



STEIN INSTITUTE FOR RESEARCH ON AGING

**ANNUAL RESEARCH REPORT
FYE 2003**

Daniel Steinberg, M.D., Ph.D.
Research Professor, Department of Medicine

I have continued my research as a Senior Investigator in Unit 3 of the UCSD Specialized Center for Atherosclerosis Research, focussing on the scavenger receptors of the macrophage in relation to atherosclerosis. In collaboration with Dr. Oswald Quehenberger, Dr. Agnes Boullier and others we have shown that CD 36, the major receptor involved in binding and uptake of oxidized LDL by macrophages, recognizes oxidized phospholipids (but not native phospholipids) in oxidized LDL. We have now narrowed down the ligand specificity, showing that the affinity is sharply reduced by removal of the choline moiety using phospholipase D. Since phosphatidylcholine in native LDL is not recognized we infer that the molecular conformation of the oxidized phosphatidylcholine is critical to recognition. These results were presented at the annual meeting of the Council on Arteriosclerosis of the American Heart Association and have been submitted for publication.

I wrote the lead article for a special focus issue of Nature Medicine (Atherogenesis in Perspective: Hypercholesterolemia and inflammation as partners in crime. 2002 Nature Medicine 8: 1211-1217) and assisted in the compiling of the focus issue.

I am continuing to work on my book reviewing the history of the 'cholesterol controversy'. Oxford University Press has expressed interest and is currently reviewing several draft chapters.



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Dr. Daniel Steinberg, M.D., Ph.D.

During academic year 2001-2002, as a member of the UCSD Specialized Center of Research on Molecular Medicine, I continued, in collaboration with Dr. O. Quehenberger, my studies of the role of oxidized LDL in atherosclerosis, the macrophage receptors for oxidized LDL and the nature of the ligands recognized by those receptors. We established that oxidized phospholipids play a key role in macrophage recognition of oxidized LDL and also in macrophage recognition of apoptotic cells. Using transfected cells, we showed that CD36 specifically recognizes oxidized phospholipids, including one previously shown to be present in oxidized LDL, namely, i-palmitoyl-2-(5-oxovaleryl)-phosphatidylcholine.

We further defined the specificity of ligand recognition using a monoclonal antibody isolated by Dr. Witztum that is specific for oxidized (but not native) phospholipids. We showed that SR-A, originally cloned as a member of the scavenger receptor family but later defined as a receptor for HDL, does in fact recognize oxidized LDL with high affinity. With Dr. Witztum I wrote a Perspectives essay for Circulation discussing the interpretation of the clinical trials of antioxidants, pointing out the inadequacy of these trials with respect to the validity of the oxidative hypothesis in humans.