pre-BCR$^+$ ALL cells. Using CRISPR-Cas9–mediated genome editing, the authors nicely showed that both BTK and B-lymphocyte kinase are relevant targets of ibrutinib in pre-BCR$^+$ ALL cells.

As a compelling follow-up to the FDA approval of ibrutinib for mature B-cell malignancies, these discoveries suggest that inhibition of pre-BCR signaling with BTK inhibitors may represent an effective therapeutic option for pre-BCR$^+$ ALL patients. Kim et al provided another important step toward clinical translation by demonstrating that single-agent ibrutinib significantly prolonged survival in mouse xenografts models of pre-BCR$^+$ ALL. Moreover, its combinations with conventional ALL chemotherapeutic agents, dexamethasone or vincristine, synergistically reduced viability and proliferation of pre-BCR$^+$ ALL cells.

Overall, the work by Kim et al exploring new insights in the activity and mechanisms of actions of ibrutinib represents a significant therapeutic advance in ALL and provides a strong rationale for the clinical development in the ALL subset with functional pre-BCR expression. Establishment of diagnostic approaches to accurately detect pre-BCR$^+$ B-ALL will help identify patients that may benefit from inhibition of pre-BCR signaling.

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

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MYELOID NEOPLASIA

Comment on Hughes et al, page 1166

# Immune reconstitution and remission in CML

**David A. Scheinberg** SLOAN KETTERING INSTITUTE

In a comprehensive and provocative report in this issue of *Blood*, with findings that were not necessarily expected, Hughes and colleagues report on the immune reconstitution that occurs as a consequence of the deepening remission achieved by patients with chronic myelogenous leukemia (CML) on tyrosine kinase inhibitors (TKIs). A significant fraction of patients with CML treated with BCR-ABL TKI achieve long-term remissions and maintain this state even after stopping the TKI. Why is this? Although the TKI itself may be contributing to this immune restoration, it is not entirely responsible as best effects are observed in those patients no longer on these drugs.[1]

The authors examined the immunophenotype and content of cells in a large series of patients with CML, beginning with diagnosis and moving through cohorts at different stages and depth of remission on TKIs, concluding with patients off of therapy and in remission. In these cohorts, the decreasing level of BCR-ABL correlated directly with the fall in levels of regulatory T cells, myeloid-derived suppressor cell, and PD-1 expression, along with their associated immunosuppressive functions. At the same time, natural killer cell and T-cell function improved; in particular, strong responses to leukemia-associated antigens, such as PRAME, WT1, PR3, and BMI-I, were noted. Responses directed to bcr/abl proteins were not examined, but specific responses to the underlying oncogenic product have been difficult to demonstrate. The cause of this immune restoration may well be the reduction in the massive immunosuppressive tumor burden, often upwards of 1 trillion CML cells at diagnosis. Furthermore, it is not yet clear whether the restoration of the antigen-specific immune response is a cause, or an effect, of the deepest remissions achieved.

The findings have important implications for therapy and the immune biology of CML. The authors ask whether the knowledge of immune recovery and its implied involvement in maintenance of remission could be used to predict which patients might successfully stop therapy. Perhaps more important is to ask whether further augmentation of the immune response to the CML cells might bring a larger fraction of patients on TKIs more rapidly into long-term unmaintained remission or even cure. These outcomes might be accomplished most immediately and crudely with a marketed checkpoint blockade antibody, or by use of a nonspecific immunostimulant such as interferon. More elegantly, and specifically, might be to treat these patients with a more selective agent that would further direct the immune system to leukemia antigens PR1 or stem cell antigens such as WT1 or PRAME. This treatment might be a vaccine[2-5] or a T-cell receptor mimic antibody[6-8] or an engineered T cell.[9,10]

In a time when immunotherapy is making great progress in hematologic cancers, and more surprisingly, in subsets of refractory solid tumors, it is especially encouraging to see possible immunological mechanistic explanations for the benefits of nonimmunologic small molecule therapies for CML, a disease that in 3 decades has moved from a relentlessly fatal illness to a chronic, and possibly curable, disease.

