More Cellular Signals for Atherogenesis?

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The potential importance of the nuclear factor κB (NF-κB) system as a key player in control of transcription of genes for mediators of a variety of inflammatory responses, from those mediated by cytokine pathways to atherosclerosis and thrombogenesis, has been a topic of broad interest. The proteins of the NF-κB family that form the inactive heterodimeric complexes in the cytoplasm of cells, the inhibitors that prevent nuclear translocation, and the stimuli that lead to release and nuclear translocation of the active uninhibited NF-κB complexes, commonly referred to as activation, have received great attention, as have the many genes subject to transcriptional activation by the various heterodimeric NF-κB complexes once translocated to the nucleus. These details are central to the goal of mapping the cellular and molecular pathways of vascular injury, including atherosclerosis, restenosis, and other vascular pathobiology. The overall schema is growing richer in detail and interpretive hypotheses. However, the answers remain elusive. A valid schema is nevertheless critically important to discovery of molecular strategies for effective and safe intervention in acute and chronic diseases of the vasculature.

In brief, this study addresses changes of gene transcription and gene product expression of the endothelial cell resulting from the dialogue between platelets and endothelial cells. This cellular embrace and exchange of signaling molecules has been suspected to be important in a number of circumstances dating from the early inflammatory hypothesis of atherosclerosis. Adhesion of platelets to the endothelial surface is observed early in the atherogenic process and had been suggested to be important for release of platelet-derived growth factor to the vessel wall and the subsequent complex events that result in vascular smooth muscle cell migration and proliferation associated with atherosclerosis (reviewed in Reference 2). Later studies have also demonstrated the early adhesion of monocytes to endothelium at local sites of atherogenesis. However, a variety of inciting factors play roles of importance in the initiation and propagation of the vascular pathology. A substantial variety of biologically active molecules are released from the activated platelet, many of which have been shown to influence endothelial cell function.

A central issue is why there are lipid-laden monocyte-derived macrophages in atherosclerotic lesions and how they get there. Issues such as the accumulation of oxidized lipids, foam cell formation, vascular cell proliferation, and attendant important events follow. The question posed in this study is how the traffic is regulated at the level of the endothelial cell, a major gatekeeper for the vessel wall.

Gawaz et al propose the hypothesis that activation of NF-κB complexes resident in the endothelial cell cytoplasm may be a particularly important initial event facilitating local monocyte adhesion and permitting monocyte traffic into the vessel wall at the site at risk for development of an atherosclerotic lesion. They have advanced the credibility of this molecular scenario by demonstration that association of activated platelets with endothelial cells, admittedly a transformed endothelial cell line in culture as a model, results in biosynthesis and secretion of monocyte chemotactic protein-1 (MCP-1) as well as of intracellular adhesion molecule-1 (ICAM-1). The former has previously been established as a potent chemoattractant for monocytes and has been shown to be produced by cells of the vessel wall. ICAM-1 is an important cell adhesion molecule, one that mediates leukocyte adhesion to the endothelium in blood under flow conditions by binding of fibrinogen, which can also be bound at the same time by activated leukocytes via the integrin αvβ3. Secretion of MCP-1 by endothelial cells after stimulation by activated platelets provides an important advance in mapping out the traffic of monocytes first to, then through, the endothelial barrier. Access to the vessel wall requires passage through the very substantial barrier presented by lateral cell-to-cell contact between these cells. The molecular biology is complex and is created by a series of carefully stacked layers of adhesive proteins (reviewed in Reference 6). Breaching of this barrier is necessary to traffic to the intima of the vessel of the monocyte destined to become, or perhaps already in the process of becoming, a foam cell. If MCP-1 is the chemoattractant for blood monocytes and ICAM-1 is providing, via fibrinogen, the anchor to the endothelial surface as the prelude to transmigration of these cells to the intima, the origin of the MCP-1 is suggested in the present study to be derived from the endothelium.

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those influencing endothelial adhesion of leukocytes hypothesized to play a significant role in atherogenesis, of a variety of cytokines, and of tissue factor, the initiating molecule of the thrombogenic cascade, a controlling role of the NF-κB system is justifiably advanced.

The present study\(^1\) shows that functionally active NF-κB is found in the nuclear extracts upon exposure of endothelial cells to activated platelets. Furthermore, transfection of cells with appropriate inhibitory NF-κB oligonucleotides resulted in nuclear localization of these oligonucleotides and not of control nucleotides, and importantly, there was significant inhibition of production of MCP-1 and also of ICAM-1 after exposure to activated platelets. These data demonstrate not only the control of these initial, seemingly required events but also the potential to inhibit these cellular events by inhibition of NF-κB through one or more mechanisms, here in a DNA therapy model in the laboratory culture flask.

Interest in this study may be aroused by the use of oligonucleotide transfer to suppress the activation of the NF-κB complex and thus the multigene activation associated with inflammatory responses. This is a “hot topic” causing considerable interest at present. In view of the broad scope of the NF-κB system in controlling important responses to injury, brief interruption might prove to be of benefit; however, the notion of chronic inhibition as a prophylactic therapy to prevent atherogenesis should be viewed with caution. Preclinical pharmacological studies in experimental animals will be needed to characterize the deficits created by such inhibition. However, the possibility that quantitative attenuation might be a therapeutically successful strategy should be explored.

**References**


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