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Review

Drug resistance mechanisms and novel drug targets for tuberculosis therapy

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ABSTRACT

Drug-resistant tuberculosis (TB) poses a significant challenge to the successful treatment and control of TB worldwide. Resistance to anti-TB drugs has existed since the beginning of the chemotherapy era. New insights into the resistant mechanisms of anti-TB drugs have been provided. Better understanding of drug resistance mechanisms helps in the development of new tools for the rapid diagnosis of drug-resistant TB. There is also a pressing need in the development of new drugs with novel targets to improve the current treatment of TB and to prevent the emergence of drug resistance in *Mycobacterium tuberculosis*. This review summarizes the anti-TB drug resistance mechanisms, furnishes some possible novel drug targets in the development of new agents for TB therapy and discusses the usefulness using known targets to develop new anti-TB drugs. Whole genome sequencing is currently an advanced technology to uncover drug resistance mechanisms in *M. tuberculosis*. However, further research is required to unravel the significance of some newly discovered gene mutations in their contribution to drug resistance.

1. Introduction

Tuberculosis (TB) has played an extremely critical role in influencing societies throughout history (Hopewell et al., 2016). This infectious disease caused by *Mycobacterium tuberculosis* is a leading cause of human morbidity and mortality globally (Tomioka and Namba, 2006; Nodieva et al., 2010). An estimated one-third of the world's population is infected with *M. tuberculosis* and 9.6 million people developed the disease in 2014 (WHO, 2015). Advances in chemotherapy have reduced the rate of death by a half in the past two decades. Despite of the advancement, 1.5 million people still died of TB in 2014, and among them 400,000 were HIV-positive subjects (WHO, 2015). Unlike most pathogens, *M. tuberculosis* has unique features making the bacillus recalcitrant to therapy with short-term antibiotics. Anti-TB therapy, in order to achieve disease cure and prevent its relapse, needs to kill actively dividing bacilli, controls semi-dormant/dormant organisms and prevents emergence of bacillary resistance to drugs.

To this end, a cocktail of different anti-TB drugs, classified as first-line and second-line drugs, plus a myriad of repurposed drugs, is in use to treat TB with different bacillary susceptibilities to therapeutic agents. This notwithstanding, drug-resistant TB has poorer treatment outcome than drug-susceptible TB.

How does drug resistance in *M. tuberculosis* arise? Following spontaneous chromosomal mutation, the drug-resistant mutants can be selected by poor physician prescription, poor patient adherence and poor supply or quality of drugs, as well as other factors such as difference of metabolism and nutrition. Thus, drug-resistant TB is largely a man-made phenomenon. The earliest published instance of drug-resistance in *M. tuberculosis* was

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associated with the use of streptomycin (S) shortly after its discovery. Then combined resistance of S with other drugs such as isoniazid (H), pyrazinamide (Z), ethambutol (E) and rifampicin (R) emerged in bacillary strains. Worldwide, the emergence of multi-drug-resistant (MDR) TB and extensively drug-resistant (XDR) TB has increasingly threatened the global control of TB. MDR-TB generally connotes disease with bacillary resistance to at least R and H, and XDR-TB is usually defined as MDR-TB with additional bacillary resistance to fluoroquinolone(s) and one or more of the second-line injectables. To worsen the drug-resistance scenarios, bacillary strains designated as totally drug-resistant (TDR) TB have been recently reported (Migliori et al., 2012).

WHO reported that there were 480,000 new cases of MDR-TB worldwide in 2014. More than a half of these cases worldwide were registered in China, India and the Russian Federation. In particular, with the high MDR-TB burden in China, the Beijing/W's family resistance genotypes become the mostly reported strains (Zhang et al., 2016). In this review, we expound and update the mechanisms of action of anti-TB drugs, briefly address some possible novel drug targets for TB therapy and discuss the roles of targets in anti-TB development.

2. First-line anti-TB drugs

Currently, over 20 drugs are used for treatment of TB, but most of them were developed more than 40 years ago. Drug-susceptible TB is effectively treatable by the use of first-line drugs: H, R, Z, E and S. Mutations in several main genes found to be associated with resistance to the first-line drugs are as follows: (i) *katG, inhA, ahpC, kasA* and *ndh* for H-resistance, (ii) *rpoB* for R-resistance, (iii) *pncA* and *rpsA* for Z-resistance, (iv) *embB* and *embC* for E-resistance, and (v) *rpsL* and *rrs* for S-resistance (Fig. 1). First-line drugs, gene names, minimum inhibitory concentrations (MICs) and resistance mechanisms are summarized in Table 1.

