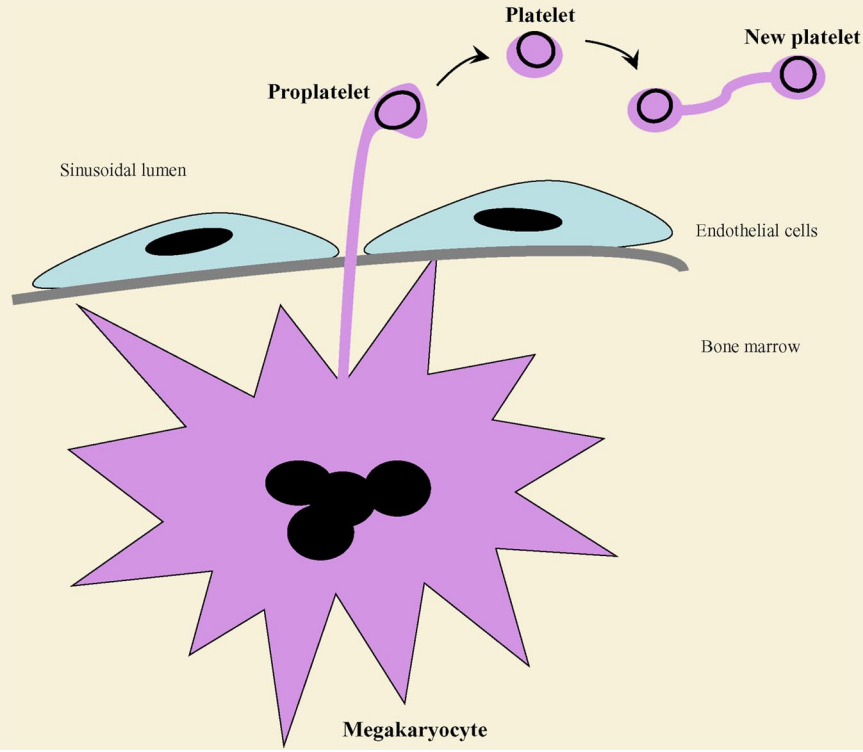

The "budding" of platelets from proplatelets, and then from mature platelets, during thrombopoiesis. Megakaryocytes in the bone marrow extend cytoplasmic projections (proplatelets) between endothelial cells into the sinusoidal lumen. The proplatelets pinch off their tips to form platelets. In a similar process, a circulating platelet is capable of extending a thin cytoplasmic projection and transferring some of its metabolic, granular, and organelle contents into an attached cell body to construct a duplicated new platelet. The dark circles in the proplatelets and platelets represent microtubules. (For an example of the platelet replication process, see Figure 1A in the article by Schwertz et al on page 3801.)

hours (in suspension culture).[5] A platelet does this by extending a thin cytoplasmic projection with a newly forming platelet at the tip of the projection. Using this maneuver, a circulating platelet can form a functioning offspring. The new platelets are equipped, through the connecting cytoplasmic projection from the parent, with organelles (including mitochondria and its DNA) and α-granules—and respond to thrombin and adenosine diphosphate (ADP).

It is an initially disconcerting concept that platelets, unequipped with nuclear DNA, can produce functional replicas of themselves. This phenomenon becomes biologically reasonable, however, because circulating platelets (1) remain active in protein synthesis and (2) contain the same molecular machinery (dynamic microtubules, actin, and myosin) that allows proplatelets (derived from megakaryocyte cytoplasm) to pinch platelet "buds" from the tips of proplatelet projections.

A proposed, expanded model of platelet production that includes the findings of Schwertz et al is presented in the figure.[5]

How will the study of Schwertz et al relate to clinical practice? The authors suggest that their observations may explain why, in some patients, platelet counts are higher than would be predicted when only few megakaryocytes are seen in bone marrow samples. It is also possible that augmentation of platelet "budding" (by methods yet to be defined) could be a novel therapeutic approach to some types of thrombocytopenia.

The work of Schwertz et al may be useful even sooner in blood banking. Platelets ex vitro continue the synthesis of proteins for as long as 10 days.[8] Schwertz et al report that the *numbers* of platelets also increase over time, as a consequence of ex vitro platelet "budding," and suggest that platelet numbers may increase during platelet storage under blood banking conditions.[5] The authors' experimental findings and provocative suggestions are likely to reinvigorate investigation of methods to optimize the preparation and "budding" of stored platelet concentrates.

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

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● ● ● RED CELLS & IRON

Comment on Ferrucci et al, page 3810

To be old is to be inflamed?

