Platelets: Unindicted Coconspirators in Inflammatory Tissue Injury
Allan M. Lefer

Circ Res. 2000;87:1077-1078
doi: 10.1161/01.RES.87.12.1077
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/87/12/1077

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/
In the 1970s, during the peak of eicosanoid research, platelets were generally considered to play a major role in mediating the cell and tissue injury known to occur in cerebral ischemia/stroke, myocardial ischemia/infarction, and traumatic injury to other organs or regions. Foremost among the platelet-derived humoral mediators of this type of tissue injury were the prostaglandins (eg, PGF$_{2 \alpha}$), the endoperoxides (eg, PGH$_2$), and thromboxane A$_2$ (TXA$_2$). TXA$_2$ and, to a lesser extent, PGF$_{2 \alpha}$ and PGH$_2$ are potent vasoconstrictors and thus can reduce blood flow to vital vascular beds. Moreover, these agents are also prothrombotic by virtue of potently stimulating platelet aggregation. These two effects can, of course, work together to constrict and obstruct microvessels. In fact, a popular and useful research protocol of that era was the intravenous injection of arachidonic acid, the precursor of thrombosis/vasoconstriction and sudden cardiopulmonary death. Because platelets are the primary source of TXA$_2$, release of TXA$_2$ aggregates other platelets and stimulates their release of additional TXA$_2$, thus propagating this response. Platelets also release serotonin, ADP, and catecholamines, which are contained within storage granules. These platelet-propagated processes are all considered to be major factors contributing to direct ischemic injury as occurs in myocardial and cerebral ischemia. With the discovery of the mechanism of action of aspirin, this area of pathophysiology was addressed in a very practical way. Presently, aspirin is widely used in transient ischemic attacks, which often are precursors of stroke, and in patients experiencing a myocardial infarction, and cerebral ischemia. With the advent of thrombolytic agents (eg, streptokinase and tissue plasminogen activator), and coronary angioplasty, reperfusion became a common practice, additionally complicating the ischemic process. The late 1980s and the 1990s were a period of intense investigation into the mechanisms of reperfusion injury, the component of the ischemic process that exacerbates ischemic injury and occurs on rapid and abrupt restoration of blood flow to a previously ischemic vascular bed. Paramount among the many factors thought to be involved in mediating reperfusion injury are leukocytes, primarily polymorphonuclear leukocytes. About this time, major discoveries were made elucidating the role of several families of cell adhesion molecules located on either the leukocyte or the endothelial cell surface. These families of adhesion molecules regulate leukocyte-endothelial cell interaction in a well-orchestrated sequence. The first phase of leukocyte-endothelial interaction, which triggers the subsequent adherence and transmigration, is leukocyte rolling (ie, a slowing of leukocytes involving a process of surface bonds attached and detached in a periodic manner), and this allows capture of leukocytes. The phenomenon of leukocyte rolling is regulated by the selectin family of adhesion glycoproteins consisting of P-selectin, E-selectin, and L-selectin. E-selectin is upregulated on the endothelial cell surface by cytokines, including tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and interleukin-1$\beta$. L-selectin is constitutively expressed on leukocyte surfaces and also contributes to leukocyte rolling. P-selectin occurs in $\alpha$-granules of platelets as well as in Weibel-Palade bodies of endothelial cells and can be translocated to the cell surface of these cells in 10 to 20 minutes by inflammatory stimuli, including thrombin, histamine, and peroxides. Moreover, P-selectin is coexpressed along with platelet-activating factor. Both are translocated to the endothelial cell surface, which contributes to leukocyte adhesion to the endothelium. P-selectin has been shown to play a major role in propagating myocardial ischemia-reperfusion injury, mesenteric ischemia-reperfusion injury, and other inflammatory states.

In the study by Carvalho-Tavares et al in this issue of *Circulation Research*, the issue of platelet-leukocyte-endothelial interactions in the cerebral microvasculature is addressed. Using the valuable technique of intravital microscopy, the authors found that the inflammatory cytokine TNF-$\alpha$ induced a significant degree of platelet adherence to the microvascular endothelium along with leukocytes. Furthermore, antibodies directed against platelets markedly attenuated leukocyte rolling and adherence to the endothelium, as did aspirin. Using P-selectin gene-deleted mice, the leukocyte rolling and adherence were markedly diminished in response to TNF-$\alpha$. Somewhat surprisingly, however, E-selectin gene-deleted mice also exhibited reduced rolling and adhered leukocytes in response to TNF-$\alpha$, suggesting that both endothelial selectins participate in the response. Both selectins share the same ligand. A major finding of this study was that platelets, in addition to polymorphonuclear leukocytes, were also recruited to the cerebral microcirculation.
tion. In fact, platelets covered 13.5% of the venules studied. The platelets appeared to act as bridges in linking some of the leukocytes to the endothelium. In a clever investigative maneuver using chimeric mice, these workers determined that the P-selectin of the endothelium was the major factor in attracting leukocytes rather than P-selectin expressed on the platelet surface.

This cooperativity among platelets, leukocytes, and the microvascular endothelium has been investigated previously, and preliminary evidence for it has been obtained in the systemic circulation, mesenteric microcirculation, and coronary microvasculature, the latter two studies during ischemia-reperfusion of these vasculatures.

It should be stated that it is very difficult to quantify leukocyte-platelet interactions and describe the precise spatial interaction between these cell types because of the dynamic nature of these interactions, disparity in their cell sizes, and host of granular-secreted inflammatory mediators generated by both cell types. Carvalho-Tavares et al have made an important contribution to elucidating the key role of the vascular selectins (i.e., P-selectin and E-selectin) in these processes, providing strong evidence of this interaction in vivo and following up on this concept postulated earlier in the development of the selectin regulation of platelet-leukocyte cooperativity.

Additional work characterizing the time course of this platelet-leukocyte cooperativity, the role of P-selectin glycoprotein ligand-1 (PSGL-1) to this interaction, and the applicability of these phenomena in other microvascular beds and to inflammatory stimuli other than TNF-α will be of great value. However, this study clearly advances the concept of platelet-leukocyte cooperativity in inflammatory states.

References