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Monocyte Rolling in Early Atherogenesis
Vital Role in Lesion Development

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The process of atherosclerotic lesion formation represents a complex interaction of a number of circulating blood cells with cells that reside within the arterial wall. Understanding the cellular mechanisms involved in this process is vital for the development of novel therapeutic strategies for prevention and treatment of coronary and carotid occlusive disease. In this issue of Circulation Research, Ramos and colleagues describe a novel in vitro search for P-selectin, a molecule that has already been used to study the kinetics of leukocyte-endothelial cell adhesion in arterioles and postcapillary venules of atherogenic mice. The authors clearly demonstrate that monocyte rolling is markedly enhanced in mice fed a high-cholesterol diet for 4 to 5 weeks. Administration of monoclonal antibodies directed against P-selectin or the P-selectin leukocyte ligand, PSGL-1, significantly attenuated monocyte rolling and adhesion. Furthermore, monocyte rolling and adherence were abrogated after administration of a monoclonal antibody that neutralizes α4 integrin. Hence, these elegant studies clearly define the role of specific leukocyte-endothelial CAMs to the monocyte rolling observed in the early stages of hypercholesterolemia preceding the development of atherosclerotic lesions. The study by Ramos et al also confirms the results of an earlier study of ApoE-deficient mice, wherein it was noted that accumulation of labeled macrophages in atherosclerotic plaques is diminished after inhibition of ICAM-1 and α4 integrin. An advantage of the intravital microscopic approach used by Ramos et al is the potential for acquisition of real-time kinetics of leukocyte interactions with the wall of lesion-prone areas of large arteries.

Monocytes and Atherogenesis
One of the characteristic features of early atherosclerotic lesions is the localized accumulation of monocyte/macrophages and T lymphocytes within the arterial intima. Monocytes are transformed into macrophages that steadily accumulate cholesterol esters and are subsequently transformed into foam cells. T lymphocytes that accumulate in the intima secrete a variety of inflammatory mediators that serve to activate vascular cells, thus contributing to atherosclerotic lesion formation.

In primates, monocyte-endothelial cell adhesion and endothelial transmigration have been shown to occur within 1 week after placement on a high-cholesterol diet. Mono-
Macrophage-derived foam cells as well as T lymphocytes. Additional evidence for the role of monocytes/macrophages in atherogenesis is provided by a recent study demonstrating that atherosclerosis is significantly retarded in mice that are genetically deficient in both macrophage colony-stimulating factor and ApoE.21

By using in vitro adhesion assay systems, many investigators22–26 have attempted to define the role of monocytes in the progression of atherosclerotic vascular disease. These studies have also served to define the cellular and molecular mechanisms responsible for monocyte/macrophage adhesive interactions with the vessel wall. It is now well appreciated that lipoproteins such as VLDL and LDL can stimulate monocyte adhesion to vascular endothelial cells in vitro.23–25 In addition, the oxidation status of lipoproteins appears to be of critical importance in the regulation of monocyte adhesion in vitro.17,22–24 Tsao et al26 have also demonstrated that the adhesion of monocytes derived from hypercholesterolemic rabbits to vascular endothelium is highly influenced by nitric oxide (NO) production. Previous studies27–29 have demonstrated that one of the earliest effects of hypercholesterolemia is a reduction in endothelial cell NO generation. Tsao et al26 reported that augmentation of NO levels with L-arginine can effectively blunt the hyperadhesivity of monocytes derived from hypercholesterolemic animals. Although all of the aforementioned studies have greatly extended our understanding of monocyte interactions with the vessel wall, additional work in animal models is needed to confirm and extend what is already known about this dynamic inflammatory process.

**Gene-Targeted Mice as Models of Hypercholesterolemia and Atherosclerosis**

Targeted disruption, deletion, or insertion of specific genes that regulate lipoprotein metabolism has resulted in the generation of a variety of novel murine models of hypercholesterolemia and atherosclerosis.30–36 Many of these animals develop arterial lesions similar in composition to those observed in humans, especially when placed on a high-fat diet.30,36 Consequently, the gene-targeted mouse models of hypercholesterolemia are considered to be more relevant to the hypercholesterolemia in humans, when compared with some of the other animal models (eg, rat) of hypercholesterolemia.

In recent years, a number of studies have used gene-targeted mice that suffer from alterations in lipoprotein metabolism to further our understanding of the pathogenesis of atherosclerotic lesion formation. The present study by Ramos et al uses the ApoE-deficient mice in combination with a high-fat Western diet as a model of hypercholesterolemia. These investigators emphasize that their model is focused on a time frame that precedes the formation of fatty lesions in large arteries, in view of the fact that the mice were maintained on an atherogenic diet for a very short period of time. Hence, this brief hypercholesteremic insult provides a unique opportunity for investigation of monocyte-endothelial cell adhesive interactions during the early stages of the atherogenic process.

**Future Directions**

The study by Ramos et al underscores the promise for an improved understanding of the atherogenic process that is offered by the application of intravital microscopic techniques to large arteries in mutant mice. Before this report, most of the available information regarding monocyte adhesion to endothelium in hypercholesterolemia and atherosclerosis was gleaned from studies of leukocyte accumulation at fixed time points during the atherogenic process or from in vitro adhesion assays that do not include the influence of shear. The dynamic images of leukocyte rolling in intact arteries exposed to physiological shear stress provide unique insights into the atherogenic process that were not previously attainable. However, there are several avenues for improvement of this powerful new tool. Highest priority should be given to applying this experimental approach to intact, arterial vessels perfused with whole, homologous blood. A recently published preliminary report,37 which demonstrated P-selectin-dependent leukocyte rolling in the intact aorta of cytokine-challenged mice, supports the feasibility of applying this approach to atherogenic mice. The development of mutant mice that express marker fluorochromes (such as green fluorescent protein) only in specific leukocyte populations (eg, monocytes) and the crossbreeding of these mutants with atherogenic mutants (eg, ApoE-deficient mice) should also enhance the utility and validity of this model system. Indeed, with the introduction of this technology to atherogenesis research, the possibilities for advancement in this important field of investigation now appear endless.

**References**


Key Words: monocyte ■ gene-targeted mice ■ hypercholesterolemia ■ cell adhesion molecule
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