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Therapeutic Targets and Rational Drug Designing for Antitubercular Drugs

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ABSTRACT

Complication in structural and chemical composition of the mycobacterial cell wall causes difficulties in the treatment of tuberculosis. Due to structural complication, mycobacterium makes many antibiotics ineffective and prevents the entry of drugs in to mycobacterial cells. Tuberculosis is still the second most imperative infectious disease worldwide due to the most important reason for this is drug resistant tuberculosis, persistent infection and synergism of tuberculosis with HIV. In present review we discussed brief introduction of tuberculosis followed by the application of currently used drug and their targets significant action against tuberculosis for the development and drug designing.

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Introduction

Tuberculosis (TB) is a one of the most chronic infectious disease caused by *Mycobacterium tuberculosis.* Currently it is the world's second common cause of death from infectious diseases, after AIDS (Ducati et al., 2006). According to the World Health Organization report, 2 million people die every year and at least 9 million are getting infected. The present chemotherapy directly observed treatment short-course (DOTS) for TB and DOTS plus Second-line TB drugs for MDR-TB (Loddenkemper et al., 2002; Perri and Bonora. 2004) not cure all the patients. Despite the fact that it is treatable and preventable, the disease has been spreading at a steady rate (Bishai and Chaisson 1997). Furthermore, the resurgence in TB is alarming due to the development of pathogenic synergy with HIV. TB commonly has a much earlier onset in AIDS patients than other pathogens and is often times difficult to detect by ordinary techniques like positive tuberculin skin test which is not possible in immune-compromised patients. The overall incidence of TB plus HIV positive patients is 50 times than the rate for HIV negative patient (Smith and Moss. 1994; Hopewell. 1994; Snider et al., 1994). In addition, the emergence of multi drug resistant (MDR-TB) and extensively drug resistant (XDR-TB) strains as a result of extended treatment, makes patient conformity difficult. The term MDR-TB is describe strains that are resistant to two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) and takes longer to treat with second-line drugs (DOT-Plus), which are more expensive and have more toxic (Bastian and Colebunders. 1999; Barry et al., 2000). XDR-TB will develop when these second-line drugs are mismanaged and also become ineffective. This

development of drug resistance has increased concern that TB may once again become an incurable disease (Joshi et al., 2006) and thus provides a strong motivation for the development of effective and affordable anti-TB drugs.

Present chemotherapy of Tuberculosis

Chemotherapy of TB started in 1940s. In 1943, anti-TB research discovered the active anti-TB agent, streptomycin. From that time, a number of drugs have been discovered and introduced in anti-TB therapy, including *p*-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethionamide (1956), rifampin (1963) and ethambutol (1962). The lack of understanding of drug action was compounded by a profound ignorance of the biochemistry of the *M.* tuberculosis (Gutierrez-Lugo and Bewley. 2008). The current short-course TB therapy used to treat drug-susceptible TB consists of 2 months' treatment with four so-called first-line drugs including rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB), followed by 4 months' treatment with RIF and INH. Infection by MDR-TB strains requires treatment with second-line drugs such as kanamycin, amikacin, capreomycin, *p*-aminosalicylate, fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin), ethionamide, and cycloserine where treatments often extend for as long 2 years (Rattan et al., 1998; Gray. 1997; Janin. 2007). An increasing incidence of deaths due to tuberculosis and the known drawbacks of the current existing drugs including the emergence of multi drug-resistant strains have led to a renewed interest in the discovery of new anti-tubercular agents with novel modes of actions. The recent researches focused on natural products have shown a useful way to obtain a potentially rich source of drug candidates,where alkaloids have been foundmore effective. The present review focuses on synergy of the disease with HIV, current therapy, available molecular targets are so important.

