developmental risk window defined in this work. What underlies the acquisition of resilience in this model? The authors speculate that platelets could limit bleeding associated with developmental vascular remodeling, as occurs during formation of mouse mesentery.[7] In that system, activated platelets maintain vascular integrity by extending filopodia at sites of gaps between endothelial cells. Do cell intrinsic changes in thrombopoiesis contribute to the development of resilience? This is the identical timeline for when murine hematopoietic stem cells undergo transcriptional reprogramming from fetal-like to adult-like.[8] How relevant are findings in this mouse model to FNAIT in humans? Although rodents are widely used as experimental models of neonatal brain injury, species differences in the timing of brain maturation can make comparisons of injury susceptibility difficult to interpret.[9] The experimental system of Farley et al is based on anti-GP1Bα, yet most cases of human FNAIT are caused by antibodies directed against GPIIb/IIIa.[2,3] Moreover, anti-GP1Bα causes both platelet clearance and perturbed GP1Bα signaling, which may enhance the severity of ICH in this model.[5] These caveats notwithstanding, this mouse model may prompt clinicians to thoughtfully consider transfusion practices in neonates with FNAIT given the potential adverse clinical outcomes associated with unneeded platelet transfusions.[10]

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

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Mahamar et al, page 2361

What causes malaria anemia?

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In this issue of *Blood*, Mahamar et al[1] report on predictors of malaria-associated anemia in a prospective study conducted in Malian children living in an area of intense seasonal malaria transmission. Across the African Sahel (the transitional area between the Sahara and the Sudanian savanna), *Plasmodium falciparum* malaria transmission is intense during the 3- to 4-month rainy season. Anemia is the main manifestation of severe malaria in these areas,[2] seen mainly in young children. During the rains, severe malarial anemia frequently necessitates blood transfusion, and it is an important cause of death in children younger than 5 years of age. In 2020, there were an estimated 627 000 deaths from malaria globally, and a large proportion of those were in children with severe malaria anemia in West Africa.[3] Now, in this area, seasonal malaria chemoprevention (monthly treatment courses of amodiaquine-sulfadoxine-pyrimethamine) is given annually during the 3- to 4-month rainy season to more than 20 million children between 3 and 59 months of age to prevent malaria and its adverse consequences. During the rainy season, malaria is ubiquitous; in many areas, mosquitoes inoculate inhabitants of this area with *P falciparum* parasites several times per week. Many of these acquired infections are asymptomatic because disease-controlling immunity is acquired during childhood. But some infections cause illness, and a few are lethal. Even after hospital admission for severe malarial anemia, there is still high mortality following discharge, which may be prevented by malaria chemoprophylaxis.[4] Severe malarial anemia is also associated with long-term neurocognitive impairment, especially in young children.[5]

So why is it that some malaria infections cause severe anemia, whereas others cause very little change in hemoglobin concentrations? In repeatedly infected children, there is little time for recovery, and progressive anemia ensues. In some other patients, a single infection causes a precipitous fall in hemoglobin.[2,6] There are 3 concomitant pathological processes (see figure).[7] First, there is the predominant clearance of unparasitized erythrocytes. Various factors are thought to contribute to this bystander destruction. These include generalized reduced red cell deformability, which may result from oxidative damage, increased splenic clearance function, and, in some cases, increased complement-mediated clearance. Second, there is bone marrow dyserythropoiesis, and third is the obligatory destruction of parasitized erythrocytes. Each of these processes is proportional to disease severity, with the first 2 reflecting host defense responses. But in most cases, this increased red cell destruction reverses rapidly. In high transmission

settings, the hemoglobin usually starts to rise as soon as the infection is controlled by antimalarial treatment. In lower transmission settings, there is a delay of several days before dyserythropoiesis resolves sufficiently for reticulocytes to increase, and for the hemoglobin to rise.

