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Full Length Research Paper

Molecular Insights into Glutathione Reductase Function in Malaria Pathogenesis

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Glutathione (GSH) is a cysteine-containing tripeptide with reducing and nucleophilic properties which play an important role in cellular protection from oxidative damage of lipids, proteins and nucleic acids. Glutathione reductase (GR) is an NADPH-dependent enzyme that reduces oxidized glutathione (GSSG) to GSH. Naturally, GR is present in human and in *Plasmodium* spp. However, the function of the GR in malarial infection is not well characterized. Here, the author used a new gene ontology technology to predict the molecular function and biological process. Using GoFigure server, the molecular function and biological process in human and *P. falciparum* GR is predicted. Comparing to the human GR, the *P. falciparum* GR has similar molecular functions as gluthathione disulfide reductase activity, oxidoreductase activity, disulfide oxidoreductase activity and metal ion binding.

Key words: Human, *Plamodium falciparum*, glutathione reductase, function.

INTRODUCTION

Glutathione (gamma-glutamyl-cysteinyl-glycine or GSH) is a cysteine-containing tripeptide with reducing and nucleophilic properties which play an important role in cellular protection from oxidative damage of lipids, pro-teins and nucleic acids (Gerard-Monnier and Chaudiere, 1996). GSH regulates the metabolism of proteins and their activities by means of thiol-disulfide exchange (Gerard-Monnier and Chaudiere, 1996). When present as a trophozoite in human erythrocytes, the malarial parasite *Plasmodium falciparum* exhibits an intense GSH metabo-lism (Becker et al., 2003). GSH plays a role not only in antioxidative defense and in maintaining the reducing environment of the cytosol (Becker et al., 2003). Many of the known glutathione-dependent processes are directly related to the specific lifestyle of the parasite (Becker et al., 2003). Proteins involved in GSH-dependent process-ses include glutathione reductase (GR), glutaredoxins, glyoxalase I and II, glutathione S-transferases, and thioredoxins (Becker et al., 2003).

GR is an NADPH-dependent enzyme that reduces oxidized glutathione (GSSG) to GSH. Naturally, GR is present in human and in *Plasmodium* spp. During deve-lopmental stages of plasmodia, profound alterations of the structure and function of host erythrocytes take place, in order to support the development and/or survival of the parasite (Mishra et al., 1994). In addition an oxidant stress is also induced by the parasite (Mishra et al., 1994). There is also an increased production of reactive oxygen species (ROS) by the parasite. This may deplete the erythrocyte of its defense mechanisms namely, superoxide dismutase (SOD), catalase, glutathione pero-xidase, NADPH, NADH, glutathione (GSH) and GR (Mishra et al., 1994). Malarial glutathione reductase, a homodimer of 110 kDa with a pH optimum of 6.8 and a high preference for NADPH over NADH, was shown to contain FAD as its prosthetic group (Krauth-Siegel et al., 1996). The N-terminal sequence, VYDLIVIGGGSGGMA, which can be aligned with residues 20-34 of human gluta-thione reductase, represents the first beta strand and the diphosphate-fixing helix of the FAD domain (Krauth-Siegel et al., 1996). Methylene blue, an inhibitor of the structurally known *P. falciparum* GR, appears to be a promising antimalarial medication when given in combi-nation with chloroquine (Mishra et al., 1994). However,

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A) HUMAN GR

EFMHDHADYG FPSCEGKFNR VIKEKRDAYV SRLNAIYQNL TKSHIEIIRG
HAAFTSDKPT IEVSGKKYTA PHILIAGGMP STPHESQIPG ASLGISDGFF
QLEELPGRSV IVGAYIAVEM AGILSALGSK TSLIRHDKVL RSFDSMISTN
CTELENAGVE VLKFSQVKEV KTLSGLEVSMVTAVPGRLPVTMIPDVD
CLLWAIGRVPNTD LSLNKLGIQT DDKGHIIVEF

