Inhibitory antibodies against factor VIII C1 domain

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In this issue of Blood, Batsuli et al demonstrate that pathogenic antibodies against the factor VIII (fVIII) C1 domain are more common than previously appreciated and that they can cause bleeding through a novel mechanism.

In contrast to most inhibitory antibodies, some anti-C1 domain antibodies increase clearance of fVIII while only modestly affecting fVIII activity. Inhibitory anti-fVIII antibodies are the most serious complication of hemophilia A therapy. Because inhibition of fVIII occurs through a variety of mechanisms, detailed studies of these antibodies has also provided remarkable insights into fVIII biology. Inhibitory antibodies against major epitopes on the A2 and C2 domains have confirmed the clinical importance of fVIII binding to fIXa and to a phospholipid surface through the respective domains (see figure panel A).

Some anti-C1 domain antibodies interfere with uptake of fVIII by scavenger receptors and processing by dendritic cells, identifying a surface involved in clearance. One anti-C1 antibody that blocks von Willebrand factor (VWF) binding prolongs plasma circulation to the same extent as VWF, confirming the relationship of the C1 domain to the clearance pathway and indicating the potential of antibodies to prolong circulation of fVIII.

Most inhibitory antibodies only partially block fVIII activity. A paradox of hemophilia A patient care is that the degree to which inhibitory antibodies inhibit fVIII activity in standard assays has poor predictive value for the risk of bleeding. Thus, the assays are used to measure the titer of antibodies but not to assess bleeding risk. This lack of correlation indicates that our current fVIII assays do not measure critical components of fVIII function.

Recent studies indicate that most clinically important inhibitory antibodies mature slowly into high-affinity immunoglobulin G4 inhibitors, and lower-affinity forms of these antibodies may be detectable many months prior to clinical bleeding. This raises the intriguing possibility that dangerous antibodies might be detected before bleeding occurs. Detecting the risk of bleeding before it occurs will require assay(s) that better measure the risk of bleeding. One approach to improving fVIII activity assays may be to measure platelet-dependent activity rather than, or in addition to, activity on phospholipid vesicles. Our laboratory recently found that fVIII binds to a complex of soluble fibrin and the αIIβ3 integrin on activated platelets rather than to phosphatidylserine. This enabled testing that showed that the degree of inhibition by 2 prototype antibodies varies 10- to 100-fold compared with phospholipid vesicle-based activity.

Batsuli and coworkers have studied a panel of monoclonal antibodies against the fVIII C1 domain. Many of these antibodies recognize epitopes that are at least partially distinct from those that were previously characterized (see figure panel B). These are adjacent to, but distinct from, regions that engage phospholipid membranes and a murine model of hemophilia A by oral delivery of antigens bioencapsulated in plant cells. Blood. 2014;124(10):1659-1668.


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VWF. They found that ≥60% of plasmas from a group of hemophilia patients with inhibitors contained antibodies that compete with anti-C1 antibodies. Thus, antibodies against this domain are likely to be much more frequent than previously anticipated.

Several of the antibodies caused bleeding, from snipped mouse tails, that was nearly as severe as complete deficiency of FVIII, even though the inhibition of FVIII activity was modest. Most prevented binding to VWF. These antibodies accelerated FVIII clearance (see figure panel A) presumably by separating FVIII from VWF and enabling clearance by scavenger receptors in the established clearance pathway. The accelerated clearance contributes to, and appears to be the major cause of, bleeding risk. This work makes it clear that the C1 domain has greater importance in providing epitopes for inhibitory antibodies than previously appreciated. It adds to the prior reports identifying bleeding that is out of proportion to inhibition of FVIII in standard assays. It also demonstrates that these antibodies can accelerate FVIII clearance as well as diminished activity.

Conflict-of-interest disclosure: G.E.G. has filed a patent application relating to measurement of FVIII activity on platelet membranes.

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