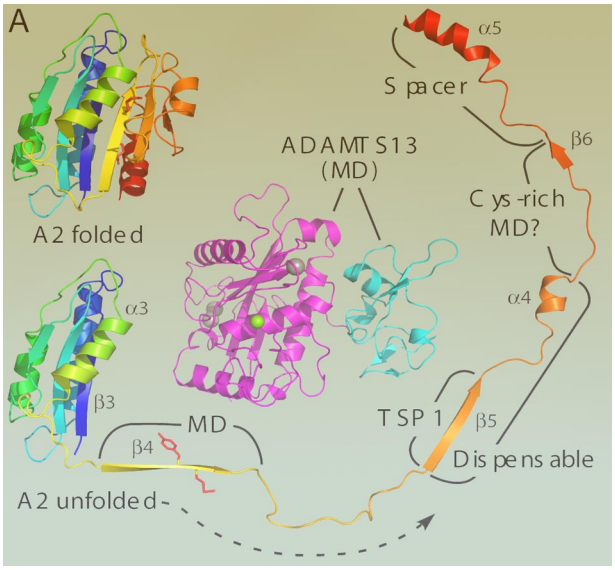

A homology model of the ADAMTS13 metalloprotease (magenta) and disintegrin-like domains (cyan) is shown (MD) to provide a sense of scale, with active site Zn2+ ion (green) and 3 structural Ca2+ ions (gray) as spheres. The VWF A2 domain is predicted to consist of a 6-stranded β-sheet surrounded by 5 α-helices. Residues Tyr^{1605}-Met^{1606} (side chains in red) are buried in strand β4. Exposure of this bond to ADAMTS13 requires substantial unfolding of domain A2; more distal segments that interact with specific domains of ADAMTS13 are labeled. The locations of these ADAMTS13 domains relative to the MD moiety are not known. Deletion of strand β5 through helix α4 (dispensable) has a minimal effect on the rate of substrate cleavage. Molecular graphics prepared with PyMOL (DeLano Scientific, Palo Alto, CA). See the complete figure in the article beginning on page 1713.

within the protease domain. This makes it poised to strike when the cleavage site is revealed by the shear-induced unfolding of the A2 domain.

Ultimately, then, such flexible proximity enables the catalytic center of ADAMTS13 to proteolyse the Tyr^{1605}-Met^{1606} bond as it becomes exposed and thereby reduces the size and reactivity of the VWF polymer. The unique preference of ADAMTS13 for a single bond contrasts with that of thrombin, the latter being an example of exosite-enhanced (almost) promiscuous proteolysis. Numerous crystal structures have given insight into the mechanisms of functional specificity of thrombin. What precisely determines the unique cleavage specificity of ADAMTS13 remains to be determined.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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HEMOSTASIS

Comment on van Schooten et al, page 1704

Where does von Willebrand factor go?

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VWF is removed from the blood by macrophages rather than scavenger receptors, suggesting a possible strategy for improving treatment of VWD and hemophilia.

In clinical hematology, von Willebrand factor (VWF) is a bit like the actor Jake Gyllenhaal: we care about him because of who clings to his arm rather than for any inherent quality. VWF is the consort for factor VIII, and many hematologists care more that VWF brings factor VIII to the party than getting to chat with VWF. This is unfair to VWF, of course. VWF is also essential for normal hemostasis and mild von Willebrand disease(VWD), due to partial deficiency of VWF, is more common than hemophilia A. However, we all know how bad bleeding can be when factor VIII is absent, so we care whether VWF is able to protect factor VIII. Thus, we also care whether factor VIII stays with VWF, even when it is removed from the blood by a clearance pathway.

VWF is an unusually large protein. It differs from most plasma proteins in that it is synthesized and secreted primarily by endothelial cells rather than hepatocytes. Rolled up like a spool of yarn, the secreted VWF travels in the blood until it unravels under vascular sheer stress or after engagement of the vascular wall. The unrolled VWF is a sticky, very long molecule. A single VWF multimer, attached to a vessel wall, can be a good deal longer than the width of an endothelial cell. As blood rushes by, the unrolled VWF thread is soon decorated by platelets that cling tightly enough to resist sheer force and the bumping of red cells. Thus, deficiency of VWF leads to bleeding problems caused by failure of platelet deposition. In a pathologic situation, excessive function of VWF is a dramatic feature of thrombotic thrombocytopenic purpura. In that disease, abnormally large VWF multimers in blood causes deposition of platelet-rich thrombi that fragment red blood cells and occlude blood flow to essential organs.

