

ICMR-BIOMEDICAL INFORMATICS RESEARCH

Completed studies

In silico analysis of isoniazid resistance in *M. tuberculosis*

Background

Altered drug binding may be an important factor in INH resistance, rather than major changes in the activity of catalase or peroxidase. The identification of the structural or functional defects in the mutant enzymes remain under explored.

Aim

- To analyse INH resistance by molecular modeling and docking

Results

In this study the differences in the binding affinity between wild-type (WT) and mutants of KatG were investigated. In this process, five mutants of KatG (Asn138Ser [N138S], Ser315Thr [S315T], Ser315Asn [S315N], Ser315Iso [S315I], Ser315Arg [S315R] and a WT [S315]) were generated by the Modeller and the mutants were docked with INH by using the software-GOLD. The heme binding score suggested that categorization of the mutants would be in the order of S315N > N138S > S315R ≥ S315T > S315I / S315I < S315T ≤ S315R < N138S < S315N in imparting resistance. INH binding score suggested that the KatG mutant models, except N138S mutant may lead to least resistance, and probably may not be associated with any resistance. These models provide the first *in silico* evidence for the binding interaction of KatG with INH and implicate the basis for rationalization of INH resistance in naturally occurring KatG mutant strains of *M. tuberculosis*.

[Contact person: Dr.N.Selvakumar (E-Mail ID: selvakumarn@trcchennai.in)]

Protein - Protein interaction of heme oxygenase-1 and p38 mitogen activated protein kinase

Introduction

Chronic kidney disease, also known as chronic renal disease, is a progressive loss of renal function over a period of months or years through five stages. Heme Oxygenase-1 (HO-1) is the rate-limiting enzyme in the catabolism of heme. To date, the mechanism by which HO-1 functions as a cytoprotective and anti-inflammatory protein remains poorly understood. Induction of HO-1 has been found to have an adaptive and beneficial response to acute renal injury secondary to ischemia-reperfusion injury, nephrotoxins, glomerulonephritis, renal transplant rejection and rhabdomyolysis, *in vitro*. Members of the p38 family of mitogen activated protein kinases (MAPK) are primarily activated by stress stimuli, but are also activated during engagement of various cytokine receptors by their ligands. A previous study reported an increase of HO-1 mRNA and protein expression by TGF- β 1 in human retinal pigment epithelial cells via p38 MAPK, and suggested that induction of HO-1 attenuates the adverse effects of elevated TGF- β 1.

Aim

- To predict the interaction of heme oxygenase-1 and p38 MAPK

Results

In the present investigation, patients with renal failure showed enhanced HO-1 expression *ex vivo*. The study hypothesized that HO-1 might have adverse effects in renal failure cases. Evidence implicates its role in fibroblast formation, which might be one of the pathways for TGF- β mediated fibrogenesis via HO-1 upregulation. Previous reports claimed that p38 MAPK signalling molecule interacts with HO-1 at the transcription level. Also, the wet lab studies showed increased expression of p38 MAPK in the patient group. In order to have a better understanding of the surface interactions between HO-1 and p38 MAPK, *in silico* studies were premeditated. The binding site of HO1 was predicted to be between 226 and 232 amino acids. Protein protein docking between HO1 and p38 MAPK was done using CDOCKER (Fig. 3).

Fig. 3: HO-1 docked into the binding site of p38 MAPK



[Contact person: Dr.Luke Elizabeth Hanna (E-Mail ID: hanna@trcchennai.in)]

Molecular modeling and docking studies of PknL

Background

PknL, a eukaryotic like serine threonine protein kinase from *M. tuberculosis*, is predicted to be involved in transcriptional regulation and cell division.

