Estimating novel potential drug targets of Plasmodium falciparum by analysing the metabolic network of knock-out strains in silico.

Fatumo S, Plaimas K, Mallm JP, Schramm G, Adebiyi E, Oswald M, Eils R, König R (2009) Estimating novel potential drug targets of Plasmodium falciparum by analysing the metabolic network of knock-out strains in silico. *Infect Genet Evol* 9(3), 351-358.

Abstract

Malaria is one of the world's most common and serious diseases causing death of about 3 million people each year. Its most severe occurrence is caused by the protozoan Plasmodium falciparum. Biomedical research could enable treating the disease by effectively and specifically targeting essential enzymes of this parasite. However, the parasite has developed resistance to existing drugs making it indispensable to discover new drugs. We have established a simple computational tool which analyses the topology of the metabolic network of P. falciparum to identify essential enzymes as possible drug targets. We investigated the essentiality of a reaction in the metabolic network by deleting (knocking-out) such a reaction in silico. The algorithm selected neighbouring compounds of the investigated reaction that had to be produced by alternative biochemical pathways. Using breadth first searches, we tested qualitatively if these products could be generated by reactions that serve as potential deviations of the metabolic flux. With this we identified 70 essential reactions. Our results were compared with a comprehensive list of 38

targets of approved malaria drugs. When combining our approach with an in silico analysis performed recently [Yeh, I., Hanekamp, T., Tsoka, S., Karp, P.D., Altman, R.B., 2004. Computational analysis of Plasmodium falciparum metabolism: organizing genomic information to facilitate drug discovery. Genome Res. 14, 917-924] we could improve the precision of the prediction results. Finally we present a refined list of 22 new potential candidate targets for P. falciparum, half of which have reasonable evidence to be valid targets against micro-organisms and cancer.

Beteiligte Forschungseinheiten

Netzwerkmodellierung

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