Biomedicine & Pharmacotherapy 103 (2018) 1733–1747

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Drug targets exploited in *Mycobacterium tuberculosis*: Pitfalls and promises on the horizon

Zubair Shanib Bhat[a,b], Muzafar Ahmad Rather[a], Mubashir Maqbool[a], Zahoor Ahmad[a,b,*]

[a] Clinical Microbiology and PK/PD Division, Indian Institute of Integrative Medicine (IIIM), Campus, Sanat Nagar, Srinagar, Jammu & Kashmir, 190005, India
[b] Academy of Scientific and Innovative Research (AcSIR), CSIR-Indian Institute of Integrative Medicine (IIIM), Campus, Sanat Nagar, Srinagar, Jammu & Kashmir, 190005, India

ARTICLE INFO

Keywords:
Tuberculosis
Drug targets
Mycobacterium tuberculosis
Drug resistance
HIV-TB
Drug discovery

ABSTRACT

Tuberculosis is an ever evolving infectious disease that still claims about 1.8 million human lives each year around the globe. Although modern chemotherapy has played a pivotal role in combating TB, the increasing emergence of drug-resistant TB aligned with HIV pandemic threaten its control. This highlights both the need to understand how our current drugs work and the need to develop new and more effective drugs. TB drug discovery is revisiting the clinically validated drug targets in *Mycobacterium tuberculosis* using whole-cell phenotypic assays in search of better therapeutic scaffolds. Herein, we review the promises of current TB drug regimens, major pitfalls faced, key drug targets exploited so far in *M. tuberculosis* along with the status of newly discovered drugs against drug resistant forms of TB. New antituberculosis regimens that use lesser number of drugs, require shorter duration of treatment, are equally effective against susceptible and resistant forms of disease, have acceptable toxicity profiles and behave friendly with anti-HIV regimens remains top most priority in TB drug discovery.

1. Introduction

Tuberculosis (TB) [1] is a leading cause of death worldwide from a single infectious agent, *Mycobacterium tuberculosis* [2,3]. Predominantly it infects lungs (pulmonary TB) but can also infect any other part of body (extra-pulmonary TB); if left untreated it destroys the body tissue by chronic inflammation and may culminate in death [4–6]. The current globally recommended chemotherapy for the treatment of drug-susceptible TB (DS-TB) involves an intensive phase of four first-line anti-TB drugs (ATD's) those include Rifampin (RIF), Isoniazid (INH), Pyrazinamide (PYZ) and Ethambutol (EMB) administered for the first 2 months followed by a continuation phase of RIF and INH for the next 4 months under directly observed treatment short course (DOTS) strategy [7] (Table 1). Although DOTS strategy is labour intensive but it ensures high rates of patient treatment [8]. Treatment success rate of 85% or more for new cases are regularly reported by WHO [9]. Since 1995 up to 2009, 41 million lives were saved under DOTS and STOP TB strategy [10,11]. However owing to various challenges that include latent TB infection (LTBI), complex and lengthy duration of chemotherapy, emergence of drug resistance and HIV-TB coinfection, TB continues to be a major global health concern in the category of infectious diseases. The global incidence of TB is alarming as about one third of the world's population is harbouring the pathogen as asymptomatic LTBI [12] (Figs. 1 and 2).

The major drawback of the current chemotherapy is its long duration that lasts for 6–9 months for drug susceptible TB (DS-TB) and up to 2 years for DR-TB. This often leads to patient nonadherence, treatment failure and resurgence. WHO Global TB report of 2017 estimates 1.67 million deaths, 10.4 million developed active TB disease, 6,00,000 new cases of rifampicin resistance (RR-TB) out of which 4,90,000 had multi-drug resiatant (MDR-TB) with 6.3 million new TB cases reported alone in 2016 [9]. Worldwide spread of extensive drug-resistant TB (XDR-TB) with only 30% success rate of treatment reflects a dangerous senario [9]. HIV-TB co-infection is a challenging setback and people living with HIV (PLHIV) are the prime victims of TB as about 1.2 million new TB cases were found in HIV positive individuals (11% of total cases) in 2015. The success rates of TB treatment in HIV positive individuals are only 78% and 0.4 million such people died in 2015. HIV promotes TB infection by modifying clinical manifestations of TB, thereby delaying its diagnosis and early treatment [14–16].