B) *P. falciparum* GR

VYDLIVIGGG SGGMAAARRA ARHNAKVALV EKSRLGGTCV
NVGCVPKKIMFNAASVHDIL ENSRHYGFDT KFSFNLPLLV ERRDKYIQRL
NNIYRQNLSKDKVDLYEGTA SFLSENRILI KGTKDNNNKD NGPLNEEILE
GRNILIAVGNKPVFPPVKGI ENTISSDEFF NIKESKKIGI VGSGYIAVEL
INVIKRLGIDSYIFARGNRI LRKFDESVIN VLENDMKKNN INIVTFADVV
EIKKVSDKNLSIHLSDGRIY EHFDHVIYCV GRSPDTENLN LGKLNVETNN
NYIVVDENQRTSVNNIYAVG DCCMVKKSKE IEDLNLLKLY
NEETYLNKKE NVTEDIFYNVQLTPVAINAG RLLADRLFLK KTRKTNYKLI
PTVIFSHPPI GTIGLSEEAAIQIYGKENVK IYESKFTNLF FSVYDIEPEL
KEKTYLKLVC VGKDELIKGLHIIGLNADEI VQGFAVALKM
NATKKDFDET IPIHPTAAEE FLTLQPWMK

Figure 1. Sequence of human and *P. falciparum* GR.

Table 1. The summary on the molecular function and biological process comparing between human and *P. falciparum* GR.

Summary	Molecular function	Biological process
Human GR	Gluthathione disulfide reductase activity Electron transporter activity Oxidoreductase activity Disulfide oxidoreductase activity Metal ion binding	Electron transport Glutathione metabolism Response to stress Response to pest/pathogen/parasite
P. falciparum GR	Gluthathione disulfide reductase activity Oxidoreductase activity Disulfide oxidoreductase activity Metal ion binding	Electron transport Glutathione metabolism

the function of the GR in malarial infection is not well characterized. A full understanding of host and parasite GR promises advances in malarial treatment. Here, the author used a new gene ontology technology to predict the molecular function and biological process of this enzyme.

MATERIALS AND METHODS

Getting the sequence

The database Unitprot (Bairoch et al., 2005) was used for data mining of the amino acid sequence for human host and *P. falciparum* GR (Figure 1).

Prediction of molecular function and biological process

The author performs prediction of molecular function and biological process of human and *P. falciparum* GR using a novel gene ontology prediction tool, GoFigure (Khan et al., 2003). GoFigure is a computational algorithm tool which is recently developed in gene ontology (Khan et al., 2003). The tool accepts an input DNA or protein sequence, and uses BLAST to identify homologous sequences in gene ontology annotated databases (Khan et al., 2003). The approach is to use a BLAST search to identify homologs in public databases that have been annotated with gene ontology terms (Khan et al., 2003). These include: SwissProt, Flybase (Drosophila), the Saccharomyces Genome Database (SGD), Mouse Genome Informatics (MGI) and Wormbase (nematode) (Khan et al., 2003). The contents of the results will show results for molecular function as well as biological process of the studied protein (Khan et al., 2003). The prediction of molecular function and biological process were presented and compared.