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In this issue of *Blood*, Ferrucci and colleagues continue their important exploration of anemia in the elderly and its causes.[1]

Along with other groups,[2] the authors previously reported that the prevalence of anemia was an astonishing 10% in those older than age 65. But the further surprise was the belated recognition that even mild anemia, at levels that most hematologists tended to ignore (hemoglobin > 110 g/L), was associated with a serious increase in morbidity and mortality, as well as impaired exercise capacity, impaired cognition, and a general decrease in measurements of quality of life.[1] Therefore, correcting this anemia would be a good idea and, as hematologists, it is hoped that we are taught to do this by identifying and treating its

cause. But identifying the cause(s) of anemia in our elderly patients with numerous comorbidities is frequently complicated. The major causes appear to be chronic kidney disease, iron deficiency anemia (IDA) likely due to subtle blood loss, and inflammatory diseases causing the well-known hematologic entity anemia of chronic disease (ACD), now called anemia of chronic inflammation(ACI).[1,3] Sadly, there is an additional large category noted by every group that has studied these patients called UA (undiagnosed anemia) that accounts for 30% to 60% of patients. Patients with UA are clearly hypoproliferative but otherwise do not fit into any recognized category or cause of anemia.[4]

It is these important clinical problems of ACD/ACI and possibly UA in the elderly that Ferrucci et al have chosen to address.[5] Their approach is based in part on the prior recognition that aging per se is a mild proinflammatory state,[6] with the elderly showing significant elevation of inflammatory markers like CRP and IL-6. The current paper is based on a well-characterized population of anemic and nonanemic community-dwelling Italians.[5] In addition to the usual measurements for analyzing anemia, the authors added measurement of urinary hepcidin. Hepcidin is a newly identified peptide that, stimulated by inflammation, particularly IL-6, acts to block iron absorption from the gut and iron release from macrophages, thus causing a fall in serum iron.[7] This hypoferremia presumably deprives infecting organisms of needed iron[8] and thus was of benefit during our evolution when most inflammation was caused by infection. Because hepcidin release is stimulated by inflammation and inhibited by iron deficiency, it was hypothesized that measurement of hepcidin in these anemic elderly persons would unambiguously identify patients with ACD/ACI (hepcidin elevated),[6] and those with iron deficiency anemia (hepcidin low). And just possibly if hepcidin were found to be elevated in those patients with UA, we might be able to conclude that the mysterious UA was a forme fruste of ACD/ACI, and a manifestation of the proinflammatory state of aging.

Because the paper deals with ACD/ACI, it is pertinent to note the practical difficulty in making the diagnosis of ACD/ACI unless there is a very obvious and substantial inflammatory insult. The usual clinical measures of serum iron, transferrin (not available in this paper), percent saturation (also not available), and ferritin are useful in uncomplicated clinical situations but can be ambiguous, particularly in the face of coexisting iron deficiency.[9,10] One approach to this diagnostic and therefore therapeutic problem is to use the ratio of serum transferrin receptor (sTfR, a good marker of overall erythropoiesis) divided by the log of the ferritin. This ratio was used apparently effectively in this paper to help distinguish between IDA and ACD/ACI. Therefore, the more general clinical use of this ratio would seem reasonable; however, the problem is that several commercial laboratories offer assay of sTfR, but they use different antibodies with different results. I suspect that the authors also wondered whether measurement of hepcidin would help resolve this diagnostic difficulty by providing an unambiguous marker of an inflammatory state and possibly even a proinflammatory state.

The findings are quite robust but I suspect were a bit of a surprise. Urinary hepcidin (serum measurements are now available) was low as anticipated in subjects with IDA as defined by low ferritin, high ratio of sTfR/log ferritin, as well as slightly low serum iron. But the hypothesis that urinary hepcidin would be increased in subjects with ACD/ACI as characterized clinically and by hypoferremia without evidence of iron deficiency, and by elevated CRP and IL-6 levels, was a bust. Further, the strong in vitro link between IL-6 and hepcidin release was not supported in these subjects considering that elevated levels of IL-6 were not associated with elevated urinary hepcidin. Further, the data provided challenge the idea that hepcidin is the master regulator of iron balance because hypoferremia in subjects with elevated CRP and IL-6 levels was not accompanied by elevated urinary hepcidin. So something other than hepcidin caused the serum iron to fall. The category of UA remains unsolved. Curiously, the subjects with chronic kidney disease had the highest levels of inflammatory markers. One wonders what sorts of renal diseases were represented.

What are the take-home messages? For the scientists, sure, hepcidin is a key player in the very important metabolism of iron, but other modulators and cytokines appear to be involved in controlling the level of serum iron. Further, only very overt sorts of inflammation lead to an increase in hepcidin. So what are the more subtle inflammatory signals that lead to an increase in IL-6 and CRP and possibly also ACD/ACI? For clinicians who provide care for these sorts of patients, UA remains unsolved. The diagnosis of ACD/ACI in the elderly is a work in progress, but if we could standardize the measurement of sTfR, the use of the ratio of sTfR/log ferritin would be helpful. Correlation with CRP and IL-6 may provide needed support for the diagnosis of ACI. And last, we still do not know whether correcting the anemia will correct some or all of the possible anemia-associated pathophysiologic events.

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