

Pharmacogenomic based miRNA Regulation in Tuberculosis: An Initiation towards the Discovery of Systemic Biomarkers to Treat Tuberculosis in Future

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Abstract

Pharmacogenomic analysis of tuberculosis in PharmGkb resulted in the association of the pharmacokinetic property of rifampin with the gene SLCO1B1. Transcription factor and microRNA association of SLCO1B1 in miRTarBase resulted in the identification of HNF1A and hsa-miR-511-5p and the possible regulatory network to understand the pharmacokinetic association of rifampin involves the gene SLCO1B1 with the transcription factor HNF1A and the miRNA hsa-miR-511-5p. Till date, HNF1A and has-miR-511-5p were not considered as vital targets for tuberculosis. In future, more experimental evidences are required address the association of tuberculosis with HNF1A and hsa-miR-511-5p. The miRNA hsa-miR-511-5p was validated experimentally. Since there is a lack of a complete crystal structure for HNF1A, homology modeling was performed in Galaxy web and the modelled structure contains 97% of amino acids in the allowed region of Ramachandran plot. The modeled structure will serve as vital target for the drug discovery of rifampin based analogs. Virtual Screening was performed in USR-VS server for identifying the best compound from the analogs of rifampin and it was identified that the analog with Zinc database Id 71049520 contain a relatively lower molecular weight compared to the parent molecule. Then the screened molecule was docked with the modeled protein using MTI AutoDock and the best pose was detected from MTI AutoDock with a minimum energy of -5.96.

Introduction

In the initial era of pre-genomics, it was estimated that about 8.7 million cases with tuberculosis were reported globally and that is an approximate of 125 cases reported per 100,000 individuals, and approximately about 1.4 million people died of the disease [1]. In order to The Stop the spread of TB, WHO recommends a standard 6-month regimen of four-drugs as the first-line therapy [2-4]. However, in some cases, the specified number cannot be administered within the targeted time period because of drug toxicity [2,5]. Furthermore, the drug induced injury in liver (DILI) can cause morbidity [6-8]. These adverse drug events can confer a substantial and additional costs associated with increased frequency of outpatient visits, laboratory tests and hospitalization in more serious cases. Second-line anti-TB medications could cause greater toxicity-related problems and are often less effective than the medications in first line and the treatment could be prolonged in spite of the attendant challenges to ensure compliance. As a result, there was a risk of treatment failure and relapse.

In the initial era of Post genomics [9], Pharmacogenetics (PGx)-based testing was anticipated to be vital across all specialties in the medical field, as a pillar towards the movement of the personalized medicine [10]. The PGx-based testing involves the assessment of risk with respect to the likelihood of patient response to a given drug to facilitating the selection of drug and its dosage [11]. The PGx-based testing is a relatively new field and will have an impact in the treatment of latent TB infection (LTBI).

Rifamycin was consistently utilized against Mycobacterium tuberculosis in both in vitro and in vivo models [12-15]. There variation of concentrations in rifamycin among patients on the

standard therapy for tuberculosis and the basis for variation is not well understood. Advanced HIV infection has been associated with the low concentrations of rifampin, but marked as a difference in patients with tuberculosis and without HIV (Figures 1-3) [16-19].

