

# Atherosclerosis: cell biology and lipoproteins Alan Daugherty

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Many aspects of the delivery and metabolism of lipoproteins within the arterial wall remain to be resolved. Initially, it was proposed that a single class of scavenger receptors was responsible for the transport of intravascular modified lipoproteins into the interior of macrophages. However, the theory of oxidatively modified lipoproteins promoting atherosclerosis is being increasingly complicated as more is discovered concerning the mode by which these particles are modified and metabolized.

Our understanding of the role of the class A scavenger receptors (SRA) was facilitated by the availability of mice in which this gene was disrupted [1]. Ling *et al.* [2<sup>•</sup>] used SRA deficient animals to determine the relative importance of this class in the removal of modified forms of LDL from the plasma compartment. Previously, modified forms of LDL were assumed to be cleared from plasma by SRA primarily located in the liver. However, this proposal was questioned with the identification of several additional receptor types that also recognize modified forms of LDL. Despite the previously assumed importance of SRA, their deficiency had no effect on the rapid removal from plasma of either oxidized or acetylated forms of LDL. Although there was some decreased metabolism of acetylated LDL by cultured hepatic endothelial cells in the absence of the receptor, the deficiency of SRA showed no effect on tissue accumulation of radiolabelled modified LDLs. SRA deficient mice were also used recently to study metabolism of acetylated LDL, apoptotic thymocytes and oxidatively damaged erythrocytes by mouse peritoneal macrophages. Oxidized LDL was previously shown to decrease binding of both oxidized erythrocytes and apoptotic thymocytes to macrophages [3]. In addition to competition by oxidized LDL, the assumption that oxidized erythrocytes are recognized by SRA was also based on competition by substances such as polyinosinic acid, fucoidan, and malondialdehyde modified albumin. However, against expectations, Terpstra *et al.* [4<sup>•</sup>] demonstrated that peritoneal macrophages from SRA deficient mice bound oxidized erythrocytes just as effectively as cells from wild-type animals of a similar strain. These two studies serve to illustrate our relative ignorance of the role of all classes of scavenger

receptors in pathophysiology. The availability of these receptor deficient animals provides considerable insight for modifying our current paradigms of the role of SRA in the metabolism of modified lipoproteins.

Recently, another member of the scavenger receptor family in the B class (SRBI) has attracted interest because of its ability to regulate HDL metabolism [5]. Murao *et al.* [6] functionally characterized the human analog of rodent SRBI, which is termed the human CD36 and LIMPII analogous (CLA-1) receptor. This protein was identified by Calvo *et al.* [7], but its biological function and tissue distribution had not previously been determined. Murao *et al.* [6] demonstrated a combination of CLA-1 binding characteristics to HDL and its expression in adrenal gland, testes and liver that is consistent with a role in HDL metabolism in humans. They also demonstrated that CLA-1 was expressed on monocytes with its presence decreasing as the cells differentiate into macrophages. Although CLA-1 may function as an HDL receptor in many cells, its potentially important function on monocyte/macrophages will need to be defined.

Given the potential importance of SRBI to lipoprotein metabolism, there is increasing focus on modes of regulation. Ng *et al.* [8] demonstrated that deficiency of lecithin:cholesterol acyltransferase greatly reduced plasma concentrations of HDL. Lecithin:cholesterol acyltransferase deficient mice had severe depletion of adrenal lipid stores associated with a 2-fold upregulation of SRBI mRNA. Therefore, the authors proposed that these findings provide further evidence that cholesterol regulates SRBI expression. Webb *et al.* [9] recently isolated an alternative form of SRBI that differs in the putative cytoplasmic domain. This arises because of alternative RNA splicing and was designated as SRBI2. There was a distinct tissue distribution of SRBI2 compared with the originally described form of SRBI1. Alternative splicing may represent an important process in the regulation of SRBI expression and function. Given the potential importance of SRBI to the metabolism of several forms of lipoproteins, further characterization of this receptor is needed.

There has been increased speculation for a role of lymphocytes in the atherogenic process [10]. This speculation is based on the abundance of lymphocytes in lesions, particularly in regions of growth and rupture. Furthermore, these lymphocytes express activation markers that infer that release of cytokines occurs from this cell type within lesions. However, the specific role of lymphocytes in

lesion formation has not been determined. Gupta *et al.* [11\*\*] provided insight into the role of this cell type by examining the extent and characteristics of atherosclerosis in apolipoprotein (apo)E<sup>-/-</sup> mice that were also deficient in interferon- $\gamma$  receptors. There was a shortcoming in their study caused by the differing genetic backgrounds of the mice deficient in both apoE and interferon (IFN)- $\gamma$  receptors compared with those with only an apoE deletion. In addition, the lack of information on statistical analysis hindered evaluation of the data. Nevertheless, the authors provide a potentially important conclusion that IFN- $\gamma$  is proatherogenic. This result may be considered a surprise, because IFN- $\gamma$  was shown to decrease scavenger receptor function and this cytokine is considered to be anti-atherogenic. The proatherogenic effects of IFN- $\gamma$  were related to effects on lipid accumulation, cell recruitment and collagen synthesis. Given the prominence of activated lymphocytes in atherosclerotic lesions that could be a source of IFN- $\gamma$ , further work is warranted to reproduce this effect in equivalent genetic strains and to define the pathways by which IFN- $\gamma$  exerts its mechanism.

## References

Papers of particular interest, published within the annual period of review, have been highlighted as:

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## Recommended reading

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 Mice that were deficient in receptors for IFN- $\gamma$  were bred into an atherosclerosis susceptible apoE<sup>-/-</sup> background and used to determine the role that IFN- $\gamma$  performs in defining both the extent and characteristics of atherosclerosis.
- Ling WH, Lougheed M, Suzuki H, Buchan A, Kodama T, Steinbrecher UP.
  - Oxidized or acetylated low density lipoproteins are rapidly cleared by the liver in mice with disruption of the scavenger receptor class A type I/II gene. *J Clin Invest* 1997; **100**:244–252.
 The kinetics of removal of modified lipoproteins from the plasma compartment were determined in scavenger receptor class A mice. Although this receptor class was previously assumed to mediate the removal from the plasma compartment, unexpectedly, scavenger receptor class A deficiency had no effect on the kinetics of clearance.
- Terpstra V, Kondratenko N, Steinberg D. Macrophages lacking scavenger
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 In addition to scavenger receptors mediating the metabolism of modified lipoproteins, they were also proposed as mediators for the clearance of oxidized erythrocytes and apoptotic thymocytes. However, peritoneal macrophages from scavenger receptor class A deficient mice had equivalent binding and uptake compared with cells from wild-type mice.