Each of the 20 to 50 subunits that make up a VWF multimer has a high affinity niche for a factor VIII molecule. When bound to VWF, factor VIII is prevented from binding to platelets and participating in the coagulation cascade. Factor VIII is also protected from spontaneous dissociation, from proteolytic degradation, and from clearance by scavenger receptors that line blood vessels. Thus, VWF substantially prolongs the plasma half-life of factor VIII. VWF has a longer plasma half-life than factor VIII and, until now, it hasn't been clear how VWF molecules are removed from the circulation or whether they take bound factor VIII molecules when they go.

In this issue of *Blood*, van Schooten and colleagues identify a cellular clearance pathway for VWF and, apparently, for VWF-bound factor VIII. The surprise is that VWF is cleared via a macrophage pathway rather than via the usual scavenger receptors that are localized primarily on hepatocytes, renal cells, and endothelial cells. It is fitting that VWF, the giant molecule, is cleared by a cellular pathway

that is better known for removing unwanted cells than the lipoprotein receptor class of scavenger receptors that remove deteriorating coagulation proteins.

One important aspect of the newly demonstrated VWF clearance pathway is that it may be susceptible to pharmacologic interruption. Interference with the clearance pathway may be a strategy to improve the half-life of VWF or infused factor VIII. This approach might be considered for patients with mild VWD or for patients with mild hemophilia. Alternatively, it might be a strategy to increase the interval between infusions of factor VIII in patients with severe hemophilia. Knowledge of the clearance pathway may also provide mechanistic insights that are useful in trying to explain why plasma VWF is low in some cases of mild VWD or why it increases during pregnancy. It may also prove useful to know the normal clearance pathway for VWF when thinking about the mechanisms of disease conditions, such as thrombotic thrombocytopenic purpura. Thus, discovery of an unexpected clearance pathway provides insight into how VWF leaves the party and suggests tricks that we might play to keep factor VIII and her consort, VWF, around longer.

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NEOPLASIA

Comment on Kujawski et al, page 1993

Genomic complexity in chronic lymphocytic leukemia

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In this issue of *Blood*, Kujawski and colleagues report that genetic complexity in CLL is associated with aggressive disease. These investigators examine the DNA of the leukemia cells from 178 CLL patients for loss or gain of genomic material using arrays capable of detecting SNPs.

A single nucleotide polymorphism (SNP) is a polymorphic variation at a single site in DNA, of which approximately 10 million have been identified in the human genome. Each person has many different SNPs that together reflect a unique DNA sequence. A DNA microarray with thousands of immobilized allele-specific oligonucleotides specific for such sequences can probe the genomic DNA for genetic polymorphisms. Such SNP arrays also can evaluate for loss of heterozygosity (LOH), a form of allelic imbalance resulting from the complete loss or increased copy number of one allele relative to the other. Using SNP-array technology, other investigators have identified LOH in many solid tumors and hematological malignancies, including chronic lymphocytic leukemia (CLL).[1,2] Kujawski et al go one step further to report that the degree of LOH complexity found in CLL cells via use of SNP arrays bears a strong relationship to the relative aggressiveness of this disease.

Prior studies using conventional techniques have found that patients with complex cytogenetics-containing CLL cells have a relatively poor prognosis.[3,4] Certain CLL cell genetic abnormalities, such as deletions in the short arm of chromosome 17 or in long arm of chromosome 11, are independent predictors of adverse outcome. Increasingly, though, there is recognition that the overall complexity of the genetic aberrations found in CLL cells is an adverse prognostic marker independent of the specific abnormalities detected.[5-8] The propensity of a CLL cell population to develop such complex genetic abnormalities might be associated with characteristics that adversely influence outcome and/or allow for secondary and tertiary genetic changes. These changes could also adversely affect the response to therapy or overall survival. In either case, the use of SNP arrays to discern such genetic complexity might offer advantages over more conventional techniques, as this method does not require complex in vitro culture conditions or use of more limited sets of probes that could yield false-negative results.

However, there are some caveats to this approach. SNP arrays are insensitive to detecting balanced translocations or genetic aberrations which are present in less than about a quarter of the cells examined. As such, the use of SNP arrays in the clinical setting might require methods for isolating leukemia cells that are not currently available to most clinical pathology laboratories. In addition, SNP arrays might be less sensitive than fluorescence in situ hybridization techniques in detecting intraclonal genetic changes that sometimes are found during CLL clonal evolution.[9] Nevertheless, the current study affirms the importance of focusing attention on the somatic genomic alterations involved in CLL pathogenesis and progression, reminding us once again that CLL, like all cancers, is truly a genetic disease.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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