Aim

- To predict the three dimensional structure of PknL

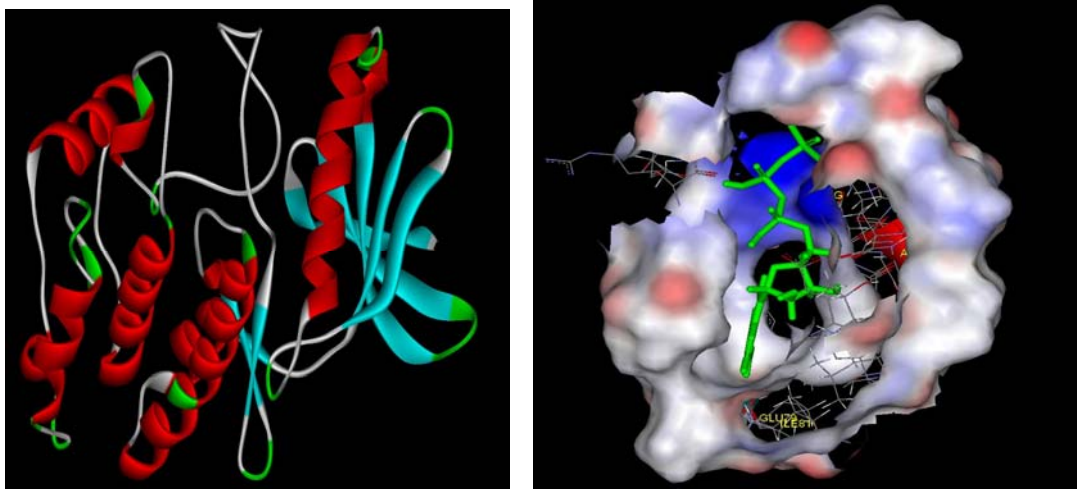
Results

In order to understand the conformational changes on binding to the ligand, the three dimensional models for apo and holo forms of PknL were predicted using two different templates (Fig. 4A). The kinase domain of PknE from *M. tuberculosis* (PDB ID 2H34) and the activation loop region of cAMP dependent protein kinase from *Saccharomyces cerevisiae* (PDB ID 1fot) was used as the structural template for building the apo structure of PknL domain. For developing a model for adenosine triphosphate (ATP) bound conformation for PknL, the

kinase domain of PknB from *M. tuberculosis* (PDB ID 106Y) and the activation loop region of phosphorylase kinase from rabbit (PDB ID 1q16) was used as the structural template. The results showed that the homology models were very similar to the template structures. Further, the ATP molecule was docked into the active site of holo model of PknL protein using CDOCKER (Fig. 4B).

Fig. 4:

A) Three dimensional model of PknL protein B) ATP docked into the active site of PknL protein using CDOCKER



[Contact person: Dr. Sujatha Narayanan (E-Mail ID: sujathan@trcchennai.in)]

Ongoing studies

Target database for drug-resistant pathogens

Emergence of drug resistance is a major threat to public health. Morbidity and mortality are higher in infections caused by resistant pathogens than those caused by susceptible ones. Drug resistance has been reported in many infectious diseases across different countries, and multi DR forms of disease are extremely difficult to treat. MDR and extensively drug-resistant TB (XDR-TB) has been reported in most parts of the world. Similarly, strains of *P. falciparum* resistant to almost all of the available drugs have evolved. Hence, there is a need to develop novel drugs for the re-emerging DR diseases.

The target database for DR pathogens (TDDRP) contains information about all current drug targets and a list of potential targets, information on metabolic pathways involving the target genes and information on drugs used for each disease. The following pathogens are being included in the database during the first phase of the project: *M. tuberculosis*, *M. leprae*, *P. falciparum*, *P. vivax*, *S. aureus*, *S. pneumonia* and *N. gonorrhoea*. This database will be a useful resource for further research in drug discovery against drug-resistant infectious diseases. Work has been completed for *M. tuberculosis*, *M. leprae* and *P. falciparum*.

[Contact person: Dr.Luke Elizabeth Hanna (E-Mail ID: hanna@trcchennai.in)]

Database for drug-resistant tuberculosis

Two billion people, equal to one-third of the world's total population, are infected with *M. tuberculosis*, the microbe that causes TB. TB kills more than 2 million people per year and is a leading cause of mortality due to infectious diseases. The increasing emergence of drug-resistant TB, especially MDR-TB (resistant to at least two frontline drugs such as INH and RMP), is particularly alarming. MDR-TB has already caused several fatal outbreaks and poses a significant threat to the treatment and control of the disease in some parts of the world, where the incidence of MDR-TB can be as high as 14%. XDR-TB occurs when resistance to second-line drugs develop; this is extremely difficult to treat, and

cases have been confirmed in all regions of the world. The rise in the prevalence and death of TB cases is also due to the coinfection of TB patients with HIV. The lethal combination of DR-TB and HIV infection is a growing problem that presents serious challenges to effective TB control. Therefore, novel drugs effective against XDR-TB need to be developed. Besides, there is also a need to prevent the emergence of MDR-TB and XDR-TB and to manage the disease. To address these issues we are developing a database for drug-resistant TB named as DDR-TB.

The DDR-TB will contain clinical information on MDR-TB and XDR-TB. The patient information will be arranged under the following heads: Basic assessment form, monthly progress report, X-ray findings, haematology results, biochemistry results, urine analysis report, drug sensitivity test report, number of missed doses, etc. The effective control of drug-resistant TB requires effective public health infrastructure that will rapidly recognize and respond to it. This database is intended to serve this purpose. Further, the database will serve as a useful tool for identifying the changing pattern of the disease, besides being an online education tool to educate medical graduates.

[Contact person: Dr.Luke Elizabeth Hanna (E-Mail ID: hanna@trcchennai.in)]