Introduction to PKD

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Erythrocytes perform a variety of functions, the most important being the binding, transport, and delivery of oxygen to all tissues. To do so, they must be capable of passage through microcapillaries – a feat that is achieved by modifications of the erythrocyte's biconcave shape. Normal human red cells survive in the circulation for approximately 120 days, using energy to maintain the electrolyte gradient between plasma and red cell cytoplasm and to keep hemoglobin and the sulfhydryl groups of the red cell enzymes and membrane proteins in the reduced state. Because of the absence of a nucleus and mitochondria, the red cell depends on the anaerobic conversion of glucose by the Embden-Meyerhof pathway (EMP or direct glycolytic pathway) and the oxidative hexose monophosphate pathway (HMP or pentose phosphate shunt). These metabolic pathways provide the cell with energy to pump ions against electrochemical gradients, to maintain its shape, to keep iron from hemoglobin in the reduced form, and to maintain enzyme and hemoglobin sulfhydryl groups. Numerous red cell enzymes are involved in these pathways, thereby providing the cell with the necessary high-energy phosphates (primarily ATP) and reducing power (NADPH). Deficiencies of any of these red cell enzymes may result in impaired ATP generation or the inability to withstand oxidative stress and, consequently, loss of function of the erythrocyte. By far the majority of these disorders are hereditary in nature.

Red blood cell enzymopathies cause a specific type of anemia designated hereditary nonspherocytic hemolytic anemia (HNSHA). Pyruvate kinase (PK) deficiency is the most common cause of chronic HNSHA. Pyruvate kinase catalyzes the conversion of phosphoenolpyruvate to pyruvate with the concomitant generation of the second molecule of ATP in glycolysis. PK thus represents one of the major regulatory enzymes of glycolysis. The two major metabolic abnormalities resulting from PK deficiency are ATP depletion and increased levels of 2,3-BPG. The latter is thought to ameliorate the anemia in PK deficiency because oxygen is more readily released to the tissues. The precise mechanisms by which the enzyme deficiency leads to increased sequestration by the spleen are unknown. The metabolic disturbances caused by PK deficiency may affect not only red blood cell survival but also the maturation of PK-deficient erythroid progenitors, resulting in ineffective erythropoiesis.

PK-deficient patients display a highly variable degree of chronic hemolysis with variable clinical severity. Clinical symptoms range from severe anemia and death at birth, severe transfusion-dependent chronic hemolysis, or moderate hemolysis with exacerbation during infection, to a well-compensated hemolysis without anemia. Splenectomy is, in general, beneficial. PK deficiency has been treated successfully by stem cell transplantation, and gene therapy strategies have been shown to be able to correct the PK-deficient phenotype in mice. Currently, small molecule activation strategies are being developed aimed at targeting the mutant enzyme.

To date, more than 230 mutations in PKLR have been reported to be associated with pyruvate kinase deficiency. Most of these mutations are missense mutations affecting conserved residues in structurally and functionally important domains of PK. Evaluating the protein structural context of affected residues using the three-dimensional structure of recombinant human tetrameric PK has provided a rationale for the observed enzyme deficiency and contributes to a better understanding of the genotype-to-phenotype correlation in PK deficiency.