Protective effect of marrow microenvironment. The Hematopoietic Inductive Microenvironment (HIM) niches include osteoblasts, stromal/mesenchymal cells, endothelial cells and extracellular matrix components. AML blast quiescence, proliferation and apoptosis are influenced by receptor kinases, adhesive receptors and signaling via matrix mediated/bound chemokines and cytokines. AMD3100 and AMD465 CXCR4 antagonists +/- sorafenib or inhibitors of VLA-4/CAM-1 interactions chemosensitize AML blasts within the HIM niches. Shh: sonic hedgehog, Notch, vascular endothelial factor and other adhesion receptors signals promote leukemic stem cell survival and expansion and can be targeted to overcome AML chemoresistance.

ERK survival pathways.\textsuperscript{15} CXCR4 inhibition partially abrogated the protection conferred by stromal cells, rendering these leukemic cells more susceptible to apoptosis when exposed to cytamine. AMD3465 led to down-regulation of FLT3 receptor expression and inhibition of KIT signaling when used in conjunction with sorafenib, a permissive tyrosine kinase inhibitor in FLT3-ITD–expressing AML cell lines (see figure). The latter observations are very intriguing and may explain in part the successful treatment of a relapsed FLT3-ITD–positive AML patient with sorafenib in the posttransplantation setting.\textsuperscript{16}

Finally, while both reports open new avenues for overcoming in vivo drug resistance in AML, it is yet unclear whether durable complete remissions can ensue from this strategy. AML is indeed a very heterogenous disease, and successful eradication of leukemic stem/progenitor cells will require blocking multiple receptors/pathways as shown in the figure, with targeted agents focused on CD44, VLA-4, CXCR4, sonic Hedgehog (shh), vascular endothelial factors VEGF, and interleukin 3 receptor alpha CD123, in addition to many factors likely not yet discovered.\textsuperscript{17-20} Progress in whole genome sequencing approaches may uncover novel target genes and signaling pathways that may radically alter our approach to therapy.\textsuperscript{11}

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the acute coronary syndromes or ischemic stroke. The hemostatic response is regulated by competing prothrombotic and antithrombotic forces. A key player in this regard is the serine protease, thrombin. In its free form, thrombin is procoagulant, activating several components of the coagulation cascade as well as converting fibrinogen to fibrin. It is also one of the most potent platelet agonists known. Conversely, thrombin bound to thrombomodulin on vascular endothelial cells can activate protein C, a potent physiologic anticoagulant.

In this issue of Blood, Li et al describe a surprising new role for thrombin: promoting the dissolution of platelet thrombi. They demonstrate that thrombin, generated at the site of vessel injury, is able to cleave a protease of previously unknown function, ADAMTS-18, which, following secretion from activated endothelium, binds to the β3 subunit of the platelet adhesion receptor integrin αIIbβ3. The thrombin-generated 45-kDa C-terminal cleavage product of ADAMTS-18 clusters the β3 integrins and induces oxidative fragmentation of the platelet, leading to thrombus dissolution. This process is dependent on the sequential activation of platelet 12- lipoygenase and NADPH oxidase, resulting in the intracellular production of reactive oxygen species (ROS) including hydrogen peroxide (H₂O₂).

Like many breakthroughs, the path leading to this discovery has been an unexpected one. It began with the seemingly unrelated observation that patients with HIV-1 infection develop autoimmune thrombocytopenia due to the presence of an antiplatelet antibody directed against the epitope GPIIa49–66 of αIIbβ3 (GPIIb–IIIa). In general, the higher the titer of antibody, the lower the platelet count. It was determined that this antibody induced thrombocytopenia by inducing platelet fragmentation via a process dependent on the generation of H₂O₂ and other ROS. The search for a physiologic ligand that could induce oxidative platelet fragmentation was undertaken using the platelet GPIIa49–66 peptide as bait in a phage surface display library. From 20 clones isolated, 1 had 70% identity with a noncleavable ADAMTS-18 expression construct and demonstrated platelet activation, 5 which begs the question as to what stage in the thrombotic process these molecules are generated and how their platelet-stimulating functions are coordinated with their ability to induce platelet fragmentation. Additionally, whether thrombin is the only (or major) proteolytic enzyme with the capacity to regulate the activity of ADAMTS-18 remains to be determined. Nonetheless, despite being one of the most intensely investigated proteases, new and unanticipated functions for thrombin continue to emerge, reinforcing its role as a master of thromboregulation.

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Is thrombin the problem or (dis)solution?

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