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Global metabolic changes and cellular dysfunction in diamide challengedg6pd-deficient red blood cells

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Glucose 6-phosphate dehydrogenase (G6PD) is essential to maintain proper nicotinamidedinucleotide hydrogen phosphate(NADPH)levels and redox homeostasis. G6PD deficiency isassociated with impaired glutathione (GSH) regeneration, and predisposes red blood cells (RBCs)to oxidative damage. The specific metabolomic pathways altered by G6PD deficiency, and therelation of these changes to the dysfunction of RBCs upon oxidant challenge are incompletelyunderstood. In this study, we investigated the changes in global metabolism of RBCs in responseto the oxidative challenge by diamide. Only minor differences were observed between themetabolome of untreated RBCs from that of normal and G6PD-deficient individuals. In contrast,significant changes in several biochemical pathways were found in G6PD-deficient RBCs,including changes in GSH metabolism, purine metabolism, and glycolysis. GSH depletion wasaccompanied by an exhaustive consumption in cellular energy due to a futile attempt to synthesizeGSH by γ-glutamyl cysteine synthetase. Accumulation of AMP and ADP led to AMPK activationand increased entry of glucose into glycolysis. However, oxidative modification of pyruvatekinase inhibited its activity leading to ineffective energy production. In addition, the diamideinduced changes led to a loss in the ability of RBCs to deform under shear stress. This loss inRBC functionality was temporary and reversible in normal RBCs, but more severe and irreversiblein G6PD-deficient RBCs. Taken together, these findings clearly demonstrate that metabolicanomalies account for diamide-induced dysfunctions of G6PD-deficient RBCs, and link theinability to counter oxidant insult by metabolism to the irreversible loss of functions of these cells.

Biography

Daniel Tsun-Yee Chiucompleted his PhD in Biochemistry at the University of California-Davis in 1976 and Postdoctoral studies from the Department of Hematology at Oakland Children's Hospital from1976-1980. He is currently a Professor as well as Dean of Research and Development of ChangGung University in Taiwan. He has published over 130 scientific papers in reputable Journalssuch as *Blood, JCI, British J of Hematology* and *ExperimentalHematology*. He is currently serving as an Editorial Board Member of Free Radical Research andan Associate Editor of *Biomedical Journal*.

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