Reconstruction of metabolic pathways for malaria parasite *Plasmodium falciparum*

Vachiranee Limviphuvadh limvip@kuicr.kyoto-u.ac.jp
Masahiro Hattori hattori@kuicr.kyoto-u.ac.jp
Minoru Kanehisa kanehisa@kuicr.kyoto-u.ac.jp

Bioinformatics Center, Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011, Japan

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1 Introduction

Human malaria is caused by infection with four species of the intracellular parasitic protozoan genus *Plasmodium* that are transmitted by *Anopheles* mosquitoes. Of these four species, *Plasmodium falciparum* is the most lethal. At present, at least 300 million people are affected by malaria globally and accounts for 0.7-2.7 million annual deaths. The development of resistance in the parasite to antimalarial drugs, the lack of any licensed malaria vaccine and the fundamental complexity inherent in the malaria parasite, mean there is an urgent need to better understand the function of *P. falciparum* genes and their biological role to support the development of effective antimalarial strategies. *P. falciparum* genome indicates the presence of 5,432 genes spread across 14 chromosomes, a mitochondrial genome and a circular plastid genome. Notably, more than 60% are hypothetical proteins [1]. This fact emphasizes the need to elucidate gene function and molecular mechanisms by somehow, new strategies.

In this research, we focus on KEGG metabolic pathways [2] in *P. falciparum*, *Anopheles gambiae* (vector) and *Homo sapiens* (host), and used chemical compounds in each organism as the initial datasets. Since these data make us to enable to reconstruct metabolic pathways for each organism, we can infer unique pathways in *P.falciparum* and incomplete pathways that can be complemented by *A. gambiae* or *H. sapiens*.

2 Method

First of all, we extracted all information of the annotation for each gene in *P. falciparum* and *H.sapiens* from the KEGG/GENES database version 29, and those in *A.gambiae* from Ensembl file last modified on 2 July 2003. Then, we created three lists of reactant and product compound pairs for possible enzymes in *P. falciparum*, *A.gambiae* or *H.sapiens*. Although there are a lot of compounds in an enzymatic reaction, only what appears in KEGG/PATHWAY is taken. And last, we applied the dept-first search to obtain chemical compound network, that is, reconstructed metabolic pathways for each organism.

3 Results and Discussion

Of 5,342 *P. falciparum* genes, we extracted 620 genes that were assigned EC numbers. For *A.gambiae* and *H.sapiens*, the numbers of EC number assigned genes are 1,712 and 2,219 respectively. The number of reactant and product compound pairs for *P.falciparum* is 674, for *A.gambiae* is 443 and for *H.sapiens* is 1,388. The numbers of chemical compounds included in the largest sub-network within each reconstructed

metabolome were 287 for *P.falciparum*, 115 for *A.gambiae* and 735 for *H.sapiens*. When we combined two networks of them, we obtained larger networks, that is, other sub-networks derived from another organism successfully complemented several sub-networks in *P.falciparum*. As a result, the largest network developed by *P.falciparum* and *A.gambiae* comprised 402 compounds and that by *P.falciparum* and *H.sapiens* consisted of 792 compounds.

Then we assigned these reactions to related KEGG metabolic pathways (Fig.1). We found that most of *P.falciparum* metabolic pathways incorporate in *H.sapiens* pathways possibly because *H.sapiens* is well annotated than *P.falciparum*. Nevertheless, we found 70 *P.falciparum* unique reactions (112 chemical compounds) that mapped onto 38 pathways in KEGG.

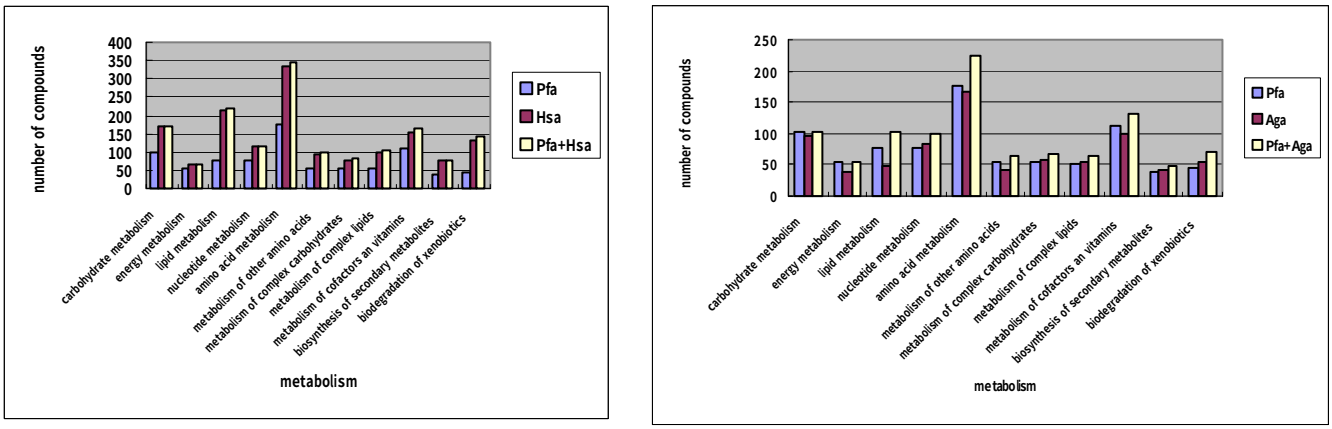

Fig 1. Distribution of networks contained chemical compounds in accordance with 11 KEGG metabolisms (Pfa; *P.falciparum*, Aga; *A.gambiae*, Hsa; *H.sapiens*)

The unique *P.falciparum* pathways we detected were most corresponding to Malaria Parasite Metabolic Pathways (http://sites.huji.ac.il/malaria/) such as Thiamine metabolism, Fatty acid biosynthesis and Pentose phosphate pathway. We now have to inspect such unique pathways in detail. On the other hand, combined networks between *P.falciparum* and *A.gambiae* increase the number of compounds that were related to amino acid metabolism and lipid metabolism. This case may occur because of the insufficient annotation for *A.gambiae*. We also need to investigate these chemical compounds in those combined networks.

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References

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