Editorial

The vascular and immune systems have to respond rapidly to injury or to invasion by a pathogen. This requires the coordinate expression of many genes. The cells begin to synthesize new cytokines, growth factors and their receptors, and also adhesion molecules—all depending on the function of the particular cell in the defense program. A central role in orchestrating the induction of these rapid-response genes is played by the transcription factor NF-κB (1). In resting cells NF-κB is located in the cytoplasm bound to proteins of the I-κB family that mask its nuclear localization signal. Cellular activation induces I-κB degradation, and the removal of this inhibitory cocoon allows the transcription factor to translocate to the nucleus where it forms a butterfly-like structure on regulatory regions of genes bearing the NF-κB binding sites (2). The signals that lead to NF-κB translocation are linked to pathogenic events or to stress. They include cytokines, mitogens, bacteria, viruses, and physical or oxidative stress (1). In this issue of *The Journal,* Andrew Weyrich and colleagues (3) report that tethering of monocytes to P-selectin also regulates NF-κB translocation to the monocyte nucleus. In addition, the authors document an increase in secretion of tumor necrosis factor-α and monocyte chemotactic protein-1 (MCP-1) (3).

P-selectin is a transmembrane adhesion receptor that, through its lectin domain, mediates binding to glycoprotein ligands present on many leukocytes. P-selectin is found in storage granules of platelets and endothelial cells. It becomes rapidly expressed on the cell surface when these cells degranulate during vascular injury or in inflammation (4). Since P-selectin is expressed only under stress or in disease, it fits very well among the other inducers that, through signaling, "chase" NF-κB from the cytoplasm to the nucleus. Through P-selectin expression, endothelial cells or platelets can rapidly communicate to contacting blood cells that they are in an activated state, i.e., there is trouble, and the blood cells should program their response accordingly.

P-selectin is not alone sufficient to induce the necessary signaling leading to NF-κB translocation. Similar to these investigators' previous report on neutrophil activation (5), a juxtacrine stimulation by platelet activating factor (PAF), a biologically active lipid, is needed. Despite the fact that PAF receptor with its seven membrane-spanning domains is linked via G-proteins to Ca^{2+} regulatory mechanisms and protein kinases, PAF alone also does not induce NF-κB translocation (3). The ligand for P-selectin, that is likely involved in the signaling, is the glycoprotein PSGL-1 (6), as antibody that inhibits binding of P-selectin to this receptor also interferes with NF-κB translocation (3). PSGL-1 is a mucin-like transmembrane glycoprotein with a single cytoplasmic domain that has no homologies to other known proteins (6). PSGL-1 is a very different molecule from the G-protein–coupled PAF receptor, and it is improbable that the two interact at the membrane level. More likely, they feed into the same signaling pathway targeting I-κB. The exact mechanism that activates I-κB destruction is not known. Several lines of evidence point to a role for reactive oxygen intermediates, as a variety of antioxidants inhibits NF-κB activation (1). It would be interesting to examine whether antioxidants inhibit the P-selectin/PAF–induced NF-κB nuclear translocation. PSGL-1 also serves as a ligand for the other endothelial selectin, E-selectin, that is expressed upon exposure to cytokines. The authors did not investigate whether the induction through PSGL-1 is P-selectin specific or whether its binding to any ligand (such as E-selectin) jointly with PAF will activate NF-κB.

In some instances it may be possible to induce gene transcription in a monocyte by binding to P-selectin only, without PAF. This was documented for tissue factor message and protein expression (7). Possibly a different signaling pathway is used here that does not involve NF-κB or perhaps an unrecognized costimulatory molecule is present in the system. The presence of such a costimulatory factor could now be addressed by examining whether NF-κB translocation occurs during P-selectin–induced tissue factor expression.

P-selectin present on activated blood vessels mediates leukocyte rolling, the first step in leukocyte extravasation (4, 8). Would rolling on P-selectin be a sufficient stimulation for initiation of NF-κB translocation? The shortest time examined for monocytes adherent to P-selectin, in the study by Weyrich and colleagues (3), was 30 min, which is longer than one would expect a leukocyte to roll. It would be interesting to know whether much shorter times during which leukocytes would be more likely to remain in rolling contact with a stimulated vessel area would be sufficient. On the other hand, it is possible for the monocytes to encounter P-selectin for prolonged periods when they are bound to activated platelets at a wound site, or after extravasation since P-selectin is likely to be expressed on the subluminal surface of stimulated endothelium as well. Although several studies have now examined signaling into leukocytes that was induced at least in part by binding to P-selectin, the effect of P-selectin engagement on endothelial cells' gene expression has been evaluated very little. It is plausible that engagement of endothelial adhesion receptors may signal changes in endothelial junctions, for example, that may facilitate leukocyte transmigration.

Although many stimuli may cause NF-κB nuclear translocation in the monocytes, P-selectin may be of special importance since the interaction of monocytes with activated platelets or endothelium is likely to occur very early in an injury or in an inflammatory process, before large amounts of cytokines or other stimulatory agents are produced. P-selectin clearly plays an important role in the recruitment of inflammatory cells to areas of acute inflammation and injury as the recruitment is drastically reduced in P-selectin–deficient mice (8). We have also observed lower recruitment of neutrophils, monocytes and, $CD4^+$ T lymphocytes in chronic inflammation. Considering the newly uncovered role of P-selectin in regulating signal transduction, the reduced recruitment of inflammatory cells in the absence of P-selectin may be due to reduced leukocyte tethering and/or to a lesser stimulation of the recruited cells to produce cytokines and chemotactic factors that would further amplify leukocyte recruitment.

The study described in this editorial (3) may also be of

J. Clin. Invest.

0021-9738/95/05/1955/02 $2.00
Volume 95, May 1995, 1955–1956

clinical relevance. MCP-1 production by monocytes is detected in atherosclerotic lesions, and P-selectin which is upregulated at these sites may be partially responsible for its induction. NF-κB translocation may be involved in the initiation of monocyte proliferation at the lesion site. For the future, there is the possibility that drugs interfering with P-selectin–mediated adhesion may have a dual effect—in that they would not only inhibit leukocyte adhesion, but also inhibit or delay NF-κB translocation to the nucleus resulting in a lesser cellular activation.

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