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SEARCH FOR NOVEL DRUG TARGETS USING BIOINFORMATICS TOOLS IN PLASMODIUM FALCIPARUM

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Abstract- *Plasmodium falciparum* and its subtypes cause malaria that has become one of the latest threatening diseases. The more we try to come out with a drug more frequently resistance is noted. There is a need to search for novel targets and then prevent multiplication by various methods. While the search is on for various targets and need a lot more understanding this review just tried to list them and understand the targets and design possible inhibitors.

Choline is in high demand as a substrate for building cellular membranes. Adenosyl-L-methionine: phosphoethanolamine *N*- methyltransferase (PfPMT) catalyzes the key step in choline (Cho) biosynthesis. PfPMT catalyzes the triple methylation of phosphoethanolamine to produce phosphocholine, which is then used for phosphatidylcholine synthesis. Disruption of enzyme activity results in severe defects in important cellular processes. Synthesis of Phosphatidylcholine from choline transported from the host plasma and metabolized by the parasite enzymatic machinery has been suggested to play an important role in parasite physiology. Thus, pathways that transport choline into the parasite and incorporate it into the parasite membranes are important for parasite growth and development. By targeting this enzyme activity with the use of herbal inhibitors may block gametocyte differentiation a key stage of transmission of disease. So there is need to employ *in-silico* bioinformatics tools such PDB and Brenda in support of pharmacological screening to expedite the drug development process with optimal success rate.

Bioinformatics provides computational tools and databases that empower efficient analysis, access and management of biologically significant information. Bioinformatics showing extensions in nearly all aspects of drug discovery, drug assessment and drug development. This growing importance lies not only in the role that bioinformatics plays in managing large volumes of data, but also in the utility of bioinformatics tools to predict, analyze and to help in interpreting clinical and preclinical findings. To prevail over the insufficient prediction of binding affinity calculated by recent scoring functions the protein-ligand interaction and compound 3D structure information are used to analysis. For the structure based drug design, several post screening analysis paying particular attention on protein-ligand interaction that has been developed for improving enrichment and effectively potential target.

Keywords- Malaria Parasite, *In silico* drug design, PDB, Brenda

Introduction and Background

Parasitic diseases today are a treatment threat to mankind around the world. Particularly Malaria has tormented and continues to thwart comprehensive control efforts. Malaria is an infectious disease caused by a parasite called *plasmodium* and transmitted through the bites of infected mosquitoes. There is vaccine being tried and to be launched in 2015 but again its efficacy is being questioned.

This pathway is also found in plant and some lower organisms use multiple methyltransferase domains for the S-adenosylmethionine reactions. Because PfPMT is essential for normal growth and survival of *Plasmodium* and is not found in humans, so it may be a potential target for drug discovery against malaria. Phosphoethanolamine N-methyltransferase (PMT) is essential for phospholipid biogenesis in the malaria parasite *Plasmodium falciparum* [1]. PfPMT involves in catalysis of phosphoethanolamine to produce phosphocholine by triple methylation, which is then used for phosphatidylcholine synthesis. The PfPMT enzyme of *Plasmodium falciparum,* the causative agent of severe human malaria, belongs to major family phosphoethanolamine methyltransferases (PMTs) also found in plants, worms, and protozoa. It also plays a critical role in the synthesis of phosphatidylcholine which involves serine decarboxylation and phosphoethanolamine methylation just like plants. Despite their important biological functions, structure of this enzyme is unknown and there is no any information about which amino acids in these enzymes are critical for catalysis and binding to S-adenosyl-methionine and phosphoethanolamine substrates.

To unsnarl the mechanism of action of the anti-malarial drugs and to give guidelines for the development of new derivatives with improved efficiency, computational study helps researcher to conclude on an idea. In Bioinformatics in order to find a possible drug targets we can begin with the natural inhibitors found in molecules designed by crystallography representing protein data bank file, followed by a general similar search in PDB, NCI and PUBMED databases resemble probable antimalarial compounds [2]. This made it possible to dock these ligand libraries with suitable software and comparing the inter-molecular interactions and scores which are given to them by the software. The highest absolute value of interactions energies can be considered the best and appropriate ligands. These can be further used for second 95% similarity search for proposed antimalarial compound which have the same mechanism as proposed target compound.