*Conflict-of-interest disclosure: D.A.S. has invented and Memorial Sloan Kettering Cancer Center has licensed a WT1 vaccine to Sellas Life Sciences. D.A.S. also serves as an advisor to and owns equity in Sellas Life Sciences and Eureka Therapeutics. Furthermore, Memorial Sloan Kettering Cancer Center has filed patent applications for antibodies on which D.A.S. is an inventor.* ■

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● ● ● PLATELETS AND THROMBOPOIESIS

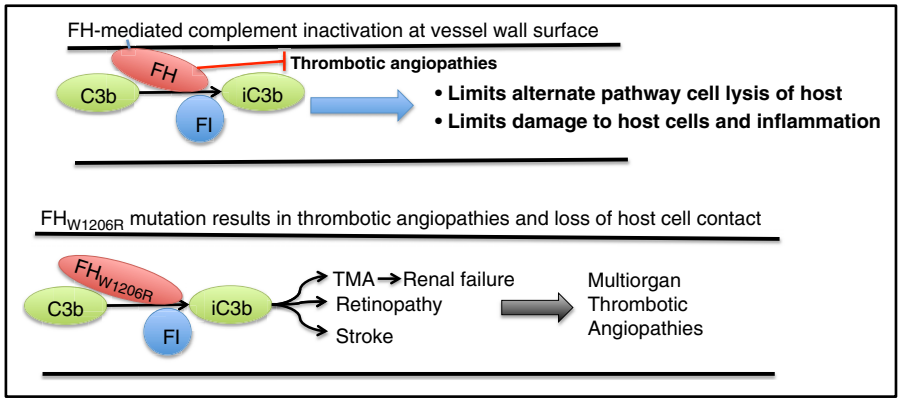
Comment on Ueda et al, page 1184

# Complement factors (H) into thrombosis

**Michael Holinstat** UNIVERSITY OF MICHIGAN

In this issue of *Blood*, Ueda et al demonstrate that a mutation in factor H (FH) disrupts host cell interactions, leading to dysregulation of complement, systemic thrombotic angiopathy, and hemolytic uremic syndrome.[1]

Complement is an innate system designed in nature to limit and fight infection through antibody-mediated immunity. The complement system has been described as a group of proteins that assist, or complement, the innate and adaptive immune systems' antibodies in killing pathogens. The primary role of the complement system is to identify common pathogens and, through a number of proteolytic cascades, lyse the pathogen and generate an inflammatory response through production and release of proinflammatory mediators.[2,3] The complement proteins, which number C1-C9, play sequential roles following antibody binding to the cell surface and result in opsonization and cell lysis. Although this is a key regulatory function for eliminating invading bacteria and pathogens, limitation of complement activation is required for prevention of lysis of the hosts' cells, including the red blood cells, endothelial cells, and other cells in the vascular space. To prevent lysis of host cell membranes, the complement system expresses factors, such as FH, that limit activity of complement and act as a cofactor for factor I (FI) to inhibit complement on the cell surface.




FH regulation of complement involves interacting with the host cell on the carboxyl terminal domains and interacting with complement C3b and FI on the amino terminal of the protein. This interaction results in inactivation of C3b (iC3b), prevention of host cell lysis and inflammation, and prevention of complement-mediated micro- and macrothrombotic angiopathies. A mutation on the carboxyl end of FH at W1206R (W1183R in human) results in a loss of host cell contact by FH without affecting regulation of complement. This loss of host cell interaction appears to result in a multiorgan thrombotic angiopathy, including stroke, retinopathy, and TMA, which leads to renal failure.

FH is a key regulator that limits complement from lysing or destroying the host cell. A number of consequences have been associated in patients with mutations in FH, including atypical hemolytic uremic syndrome (aHUS).[4-6] Although hemolytic uremic syndrome is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure, aHUS has the added characteristic of not being associated with infection of *Escherichia coli* commonly found with HUS. aHUS results in damage to the microvasculature and endothelium because of rare genetic defects in FH. One of the most common vascular dysfunctions observed with aHUS is thrombotic microangiopathies (TMAs), a serious disease originally observed in children and often resulting in anemia, renal failure, and death. It is now appreciated that aHUS can present in adults as well as in children and can be treated with anticomplement therapy such as eculizumab when properly diagnosed.[7] However, the underlying mechanism by which FH mutations result in TMAs is not well understood.

The focus of the article by Ueda et al is to assess the importance of a rare mutation in FH that results in impairment of its interaction with host cells and determine how this mutation identified as a W1183R (W1206R in mouse) change in human patients regulates both atypical complement on the host cell as well as that of the plasma complement activity.[8] Because of the role of FH in regulating complement by acting as a cofactor for FI and