Editorial

Inflammation and Thrombosis
The Clot Thickens

Peter Libby, MD; Daniel I. Simon, MD

Textbooks often portray thrombosis as a bland protective mechanism critical for stanching blood loss after injury: the prick of a lancet, the wound of a scalpel, or the predator’s fangs neatly trigger a proteolytic cascade culminating in fibrin formation and cross-linking. However, in diseases such as atherosclerosis, the picture differs substantially from this simplistic model. In the natural history of atherosclerosis, thrombosis involves an inciting injury more subtle than a wound. In such pathological states, the importance of an intricate interface between inflammation and thrombosis becomes apparent.

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Septic Shock: An Extreme Example of Inflammatory Activation of the Endothelium
Consider the case of septic shock, a dramatic example of the link between inflammation and thrombosis. When Gram-negative bacteria release their endotoxin into the bloodstream, the lipopolysaccharide can change endothelial lining of blood vessels from an anticoagulant, profibrinolytic surface into one that promotes thrombosis. Bacterial endotoxin potently stimulates expression of the gene encoding tissue factor, a procoagulant molecule that multiplies manyfold the activity of coagulation factors VIIa and Xa. Endotoxin also can augment endothelial cell production of fibrinolytic inhibitor plasminogen activator inhibitor-1 (PAI-1). These alterations in endothelial function lead to the frequent clinical scenario of disseminated intravascular coagulation, a common concomitant of Gram-negative sepsis.

Less-global endothelial activation may contribute to thrombosis in situ in more-chronic diseases such as atherosclerosis. Many inflammatory mediators found in human atherosclerotic plaques can augment tissue factor gene expression by endothelial cells. For example, interleukin-1 (IL-1) or tumor necrosis factor not only augment tissue factor gene expression but also PAI-1 production by human endothelial cells. Bacterial endotoxins within atheroma conceivably could derive from local Chlamydia pneumonia or other microbial infection. Endotoxin-induced expression of tissue factor and PAI-1 by endothelium thus may provide a stimulus that promotes thrombotic complication of “active” atherosclerotic plaques. In this manner, endogenous or bacterial inflammatory mediators can critically mediate functions of endothelial cells that promote systemic or local thrombosis in disease.

Inflammatory Leukocytes as a Source of Thrombogenic Stimuli
In the atheromatous plaque, macrophages often localize under the endothelial layer. A subpopulation of foamy macrophages in human atheroma express tissue factor. When plaques rupture, allowing contact of the blood with these tissue factor–bearing macrophages, thrombosis can ensue. Blood monocytes and resting tissue macrophages do not express tissue factor. However, when stimulated by certain inflammatory mediators, these mononuclear phagocytes transcribe the tissue factor gene. Bacterial endotoxin potently stimulates tissue factor gene expression in human mononuclear phagocytes. But what nonmicrobial stimuli might elicit tissue factor gene expression in atherosclerotic plaques? Unlike human endothelial cells, human mononuclear phagocytes do not augment tissue factor gene expression appreciably in response to soluble mediators such as IL-1 or tumor necrosis factor. Recent work has identified a cell surface–based signaling system, CD154 (CD40 ligand), binding to its receptor CD40 on the leukocyte, that can induce tissue factor expression. Because several cell types in atheroma bear CD154, this novel pathway probably contributes to macrophage tissue factor expression in the human atheroma.

Smooth Muscle Cells: Source of Procoagulants and Amplifier of Inflammatory Responses During Thrombosis
The smooth muscle cell is not commonly implicated in clotting. However, smooth muscle cells, like endothelial cells and macrophages, can express tissue factor procoagulant. Indeed, in superficial arterial erosion accounting for some fatal coronary thrombi, tissue factor expressed by smooth muscle cells uncovered by the endothelial erosion may contribute to thrombogenesis. Like the macrophage, for smooth muscle cells, CD154 may represent an important pathway of procoagulant activation of relevance to atherosclerosis.

The smooth muscle cell not only produces procoagulant but also can undergo inflammatory activation when exposed to thrombin and products of thrombosis. For example, thrombin stimulation causes smooth muscle cells to produce IL-6 abundantly. Platelet-derived growth factor, released from platelet alpha granules during thrombosis, can also markedly augment IL-6 production by smooth muscle cells. IL-6, in turn, can induce the acute phase response. Altering the pattern...

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of hepatic protein synthesis from everyday “housekeeping” to the proteins in acute-phase response, IL-6 can increase plasma concentrations of fibrinogen, PAI-1, and the inflammatory marker C-reactive protein. Thus, local thrombotic stimulation of smooth muscle cells in the artery wall can amplify inflammatory response and promote a systemic procoagulant effect due to increased fibrinogen and PAI-1 levels in the circulation.

New Roles for the Platelet in Inflammation

Although physicians readily acknowledge the key function of platelets in arterial thrombosis, most relegate platelets to a limited role as a responder to thrombotic stimuli. Platelets are nonnucleated and incapable of protein synthesis, and few researchers have accorded a regulatory role to these cell fragments. We now increasingly appreciate that the lowly platelet can take its rightful place beside its nucleated brethren as a source of inflammatory mediators. For example, platelet factor 4, long recognized to be a platelet product, belongs to the CXC chemokine family of inflammatory mediators. Curiously, one particular chemokine (stromal cell–derived factor-1) can potently stimulate platelet aggregation; thus, platelets can both produce and respond to chemoattractant cytokines. Recent work has established that platelets can express CD154, the very molecule that regulates cell–cell interaction.

Examples of Inflammatory Modulators Produced by Platelets

<table>
<thead>
<tr>
<th>Modulator</th>
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<tbody>
<tr>
<td>Platelet-derived growth factor</td>
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<tr>
<td>Platelet factor 4</td>
</tr>
<tr>
<td>CD 154 (CD40 ligand)</td>
</tr>
<tr>
<td>RANTES</td>
</tr>
<tr>
<td>Thrombospondin</td>
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<tr>
<td>Transforming growth factor-β</td>
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<td>Nitric oxide</td>
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Accumulating data linking inflammation and thrombosis support the hypothesis illustrated here that anti-inflammatory therapies may limit thrombosis and that antithrombotic therapies may reduce vascular inflammation.

Inflammation and Thrombosis: Intertwined in Vascular Pathology

The examples above illustrate how major cell types involved in vascular diseases express multiple functions at the interface of thrombosis and inflammation. Inflammation can beget thrombosis and thrombosis can amplify inflammation. Thus, we can regard anti-inflammatory therapies as potentially antithrombotic, obvious in the case of aspirin but a useful framework for rethinking mechanisms of benefit of other strategies (Figure 1). In addition, antithrombotic treatment may suppress inflammation and help break the vicious cycle of the acute coronary syndromes by limiting the local and systemic amplification loops described above. The biology of the diseases that preoccupy us in the clinic guide us in adjustment of our classic textbook categorizations of cells and their functions.

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References


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