An in silico Approach to Detect Efficient Malaria Drug Targets to Combat the Malaria Resistance Problem

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Abstract:
Resistance to malaria drugs is a major challenging problem in most parts of the world especially in the African continent where about ninety per cent of malaria cases occur. As a response to this alarming problem, the World Health Organisation (W.H.O) recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine–pyrimethamine, should use combination therapies [1]. Therefore there is a need to discover new drug targets that are able to target the malarial parasite at distinct pathways for an efficient malaria drug. In this paper, we presented a machine-learning tool which is able to identify novel drug targets from the metabolic network of Plasmodium falciparum. With our tool we identified among others 19 drug targets confirmed from literature which we analyzed further with a sophisticated gene expression analysis tool. Our data was clustered using common distance similarity measurements and hierarchical clustering to propose a profound combination of drug targets. Our result suggests that two or more enzymatic reactions from the list of our drug targets which span across about ten pathways (Table 2) could be combined to target at distinct time points in the parasite's intraerythrocytic developmental cycle to detect efficient malaria drug target combinations.

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I. Introduction

Malaria is one of the most devastating tropical diseases despite the availability of numerous drugs acting against the protozoan parasite Plasmodium in its human host. However, the development of drug resistance renders most of the existing drugs useless. It is currently estimated that 90% of global episodes of clinical malaria and 90% of global malaria mortality occur in sub-Saharan Africa. Malaria control efforts in the region have been greatly affected by the emergence and spread of chloroquine resistance. This was first recorded in 1979 in East Africa, but has now been reported from almost all malaria endemic countries of Africa [2]. Sulfadoxine-pyrimethamine (SP) was, until recently, seen as the obvious successor to chloroquine. However, resistance to SP is developing quickly even with its current use [3][4] thus reducing the useful therapeutic life of this drug. Resistance to antimalarial drugs arises as a result of spontaneously-occurring mutations that affect the structure and activity at the molecular level of the drug target in the malaria parasite or affect the access of the drug to that target [5]. The evolution of drug resistance in Plasmodium is not fully understood although the molecular basis for resistance is becoming clearer. Increasing resistance to chloroquine and sulfadoxine/pyrimethamine will probably lead to an increase of malaria morbidity and mortality, particularly in children, and urgent action is needed to replace antimalarial drugs which have become, or are rapidly becoming, ineffective. The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination. Currently, the availability of genome data can be assembled and combined with an in silico analysis of the metabolic network.

Keywords

- Diseases, Drugs, Immune system, Biochemistry, Bioinformatics, Genomics, Africa, Springs, Medical treatment, Organisms
- pest control, drug delivery systems, drugs
- intraerythrocytic developmental cycle, in silico approach, malaria drug target detection, malaria resistance problem, African continent, World Health Organisation, monotherapies, chloroquine, amodiaquine, sulfadoxine-pyrimethamine, combination therapies, malarial parasite, machine-learning tool, Plasmodium falciparum, gene expression analysis, hierarchical clustering, enzymatic reactions
- life cycle, Resistance, Malaria, drug targets

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