influence the choice of therapeutics to treat malignancies for which alternate therapies are available. They also provide preliminary insights into mechanisms of leukemogenesis, which may facilitate development of targeted therapies for t-AML.

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Comment on Patel et al, page 856

It really IS the red cell

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In this issue of Blood, Patel and colleagues demonstrate that placental growth factor derived from hemoglobin S erythroid cells upregulates the expression of both ET-1 and ET-BR via HIF-1α in the absence of hypoxia.

It has become increasingly clear that the process leading to vaso-occlusion in sickle cell disease (SCD) is quite complex and likely brings into play not only red-cell adhesion and red-cell sickling, but also leukocyte adhesion and activation, cytokine production, activation of coagulation, and induction of endothelial-cell activation. Together, these processes lead to further exacerbation of the occlusive process, hypoxia reperfusion injury, and extension of tissue damage. Thus, many investigators have focused recently on the role played by the nonerythroid cells and factors involved in these processes. Attention has been paid to the role of leukocytes, the elevated levels of proinflammatory cytokines, the activation of thrombogenesis, and platelet activation. And yet, one must ask: do all these cells and processes become involved just because sickled red cells become stuck in small vessels?

Patel and colleagues in this issue of Blood now redirect our attention to the primary cause of sickle cell disease and vaso-occlusion—the red blood cell. Sickle cell disease is, after all, a disease of hemoglobin (Hb), whose expression is restricted to red blood cells. While the propensity of cells with predominantly Hb S to sickle at low oxygen tension and to adhere to endothelial cells was described decades ago, the degree to which abnormal red cells play a truly dynamic role in sickle cell disease is only now being appreciated.

Connecting the dots, Patel and colleagues have now discovered an intriguing pathway that may explain a great deal, especially about the process of lung and pulmonary vascular injury in SCD. Tordjman et al showed in 2001 that erythroblasts were the only bone marrow hematopoietic cells that coexpressed 2 angiogenic factors, VEGF-A and PlGF; moreover, they showed that expression of these factors increased during erythroid maturation, and that erythroblasts secreted these factors and thus were capable of inducing migration of both monocytes and endothelial cells.1 PlGF is a member of the vascular endothelial growth factor (VEGF) family of proteins. It is typically secreted and interacts with several receptor tyrosine kinases in the VEGFR family. In addition to being a proangiogenic factor, it is also proinflammatory and may play an important role in the instability of atherosclerotic plaques, as well as in tumor neovascularization.

In 2003, companion papers by Perelman et al2 and Selvaraj et al3 showed that levels of PlGF were increased in SCD at least roughly proportionately to the frequency of vaso-occlusive episodes. They also showed that PlGF directly activates monocyte chemotaxis and mRNA levels of interleukin-1, interleukin-8, monocyte chemoattractant protein-1, and VEGF. Furthermore, Hb SS erythrocytes appear to contain more PlGF per cell than do normal cells, and this is hypothesized to account for the increased PlGF levels in SCD.4 Investigation of the mechanism whereby PlGF stimulated monocytes revealed that PlGF activates the monocyte Fc-1, which then leads to activation of PI2 kinase/akt and ERK-1/2 signaling.

In their paper in this issue of Blood, Patel and colleagues have now shown that the pathways activated by PlGF are potentially involved in the development of SCD-associated pulmonary hypertension, a grave complication affecting approximately one-third of adults with SCD. They showed not only that PlGF induces increased expression of endothelin-B receptor (ET-BR) by monocytes, but also that it induces expression of endothelin-1 (ET-1), an ET-BR ligand, by human microvascular endothelial cells. ET-1 is known to be increased in SCD and to become further elevated during vaso-occlusive episodes and acute chest syndrome.4 Interestingly, the effects of PlGF on endothelial cells and monocytes occurred via activation of PL-3 kinase and also involved hypoxia-inducible factor-1α (HIF-1α) in the absence of hypoxia. These effects potentially constitute a double whammy that may lead to a vicious cycle of both vasoconstriction and inflammation in the pulmonary circulation.

