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Sickle cell anemia as an inflammatory disease

Orah S. Platt

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Commentary

The classical view of sickle cell anemia has always focused on the primary genetic defect — the abnormal sickle hemoglobin that polymerizes when deoxygenated. Polymerization within the red cell causes it to deform, to become rigid, to obstruct blood flow, and to produce acute and chronic tissue damage because of poor perfusion. A more holistic view sees the sickle red cell with its abnormal contents and membrane in a larger context — as it interacts with, damages, and stimulates the vascular endothelium and surrounding tissues and cells. This view allows examination of the hypothesis that the sticky, stiff, oxidizing sickle red cell is an irritant that provokes an inflammatory response as it obstructs flow. The tissues are not only under-perfused, but also exposed to inflammatory cytokines, growth factors, and the actions of the activated cells that respond to and produce them. The article by Kaul and Hebbel in this issue of the JCI (1) suggests that reperfusion injury plays a major role in sickle pathophysiology and provides new insights that contribute to this broader view of the disease process. Using a transgenic sickle mouse model and directly visualizing the microcirculation in a living open cremaster muscle preparation, the authors make three key observations that implicate reperfusion injury (1). First, after 3 hours of mild hypoxia followed by reoxygenation, the vascular […]

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Orah S. Platt

Harvard Medical School, Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA.
Phone: (617) 355-6347; Fax: (617) 713-4347; E-mail: orah_platt@hms.harvard.edu.

The classical view of sickle cell anemia has always focused on the primary genetic defect — the abnormal sickle hemoglobin that polymerizes when deoxygenated. Polymerization within the red cell causes it to deform, to become rigid, to obstruct blood flow, and to produce acute and chronic tissue damage because of poor perfusion. A more holistic view sees the sickle red cell with its abnormal contents and membrane in a larger context — as it interacts with, damages, and stimulates the vascular endothelium and surrounding tissues and cells. This view allows examination of the hypothesis that the sticky, stiff, oxidizing sickle red cell is an irritant that provokes an inflammatory response as it obstructs flow. The tissues are not only underperfused, but also exposed to inflammatory cytokines, growth factors, and the actions of the activated cells that respond to and produce them. The article by Kaul and Hebbel in this issue of the *JCI* (1) suggests that reperfusion injury plays a major role in sickle pathophysiology and provides new insights that contribute to this broader view of the disease process.

Using a transgenic sickle mouse model and directly visualizing the microcirculation in a living open cremaster muscle preparation, the authors make three key observations that implicate reperfusion injury (1). First, after 3 hours of mild hypoxia followed by reoxygenation, the vascular bed of the sickle mouse (but not control) showed a distinct inflammatory response with increased leukocyte rolling, adhesion, and emigration. Second, the reoxygenation resulted in conversion in endothelial cells of the oxidant-sensitive probe dihydrorhodamine to the fluorescent compound rhodamine, suggesting local production of H_2O_2. Third, the abnormal rolling, adhesion, and migration of leukocytes were prevented by infusion with a monoclonal murine P-selectin antibody before reoxygenation. This theme of reactive oxygen species generation and P-selectin–sensitive leukocyte adhesion and migration is consonant with a variety of reperfusion injury models. The implication is that once oxygen is restored to ischemic tissues, oxygen radicals are formed, and inflammatory endothelial and tissue injury occurs. This is a particularly attractive model for sickle cell anemia — especially for the chronic subliminal organ damage that typically occurs in the spleen, lung, and kidney.

In the vascular beds of these organs, young reticulocytes periodically attach to endothelial cells and, if conditions are right, cause a transient logjam of relatively rigid deoxygenating mature red cells in their wake (2). As the obstruction eventually clears, the reperfusion pathophysiology plays out, escalating the likelihood of additional rounds of reticulocyte adhesion to the inflamed endothelium that is becoming increasingly decorated with large unyielding leukocytes. These repetitive episodes of localized ischemia and reperfusion can set up a low-grade chronic inflammatory tissue-injuring state.

The finding that reperfusion injury contributes to sickle pathophysiology builds on the hypothesis that the sticky, stiff, oxidizing sickle red cell provokes inflammation as it obstructs blood flow

The authors support the concept of chronic inflammation by pointing out the abnormally high base-line leukocyte count in the sickle mouse, an abnormality that is also found in humans with sickle cell disease (3). Even more impressive is the increasing number of epidemiological studies that implicate base-line leukocyte count as a major risk factor for severity in sickle cell anemia. Despite the fact that all individuals with sickle cell anemia have the identical *globin* gene mutation, there is a wide range of clinical severity. For example, the most common clinical manifestation of the disease, the pain crisis, varies tremendously among individuals, with rates ranging from 0 per year to more than 10 per year (4).

It was no surprise to discover that some of the typical clinical complications of sickle cell anemia were less common among those individuals with higher levels of fetal hemoglobin (4–6). What has been surprising is the emerging evidence that the base-line leukocyte count is also a very important independent risk factor for disease severity. Patients with high base-line leukocyte counts are more likely to die at a younger age (5). Such patients are also more susceptible to the acute chest syndrome, an effect that is of similar magnitude to that of fetal hemoglobin over the range of fetal hemoglobin and leukocyte counts in the population (6). Base-line leukocyte counts are also risk factors for the development of silent brain infarcts (7). Most recently, the base-line leukocyte count was shown to be a strong predictor of which infants with sickle cell anemia will develop clinically severe disease (8). In the context of these epidemiological studies, it is impossible to determine whether the base-line leukocyte count simply reflects ongoing base-line chronic inflammation, or whether it indicates the propensity to develop an inflammatory response to a given stimulus. The observation that base-line leukocyte count has a heritability estimate

of 0.62 in the general population (9) suggests that a genetic modulator of inflammatory response may be related to the clinical variability of sickle cell anemia.

Exploring the role of inflammation in the pathophysiology of sickle cell anemia is of critical importance as we search for new therapeutic approaches. The paper by Kaul and Hebbel (1) sets the stage for therapies designed to interfere with P-selectin in order to decrease leukocyte-endothelial interactions. This is just the beginning.

Acknowledgments

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