A vision of transition from stopping TB to ending TB is turning bleak. However, advances in understanding the biology of *M. tuberculosis* along with availability of its complete genome sequence has provided researchers with a platform of wide range of novel drug targets

* Corresponding author at: Clinical Microbiology PK/PD/Laboratory, Indian Institute of Integrative Medicine, Sanat Nagar, Srinagar, 190005, India.
E-mail address: zahoorap@iiim.ac.in (Z. Ahmad).

https://doi.org/10.1016/j.biopha.2018.04.176
Received 14 November 2017; Received in revised form 24 April 2018; Accepted 24 April 2018

Table 1
Mechanism of action of standard first line anti-TB drugs and their adverse effects.

Drug Discovery	Target	Mechanism of Action	Description	Adverse Effects
Rifampicin (RIF) (1963)	Bacterial RNA polymerase (RNAP)	Bactericidal-Inhibits Transcription RIF-inhibits bacterial DNA-dependent RNA polymerase by forming a stable enzyme-drug complex with the ß-subunit of RNA polymerase (RNAP-Rif), *rpoB* gene. Broad antibacterial spectrum, including activity against several forms of *Mycobacterium*.	RIF- Semi-synthetic; A member of the Rifamycin group of antibiotics produced from *Streptomyces mediterranei*. The most powerful anti-TB agent currently available.	Hepatitis, Joint pain, Fever, Flu syndrome Headache Haemolysis, Exanthema, Thrombocytopenia
Isoniazid (INH) (1952) (Prodrug Peroxidative activation by *M.tb* KatG)	InhA [Enoyl-(acyl-carrier-protein) reductase]	Bactericidal- Cell envelope disruption INH-Inhibits mycolic acid biosynthesis, an essential component of *M. tuberculosis* cell envelope. It specifically inhibits InhA, the enoyl reductase of *M. tuberculosis*, by forming a covalent adduct with the NAD cofactor. The INH-NAD adduct acts as a slow, tight-binding competitive inhibitor of InhA	INH-belongs to Pyridine- carboxylic class of drugs, containing a pyridine ring bearing a carboxylic acid group. Highly active against replicating but not dormant or near dormant bacilli	Psychiatric disorders Restlessness, Insomnia, Muscle twitching
Pyrazinamide (PYZ) (1954) (Prodrug- PZA converted by Pyrazinamidase (PZase) to POA)	S1 Component of 30S Ribosomal subunit	Bactericidal-Acidifies cytoplasm; Inhibits translation and trans-translation. The active moiety of pyrazinamide is pyrazinoic acid (POA). POA is thought to disrupt membrane energetics and inhibit membrane transport function at acid pH. Its analogs have been shown to inhibit the activity of purified FAS I.	Z- A pyrazine based compound active against tubercle bacilli in acidic inflammatory lesions	Elevated Uric acid, Gastrointestinal upsets, Anorexia, Arthralgia, Gout, Skin sensitivity to light
Ethambutol (EMB) (1961)	Inhibits Arbinosyl-Transferase	Bacteriostatic- Cell wall disruption Ethambutol disrupts arabinogalactan synthesis thereby preventing the interaction of 5'-hydroxyl groups of D-arabinose residues of arabinogalactan with mycolic acids that form mycolyl-arabinogalactan-peptidoglycan complex of *M. tuberculosis* cell wall	E- 1,2-Aminoalcohols based compound; Active during the early, intensive phase of treatment and may enhance the activity of other anti-TB agents by enhancing the mycobacterial cell wall permeability	Optic neuritis, Peripheral neuritis, Reduction in visual acuity, Low platelet count