Molecular targets

Many well-known anti-TB drugs are known to target the biosynthetic pathways that involve the production of macromolecules such as proteins, nucleic acids, or cell wall polymers. In selecting targets for antitubercular agents, it is advantageous to avoid targets that are close to the counterparts in mammalian cells]. The new targets should be specific to Mycobacteria to limit the transfer of resistance factors from other bacteria. New drugs must act on a target essential for bacterial survival and ideally be active against Mycobacterium throughout its growth cycle both inside and outside the mammalian cells during infection. The intensive efforts of medicinal chemists to develop antitubercular agents based on inhibition of protein synthesis have suggested that the ribosome may not be an efficient target for novel anti-TB drugs (Zang et al., 2006; Zhang, 2004; Zhang, 2005 Zhang and Amzel, 2002). Many of the inhibitors of protein synthesis like tetracycline, chloramphenicol and macrolides do not show activity against *M. tuberculosis*. An aminoglycoside, streptomycin being used for widespread treatment of TB, is known to disrupt bacterial protein synthesis. However, mutation altering the 16s ribosomal subunit in RNA, results in drug resistance to *M. tuberculosis*. A detailed study of enzymes involved in tetrahydrofolate biosynthesis may lead to a rational design of new and novel anti-TB drugs. The anti-TB drug p-amino salicylic acid initially designed as competitive inhibitor of salicylic acid has been reported to act on the tetrahydrofolate pathway as well as salicylate dependent biosynthesis of mycobactins, required for iron transport. Sulphonamides, the structural analogs of p-amino benzoic acid, inhibit biosynthesis of tetrahydrofolic acid, and thereby block the production of purine and pyrimidine bases required for nucleic acid biosynthesis in microbes. A type II topoisomerase, DNA gyrase, involved in many reactions including ATP-dependent negative supercoiling of closed circular double stranded DNA, ATP independent relaxation of negatively supercoiled DNA is a promising target for development of novel antitubercular drugs (Ducati et al., 2006; Loddenkemper et al., 2002; Perri and Bonora. 2004; Bishai and Chaisson. 1997; Smith and Moss. 1994). Recently, gyr A and gyr B have been cloned from M. tuberculosis and M. smegmatis. A stretch of 165 amino acids found in E. coli gyr B is absent from mycobacterial gyr B and thus any drug acting against gyr B would be specific to Mycobacteria. Inhibition of its activity prevents supercoiling, as subsequent process such as replication and transcription are DNA topologically dependent. Nucleotide biosynthesis has been reported to be a good target particularly for TB in HIV cases. In this regard, thymidine monophosphate kinase (dTMKase) has been suggested as validated target to develop new anti-tubercular agents particularly for the treatment of MDR TB and TB in HIV infected patients. This enzyme is an essential enzyme of nucleotide metabolism that catalyzes the reversible phosphorylation of thymidine

monophosphate (dTMP) to thymidine diphosphate (dTDP). Detailed structural elucidation of this enzyme is known and the well-known anti-HIV drug AZT has lowaffinity and this has led to the design and synthesis of more potent nucleoside analogs to develop new anti-TB agents (Hopewell. 1994; Snider et al., 1994; Bastian and Colebunders. 1999; Barry et al., 2000). Based on recent advances in ultra-structure and biochemistry, the three basic structural components of the M. tuberculosis cell, the plasma membrane, the cell wall, and the capsule have been identified as the most important target to develop new anti-TB drugs. The two layered cell wall in M. tuberculosis and M. leprae is very complex and poorly permeable. Classical studies carried out over many years identified that the peptidoglycan, the arabinogalactan, and the mycolic acids are the main structural components of the M. tuberculosis cell wall. Beyond the membrane peptidoglycan (PG) layer is covalently linked to arabinogalactan (AG), which in turn, is attached to large mycolic acids with their long meromycolate and short α-chains. These three constitute the cell wall core, the mycolyl arabinogalactan–peptidoglycan (mAGP) complex. Moreover, D-amino acids are important constituents of the mycobacterial cell wall. A cytoplasmic enzyme D-alanine racemase is required in the initial step of peptidoglycan biosynthesis to convert natural L- to D-alanine and has been identified as a novel target for antitubercular drug development (Joshi et al., 2006; Rattan et al., 1998; Bocanegra-García et al., 2010). The ability of M. tuberculosis to survive within an inhospitable environment has been attributed to its robust cell wall that comprises complex glycolipids including mycolyl-arabinogalactanpeptidoglycan (mAGP) and lipoarabinomannan. Lipoarabinomannan facilitates the entry of bacterium into macrophages, prevents macrophage activation, and protects M. tuberculosis from damage by superoxide and hydroxyl radicals. Although macrophages also produce H_2O_2 during a respiratory burst, the effect of H_2O_2 on LAM was not reported alongside the studies on superoxide and hydroxyl radicals. Many other extractable lipids including glycolipids (glycopeptididolipids, lipooligosachharide) (Gray. 1997; Gutierrez-Lugo and Bewley 2008; Janin. 2007), phenolic glycolipids (PGL), and other classes of free lipids (sulpholipids, phthiocerol dimycocerosate) are very important in pathogenesis and survival of M. tuberculosis in the host macrophages (Kishore et al., 2009).

Anti-TB drug targets

Despite the relative efficacy of current treatment, the various antibiotics that constitute first and second-line drugs for TB therapy target only a small number of core metabolic processes such as Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) synthesis, cell wall synthesis, and energy metabolism pathways (Zhang, 2005). New classes of drugs with additional drug targets that are difficult to overcome by mutation are urgently needed. Desirable new targets should be involved in vital aspects of bacterial growth, metabolism and viability whose inactivation would lead to bacterial death or an inability to persist, thus therapy could be shortened and drug resistant strains could be eliminated or drastically reduced (Mdluli and Spigelman, 2006; Duncan, 2004). Moreover, targets involved in the pathogenesis of the disease process should also be considered for drug development (Zhang et al., 2006; Palomino et al., 2009). The discovery of the complete genome sequence of TB bacteria helped to identify several important drug targets (Cole et al., 1998). Various groups have used this genomic information to identify and validate targets as the basis for development of new Anti-TB agents. Besides, mycobacterial genetic tools, such as transposon mutagenesis, gene knockout, and gene transfer, greatly facilitate target identification.