In Silico Drug Design

Bioinformatics provides information to elucidate the structure and function of proteins based on similarities in nucleotide sequences this can help in designing structure-based drugs that can act against malaria effectively [3]. At a basic level, this problem gives an oration by providing external links to other databases like in PDB for individual structures direct the user towards corresponding entries in the PDB, NDB, CATH and SWISS-PROT databases. Through structure-based drug design, interactions between a potential drug and its proposed target can be conceptualize and this helps the drug development companies to refine a promising molecule to escalate its attributes, thus making it effective, specific or to improve pharmacokinetic properties [4]. Given the nucleotide sequence, the probable amino acid sequence of the encoded protein can be determined using translation software. Sequence search techniques can be used to find homologues and based on sequence similarity. It is possible to model the structure of the protein on experimentally characterized structures. Now docking algorithms could design molecules that could bind the model structure, which leads for biochemical assays to test their biological activity on the actual protein. This approach has been used in the development of many drugs and some of them include the HIV1 protease inhibitors, Captopril (for treating high blood pressure, heart failure and for preventing kidney failure due to high blood pressure and diabetes), anti-bacterial agent (Norfloxacin).

Aminoacyl-tRNA synthetase enzymes that catalyzes the esterification of a specific amino acid or its precursor to one of all its compatible cognate tRNAs are essential for protein synthesis can be a good target for drug discovery for *Plasmodium.* They have recently been recognized as promising drug targets across a broad range of microbes, and scientist have recently identified *Plasmodium* aminoacyl-tRNA synthetase that are potential targets for new drugs to treat malaria. *Plasmodium* aminoacyl-tRNA synthetase enzymes differ from those of humans, so there is hope to develop drugs specific for *Plasmodium*. *In silico* molecular modeling methods, like docking can help in the process of drug discovery by discern the binding affinities of existing and hypothetical compounds towards the human isoform of this enzyme. The main goal is to develop tools and resources that help in the analysis of data. Likewise having sequenced a particular protein, it is of interest to compare it with previously characterized sequences.

Current Anti-Malarial Drugs

The chemotherapy drugs that are being used specifically target a particular enzyme unique to the parasite and inhibit it. Many factors may lead to such specificity like presence of unique target in parasite, ability to discriminate between the host and the parasite

The most pharmaco kinetically studied drug probably are quinine, along with its dextroisomer quinidine, Lumefantrine and Amodiaquine [5]. Primaquine is another popular anti malarial drug. This drug has primarily been used against gametocytes and hypnozoites. It has been suggested that the drug works by inhibiting the electron transport chain of the parasite. The complication though is that the use of Primaquine for prophylactic treatment against *Plasmodium falciparum* infections is known to cause glucose-6-phosphate dehydrogenase deficiency on rare cases. Antibiotics mainly tetracycline are also used in combination with other drugs to combat the disease. Besides this, resistance to antimalarial medicines is a deep-rooted problem. It can be defined as ability of a parasite strain to survive and multiply despite the administration and absorption of a drug given in doses as recommended, but within the limits of tolerance of the patients. To overcome from this problem combination therapy with antimalarial drugs can also aid the treatment in effective way. It uses two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite. The goal is to improve efficacy and to slack up the development of resistance to the individual components of the combination.

Now the question arises that how the bioinformatics can help in target identification and for antimalarial drug development. Here so we can say Bioinformatics is a tool by which we can proceed to our goal. This provides us a wide range of data and several BI tools to identify unique genes of parasite. The study of homologous & orthologous genes, gene order, gene clusters, molecular pathways and wire diagrams, gene ontology pledge the comparative genomics of malarial parasites which anticipate the source for identification of new target molecules.

The rapidly growing parasite requires large amounts of lipids. The presence of a fatty acid biosynthetic pathway in apicoplast of *Plasmodium falciparum* can be a better indication in the way to developing drug strategy. This pathway represents the type II pathway similar to plant chloroplasts and bacteria but recognizably different from the type I pathway of animals including humans. Specific inhibitors of the type II pathway, thiolactomycin and triclosan, have been observed to target this pathway. A compound belonging to chlorinated aromatic compounds which have functional groups representative of both ethers and phenols was modeled. Its ADMET properties conformed to those of most traded drugs. However, *in vitro* and *in vivo* efficacy has not been tested. In the food vacuole the aspartic acid proteases of *Plasmodium* species are involved in the haemoglobin degradation which are also known as plasmepsins. These are the probable target for quinine analogs as drugs against malaria parasite.

Conclusion and Future Directions

The review is looking at two major aspects of malaria and new drugs for it, firstly a record of what drugs have been used until now and later a review of the various targets that can be used for the development of the drugs.