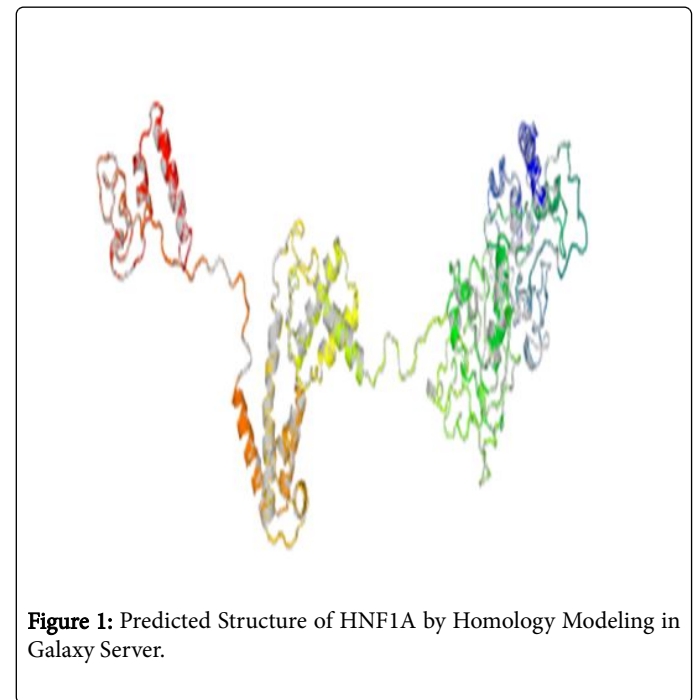


Figure 1: Predicted Structure of HNF1A by Homology Modeling in Galaxy Server.

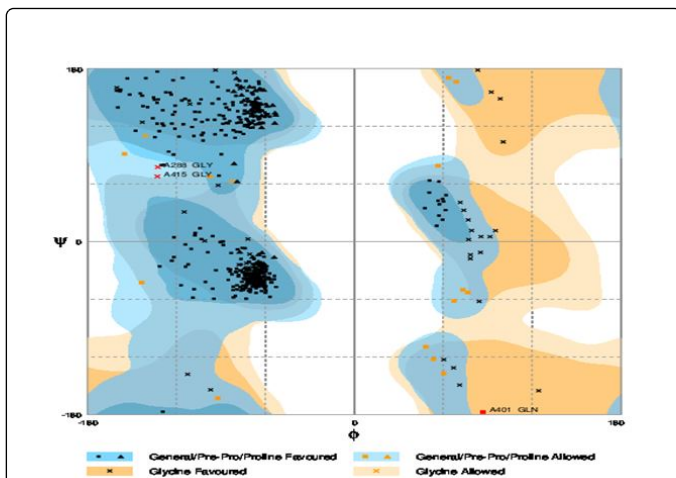


Figure 2: Validation of HNF1A in Rampage Server (97% of residues in allowed region of Ramachandran Plot).

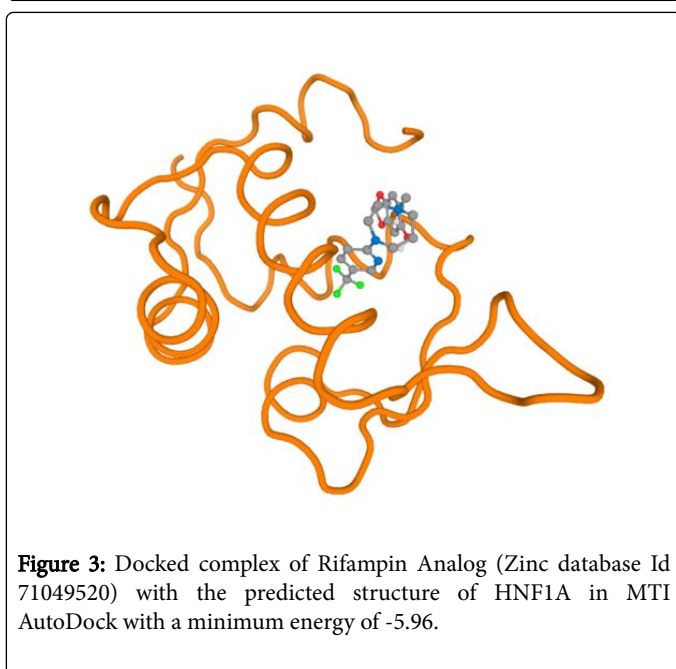


Figure 3: Docked complex of Rifampin Analog (Zinc database Id 71049520) with the predicted structure of HNF1A in MTI AutoDock with a minimum energy of -5.96.

A novel approach to identify a therapeutic target was initiated in this manuscript. In this approach, two novel therapeutic targets (HNF1A and hsa-miR-511-5p) to diagnose and treat tuberculosis were identified by a rational approach of data mining with bioinformatics. Since we do not have a crystal structure of HNF1A, homology modeling was done and the best analog of rifampicin (Zinc database Id 71049520) was docked with HNF1A to find the compatibility of binding and the molecule have a maximum probability to be considered as a lead molecule in the process of ration drug design of tuberculosis.

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