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From biochemistry to validated drug targets in *Plasmodium falciparum* infected red blood cells

Lactic acidosis and hypoglycemia are the best predictors of poor prognosis and subsequent death in *P. falciparum*-infected children, but the etiology of these metabolic disorders is only partially understood. *Plasmodium*-infected red blood cells (iRBC) have a 30 to 100-fold increase in glucose metabolism and a rational approach on the basis of this increased glucose metabolism was followed to identify drug targets that are specific for iRBC.

Each enzymatic step in *P. falciparum* glycolysis was kinetically characterized. The kinetic data were used to construct a detailed mathematical model, which correctly predicts the glycolytic flux and intermediate levels of the pathway in the intact isolated trophozoite. To simulate the iRBC, the trophozoite model was merged with a mathematical model of the RBC central carbon metabolism. This combined model correctly predicted the glycolytic flux in the iRBC/trophozoite stage.

Through differential control analysis, a number of potential drug targets were identified upon whose inhibition the non-infected RBC is not affected while in the infected RBC glucose flux is strongly reduced. One of the predicted targets, the glucose transporter, was successfully tested experimentally. Inhibition of the malaria and RBC glucose transporter by cytochalasin B titration inhibited the isolated trophozoite and iRBC glycolytic flux but did not affect the non-infected RBC. The model correctly predicted the extent of glycolytic flux inhibition in the intact cells as a function of the glucose transport inhibition.

This work not only highlights the importance of the glucose transporter as a drug target within *P. falciparum*, but also the relevance and importance of differential control analysis as a general tool for drug target identification.