Rational design is aim in particular direction, but it depends on the knowledge of the mechanisms of the parasite. Probable target would be search using internet and specially site known as PDB. This will be reveal 3D structure and amino acid sequence arrangement. After that there will be need to study their specific active sites and their best Lock and key fit arrangement that describe in further inhibition of Plasmodium growth.

In-depth analysis of corresponding enzymes (complexes) will be essential to identify key pathways to be deregulated via administration of epi-drugs. While much remains to be uncovered, our current knowledge suggests that the epigenome is a “weak spot” unless the parasite has additional tricks up his sleeves.

References

[1] Benson D.A., Karsch-Mizrachi I., Lipman D.J., Ostell J., Rapp B.A. and Wheeler D.L. (2000) *Nucleic Acids Research*, 28(1), 15-18.

[2] Jullian V., Bourdy G., Georges S., Maurel S. and Sauvain M. (2006) *Journal of Ethnopharmacology*, 106(3), 348-352.

[3] Barton S. (2006) *Nature Reviews Drug Discovery,* 5, 375.

[4] Catteruccia F., Benton J.P. and Crisanti A. (2005) *Nature Biotechnology,* 23(11), 1414-1417.

[5] Baton L.A. and Ranford-Cartwright L.C. (2005) *Malaria Journal,* 4(1), 15.

[6] Kumar K.A., Sano G.I., Boscardin S., Nussenzweig R.S., Nussenzweig M.C., Zavala F. and Nussenzweig V. (2006) *Nature*, 444(7121), 937-940.

[7] Bairoch A. and Apweiler R. (2000) *Nucleic Acids Res.,* 28(1), 45 -48.

[8] Barford D., Das A.K. and Egloff M.P. (1998) *Annual Review of Biophysics and Biomolecular Structure*, 27(1), 133-164.

[9] Berman H.M. (2000) *Nucleic Acids Res.,* 28(1), 235-242.

[10] Blandin S., Moita L.F., Köcher T., Wilm M., Kafatos F.C. and Levashina E.A. (2002) *EMBO Reports*, 3(9), 852-856.

[11] Borthwick E.B., Zeke T., Prescott A.R. and Cohen P.T.A. (2001) *FEBS Letters*, 491(3), 279-284.

[12] Chauhan V.S. and Bhardwaj D. (2003) *Current Adv. Biochem. Eng. Biotechnology*, 84, 143-182.

[13] Checchi F., Piola P., Kosack C., Ardizzoni E., Klarkowski D., Kwezi E., Priotto G., Balkan S., Bakyaita N., Brockman A. and Guthmann J.P. (2004) *Trop. Med. Int. Health*, 9(4), 445-450.

[14] Chen M.S., Silverstein A.M., Pratt W.B. and Chinkers M. (1996) *Journal of Biological Chemistry*, 271(50), 32315-32320.

[15] Chen M.X., McPartlin A.E., Brown L., Chen Y.H., Barker H.M. and Cohen P.T. (1994) *EMBO*, 13, 4278-4290.

[16] Chen M.X. and Cohen P.T.W. (1997) *FEBS Letters*, 400, 136-140.

[17] Dame J.B., Williams J.L., McCutchan T.F., Weber J.L., Wirtz R.A., Schneider I. and Roberts D. (1984) *Science*, 225(4662), 593-599.

[18] Dean D.A., Urban G., Aragon I.V., Swingle M., Miller B., Rusconi S. and Honkanen R.E. (2001) *BMC Cell Biology*, 2(1), 6.

[19] Desai P.V., Patny A., Gut J., Rosenthal P.J., Tekwani B., Srivastava A. and Avery M. (2006) *J. Med. Chem*., 49(5), 1576-1584.

[20] Desai S.A., Bezrukov S.M. and Zimmerberg J. (2000) *Nature,* 406, 1001-1005.

[21] Desakorn V., Dondorp A.M., Silamut K., Pongtavornpinyo W., Sahassananda D., Chotivanich K., Pitisuttithum P., Smithyman A.M., Day N.P. and White N.J. (2005) *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 99(7), 517-524.

[22] Holder A.A. (2007) *Proceedings Natl. Acad. Sci.*, 16, 96(4), 1167 -1169.

[23] Hyde J.E. (2002) *Microbes and Infection*, 4(2), 165-174.

[24] Jambou R., Legrand E., Niang M., Khim N., Lim P., Volney B., Ekala M.T. and Bouchier C. (2005) *Lancet*, 366(9501), 1908-1909.

[25] Kaestli M., Cockburn I.A., Cortes A., Baea K., Rowe J.A. and Beck H.P. (2006) *J. Infect. Dis*., 193(11), 1567-1574.