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Structural characterization and comparison of bifunctional HPPK-DHPS enzyme with pathogenic microbes

Content

Despite the recent advances in controlling and elimination of malaria, it still remains a major public health concern. Also, the rapid surge in reports of drug resistance in malaria threatens the gains achieved so far in its control and elimination agenda; putting the millions of people life at risk. Tetrahydrofolate- the end product of the folate bio-pathway is required as a cofactor in multiple pathways. The two main enzymes of folate pathway – dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) are already validated targets of the known drugs sulfadoxine (a sulfa drug-Sdx) and pyrimethamine (Pyr) respectively 1. Plasmodium species and other bacterial species possess the ability to synthesize their own tetrahydrofolate while humans derive folates from their diet. DHPS in Plasmodium species is bifunctional and fused with 6-hydroxymethyl, 7,8-dihydropterin pyrophosphokinase (HPPK) enzyme. The reports of resistance in Pf/Pv DHPS and DHFR resistance have been emerging across the globe 2. Here, we present the global spread of resistance against Sdx and Pyr. Further, the crystal structures of the HPPK and DHPS across all pathogenic species were compared and virtual screening of potential compounds for the HPPK active site was performed. Briefly-

1. The fully- and super resistance mutants – quintuple (IRN-GE) and sextuple (IRN-GEG) are widespread in multiple African countries along South Asian countries and a few regions in India as well 2.

2. Structural analyses of DHPS protein in complexes with substrates/drugs have revealed that resistance mutations map proximal to sulfa drug binding sites. The importance of conformation changes in the protein results in similar changes in the active site of the enzyme.

3. The effective target compounds against HPPK enzyme of the pathogenic species will not allow the incorporation of 6-hydroxymethyl, 7,8-dihydropterin pyrophosphate in the DHPS enzyme that ultimately will lead to inhibition of folic acid pathway.

The top hits screened utilizing the in silico approaches against Pf/Pv HPPK pterin-binding site will be further evaluated in vitro and in vivo. It is to note that the residues involved in the active sites of HPPK and DHPS are highly conserved among pathogens. Further, to counteract the rising SP drug resistance, it is imperative to discover novel inhibitors that could target the validated enzymes of pathogens.

Reference:

1. Gregson A, Plowe C V. Mechanisms of resistance of malaria parasites to antifolates. Pharmacological Reviews. 2005;57: 117–145

2. Chaturvedi R, Chhibber-Goel J, et al. Geographical spread and structural basis of sulfadoxine-pyrimethamine drug-resistant malaria parasites. Int J Parasitol 2021 Jun;51(7):505-525.

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