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Misguided leukocyte adhesion.

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Editorial

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During inflammation leukocytes roll on the endothelium, then spread and adhere more tightly, and finally emigrate into the underlying tissues. The recruitment of leukocytes, although essential for eradication of microbial pathogens, can also lead to tissue destruction if improperly regulated. Recently, there has been an extraordinary increase in information concerning the molecular mechanisms that mediate leukocyte–endothelial cell interactions during inflammation (1). Two papers in this issue of *The Journal* illustrate how quickly this information is being used to study the roles of newly characterized adhesion proteins in inflammatory disorders (2, 3).

Leukocyte recruitment requires cooperation of both adhesion and signaling molecules. Transient adhesion of leukocytes to regionally activated endothelium is mediated by receptors called selectins. The loosely adherent leukocytes are then activated, resulting in upregulation of integrins that tighten adhesion and direct emigration (1). The selectins are three related membrane proteins that interact with cell-surface carbohydrate ligands (4). E- and P-selectin, expressed on activated endothelium, bind to myeloid cells and subsets of lymphocytes. L-selectin, expressed on most leukocytes, binds to inducible ligands on the endothelium. The selectins are uniquely capable of forming adhesive bonds under the shear forces found in the venular circulation. However, firm adhesion requires that the leukocyte integrins undergo activation-induced increases in avidity for immunoglobulin-like counter-receptors such as intercellular adhesion molecule (ICAM)-1, ICAM-2, and vascular cell adhesion molecule (VCAM)-1 on the endothelial cell surface. All leukocytes express one or more of the three $\beta 2$ integrins; mononuclear cells, eosinophils, and basophils also express the $\alpha 4\beta 1$ or $\alpha 4\beta 7$ integrins. In physiologic inflammation, signaling and adhesion molecules are transiently expressed, limiting the recruitment of leukocytes. The subsets of leukocytes recruited and the kinetics of their emigration from the bloodstream probably reflect the expression of specific combinations of adhesion and signaling molecules.

Two major predictions can be made from the above scheme. First, blockade of either the selectin or integrin pathways will prevent stable leukocyte adhesion to endothelium. Second, inappropriate display of signaling molecules will cause dysregulated expression of adhesion molecules, resulting in excessive leukocyte recruitment.

Although the selectins initiate leukocyte adhesion, the integrins were discovered first and their functions have been more extensively studied in animal models of inflammatory disease (5). For example, infusion of antibodies to the $\beta 2$ integrins significantly reduces tissue necrosis in models of ischemia-reperfusion injury in which neutrophils have been implicated as key participants. In this issue, Weyrich et al. demonstrate that a monoclonal antibody to P-selectin is equally effective in reducing necrosis in a feline model of coronary ischemia-reperfusion injury (2). P-selectin is a good candidate for involvement in the early stages of acute inflammation (6). The protein is constitutively synthesized by megakaryocytes and venular endothelial cells where it is sorted into storage granules: the α granules of platelets and the Weibel-Palade bodies of endothelial cells. Physiologic agonists such as thrombin or histamine induce rapid redistribution of P-selectin to the cell surface as granule membranes fuse with the plasma membrane. Peak expression of P-selectin on the endothelial cell surface occurs within 10 min after stimulation and then declines over the next 30–60 min as the protein is endocytosed. Pathologic mediators such as complement and oxygen radicals, which may be elaborated during ischemia-reperfusion, also induce surface expression of P-selectin. Oxygen radicals cause sustained surface display of P-selectin over several hours, perhaps due to impairment of endocytosis. Weyrich et al. demonstrate that ischemia-reperfusion causes P-selectin–dependent adhesion of neutrophils to coronary artery endothelium ex vivo, consistent with surface mobilization of the receptor. Immunohistochemical staining for P-selectin is more intense in venules of the heart during early reperfusion; it is not clear whether this is due to increased protein synthesis in response to certain cytokines (7), or to surface mobilization of the protein that enhances accessibility of the antibody epitope in the tissue sections (8).

Grober et al. (3) use an entirely different approach to assess the roles of adhesion molecules in a chronic inflammatory disease, rheumatoid arthritis. The method measures adhesion of leukocytes to the microvasculature of frozen sections of human tissues on an agitator that introduces shear forces. The authors find that monocytes adhere to the venular endothelium of synovitis specimens from patients with rheumatoid arthritis, but not to endothelium of noninflamed tissues such as placenta. Monocyte adhesion is completely blocked by a monoclonal antibody to P-selectin and partially blocked by antibodies to other adhesion molecules. Because P-selectin is stored in granules inside endothelial cells, measurement of leukocyte adhesion to tissue sections is particularly difficult because the cells may bind to intracellular P-selectin that is exposed by sectioning. Using confocal microscopy, the authors suggest that monocytes bind only to P-selectin expressed on the apical surface of the endothelium. Although this ex vivo adhesion assay has clear limitations, the data imply that P-selectin plays a prominent role in pathologic monocyte recruitment in at least some phases of rheumatoid arthritis. Furthermore, P-selectin, although rapidly mobilized during acute inflammation, may also be expressed for longer periods during chronic inflammation. As Grober et al. point out, this may reflect repeated release of acute inflammatory mediators, generation of oxygen radicals that cause persistent display of P-selectin, and release of cytokines that increase P-selectin synthesis.

Recent papers also support roles for P- or E-selectin in models of lung injury and asthma (5, 8). We can expect that our increasing knowledge of the adhesion and signaling molecules that direct leukocyte recruitment will be exploited rapidly to study the pathogenesis of inflammatory disorders. This information may lead to more effective treatment strategies for these diseases.

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