have suggested that blockade of BAFF by blocking reagents such as TACI-Ig, BAFF-R-Ig, or BR3-Fc may be an effective therapeutic approach for autoimmune diseases.[1]

Immune thrombocytopenia (ITP) is an autoimmune disorder in which antiplatelet autoantibodies bind to platelets and cause their premature destruction by Fc-mediated phagocytosis within the spleen.[7] The autoantibodies are usually of the IgG class with specificity for platelet GPIIb/IIIa and/or GPIb/IX.[7] ITP is also associated with several abnormalities of T cells such as enhanced IFN-γ production and a deficiency of T regulatory cells that are responsible for loss of tolerance and the production of the platelet autoantibodies.[7] The nature of these immune abnormalities and the important role that BAFF plays in autoimmunity led Zhu et al[8] to examine BAFF in patients with ITP.

The authors measured levels of BAFF in 45 patients with chronic ITP. They found that patients with active disease had higher levels of plasma BAFF and BAFF mRNA than patients in remission and controls. Using in vitro assays, they found that addition of recombinant human BAFF to the culture not only promoted the survival of $CD19^+$ B cells and $CD8^+$ T cells but increased the apoptosis of platelets and the secretion of IFN-γ. They then examined how an inhibitory BAFF-receptor-Fc fusion protein (BR3-Fc) affected the above responses and found that BR3-Fc successfully corrected the above effects of recombinant human BAFF. These findings suggest that not only does BAFF play a pathogenic role in ITP by promoting the survival of both B and T cells, but blockade of BAFF signaling by BR3-Fc might be a promising therapeutic approach for ITP.

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

REFERENCES

1. Mackay F, Browning JL. BAFF: a fundamental survival factor for B cells. *Nat Rev Immunol*. 2002;2(7):465-475.
2. Schneider P, MacKay F, Steiner V, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J Exp Med*. 1999;189(11):1747-1756.
3. Moore PA, Belvedere O, Orr A, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science*. 1999;285(5425):260-263.
4. Sutherland AP, Mackay F, Mackay CR. Targeting BAFF: immunomodulation for autoimmune diseases and lymphomas. *Pharmacol Ther*. 2007;112(3):774-786.
5. Bossen C, Schneider P. BAFF, APRIL and their receptors: structure, function and signaling. *Semin Immunol*. 2006;18(5):263-275.
6. HGSI and GSK Joint Press Release. Human Genome Sciences and GlaxoSmithKline announce full presentation at ACR of positive phase 3 study results for BENLYSTA in systemic lupus erythematosus. http://www.pressreleasepoint.com/human-genome-sciences-and-glaxosmithkline-announce-positive-results-second-two-phase-3-trials-benlys. Accessed October 20, 2009.
7. Semple JW. Infections, antigen-presenting cells, T cells, and immune tolerance: their role in the pathogenesis of immune thrombocytopenia. *Hematol Oncol Clin North Am*. 2009;23(6):1177-1192.
8. Zhu X-j, Shi Y, Peng J, et al. The effects of BAFF and BAFF-R-Fc fusion protein in immune thrombocytopenia. *Blood*. 2009;114(26):5362-5367.

THROMBOSIS & HEMOSTASIS

Comment on Shavit et al, page 5368

A mischief of mice

Thomas J. Kunicki THE SCRIPPS RESEARCH INSTITUTE

In this issue of *Blood*, Shavit and colleagues take advantage of major differences in von Willebrand factor gene (*VWF*) expression between inbred mouse strains to identify both a *VWF* locus alteration (*Mvwf5*) and 2 unlinked modifier gene loci (*Mvwf6-7*) that regulate plasma VWF levels.[1]

Plasma von Willebrand factor (VWF) plays a key role in hemostasis. In areas of blood vessel injury, it acts as an adhesive link between platelets and components of the extracellular matrix. In addition, it is a carrier for coagulation factor VIII and it serves with fibrinogen as a mediator of platelet-platelet cohesion (aggregation). The inherited disorder of VWF function, von Willebrand disease (VWD), is the most common inherited bleeding disorder in humans and results from quantitative deficiencies in or qualitative abnormalities of VWF. The diagnosis of VWD can often be difficult because of the variety of bleeding symptoms, its variable expressivity, and the incomplete penetrance of VWF mutations. The genetic regulation of VWF expression is complex, not only in humans but also in numerous other mammalian species in which it has been studied. A systematic study of differences in VWF expression between inbred mouse strains has begun to uncover a variety of intriguing mechanisms that control the levels of this important protein. The variety of genetic factors that influence VWF expression is sizable and extends far beyond mutations in the coding sequence or promoter region that directly affect protein function or the rate transcription.

