Computer Simulation of Enzyme Deficiencies in Human Erythrocyte using the E-CELL Simulation System

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We previously constructed a computer model of the human erythrocyte using E-CELL simulation system.
The model has three major metabolic pathways, including glycolysis, the pentose phosphate pathway, and nucleotide metabolism, as well as Na+/K+ pumps, some transport systems, and magnesium complexation. All enzymes were modeled using experimental kinetic data published in the literature. The model has reached the steady state in which concentrations of metabolic intermediates are very closed to the real erythrocyte.

In this work, we carried out the simulation of enzyme deficiencies such as that of Glucose-6-phosphate dehydrogenase (G6PD). G6PD is a key enzyme that produces NADPH in the Pentose Phosphate Pathway. NADPH is required for the reduction of glutathione disulfide (GSSG) by glutathione reductase. A major function of glutathione (GSH) in the erythrocyte is to eliminate H2O2 and organic hydroperoxides. Peroxides are eliminated through the action of glutathione peroxidase, yielding GSSG.

We expanded this model to simulate G6PD deficiencies, including the export system of GSSG and de novo synthesis of GSH. We also modified the kinetic parameters of G6PD to fit for the mutant, and the simulation experiments were carried out with the initial concentrations corresponding to those of the normal erythrocyte. A sequential decrease in the quantity of NADPH, GSH, and ATP was observed in the simulation experiments. The longevity of our computer model in these experiments turned out to be much shorter than that of the real erythrocyte with G6PD mutation. This difference is presumably due to inadequate parameters of the pathway producing GSH. We are now trying to estimate the parameters to fit for the

experimental data.

We also plan to expand our simulation model to achieve greater accuracy by taking into account isozymes of rate-determining enzymes, metabolite diffusion and localization, and dynamic changes of the cell shape.