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Structural Characterization of Histone Deacetylase from Plasmodium Falciparum

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Abstract **– Histone deacetylase (HDAC) is the key enzyme responsible for epigenetic regulation of an organism. This protein has been involved in transcriptional regulation of many proteins associated with chromatin remodelling. Homologs of histone deacetylase are also found in malaria parasite Plasmodium falciparum where it plays major role in regulation of key pathways of parasite. In this study, we determined the three-dimensional structure of histone deacetylase from Plasmodium falciparum (PfHDAC) by using homology modelling tools available at Swiss Modeller server and Modweb. Modelled structure was validated using Ramachandran plot and active site determination was performed using CASTp. We believe that structural analysis of PfHDAC could be pivotal in discovering new drug like molecules against malaria parasite.**

Keywords: **HDAC, Transcription regulation, molecular modelling, malaria, drug discovery**

I. Introduction

Malaria is one of the major problems in many developing countries which are caused by the protozoan parasite Plasmodium. Several cases are reported annually. Many drugs have been invented against malaria but developing resistant in malaria parasite has raised the concern of identifying new protein molecules which can be treated as viable drug target. There are many pathways crucial for parasite survival and some of them are very unique to Plasmodium. Regulation of transcription remains the major pathway in survival of any organism including malaria parasite where post-translational modification of histone proteins are very critical. Histone acetyl transferase (HAT) and histone deacetylase are two major enzymes involved in transcriptional regulation [1]. HAT catalyzes acetylation on histone lysine residue whereas HDAC does the removal of acetyl group from histone leads to chromatin condensation and transcriptional repression. Histone deacetylases (HDACs) is the enzyme generally localized in the nucleus [2]. HDACs are classified into various classes and sub-classes based on their catalytic centre [3]. Several studies have shown that HDACs play crucial role in cell survival and proliferation [4]. Many other proteins along with the histones, which are involved in the cell migration, cell proliferation and cell death, are target of HDACs. When interact with histones, these proteins catalyze the deacetylation of α-acetyl lysine at the N-terminal of histone core. Inhibition of HDACs activity has been established as a proven cancer therapy [5].

Malaria parasite Plasmodium harbour many histone deacetylases (PfHDACs), which have been shown to regulate the transcription of many genes. Inhibition of PfHDAC resulted in the change of expression profile of many genes from all the developmental stages of asexual life cycle of parasite viz. ring, trophozoite and schizont [6]. The level of acetylation and chromatin structure was also altered. Though, biochemical data on PfHDACs are available, structural characterization remain obscure. Hence, in this study, we evaluated the structural properties of PfHDAC using in-silico structure determination method and dissected the structure with identification of active site. Our studies provided the structural framework of PfHDAC in three-dimension space which can be utilized for high-through put drug screening against malaria parasite.

II. Materials and Methods

The sequence of PfHDAC was retrieved from PlasmoDB (PFI1260c). 3MAX pdb structure was used as a template for homology modeling. Identification of template structures was carried out using NCBI BlastP. Modeller [7]. and Swiss Model Server were used to build the in-silico structure of PfHDAC. Structure validation was performed with Ramachandran plot using online server RAMPAGE [8]. Modelled structure of PfHDAC was submitted to CASTp [9]. for active site prediction. Figures and images were developed using CHIMERA [10].

III. Results and Discussion

The modelled structure of PfHDAC is shown in Figure 1 with ribbon diagram along with surface topology representation. Structure of PfHDAC is broadly divided into rossman like fold and zinc binding fold. Bound zinc residues

