Absence of EC-SOD Does Not Promote Atherogenesis in Mice
Have We Lost Yet Another Player?

Jan Nilsson

A convincing body of cell culture, animal, and epidemiological studies have provided support and plausible biological mechanisms of a role for lipid oxidation in atherogenesis.\(^1,2\) Oxidized structures associated with lipoproteins, primarily LDL, have been shown to be abundant in atherosclerotic plaques.\(^3\) The observation that cultured macrophages take up oxidized LDL through a family of scavenger receptors, receptors that appear to be part of a more general “cleaning up” function of the immune system, provides a good explanation for the formation of foam cells in plaques. The generation of cytotoxic and immunogenic structures associated with oxidation of lipoprotein lipids offers an apparent cause of the inflammatory activity in the arterial intima that characterizes almost all stages of atherosclerosis.\(^4\) A large majority of experimental animal studies show that antioxidants inhibit the development of atherosclerosis.\(^5\) Epidemiological data suggest that a low intake of antioxidant vitamins is associated with an increased risk of developing cardiovascular disease.\(^6\) With all this knowledge at hand, it is frustrating to admit that we still have yet to identify how lipoproteins become oxidized in vivo and how we can prevent it.

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Assuming that the lipid oxidation hypothesis is correct, it would be expected that antioxidant vitamins such as vitamins E and C and β-carotene should be able to prevent cardiovascular disease. However, the results of the clinical intervention trials, including the recent HOPE and GISSI trials, have been largely disappointing. Even if these studies do not exclude a role for antioxidant vitamins in the protection against atherosclerosis, they clearly suggest that other antioxidative defense systems may be more important. Extracellular superoxide dismutase (EC-SOD) represents an ideal candidate in this respect. SOD is the major enzymatic defense against superoxide anions, an extremely powerful and common oxidant.\(^7\) There are a number of oxidases and other enzymes in the vascular wall that produce superoxide anions. EC-SOD is the only extracellular form of SOD, it is present in particularly high concentrations in the vascular intima, and the concentration is further increased in arteries affected by atherosclerosis. Moreover, in the intima, EC-SOD is tightly bound to heparin sulfate proteoglycans, the same location where LDL particles accumulate and oxidation of LDL is believed to occur. Colocalization between epitopes for oxidized LDL and expression of EC-SOD has also been demonstrated in human atherosclerotic lesions.\(^8\) In cell culture studies, EC-SOD markedly reduced LDL oxidation by endothelial cells.\(^9\) It almost looks like EC-SOD was made just to protect intimal LDL from being oxidized by superoxide anion.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Sentman and coworkers\(^10\) have published a study in which the role of EC-SOD in atherosclerosis has been evaluated by exposing EC-SOD–null, apo E–null, and various combined-genotype mice to atherogenic or control diets. In contrast to what would be expected, EC-SOD\(^-\) apo E\(^-\) double-knockout mice were not found to be more prone to develop atherosclerosis than mice lacking only the apo E gene. Indeed, after 1 month of the atherogenic diet, lesions were even smaller in the double-knockout mice, whereas no difference was observed after 3 months of the atherogenic diet or 8 months of normal chow. One could argue that the lesions caused by the absence of apo E may not evolve through the mechanisms otherwise responsible for the development of atherosclerosis and that this is the reason why the absence of EC-SOD did not increase atherogenesis in an apo E–null background. However, when the authors compared lesion formation in wild-type C57BL/6 mice and EC-SOD–null mice (on a C57BL/6 background) given an atherogenic diet, they also find no difference.

Why was there no effect? It all looked so promising and logical. The most obvious explanation is, of course, that offered by the authors: superoxide anion is not what does it. Oxidation of LDL in the arterial wall is mediated by other factors. This conclusion is also supported by recent observations that disruption of neutrophil-type superoxide radical–producing oxidase genes does not inhibit atherosclerosis in apo E–null mice.\(^11,12\) However, the real truth may also be much more complicated than that. The generation of reactive oxygen intermediates and the antioxidative defense involve a number of different factors and backup systems in a complex interplay. Removing 1 of them may just not have that much effect.

Is this study yet another blow to the lipid oxidation hypothesis? I don’t believe so; epitopes for oxidized LDL were equally prevalent in lesions of EC-SOD–null mice and apo E–null control mice. The urinary excretion of the lipid peroxidation marker 8-iso-prostaglandin F\(_{2α}\) showed an association with the rate of atherogenesis. It does, however, suggest that superoxide anion and EC-SOD are not the major

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players in this process. The outcome of this study may be disappointing at first glance, but limiting the number of factors that may be involved in the oxidative modification of LDL in vivo will also help us to reach a better understanding of this complex disease.

References
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