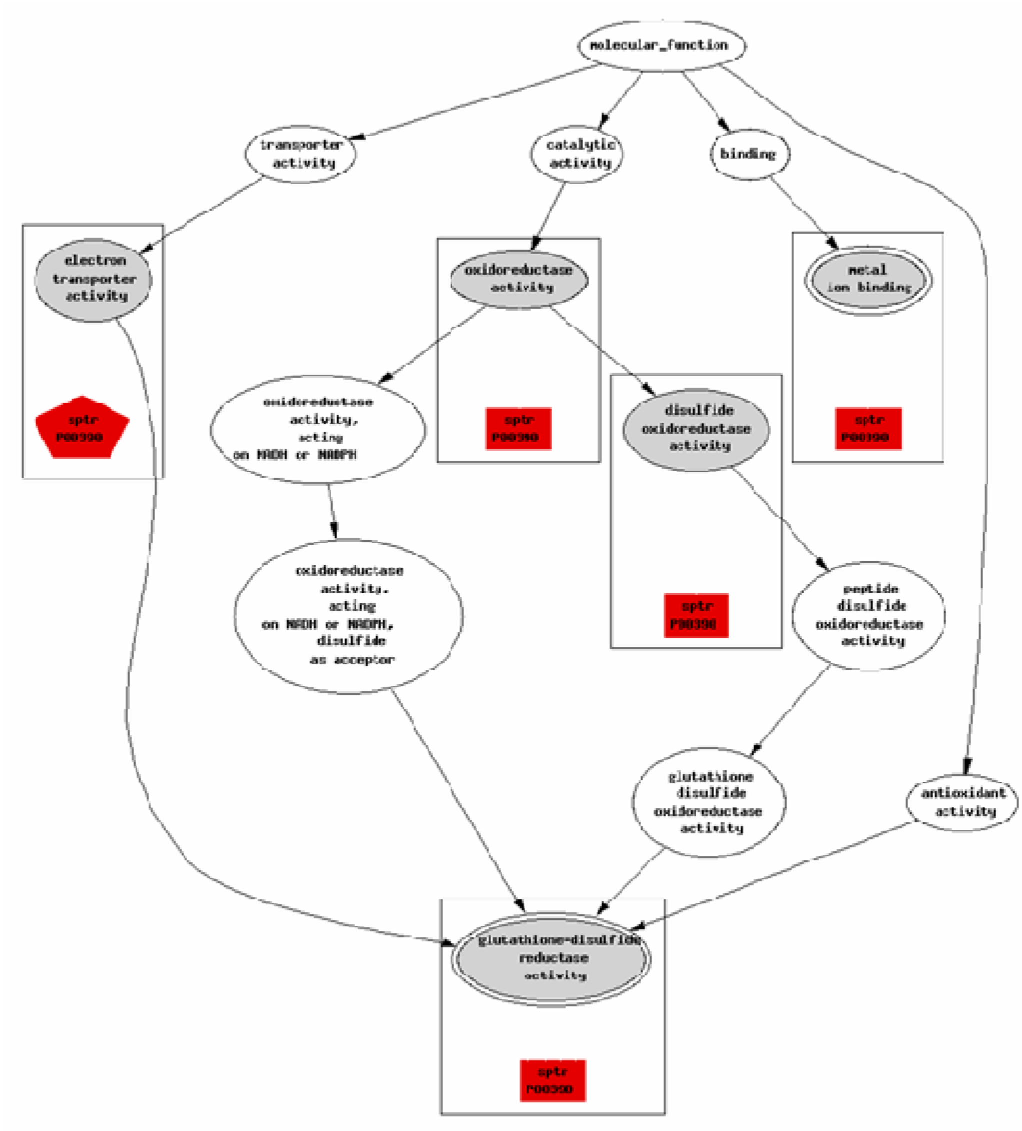

Figure 2. Expected molecular function of human GR.

of human and P. falciparum GR are presented in Figures 2 and 3, respectively. The summary on the molecular function and biological process comparing between human and P. falciparum GR is presented in Table 1.

DISCUSSION

GR is an enzyme that is believed to have a significant role in malarial infection. Roles of both host and parasite GR in cellular level metabolism during a malarial infection have been proposed. Physiologically, GSH, which is known to guard P. falciparum from oxidative damage, may have an additional protective role by promoting heme catabolism (Davioud-Charvet et al., 2001). An elevation of GSH content in parasites leads to increase resistance to chloroquine (CQ), while

Figure 3. Expected biological process of *Plasmodium falciparum* GR.

GSH depletion in resistant P. falciparum strains is expected to restore the sensitivity to CQ (Davioud-Charvet et al., 2001). High intracellular GSH levels depend on the efficient reduction of GSSG by glutathione GR (Davioud-Charvet et al., 2001). Since the malarial parasite *P. falciparum* is known to be sensitive to oxidative stress, and thus the antioxi-dant enzyme GR has become an attractive drug target for antimalarial drug development (Sarma et al., 2003).Until present, the functional of *P. falciparum* GR, correlating to human GR, is not well explored and there is a need for better understanding on these proteins' function.

Based on the recent advance in the genomics technology, current microarray technologies permit the examination of gene expression patterns of tens of thousands of genes (Bairoch et al., 2005). One challenge facing the biologist interpreting such data is recognizing the function of many of the hits identified in a single experiment (Khan et al., 2003). While one can check the literature, a rapid means to get some idea of potential function of a gene product is to obtain the ontology terms that describe the gene (Khan et al., 2003). The gene ontology is developed for this specific purpose. Many genes ontology tools have been constructed and laun-ched. Here, the author used a gene ontology tool to perform a comparative study on the predicted function of human and *P. falciparum* GR. omparing to human GR, the *P. falciparum* GR has similar molecular functions as gluthathione disulfide reductase activity, oxidoreductase activity, disulfide oxidoreductase activity and metal ion binding. Although the basic sequences for human and *P. falciparum* GR are totally different, the molecular functions are similar. This implies that any treatment aiming at blocking the functions of *P. falciparum* GR can affect human GR. Thus any drug targeting at *P. falciparum* GR might not be a magic ballet. The more specific structural antagonist that can directly block at amino acid of *P. falciparum* GR is more favorable. However, further experimental studies are needed before making a conclusion on this topic. The finding in this study is not only supports the previous knowledge on malarial GR but also gives the new view on the function of malarial GR.

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