dissemination, enhancing immune activation, or mediating direct pathogen killing. Interestingly, this current work appears to demonstrate delineation between virus-mediated platelet activation and thrombosis. Although virally activated platelets have increased adherence to leukocytes and collagen (a molecule frequently associated with the initiation of coagulation in response to the exposure of the subendothelium following vascular damage), TLR7-mediated platelet activation failed to induce platelet-platelet aggregation or thrombosis. This finding is similar to that observed in a model of intravascular infection with *Bacillus cereus* and suggests it may be possible to functionally “uncouple” the hemostatic and immune functions of platelets.

Perhaps the most important finding in the current work is that platelet TLR7 contributes to host survival following viral infection. Mice deficient for TLR7 or depleted of platelets succumbed to the virus more rapidly than wild-type mice. The authors then went on to demonstrate that protection could be conferred to TLR7-deficient mice following transduction of wild-type platelets. This surprising finding raises one critically important question: How? Is it that platelets are simply able to capture and sequester viral particles, targeting them for destruction through granulocyte phagocytosis? Or do platelets play a more active role in helping drive host antiviral immunity? Platelets have been shown to modulate cellular adhesion within the vasculature and enhance leukocyte activation through the release of soluble mediators such as sCD40L, potentially helping to regulate the host immune response to virus. More recently, platelet adherence to neutrophils has been shown to trigger the release of neutrophil extracellular traps within the vasculature. These structures, previously associated with antibacterial and antifungal immunity, have also been shown to protect from viral infection and as such potentially represent an additional mechanism by which platelets can contribute to antiviral immunity.

As studies into platelet-mediated immunity advance, it is unlikely any one single mechanism will account for the protective functions of platelets, but rather it will likely be a battery of overlapping immune processes that allow the platelet to respond to a diverse array of potential pathogens. This adaptability places the platelet as a key player in host immunity to viruses.

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

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Comment on Liu et al, page 803

**KLF1: when less is more**

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In this issue of *Blood*, Liu et al gain an understanding of phenotypic variability in hemoglobinopathies. They find that mutations in Krüppel-like factor-1 (KLF1) are significantly more prevalent in patients with β-thalassemia than previously
recognized and correlate with a milder phenotype. This supports the emerging concept that monoallelic KLF1 mutations can play a modulatory role in hemoglobinopathies.

β-thalassemia is a quantitative globin disorder that results from decreased levels of β-chain synthesis. The uncoupled α-chains form insoluble aggregates leading to ineffective erythropoiesis and shortened red cell survival. Iron overload from increased absorption and red cell transfusions contributes to end-organ damage. Globally, it is estimated that 1% to 5% of people are carriers, with certain geographical areas exhibiting a greater prevalence. The large clinical and hematologic variability can be partly accounted for by the concomitant milder phenotype seen in patients with a variability can be partly accounted for by the concomitant milder phenotype seen in patients with a 

The concept that monoallelic KLF1 mutations can play a modulatory role in hemoglobinopathies.

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The present analyses strongly suggest that elevation of Hbf and HbA2 levels, coupled with a decrease in CD44 expression, can be used as a basis to screen for KLF1 mutation. Identification of KLF1 mutations in individuals with β-thalassemia mutations can now be used along with other currently known predictors of disease severity to address prognosis and inform genetic counseling. Further, these types of analyses could well be directed at sickle cell disease patients, as a corollary to the present study is that monoallelic KLF1 mutations may also ameliorate the phenotype severity in that population. In addition, including more of the KLF1 promoter region and introns in the analysis could also provide an additional source of mutation discovery relevant to alteration of expression. As with the present impressive study, it would be most optimal to characterize a large population of carefully characterized individuals.

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

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Comment on Hazenberg and Spits, page 700, and on Munneke et al, page 812

Innate protection from graft-versus-host disease

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In this issue of Blood, Hazenberg and Spits provide a detailed overview of human innate lymphoid cell (ILC) subsets and their development and distribution
KLF1: when less is more

Deepa Manwani and James J. Bieker