

How might our view of vascular injury or atherosclerosis have changed if thrombin had been identified as the critical serum-derived growth factor (SDGF) before platelet-derived growth factor (PDGF)? Knowledge that advanced atherosclerotic plaques show evidence of repeated thrombotic/coagulative events led Ross to argue that platelet factors play a key role in atherosclerosis (1). Thrombin may be a more tempting candidate, especially in regard to the problem of restenosis after angioplasty. First, Hatton showed that thrombin activity remains elevated over balloon-injured vessels in animals for weeks after injury (2); in contrast, the platelet response is over in one to two days (3). Moreover, indirect evidence implies that thrombin is functioning in vivo after balloon injury. We showed that the pattern of gene expression for the PDGF-receptors and PDGF-A chain after balloon injury in vivo closely follows the pattern seen when cultured smooth muscle cells are treated with thrombin (4). Other growth factors and vasoactive molecules do not reproduce this pattern. When PPACK was infused into baboons after angioplasty, most of the elevation of expression of PDGF-A chain was abated (4). This effect on PDGF is especially interesting given reports in vitro that autocrine PDGF-A chain is a co-mitogen rather than a complete mitogen (5-7). Activation by thrombin might also explain the synthesis of PDGF-B by endothelial cells and by macrophage within advanced atherosclerotic plaques (8, 9). Second, via its proteolytic activity, thrombin may activate or deactivate other molecules implicated in the response to injury, including plasmin and bradykinin (10, 11). Thus, one might imagine thrombin having both a direct and an indirect role in the proliferative response of vessels to injury. Finally, thrombin might play a major role in spasm. Thrombin stimulates endothelial cells to produce endothelium-derived relaxing factor, and endothelium-derived relaxing factor results in smooth muscle relaxation and possibly growth inhibition. In contrast, thrombin acts directly on the smooth muscle cells as a vasoconstrictor. It seems likely that such a mechanism plays an important role in the ability of small vessels to contract at sites of vascular injury while neighboring vessels, their endothelium still intact, are stimulated to increase their blood flow. Similar mechanisms might contribute on the one hand to vasospasm and on the other hand to control of blood flow through the adventitial vessels that supply the base of the atherosclerotic plaque (12).

Obviously, we do not know that thrombin is active in plaques or that it is an in vivo mitogen. By contrast, in vivo studies show that PDGF is chemotactic but weakly mitogenic (9, 13). Indeed, McNamara and colleagues (14) lose mitogenic activity in the presence of serum. Infusion studies with thrombin receptor oligopeptides would be valuable. However, the peptides will only mimic activity of the thrombin receptor and may clear too quickly. Moreover, there is evidence that non-proteolytic domains of thrombin have their own activities (15, 16). The protease itself may have different substrate specificities depending on occupation of the exosite, binding to thrombomodulin, or, perhaps, binding to as yet undefined protease nexins within the vessel wall. The critical step in focusing on particular thrombin activities may well depend on use of specific inhibitors. The most impressive published data so far is the work of Sarembock et al. showing that hirudin inhibited intimal thickening following balloon injury in rabbits (17).

Unfortunately, the data did not clearly distinguish between the effects of hirudin on coagulation in the acute stages after balloon injury and its effects on inhibiting the formation of the intima. Nor do we know whether effects were due to inhibition of replication, inhibition of migration, or any of the other effects discussed above. Undoubtedly, McNamara et al.'s paper in this issue, as well as earlier studies implicating thrombin as a very potent in vitro mitogen (18), will lead to new and critical in vivo experiments.

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