At this point, definite links between PI GF–induced processes and pulmonary hypertension have not been established. For example, serum PI GF levels during pregnancy peak at

Table 1. Characteristics of the pathogenic sickle red cell

<table>
<thead>
<tr>
<th>Red cell characteristic</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Cell dehydration</td>
<td>Increased dynamic rigidity; increased hemoglobin polymer formation and sickling; increased blood viscosity</td>
</tr>
<tr>
<td>Hemoglobin polymer formation</td>
<td>Sickled shape; mechanical obstruction of small-caliber vessels; hemolysis; vaso-occlusion</td>
</tr>
<tr>
<td>Young age</td>
<td>Increased expression of adhesion receptors; increased content of signaling molecules; activation of adhesion receptors</td>
</tr>
<tr>
<td>Surface phosphatidylserine exposure</td>
<td>Thrombogenic potential; activation of coagulation cascade; adhesion</td>
</tr>
<tr>
<td>Adhesive properties</td>
<td>Abnormal interactions with other blood cells (monocytes, neutrophils, platelets) and endothelium; vaso-occlusion; inflammation</td>
</tr>
<tr>
<td>Oxidatively damaged membrane</td>
<td>Defect in NO transport and delivery; abnormal cell rheology; vasoconstriction; inflammation</td>
</tr>
<tr>
<td>Abnormal cell-cell signaling</td>
<td>Activation of endothelial cells and monocytes; inflammation; vasoconstriction</td>
</tr>
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The irony of host defense

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Macrophages from flatiron mice, with functional defects in the iron exporter ferroportin, support increased bacterial growth when infected by Chlamydia psittaci, Chlamydia trachomatis, and Legionella pneumophila. The oral iron chelators deferriprone and desferasirox reduced intracellular bacterial growth, suggesting a new approach to antimicrobial therapy.

Iron is essential for both pathogenic microbes and their hosts. Bacterial infections are often associated with a reduction in circulating iron, a calibrated host defense mechanism that deprives microorganisms of a nutrient required for their growth and virulence. The recent elucidation of the function of the iron regulator hepcidin suggests that the molecular basis for the hypoferremia of infection resides in the ability of this liver hormone to bind and down-regulate the iron exporter ferroportin, thereby reducing extracellular iron availability to pathogens.

The role of ferroportin’s iron export function in macrophages poses a unique dilemma, because the hepcidin response is predicted to increase intracellular iron in cells of the reticuloendothelial system. Thus, although growth of extracellular bacteria may become limited by host iron sequestration, obligate intracellular pathogens that reside within macrophages could potentially find a rich supply of iron. In this issue of Blood, Paradkar and colleagues took advantage of flatiron mice, a strain heterozygous for a loss-of-function ferroportin mutation, to study growth of the intracellular pathogens Chlamydia and Legionella, both of which require iron for replication. Compared with macrophages from control mice, flatiron macrophages supported enhanced microbial growth. In addition, Paradkar and coworkers found that exogenous hepcidin promoted bacterial growth in control macrophages, consistent with the idea that loss of ferroportin’s iron export activity is associated with increased infection. Importantly, flatiron macrophages did not respond to hepcidin. These observations imply that certain bacterial infections may be promoted by intracellular iron retention due to loss-of-ferroportin iron export activity and/or its regulation by hepcidin in human patients with ferroportin disease, a type of hereditary hemochromatosis.1

The new data are consistent with previous studies showing that changes in ferroportin expression and intracellular iron levels can influence growth of Salmonella2,3 and Mycobacteria.4 Combined, this body of research points to a close association between macrophage iron export by ferroportin, intracellular iron retention, and infection by obligate intracellular pathogens. Using 2 oral iron chelators recently approved for human use, Paradkar et al further tested the possible therapeutic application of reducing macrophage iron levels. Both deferriprone and desferasirox reduced bacterial growth in control and flatiron macrophages, raising the possibility that these drugs might be effective in treating bacterial infections. However, caution is warranted; although iron supplementation may be detrimental to disease outcome, manipulation of iron status to deplete the host’s supply could result in adverse consequences due to iron deficiency induced outside of the body’s normal regulatory responses. Clearly, further study is needed to evaluate the ability of oral iron chelators to modulate host defense and infection. As a ferroportin disease model, flatiron mice may shed light on using this approach in at least one important clinical setting—hereditary hemochromatosis—wherein regulation of iron status by the hepcidin/ferroportin axis can be disrupted.

REFERENCES
It really *IS* the red cell

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