Scavenger Receptors in Atherosclerosis

New Answers, New Questions

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The existence of a cell surface receptor, now known as the macrophage scavenger receptor A I/II (MSR-A), was inferred from early studies based on ligand binding analyses. Description of this binding activity, with acetylated low density lipoprotein (LDL) used as a ligand, was important because it provided a mechanism for the formation of foam cells in vivo and because the activity of this receptor was not downregulated by expanding cellular cholesterol stores as had been recently shown for the LDL receptor. The presence of acetylated LDL receptor binding activity, predominantly on macrophage-type cells, helped to underscore the importance of the macrophage in atherogenesis and stimulated further investigation of macrophage function in the vessel wall. The description of this activity also helped to fuel investigative efforts to identify a potential in vivo ligand, and the various forms of oxidized LDL were soon suggested as physiological ligands for this receptor. Thus, the MSR-A has already shaped investigative efforts into the mechanisms of atherosclerosis. Now that MSR-A has been cloned, attempts to further understand its role in atherogenesis with the use of mice deficient in its expression have been undertaken.

In a subsequent report, the effect of eliminating MSR-A expression was examined for atherosclerosis in an LDL receptor–deficient background. Double-knockout mice in that study showed a significant decrease in lesions; however, this decrease was smaller than that reported previously (≈20%). In still another study, the effect of MSR-A deficiency was examined on atherosclerosis in the apoE Leiden transgenic mouse fed a high fat diet. In that study, there was no decreased lesion formation as a result of MSR-A deficiency. In fact, lesions actually tended to be larger and somewhat more complex in the apoE3 Leiden/MSR-A–deficient animals. As a result of the above reports, it has been suggested that an antiatherogenic role of the MSR-A depends on the mouse model used to provide the atherogenic background and that an interaction between MSR-A and apoE, perhaps in modulating macrophage cholesterol homeostasis, is a modifying factor.

A recent study by Babaev et al in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* provides new and important information regarding MSR-A involvement in atherogenesis. In their study, the authors used MSR-A–deficient mice on a C57BL/6 background challenged with a butterfat diet. The MSR-A–deficient mice had ≈60% less atherosclerosis. The authors then repeated this observation with use of the C57BL/6 diet-induced model but with the transplantation of MSR-A–/– or MSR-A–/+ fetal liver cells into lethally irradiated recipients. They again noted a substantial and significant decrease in atherogenesis in the animals receiving the MSR-A–deficient cells. In yet another approach, the authors used fetal liver cells transplanted into LDL receptor–deficient mice on a high fat diet. Using this model, they again demonstrated a substantial and significant decrease (again ≈60%) in lesion formation in the mice receiving the MSR-A–deficient cells. On the basis of these results, the authors conclude that MSR-A expression in macrophages significantly contributes to atherosclerotic lesion formation and that a mixed genetic background in animals may have contributed to the smaller effect on atherosclerosis previously reported in LDL receptor–/– mice and to the absence of effect previously reported in apoE Leiden transgenic mice. More specifically, they point out that the mating of MSR-A–deficient mice (129/ICR) with LDL receptor–deficient mice (129/C57BL/6) or apoE Leiden mice (C57BL/6) produced hybrids that likely differed in the segregation of loci for atherosclerosis susceptibility.

There are several issues to be considered in integrating these new observations. As the authors suggest, the issue of genetic background can be an important source of unpredictable and/or inconsistent results in studies using
transgenic or gene-targeted mice. This issue has been recently reviewed in *Arteriosclerosis, Thrombosis, and Vascular Biology*.

For atherosclerosis studies, the issue of genetic variability can be separated into distinct considerations. Because mice do not spontaneously develop atherosclerosis, a common study design begins with a mouse strain genetically manipulated to produce atherosclerosis. Atherosclerosis-prone models are produced on mice of different genetic backgrounds, and these variable backgrounds are a potential source of inconsistent results. To investigate the involvement of a specific gene in atherosclerosis, these atherosclerosis-prone mice are usually mated to another strain of mice, deficient in the gene of interest. An important question for the generalization of the results of such studies is whether the experiment has been designed so that (single knockout or transgenic) control mice (ie, the proatherogenic model) are genetically identical to the experimental mice (bearing the new deletion on the atherosclerotic background) in every way except for deletion of the gene of interest. The next issue is the nature of the proatherogenic manipulation itself. It is entirely conceivable that manipulating the expression of a specific gene might have different effects on atherosclerosis depending on the mechanism and potency of the specific gene might have different effects on atherosclerosis depending on the mechanism and potency of the proatherogenic milieu selected for study.

Again, the study by Babaev et al helps to deal with some of these complexities, as noted by the authors. An important advantage of their present study is the examination of 2 different proatherogenic models, a diet-induced C57/BL6 and an LDL receptor–deficient model. Consistent results were obtained between these models. Furthermore, the use of the transplant approach provides potential advantage with respect to eliminating genetic background variability. By transplanting cells from engineered donor mice into genetically homogeneous hosts for experimental comparisons, potentially confounding genetic factors expressed in the donor animals (but not expressed in the transplanted cells) are eliminated. Therefore, the authors convincingly demonstrate the involvement of MSR-A in atherosclerosis.

As the present study of Babaev et al shows, many confounding issues that could contribute to unpredictable and/or variable results in mouse atherosclerosis studies are amenable to experimental elimination. In fact, with a systemic approach, the use of well-characterized and genetically distinct lines of mice can be used to advantage to identify modifier genes for atherosclerosis. Such an approach has been proposed for investigating the large differences in atherosclerosis observed in apoE-deficient C57BL/6J mice compared with apoE-deficient FVB/NJ mice.

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