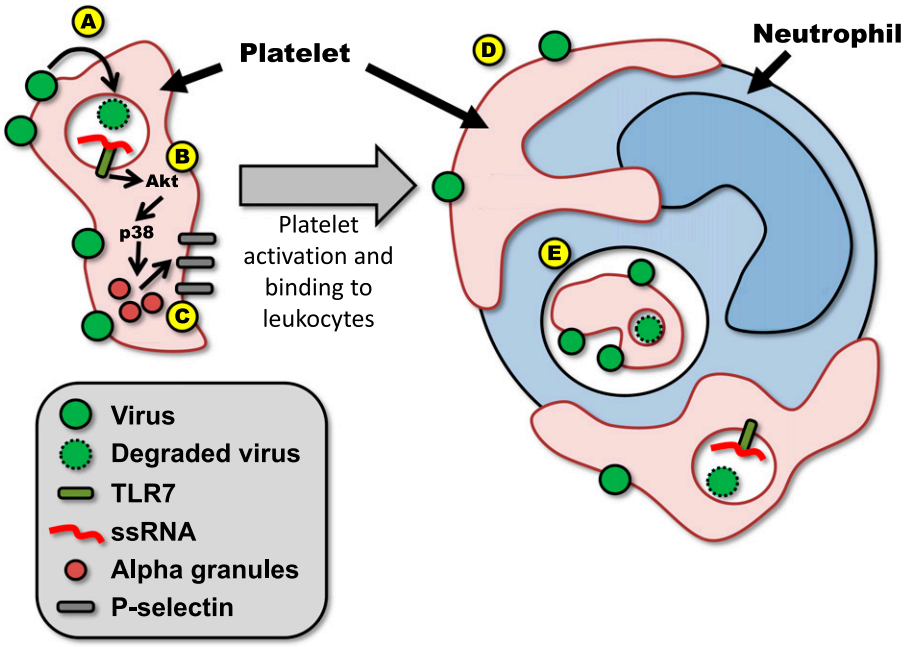

(A) Virus is bound by platelets and internalized. (B) Viral particles are degraded, releasing ssRNA, which binds TLR7, and initiating signaling through Akt and p38–mitogen-activated protein kinase (MAPK). (C) Platelet activation results in morphological changes and release of α-granules, leading to increased expression of molecules such as P-selecting on the platelet surface. (D) Activated platelets bind to leukocytes in the circulation such as neutrophils. (E) Bound platelets (or fragments derived from bound platelets) are then phagocytosed by the neutrophil.

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*[7] 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.[1] 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 transfusion 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[8] and enhance leukocyte activation through the release of soluble mediators such as sCD40L,[9] 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.[10] 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.[3]

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. It is this adaptability that places the platelet as a key player in host immunity to viruses.

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

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● ● ● RED CELLS, IRON, & ERYTHROPOIESIS

Comment on Liu et al, page 803

KLF1: when less is more

Deepa Manwani[1] and James J. Bieker[2] [1]ALBERT EINSTEIN COLLEGE OF MEDICINE, [2]MOUNT SINAI SCHOOL OF MEDICINE

In this issue of *Blood*, Liu et al gain an understanding of phenotypic variability in hemoglobinopathies.[1] 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.[2,3] 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.[2] The large clinical and hematologic variability can be partly accounted for by the milder phenotype seen in patients with a concomitant α-thalassemia mutation or with a compensatory increase in levels of the normally repressed γ-globin chain (hereditary persistence of fetal hemoglobin [HbF]), leading to clinically significant levels of HbF.[3] Although some of the hereditary persistence of HbF mutations map to the globin locus, a significant focus of recent small- and large-scale genetic studies has been to identify nonlinked loci that achieve the same result.[4]

KLF1 (formerly known as EKLF) is an erythroid-enriched transcription factor that plays a critical global role in red cell gene regulation.[5] Among its targets are genes within the β-like globin locus, where it directly (adult β-) and indirectly (fetal γ-) regulates the β-like globin switch during mammalian ontogeny.[6] Although ablation of *KLF1* is lethal, haploinsufficiency is benign but leads to altered gene expression of specific targets that are highly sensitive to KLF1 levels, such as the *Lu* antigen. Of relevance to the present study, another sensitive target is the *Bcl11a* gene, a repressor of γ-globin expression,[7] whose levels are decreased such that HbF levels increase when KLF1 expression is lowered because of monoallelic disruption.[8]

The article focuses on the significant prevalence of *KLF1* mutations and the evidence that these are linked to amelioration of the severity of β-thalassemia in those regions with high incidence; in the present case, the southern China provinces of Guangxi and Guangdong. Several aspects of this analysis are notable. Although there have been reports of *KLF1* mutation occurring in patients with hemoglobinopathies, this is the first large population study to address how common this finding is. As a result, a major strength of the study is the large number of individuals surveyed (~5000 total). This enabled significant conclusions to be made from a comparison of β-thalassemia endemic region (~3800) vs non- thalassemia region (~1200) samples, primarily that the *KLF1* mutation prevalence was dramatically higher in the endemic samples. These numbers also allowed a comparison to be made of the median time to first transfusion between cohorts to show that patients with *KLF1* mutations were significantly favorably affected. Perhaps surprisingly, patients with KLF1 mutations had a stronger ameliorative effect on severity than mutations within the β-locus, the *HBS1L-MYB* intergenic region, or in *BCL11A*. This resulted in patients who, although genetically β^0-thalassemia homozygous (or compound β^0-thalassemia heterozygotes) and therefore expected to have a thalassemia major phenotype, exhibited only a mild β-thalassemia intermedia phenotype and were largely transfusion-independent. Strikingly, 20% of nonthalassemic subjects with elevated HbA2 and HbF levels harbored KLF1 mutations.

Previously identified and novel KLF1 coding variants are described, and it is of interest that almost all mutations gave rise to truncation variants or were within the KLF1 zinc finger region, thus rendering 1 allele not expressed or functionally inactive.[5]

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 phenotypic severity in that population.[9] 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.[10] As with the present impressive study, it would be most optimal to characterize a large population of carefully characterized individuals.

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● ● ● TRANSPLANTATION

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

Innate protection from graft-versus-host disease

Tom Cupedo ERASMUS UNIVERSITY MEDICAL CENTER

In this issue of *Blood*, Hazenberg and Spits provide a detailed overview of human innate lymphoid cell (ILC) subsets and their development and distribution