From a genotypic and phenotypic standpoint, inbred mouse strains vary considerably, and one reflection of this genetic divergence is a wide variation in VWF levels, which can range 10-fold or greater between the most divergent strains.[2] The Ginsburg group has had unparalleled success in the exploitation of this divergence to dissect many aspects of the genetic basis for VWF variation in mice, and their findings provide new insights into the comparable but even more complex genetic regulation of VWF expression in humans.

In previous work from the Ginsburg group,[3] 2 major regulators, *Mvwf1* and *Mvwf2* (modifier of VWF), were discovered. The second regulator *Mvwf2* is a natural *VWF* variant that alters biosynthesis. The discovery of *Mvwf1*, however, provided new insight into the indirect but profound influence of modifier genes. The culpable gene in *Mvwf1* is a glycosyltransferase that influences clearance of VWF. Its influence would otherwise have escaped attention, had it not been for these elegant analyses of inbred mice.

The theme of modifier loci is particularly intriguing and relevant to human disease. Subsequent studies of different mouse strains by the Ginsburg group have uncovered 4 more modifier gene loci that lie outside of the *VWF* gene: *Mvwf3-4*[4] and now *Mvwf6-7*.[1] The existence of such loci is certainly not unique to the mice, and their discovery has implications for the biology of human VWF. Three of these murine loci correlate with potential human modifier loci that exist in the corresponding (syntenic) chromosomal regions. For example, the region that encompasses the human ortholog of *Mvwf6* overlaps a region identified as a VWD quantitative trail locus (QTL) in the Genetic Analysis of Idiopathic Thrombophilia (GAIT) study.[5] In addition, it overlaps potential human VWD modifier loci that were identified in a large Amish pedigree.[6]

The newly discovered murine loci are admittedly large, each encompassing several

genes. Nonetheless, the Ginsburg group has already shown that positional cloning is likely to identify candidate genes within these loci that will point the way to the discovery of additional human genes that influence risk for bleeding or thrombosis. This sentinel body of work demonstrates how great benefits to mankind can follow from a mischief of mice.

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

REFERENCES

1. Shavit JA, Manichaikul A, Lemmerhirt HL, Broman KW, Ginsburg D. Modifiers of von Willebrand factor identified by natural variation in inbred strains of mice. *Blood*. 2009;114(26):5368-5374.

2. Westrick RJ, Ginsburg D. Modifier genes for disorders of thrombosis and hemostasis. *J Thromb Haemost*. 2009;(7 suppl 1):132-135.

3. Mohlke KL, Purkayastha AA, Westrick RJ, et al. Mvwf, a dominant modifier of murine von Willebrand factor, results from altered lineage-specific expression of a glycosyltransferase. *Cell*. 1999;96(1):111-120.

4. Lemmerhirt HL, Broman KW, Shavit JA, Ginsburg D. Genetic regulation of plasma von Willebrand factor levels: quantitative trait loci analysis in a mouse model. *J Thromb Haemost*. 2007;5(2):329-335.

5. Souto JC, Almasy L, Soria JM, et al. Genome-wide linkage analysis of von Willebrand factor plasma levels: results from the GAIT project. *Thromb Haemost*. 2003;89(3):468-474.

6. Di Paola J, Rickard M, Murray J, Burns T, Wang K, Shapiro A. A genome-wide linkage scan of a large Amish pedigree with von Willebrand disease (VWD) identified several chromosomal regions that may contain potential modifiers of von Willebrand factor (VWF) levels and disease variability [abstract]. *Blood*. 2006;108(11): Abstract 176.