Mahamar et al conducted a pilot quantitative proteomic screen of a very large number of potential blood markers in 9 Malian children with different hematological responses to *P falciparum* infection to try to understand why these different hematologic responses occur. The lead candidates were then evaluated in a prospective series of more than 70 children from the same cohort. The study excluded children with hemoglobin AS or AC, but did not exclude G6PD deficiency, which may exacerbate malaria-associated hemolysis.[8] Higher plasma levels of circulating 20S proteasome and lower levels of insulin-like growth factor-1 were confirmed in children with reduced hemoglobin. The investigators speculated that circulating 20S proteasome may contribute to hemolysis by digesting erythrocyte membrane proteins modified by oxidative stress, whereas decreased insulin-like growth factor-1, which is important for erythroid maturation, might contribute to inadequate erythropoiesis. Of course, association does not necessarily mean causation, so further studies are warranted to elucidate these very interesting findings. These should focus on quantitating the preceding malaria parasite biomass, which is reflected poorly by the parasite density at the time of anemia, and characterizing the sequence of events that preceded the reduction in hemoglobin.

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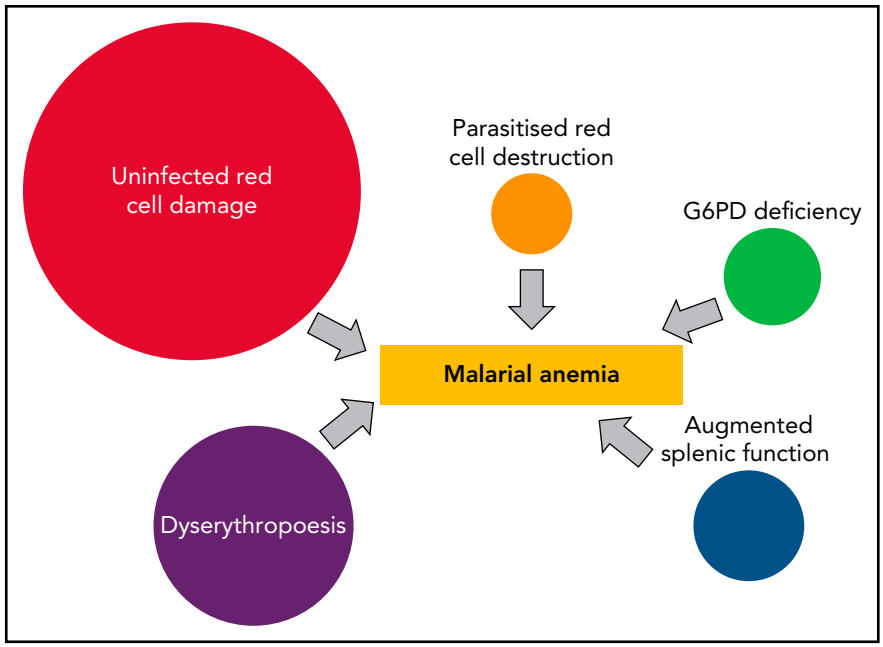

Direct contributors to malarial anemia. The proportions vary but, in general, uninfected erythrocyte hemolysis is the major contributor to acute anemia, whereas dyserythropoiesis is a major contributor to subacute anemia in children in high transmission settings.

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THROMBOSIS AND HEMOSTASIS

Comment on Cointe et al, page 2377

Therapeutic potential of granulocyte microvesicles in sepsis

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The study by Cointe et al[1] in this issue of *Blood* shows that microvesicles (MVs) from human granulocytes express urokinase plasminogen activator receptor (uPAR) and when loaded with urokinase (uPA) lyse clots in vitro and reduce microthrombi in kidneys and lungs of septic mice and increase their survival. In addition, neutrophil elastase (NE) increased fibrinolysis by degrading plasminogen activator inhibitor 1 (PAI-1).

Extracellular vesicles are small membrane vesicles (0.1-1 μm), which includes MVs and exosomes, that are highly abundant in blood.[2] The study of extracellular vesicles has exploded in recent years, with the therapeutic potential of extracellular vesicles being particularly exciting. Extracellular vesicles can be considered minicells that express cell-surface receptors from their parent cell and contribute to