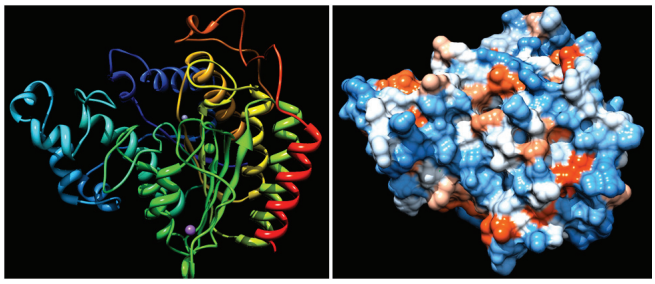

Fig. 1 : Modelled structure of PfHDAC.
A) Ribbon diagram; B) Surface topology

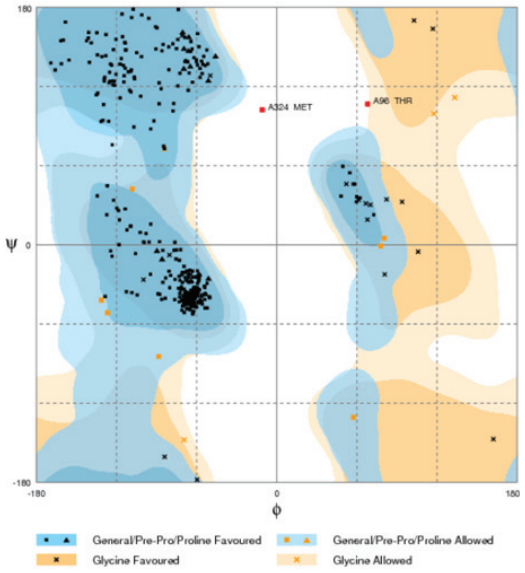

Fig. 2 : Ramachandarn plot PfHDCA using RAMPAGE

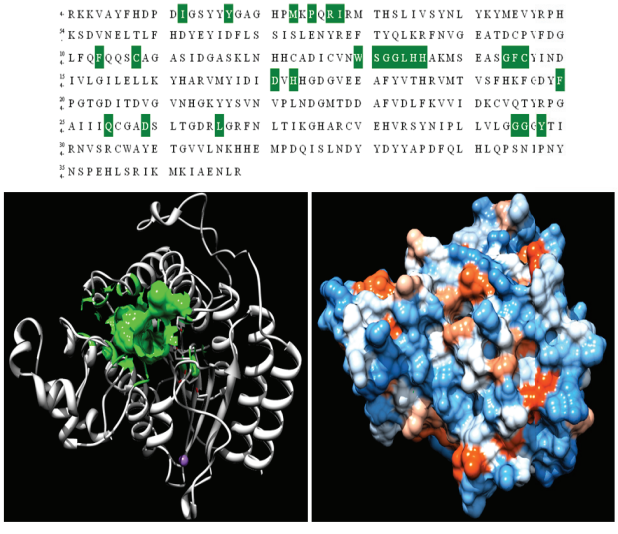

Figure-3: Prediction of active site of PfHDAC using CASTp. A) Active site prediction using CASTp where active site residues shown in green colour in between amino acid sequence of protein; B) & C) Position of active site residues are shown in three-dimensional space in ribbon form and surface topology respectively using CHIMERA.

are also shown in structure. Modelled PfHDAC structure is helical dominant with intermittent loops are hanging out and middle part of the structure is mostly occupied by beta sheets. Surface topology diagram shows the patches of negatively charges residue all over the surface probably required for interaction with positively charged histone proteins.

A large cavity is predicted to be active site of the enzyme PfHDAC with the cavity size of volume 409 and area of 401 angstrom. The cavity is shown with the green color in the diagram (Fig. 3). A zinc residue is also seen near active site, helps in the catalysis of the enzyme. Overall the compact active site with zinc residue perfectly setup the platform for deacetylation to occur. In addition, structure validation was done by using Ramachandran plot which shows that most of the residues are in favoured and allowed region to prove the authenticity of homology modeling (Fig. 2).

IV. Conclusion

Biochemical characterization of HDAC from Plasmodium falciparum has been done but structural information was missing. This lack of information clearly blocks the possibility of transferring available facts of transcription regulation for development of new anti-malarial drugs. Thus, an in-silico approach is the most efficient way of structural characterization of proteins. Molecular modeling of the PfHDAC provided us the 3D structures of the protein. Three-dimension structure of the parasite protein could act as a staring material for the in-silico drug screening. Not only that, but the prediction of the active site might also be useful in understanding the enzymatic activity of the protein which is crucial in deciphering the regulation of transcriptional control. In addition, modelled PfHDAC can be compared with its human counterparts for structural discrepancy, which could also fasten the process of drug development against malaria parasites.

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