vivo considering that C3 depletion increases the therapeutic activity of an anti-idiotype antibody in a syngeneic lymphoma model.

The work of Wang and colleagues is important because it presents the first evidence that complement activation can have a detrimental effect on the antitumor activity of a therapeutic mAb in vivo. It favors the idea of modifying antibodies, for example through point mutations, to inhibit their complement-activating function and thus augment ADCC activity. Several new-generation anti-CD20 antibodies have already been designed, originally aimed at diminishing the acute side effects related to complement activation.2

Clearly, these in vivo findings will have to be extended to other mouse models and different therapeutic mAbs including rituximab, because different murine models have been widely contradictory with regard to the role of complement or immune cells in the activity of anti-CD20 antibodies. In support of this report, in a recent study of B-cell depletion using rituximab in mice transgenic for human CD20, a small inhibitory effect of complement was observed.3 Nonetheless, there are a number of caveats regarding the conclusions reached by Weiner’s group.1 One is their use of an intraperitoneal route of tumor inoculation. Previous evidence suggests that normal peritoneal B cells are more resistant to depletion by anti-CD20 and that resistance can be overcome by inducing inflammation at this site.4 Because CVF cleaves C3 in the soluble phase and complement fragments have multiple functions, alternative explanations for the data of Wang et al are possible. CVF treatment in the peritoneum may have attracted or activated effector cells at this site, thus enhancing the antibody effect. Indeed the mechanism of enhancement of therapeutic activity by complement depletion in vivo still needs to be investigated in more detail, verifying the role of different immune cell populations. Another caveat is that Wang et al used anti-CD20 in vitro and anti-idiotype antibody in vivo, which may not have identical mechanisms of action.

Finally, the significance of the findings to the clinic need to be verified. A role of ADCC in patients treated with rituximab is indicated by the correlation between CD16 polymorphism and clinical response of FL patients to rituximab.5 In addition, a C1qA polymorphism associated with low C1q levels correlated with prolonged response of FL patients to rituximab,6 supporting a negative role of complement activation in humans. In contrast to these data, some authors have suggested that coadministration of fresh frozen plasma (a source of complement) with rituximab improves the response of B-CLL patients refractory to the drug.7 Probable light will be shed by the clinical results obtained with new-generation anti-CD20 antibodies that have entered the clinic and have enhanced capacity to induce CDC, ADCC, or programmed cell death.2

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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.2 The autoantibodies are usually of the IgG class with specificity for platelet GPIIb/IIIa and/or GPIIb/IX.3 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.4 The nature of these immune abnormalities and the important role that BAFF plays in autoimmunity led Zhu et al.5 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 increased the apoptosis of platelets and the secretion of IFN-γ by T cells but increased the apoptosis of B cells and the secretion of IFN-γ in B cells and T cells, and immune tolerance: their role in the pathogenesis of immune thrombocytopenia. Hematol Oncol Clin North Am. 2009;23(6):1177-1192.

In this issue of Blood, Shavit and colleagues take advantage of major differences in von Willebrand factor (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 of 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 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 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 trait 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
ITP has elevated BAFF expression

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