment.

The ability of CD36 to facilitate long chain fatty acid uptake by cells, and to lead to phenotypes associated with differences in fatty acid oxidation and storage, remains incomplete owing to the lack of delineation of the precise mechanism for the actual facilitated uptake event. Regulation of CD36 expression by insulin, exercise, and AMP kinase (among others), correlating with differences in fatty acid uptake and oxidation, and associated changes in energy resources in CD36 null mice and people, suggest an important role in homeostasis as well as in metabolic disease states. A role for CD36 in lipoprotein formation and secretion in the gut has been demonstrated based on expression analyses and composition of chylomicrons, and more recent work has identified CD36 as an intestinal receptor for very long chain fatty acids. CD36 expressed on taste buds in the mouth signal to ready the gut for a fatty meal. Other signaling events mediated by CD36 alone or in collaboration with other receptors lead to uptake of oxLDL, βamyloid, macrophage secretion of reactive oxygen species and cytokines, platelet activation, and apoptosis in endothelial cells resulting in inhibition of angiogenesis.

Luangrath and colleagues investigated the role of CD36 on LDL and oxLDL metabolism in liver. Study of CD36 in liver is complicated by the fact that all major cell types, hepatocytes, endothelial cells, and Kupffer cells, express CD36. It was previously believed that expression of hepatocyte CD36 was low. Luangrath et al. show evidence for appreciable expression of CD36 in isolated hepatocytes, and complimentary data in vitro to support the in vivo work. Using mice deficient in CD36, SR-BI, or both, and holoparticle or cholesterol ester radiolabeling, their studies demonstrate a role for CD36 in retardation of LDL clearance by hepatocytes, and a significant role for CD36 in oxLDL clearance. In the absence of SR-BI, CD36 could facilitate LDL cholesterol ester selective uptake. Although the oxLDL data are perhaps as expected (with the caveat that many would have believed that Kupffer cell CD36 would have been the predominant site of uptake), the influence of CD36 on LDL holoparticle and cholesterol ester selective uptake is a surprise, given the expression of the LDL receptor in liver. In fact, using an overexpression adenovirus strategy, but examining only lipoprotein profiles, de Villiers and colleagues found no role for CD36 in LDL metabolism.

Thus Luangrath et al. provide important potential in vivo relevance for the previously defined interactions of CD36 with LDL. A role for CD36 in native lipoprotein particle clearance was also recently suggested by Densupsoontorn et al, who studied the fate of (n-3) fatty acid-enriched triglyceride-rich particles from blood. In another study, Love-Gregory et al. surveyed CD36 tagged SNPs in human populations of African descent, where CD36 polymorphisms are widespread. SNPs for CD36 correlated with increased levels of plasma HDL and decreased levels of triglycerides and with protection against metabolic syndrome. Our work showed increased HDL levels and protection against insulin resistance in CD36 null mice. These vastly different approaches provide support for a role for CD36 in the metabolism of several apparently native lipoprotein classes.

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**CD36 Goes Native**

Maria Febbraio

From the Cleveland Clinic, Lerner Research Institute, Department of Cell Biology, Cleveland, Ohio.

Correspondence to Maria Febbraio, Cleveland Clinic, Lerner Research Institute, Department of Cell Biology, 9500 Euclid Avenue, NC 1-139, Cleveland, Ohio 44195. E-mail febbram@ccf.org


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Much of science leads to more questions, and so it is these new studies. For example, what is the mechanism underlying the recognition by CD36 for native as well as aberrant lipoproteins, and lipoproteins of different types? Although CD36 was previously identified as an anionic phospholipid receptor, this has been reevaluated because care to guard against oxidation of phospholipids in earlier studies was probably not taken. Could it be that in “native” lipoproteins, there is a trace amount of the CD36 recognition motif? Indeed, previous studies showed that a very small mole percent of oxidized phospholipid could trigger recognition by CD36, and Thorne et al demonstrated CD36 to be a receptor for oxidized HDL. Does the amount of these oxidized phospholipids then determine cellular trafficking and subsequent outcomes? Or do these changed lipoproteins carry with them the ability to oxidize other lipids and proteins, or trigger intracellular signaling events, and thus affect subsequent outcomes? Is there physiological relevance to the retardation of LDL uptake mediated by CD36, and does it contribute to the pathophysiology of steatosis induced by diet, alcohol, and other conditions? Do cells recognize lipoproteins based on fatty acid subtypes and does CD36 have a role? Are differences in lipoprotein metabolism observed in CD36-deficient states secondary to other CD36 effects? For example, in CD36 deficient states, the increase in plasma fatty acids can inhibit lipoprotein lipase, leading to inhibition of lipoprotein catabolism. And finally, how can we exploit what we now know to develop therapies? The work of Luangrath et al thus takes what seems like something old to a new relevance that will result in new hypotheses to be tested to reconcile the observations concerning this very versatile protein. It seems like CD36 is shorthand for Can Do 36 things.

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I sincerely regret that space precludes the citation of all colleagues whose work was mentioned, but I humbly acknowledge their contributions to our knowledge of CD36 here.

Disclosures

None.

References

10. Thorne RF, Mhaidat NM, Ralston KJ, Burns GF. CD36 is a receptor for oxidized high density lipoprotein: implications for the development of atherosclerosis. FERS Lett. 2007;581:1227–1232.
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Maria Febbraio

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