Cell wall biosynthesis related targets

Cell wall biosynthesis is a particularly good source of molecular targets because the biosynthetic enzymes do not have homologues in the mammalian system (Mdluli and Spigelman, 2006). The cell wall of *M. tuberculosis* is very important for its survival within constrained conditions such as those inside of human macrophages. The biosynthesis of the cell wall components involves many important stages and different enzymes that are absent in mammals and could be attractive drug targets (Khasnobis et al., 2002; Brennan and Crick, 2007; Sarkar and Suresh, 2011). Recently, the 2C-methyl-D-erytrol 4-fosphate (MEP) pathway was found (Eoh et al., 2009) as a potential drug target since the end product of the pathway leads to the formation of isoprenoids, which are responsible for the synthesis of several cell wall components (Mahapatra et al., 2005; Anderson et al., 1972). Peptidoglycan biosynthesis is another source of potential drug targets. For instance, alanine racemase and D-Ala-D-Ala-ligase catalyze the first and second committed steps in bacterial peptidoglycan biosynthesis, and since these steps are essential for important polymers, they are good drug targets. Both

alanine racemase and D-Ala-D-Ala ligase are inhibited by Dcycloserine, a second line anti-TB drug (Strych et al., 2001; Feng and Barletta, 2003). Another good drug target is the pyridoxal 5'-phosphate containing enzyme Alr that catalyzes the racemization of L-Alanine into D-Alanine, a major component in the biosynthesis of peptidoglycan (LeMagueres et al., 2005). Arabinogalactan biosynthesis, a novel arabionofuranosyl transferase that catalyzes the addition of the first key arabinofuranosyl redisude of the galactan core, is not sensitive to EMB, but is essential for viability (Sassetti et al., 2003). The ribosyltransferase that catalyzes the first committed step in the synthesis of decaprenyl-phosphoryl-D-arabinose, the lipid donor of mycobacterial d-arabinofuranosyl residues, has also recently been characterized and shown essential for growth (Huang et al., 2005)

Mycolic acid biosynthesis related targets

Within the mycobacteria lipid metabolism, mycolic acids are essential structural components of the mycobacterial cell wall. The early stage of fatty acid biosynthesis, which generates the precursors of mycolic acids, is a rich source of antibacterial targets (Heath et al., 2001). It is also the site of action of INH and ethionamide (Quemard et al., 1995; Larsen et al., 2002). *M. tuberculosis* has both types of fatty acids synthase (FAS) systems found in nature, FAS-I and FAS-II. FAS I is the system responsible for de novo synthesis of C16-C26 fatty acids and the FAS II system extends these fatty acids up to C56 chains to make precursors of mycolic acids, which are essential for growth. Since en oil-ACP reductase (InhA) is the target of INH, it is reasonable to assume that all steps in the FAS-II pathway will be essential for the viability of *M. tuberculosis.* Many of the individual enzymes of the FAS-II system have been expressed, purified and characterized (Kremer et al., 2001; Choi et al., 2000; Scardale et al 2001; Benerjee et al 1998; Marrakchi et al., 2002; Marrakchi et al., 2000; Slayden and Barry, 2002).

Energy production related targets

Isocitrate lyase (ICL) is an important enzyme in this category and also an important drug target. ICL is involved in energy production via the metabolism of acetyl-CoA and propionial CoA of the glyoxilate pathway. Inactivation of the *icl* gene leads to attenuation of both persistent and virulent strains of *M. tuberculosis*. However, *M. tuberculosis* has a salvage pathway, so a suitable anti-TB drug for this target must address both the main and salvage pathways (McKinney et al., 2000; Savi et al., 2008)

Amino acid biosynthesis related drug targets

Amino acid biosynthesis is another important target for developing anti-TB drugs. The shikimate pathway is very important and is involved in the synthesis of aromatic amino acids in algae, fungi, bacteria, and higher plants; however, it is absent in the mammalian system (Sarkar and Suresh, 2011). The final product of the shikimate pathway, chorismate, is a key biosynthetic intermediate involved in generating aromatic amino acids and other metabolites. The entire pathway is essential in *M. tuberculosis* (Parish and Stoker 2002). This feature makes the pathway an attractive target for developing anti-TB drugs with minimum cross reactivity (Ducati et al., 2007). Other enzymes of this pathway are also likely to be essential, and shikimate dehydrogenase (Magalhaes et al., 2002), and 5-enolpyruvylshikimate 3-phosphate synthase (Oliverira et al., 2001) have been characterized in detail. The biosynthesis of non-aromatic amino acids is also emerging as a potential drug target. The impact of amino acids such as lysine (Pavelka and Jacobs, 1999), proline, tryptophan and leucine (Smith et al., 2001) is evident from the fact that knocked out *M. tuberculosis* strains of the genes required for amino acid biosynthesis showed less virulence (Pavelka et al., 2003; Smith et al., 2001). Another attractive target of the lysine biosynthesis pathway is the enzyme dihydrodipicolinate reductase, for which potent inhibitors have been identified (Paiva et al., 2001).

