LFA-1 is strictly required for neutrophil migration at the initiation phase of K/BxN arthritis, other pathways can often compensate for β2 integrin deficiency in the context of bacterial infection. Because we found that Ly6G ligation attenuated β2 integrin–dependent migration, but not β2 integrin–independent migration, it is not clear that an effect would have been expected in the Staphylococcus aureus cellulitis model used by Drs Yipp and Kubes.

However, we recognize that divergent dependence on β2 integrins cannot be the whole story. The Kubes laboratory has employed conjugated anti–Gr-1 as an in vivo tool in several important studies using models of sterile inflammation in which β2 integrins play a demonstrable role. Further investigation will be required to determine the relevant differences between these experimental systems and those used in our work.

We therefore interpret the findings of Drs Yipp and Kubes as complementary to, rather than in conflict with, our own. Together, these studies raise new and interesting questions. What are the conditions under which Ly6G-binding ligation alters migration? What is the role of Ly6G in the normal course of neutrophil physiology? What does this role of Ly6G tell us about human neutrophil biology? We look forward to working with the Kubes laboratory and others to answer these important questions.

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To the editor:

Lactate dehydrogenase and hemolysis in sickle cell disease

Lactate dehydrogenase (LDH) is one of the enzymes of the glycolytic pathway that catalyzes the conversion of pyruvate to lactate with concurrent conversion of NADH to NAD+. It is a ubiquitous enzyme found in all tissues. Serum LDH exists in 5 separable isoenzymes numbered 1-5 according to their electrophoretic mobility. The distribution of the 5 isoenzymes is not uniform across body tissues. LDH1 and LDH2 are found primarily in RBCs and heart muscle; LDH3 is highest in the lungs; LDH4 is highest in the kidneys, placenta, and pancreas; and LDH5 is highest in skeletal muscle and liver. The routine determination of serum LDH includes all of its isoenzymes.

Along with reticulocyte count, indirect bilirubin level, and serum haptoglobin level, and serum hemoglobin, LDH has been used as a marker of hemolysis. Serum LDH is usually elevated in sickle cell anemia in the steady state (SS). During painful vasoocclusive crises (VOCs), the LDH may increase further in some patients because of hyperhemolysis, as shown by RBC survival studies. However, the increase in LDH during VOCs is not always because of hemolysis. Neely et al found that the increase in serum LDH was not correlated with plasma Hb level, indicating that the source of LDH is not secondary to hemolysis but rather to tissue damage, most likely BM infarction.

A prospective descriptive cohort study in children showed that the LDH level increases significantly during VOCs compared with steady-state values and that there is a significant positive correlation between LDH levels and the severity of pain but not between LDH and Hb. Moreover, elevated LDH levels at admission for VOCs were associated with severe outcome, including death and worsening clinical state requiring transfer to the intensive care unit, in adult patients with sickle cell disease (SCD).

A retrospective review of 40 patients with SS between the ages of 5 and 19 years determined correlates of microalbuminuria and proteinuria including age, sex, height, body mass index, serum creatinine, Hb level, fetal Hb, LDH level, reticulocyte count, blood pressure, history of blood transfusion, history of hydroxyurea, and history of splenectomy. The prevalence of microalbuminuria and proteinuria among the patients studied was 15% and 5%, respectively. Univariate and multivariate analyses showed a significant correlation between LDH level and microalbuminuria and proteinuria. Kato et al reported an association between hemolysis and clinical subphenotypes of SCD, including pulmonary hypertension (PH), but the diagnosis of hemolysis was based on LDH levels. Conversely, Ataga et al reported a significant correlation between PH and microalbuminuria, but no correlation with parameters of hemolysis.
These data suggest that it is the LDH level that is most likely associated with PH and microalbuminuria irrespective of the severity of hemolysis. However, unless the association between hemolysis and PH and other complications of SCD is proven by RBC survival studies, this remains a hypothesis. Elevated levels of serum LDH are a marker of nonspecific tissue damage. The clinical picture and the level of LDH isoenzymes may provide clues to its source.

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References

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