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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 nonsperocytic hemolytic anemia due to a heat-unstable HK variant[4] show the same defect in platelets[4] and fibroblasts[5] as an HK variant with abnormal kinetic properties,[6] which has the same properties as the corresponding fibroblast HK.[5] 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 HK[4-7] excludes the possibility that the multiple forms of RBC HK are separate gene products independently regulated.

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REFERENCES

1. Murakami K, Blei F, Tilton W, Seaman C, Piomelli S: An isozyme of hexokinase specific for the human red blood cell (HK_R). Blood 75:770, 1990

2. Magnani M, Chiarantini L, Serafini G, Stocchi V, Dachà M, Fornaini G: Human erythrocyte hexokinase are immunologically related. Arch Biochem Biophys 245:540, 1986

3. Magnani M, Serafini G, Stocchi V: Hexokinase type I multiplicity in human erythrocytes. Biochem J 254:617, 1988

4. Magnini M, Stocchi V, Cucchiarini L, Novelli G, Lodi S, Isa L, Fornaini G: Hereditary nonspherocytic hemolytic anemia due to a new hexokinase variant with reduced stability. Blood 66:690, 1985

5. Magnani M, Chiarantini L, Stocchi V, Dachà M, Fornaini G: Glucose metabolism in fibroblasts from patients with erythrocyte hexokinase deficiency. J Inher Metab Dis 9:129, 1986

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6. Magnani M, Stocchi V, Canestrari F, Dachà M, Balestri P, Farnetani MA, Giorgi D, Fois A, Fornaini G: Human erythrocyte hexokinase deficiency: A new variant with abnormal kinetic properties. Br J Haematol 61:41, 1985

7. Rijksen G, Akkerman JWN, ven den Wall Bake AWL, Pott Hofstede D, Staal GEJ: Generalized hexokinase deficiency in the blood cells of a patient with nonspherocytic hemolytic anemia. Blood 61:12, 1983

RESPONSE

In our report[1] we indicated that HK_I and HK_R, although sharing some common structure recognizable by the same antibody,[2] 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,[3] HK_I (the cathodal subtype) was missing, but HK_R (the anodal subtype) was present. Similarly, in the RBCs of the case reported by Magnani et al[4] as HK_{Melzo}, HK_R was by far the most preponderant subtype. In the platelets in both cases, HK activity appeared also reduced. In cultured fibroblasts from HK_{Melzo}, abnormal kinetics were observed.[5] As expected, in all these cases, the abnormality of HK_I was expressed in all tissues that contain it. (In another patient reported by Magnani et al[6] as HK_{Napoli}, 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 HK_I and certainly does not suffer from chronic hemolytic anemia.)

However, the opposite situation was observed in the case reported by Altay et al[7]: in their RBCs, HK_R (the anodal subtype and related minor bands) was missing, but HK_I (the cathodal subtype) was present. There was no abnormality in other tissues, as is expected if HK_R is RBC-specific.

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

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

1. Murakami K, Blei F, Tilton W, Seaman C, Piomelli S: An isozyme of hexokinase specific for the human red blood cell (HK_R). Blood 75:770, 1990

2. Magnani M, Chiarantini L, Serafini G, Stocchi V, Dacha M, Fornaini G: Human erythrocyte hexokinase are immunologically related. Arch Biochem Biosphys 245:540, 1986

3. Rijksen G, Akkerman JWN, van den Wall Bake AWL, Pott Hofstede D, Staal GEJ: Generalized hexokinase deficiency in the blood cells of a patient with nonspherocytic hemolytic anemia. Blood 61:12, 1983

4. Magnani M, Stocchi V, Cucchiarini L, Novelli G, Lodi S, Isa L, Fornaini G: Hereditary nonspherocytic hemolytic anemia due to a new hexokinase variant with reduced stability. Blood 66:690, 1985

5. Magnani M, Chiarantini L, Stocchi V, Dacha M, Fornaini G: Glucose metabolism in firbroblasts from patients with erythrocyte hexokinase deficiency. J Inher Metab Dis 9:129, 1986

6. Magnani M, Stocchi V, Canestrari F, Dacha M, Balestri P, Farnetani MA, Giorgi D, Fois A, Fornaini G: Human erythrocyte hexokinase deficiency: A new variant with abnormal kinetic properties. Br J Haematol 61:41, 1985

7. Altay C, Alper CA, Nathan DG: Normal and variant isoenzymes of human blood cell hexokinase and the isoenzyme patterns in hemolytic anemia. Blood 36:219, 1970

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