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By John Ashkenas, Science Editor

Vascular thrombosis viewed in real time

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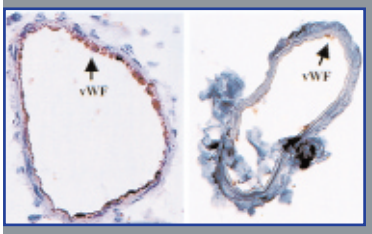
Intravital microscopy provides a direct view of the interactions of fluorescently labeled cells within the vasculature of a living animal. Using this approach, Ni and colleagues have studied the loss of endothelial cells from arterioles treated locally with ferric chloride, as well as the thrombosis and occlusion that occur in these wounded vessels. Clot formation is believed to occur in two steps, involving different platelet surface receptors and different adhesive ligands. The first, mediated by von Willebrand factor (vWF) and its receptor, slows the flow of platelets past the wounded area and activates the second receptor, the integrin $\alpha_{IIb}\beta_3$. This receptor binds fibrin, bringing the platelet to a halt and setting the stage for the aggregation of additional platelets onto those already bound. By means of these and other adhesive interactions, platelets in normal animals bind to, and initiate clot formation on, the wounded subendothelial tissue within minutes of denudation. Ni et al. report here that neither vWF nor fibrinogen (Fg) is strictly necessary for clot formation in this system, although clots in animals lacking Fg tend to break off from the site where they form and to cause occlusion downstream of the wounded area. Even animals deficient for both Fg and vWF can form such fragile clots, albeit with slow kinetics. The authors note that when Fg is lacking, fibronectin, another known ligand of $\alpha_{IIb}\beta_3$, accumulates to unusual levels in the secretory granules of platelets. They suggest that this adhesive molecule is secreted by platelets when they bind at the wounded site, thus partially compensating for the lack of Fg.



Substrate-specific blockade of proteasomal activity

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Simons and his associates have previously reported that the biologically active peptide PR39 blocks the proteasome-dependent turnover of the regulatory protein HIF-1α. Here, these same authors identify IκBα as another protein that is stabilized by PR39 treatment, and they provide insights into the mechanism by which these proteins escape degradation, despite undergoing ubiquitination in the normal manner. PR39, they show, binds directly to one of the subunits of the 26S proteasome, apparently interfering with its recognition of ubiquitinated IκBα. As a consequence, NF-κB is retained in the cytoplasm, where it cannot mediate the cellular response to proinflammatory signals. With respect to the NF-κB pathway, PR39 treatment is similar to other known inhibitors of the proteasome, but PR39 does not affect either the overall cellular level of proteasomal activity or the essential turnover of cell cycle regulatory proteins, and it does not appear to be toxic. Indeed, transgenic mice tolerate the constitutive expression of PR39 in their cardiac myocytes. Because they cannot induce NF-κB or its dependent genes in response to cardiac ischemia-reperfusion injury, these mice are somewhat protected from the effects of coronary ligation, suffering significantly smaller infarctions than do normal mice. The full range of cellular proteins whose degradation is blocked by PR39 is unknown, but these findings suggest that this or other substrate-specific inhibitors of proteasomal activity could be used for therapeutic purposes to influence the fate of key cell-regulatory proteins.

The angiotensin II type 2 receptor in cardiac hypertrophy

(See article on pages R1–R5)

Faced with increasing systolic blood pressure, the left ventricle of the heart undergoes a stereotyped morphological change in which the ventricle walls thicken, as the deposition of interstitial collagen increases and cardiac myofibrils become more massive. Left ventricular hypertrophy (LVH) can be induced consistently in wild-type mice by constricting the aorta to increase blood pressure. However, the heart appears to be poised to undergo this transition, since a wide variety of transgenes, some probably acting indirectly, predisposes mouse hearts to hypertrophy and the associated cardiomyopathy. Drug studies suggest that inhibition of angiotensin-converting enzyme blocks LVH, but the signaling pathway through which angiotensin II stimulates this process has been controversial. Senbonmatsu and coworkers now show that mice lacking the gene for the angiotensin II type 2 receptor (AT_2) fail to undergo LVH, even in the face of chronic aortic constriction, and they identify a candidate mediator of this signal, the kinase $p70^{S6k}$. The crucial role of AT_2 is consistent with recent reports that AT_1, the other major angiotensin II receptor, is not required for hypertension-induced LVH. Senbonmatsu et al. show that despite their resistance to the normal hypertrophic response, AT_2^- hearts maintain normal ventricular function even after aortic banding, suggesting a pathological rather than a desirable homeostatic role for LVH. If blocking hypertrophy proves benign, local inhibition of AT2 or $p70^{S6k}$ might be tested as a means to forestall the cardiomyopathy seen in various diseases.