HEXOKINASE: ONE GENE OR TWO

To the Editor:

In the article by Dr Murakami et al in the February issue of Blood,¹ it was reported that human red blood cells (RBCs) contain a specific hexokinase (HK) isozyme based on its unique chromatographic behavior. These data are very similar to those we have previously reported and are cited in the reference list by Murakami et al. However, our conclusions differ significantly. Several lines of evidence suggest that not one of the RBC HK multiple forms is a specific RBC isozyme. Rather, each is a post-translational modification of the isozyme type I present in a number of cells and tissues. In fact, an antibody that recognizes human HK type I, but not HK types II and III, is also able to recognize all the multiple HK forms present in human RBCs.² By Western blotting experiments, the multiple forms of HK show all the same molecular weight.³ Patients with nonspherocytic hemolytic anemia due to a heat-unstable HK variant⁴ show the same defect in platelets⁴ and fibroblasts⁵ as an HK variant with abnormal kinetic properties,⁶ which has the same properties as the corresponding fibroblast HK.⁷ In conclusion, our results are in agreement with the data reported by Murakami et al regarding the multiplicity of RBC HK, but the evidence that the same genetic defect present in RBC HK can also be found in platelets and fibroblasts HK⁴-⁷ excludes the possibility that the multiple forms of RBC HK are separate gene products independently regulated.

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RESPONSE

In our report, we indicated that HK₁ and HK₇, although sharing some common structure recognizable by the same antibody, have an obvious difference in molecular weight by BioGel chromatography and appear to be regulated independently. This hypothesis was put forward by us on purely biochemical evidence. The observations in patients with nonspherocytic hemolytic anemia associated with HK-deficiency also support the hypothesis of two independent genes, quite to the contrary of the argument of Magnani and Stocchi.

In the RBCs of the case reported by Rijksen et al., HK₁ (the cathodal subtype) was missing, but HK₇, (the anodal subtype) was present. Similarly, in the RBCs of the case reported by Magnani et al. as HK₇, HK₇₇ was by far the most preponderant subtype. In the platelets in both cases, HK activity appeared also reduced. In cultured fibroblasts from HK₇, abnormal kinetics were observed. As expected, in all these cases, the abnormality of HKₗ was expressed in all tissues that contain it. In another patient reported by Magnani et al., HKₗ, HK₇, abnormal kinetics were reported in both RBCs and fibroblasts. It must be noted that this patient is most likely just a carrier of a variant HK₁ and certainly does not suffer from chronic hemolytic anemia.

However, the opposite situation was observed in the case reported by Altay et al.: in their RBCs, HK₇, (the anodal subtype and related minor bands) was missing, but HK₁ (the cathodal subtype) was present. There was no abnormality in other tissues, as is expected if HK₇, is RBC-specific.

Therefore, the observations in all these patients appear precisely consistent with our hypothesis that the HK₇ gene is independently regulated from the gene for HK₁ and is specific to the RBCs. They show distinct congenital defects for HK₁ and HK₇, respectively, as expected from mutations at two independent loci:

1. When HK₁ is affected (absent or reduced), the defect can be expressed in the RBCs as well as in other tissues that usually contain HK₁.
2. When HK₇ is affected, the defect can be expressed only in the RBCs.

The hypothesis of post-translational modification proposed by Magnani and Stocchi is not supported by the current evidence.

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Hexokinase: one gene or two [letter; comment]

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