Inflammation and Thrombosis

The Clot Thickens

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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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Seventy years ago, the innate immune response to injury, with its array of regulatory feedback loops, was thought to consist of a system with two outcomes: heal or die. More recently, the concept that inflammation is the ‘unResolved Response to Injury’ has been advanced. In this new paradigm, inflammation is no longer seen as a monolithic system with two outcomes; rather, it is a complex network of overlapping and diverging feedback loops, which include vasoactive mediators and their receptors, transcription factors, gene expression, and the role 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 foam cells expresses tissue factor expression in human mononuclear phagocytes. 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...
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 (Table). 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–derived factor-1 (RANTES), can participate in macrophage adhesion to endothelial cell by functioning as a bridge. Precedent for this kind of function for chemokines bound to the surface of endothelial cells and leukocyte adhesion exists in the cases of other chemokines, including macrophage chemoatractant protein-1 and IL-8.

The new observations of von Hundelshausen and colleagues extend our appreciation of the links between thrombosis and inflammation. 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.

### Examples of Inflammatory Modulators Produced by Platelets

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<th>Platelet-derived growth factor</th>
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### References


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