2.1. Isoniazid (H)

H, a pro-drug, is activated in *M. tuberculosis* by a catalase-peroxidase (KatG) encoded by *katG* gene (*Rv1908c*) to form a hypothetical isonicotinoyl anion or radical (Dessen et al., 1995; Quemard et al., 1995). The anion reacts with NAD^+ to form an H-NAD adduct, which binds to the active site of the NADH-dependent enoyl-ACP reductase InhA (Rv1484) (Rozwarski et al., 1998). Then the H-NAD adduct inhibits InhA (Lei et al., 2000), which causes the disruption of mycolic acid biosynthesis and leads to cell death (Winder and Collins, 1970; Wilming and Johnsson, 1999; Vilchèze et al., 2006).

Mutations in *Rv0340-0343, fadE24, efpA* and *kasA* encoding ketoacyl acyl carrier protein synthase are linked to H-resistance in *M. tuberculosis.* These mutations occur simultaneously in all these genes or in *katG* and/or *inhA* promoter, but these are also present in H-sensitive clinical isolates of *M. tuberculosis*, which makes it difficult to clarify their exact function in conferring drug resistance (Vilchèze and Jacobs, 2007). For example, it is well documented that

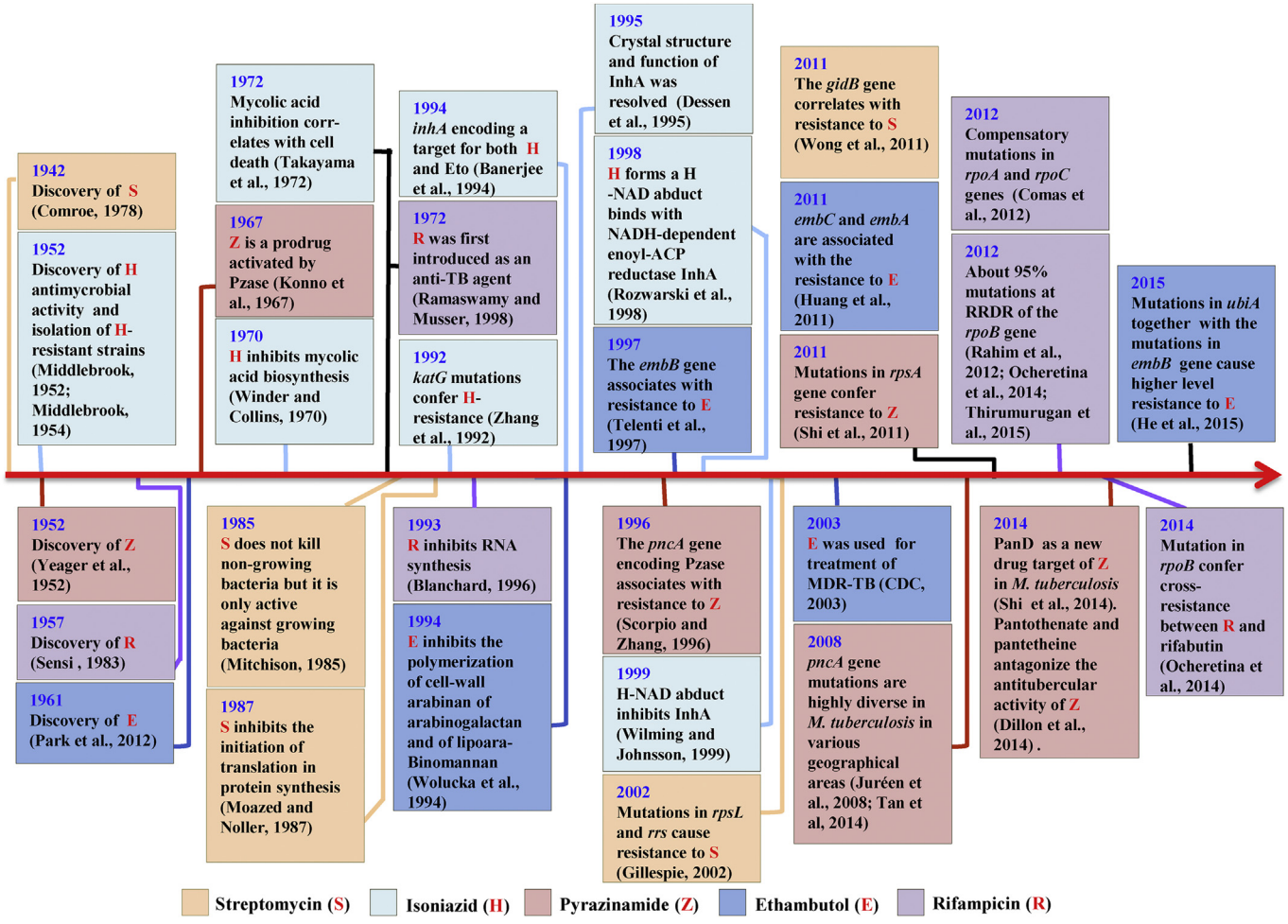

Fig. 1. First-line anti-TB drugs and their resistance mechanisms.