Reviewer's report

Title: Regulation and Splicing of Scavenger Receptor Class B Type I in Human Macrophages and Atherosclerotic Plaques.

Version: 1 Date: 12 March 2005

Reviewer: David Rhainds

Reviewer's report:

General comments.

The role of scavenger receptors, and especially scavenger receptor BI, in the development of atherosclerosis deserve careful and thorough investigation of their role at different stages of the atherosclerotic process. The study by Svensson and coll. uses macrophages derived from monocytes of carefully selected subjects with subclinical atherosclerosis from the INTERGENE study in Göteborg area, Sweden. While their findings on SR-BI regulation in macrophages may apply to early stages of atherosclerosis in families with a documented history of CHD, studies on macrophages derived from atherosclerosis subgroup are limited by the time required to differentiate monocytes, resulting in a blurring of potential variation of SR-BI vs. control subjects, if any. Recent reports suggest that expression of SR-BI in monocytes is low and that differentiation in vivo into macrophages raises SR-BI expression (Chinetti et al., Circulation 2000, 101:2411-7). This could lead to identical levels in both control and atherosclerotic subgroups in the present study.

Another limitation of the study on macrophages is the absence of experiments devoted to the interaction of hypoxia and circulating mmLDL. What is the predominant signal to raise (mmLDL) or decrease (hypoxia) SR-BI expression in macrophages? How can the effect of hypoxia and/or mmLDL on SR-BI expression be related to progression of atherosclerosis? In addition, Western blots for SR-BI isoforms (SR-BI and BII antibodies are available) would have strengthened the results and eventually discriminated between differential expression of isoforms, which has been demonstrated for SR-BI/BII (Graf et al., J Lipid Res 2001,42:1444-9).

Studying the expression of SR-BI in macrophages and atherosclerotic plaques reveals a third isoform of the receptor, called SR-BIII. This finding is important and deserves further investigation or its cellular and molecular biology. Is this isoform expressed as a protein at high levels and in which tissues? (SR-BII is generally not). Does SR-BIII exhibit similar lipid transport activities compared to SR-BI?

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors should discuss (and not only mention) their findings on mmLDL increasing SR-BI expression in macrophages in relationship with other studies (i.e. Hirano (cited) and Han et al. J Biol Chem 2001 276:16567-72) that show a reduction of SR-BI expression with OxLDL, also considering different types and degrees of LDL oxidation. Discussion and review of the literature are overall skinny and do not integrate recent advances obtained from mouse models on the role of macrophage SR-BI in atherosclerosis.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
author can be trusted to correct)

1) Figures 4AB and 5 (some details) do not reproduce clearly (streaky bands, arrows and letters) when printed and has to be adjusted for higher resolution. By comparison, figure 6 is crystal-clear.

2) Missing word "donors" in line 2 of legend to figure 2.

Discretionary Revisions (which the author can choose to ignore)

In figure legends, "normalized" or "standardized" would be preferable to "related".

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No