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Sickle cell disease: a step closer to the dream.

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Editorial

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The last few years have been exciting ones for clinicians and scientists interested in sickle cell disease and hopeful times for patients suffering with the disease. Building upon fundamental studies carried out over the last few decades on the regulation of globin gene expression, erythroid progenitor cell proliferation, sickle hemoglobin polymerization, and membrane transport physiology, rational new therapeutic approaches for the efficacious treatment of this mortal disease have been initiated (1).

The most promising of these approaches has been the recently concluded multicenter study of hydroxyurea in sickle cell anemia which tested the effects of hydroxyurea on the frequency of painful crises in 299 adult patients with histories of three or more crises per year (2). The results of this study conclusively demonstrated decreased number of crises in the hydroxyurea-treated group compared with the control group. It was also noted that hydroxyurea treatment resulted in a reduction in the frequency of blood transfusions and of acute chest syndrome. The observed beneficial effect is most likely the result of stimulation of fetal hemoglobin synthesis after treatment with hydroxyurea and consequent reduction in the propensity of deoxygenation induced polymerization of sickle hemoglobin and the attendant cellular abnormalities. While these results are encouraging, it is clear that other therapeutic strategies are needed and should be pursued.

In this issue of *The Journal*, Brugnara and colleagues describe another realistic anti-sickling strategy for treatment of sickle cell disease based on our understanding of red cell transport physiology (3). As both the kinetics and the extent of sickle hemoglobin polymer formed upon deoxygenation are critically dependent on the state of cell hydration, it has been a long sought goal of investigators to devise therapeutic strategies for inhibiting the dehydration of sickle red cells (1, 4). As it has long been known that the Ca^{2+}-activated K^+ channel (Gardos channel) contributes to the deleterious dehydration of sickle red cells, Brugnara and colleagues set out to determine whether treatment with oral clotrimazole, a specific Gardos channel inhibitor, could prevent water loss via this channel. In five patients treated with 20 mg clotrimazole/kg/d, the red cell Gardos channel was inhibited, cell K^+ content increased, red cells became less dehydrated, and a very modest increase in hemoglobin levels was noted. This study demonstrates for the first time that the Gardos channel indeed plays a role in sickle cell dehydration.

The significance of this study is that it offers a novel and a different therapeutic strategy for the treatment of sickle cell disease. The strategy used is based on well-founded understanding of red cell transport mechanisms. However, while the data outlined clearly show that oral clotrimazole inhibits red cell Gardos channel in vivo, the observed effects on the state of cell hydration are very modest compared with that seen after successful treatment with hydroxyurea. In fact, it is unclear if the observed changes in the state of sickle red cell hydration could have significant impact on the clinical course. The authors rightfully state that this is a short-term study designed to evaluate the cellular effects and possible toxicity of oral clotrimazole in subjects with sickle cell disease and that long-term clinical trials are needed to objectively test the efficacy of this agent in treatment of this serious chronic disease.

What can we conclude from the present study and the hydroxyurea study? Although it has been almost 50 yr since the molecular basis for this disease was first defined, we are still a long way from finding an effective cure. As such, the sickle cell disease should serve as a constant reminder that the exaggerated claims we constantly read that the identification of the genetic basis of a particular disease will soon lead to a cure cannot be taken seriously. Similarly, the promise of gene therapy for treatment of hemoglobinopathies has also failed to materialize. The modest progress that has been made to date in the treatment of sickle cell disease is the result of applying knowledge regarding physiology of red cells and of erythropoiesis with careful clinical investigation. As such, these studies should serve as reminders that while molecular biology can provide critical information regarding the molecular basis of human diseases, understanding the pathobiology of cells and the pathophysiology of the disease are still key to devising effective therapeutic strategies. Furthermore, it is clear that a combination of therapeutic approaches may be necessary to effectively treat the multiple clinical manifestations of a chronic disease such as sickle cell anemia.

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