Cofactor-related drug targets

Several cofactor biosynthetic pathways and pathways requiring some cofactors are good candidates for identification of new drug targets. Folate derivatives are cofactors utilized in the biosynthesis of essential molecules including purines, pyrimidines, and amino acids. While bacteria synthesize folate de novo, mammals must assimilate preformed folate derivatives through an active transport system (Mdluli and Spigelman, 2006). Dihydrofolate reductase, which catalyses the reduction of dihydrofolate to tetrahydrofolate, a key enzyme in folate utilization whose inhibition may affect the growth of *M. tuberculosis* (Gerum et al., 2002), and dehydropteroate synthase are validated targets of the widely used antibacterial sulfonamide, trimethoprim (Huovinen et al., 1995). Two enzymes involved in the de novo biosynthesis of NAD that affects the

NADH/NAD+ ratio upon which *M. tuberculosis* is dependent, have been studied as possible drug targets (Bellinzoni et al., 2002). Genomic analysis studies have suggested that the riboflavin biosynthesis pathway is essential in *M. tuberculosis* (Morgunova et al., 2005) and the lumazine synthase pathway has been validated as a target for anti-TB drug discovery.

DNA metabolism

Differences in mammalian and mycobacterial thymidin monophosphate kinase have been studied and exploited in an attempt to find selective inhibitors for this drug target (Haouz et al., 2003; Vanheusden et al., 2002). Other targets are ribonucleotide reductases that catalyze the first committed step in DNA synthesis and have differences with corresponding mammalian enzymes (Yang et al., 1994; Yang et al., 1997); DNA ligases, that play an important role in the replication and repair of DNA, are classified as NAD+ or ATP dependent. NAD+ dependent ligases are only found in some viruses and eubacteria (Mdluli and Spigelman, 2006). LigA is essential for growth of *M. tuberculosis* (Gong et al., 2004) and inhibitors that distinguish between the two types of ligases and have anti-TB activity have been identified (Srivastava et al., 2005). DNA gyrase has also been validated as a target for *M. tuberculosis*, since this is the only type II topoisomerase that it possesses (Cole et al., 1998). Its inhibition by fluoroquinolones results in highly mycobactericidal activity.

Other potential drug targets in *M. tuberculosis*

The tubercle bacillus produces no less than 20 cythochrome p450 enzymes, some of which appear to play essential roles (Cole and Alzari, 2007). Antifungal azole drugs target these enzymes and the cytochrome p450 homologues in the bacteria. Drugs like miconazole and clotrimazole are active against *M. tuberculosis* (McLean et al., 2007; Ahmad et al., 2006; Sun and Zhang, 1999). Subsequent crystallization studies of the *M. tuberculosis* cytochrome p450 enzyme system evoked studies to evaluate new drugs (Leys et al., 2003). Peptide deformylase inhibitors may be effective against *M. tuberculosis* since peptide deformylase catalyzes the hydrolytic removal of the B-terminal formyl group from nascent proteins. It is a metalloprotease essential for maturation of nascent polypeptides in bacteria but not essential for humans, making it an attractive target for antibacterial drug development (Teo et al., 2006); however, it has little effect on slow growing TB bacteria (Khasnobis et al., 2002). Another important set of emerging drug targets are the components of the siderophore biosynthesis of *M. tuberculosis* (Monfeli et al., 2007). Upon infection, as a part of the defense mechanism, the host has several mechanisms to withdraw or control the free extracellular, as well as intracellular, iron concentration (Weinberga and Miklossy, 2008; Ferreras et al. 2005). Mycobacteria have an unusual reliance on serine/threonine protein kinases as the main component of signal transduction pathways (Av-Gay and Everett, 2000), and there is considerable activity around this transduction system since some of these enzymes are essential for growth (Fernandez et al., 2006). *M. tuberculosis* synthesizes mycothiol in a multistep process involving four enzymatic reactions for protection against the damaging effects of reactive oxygen species. This pathway is absent in humans, and it has been shown to be essential to *M. tuberculosis* (Sareen et al., 2003).

Rational drug design

One of the design strategies for new anti-TB compounds is based on the development of analogs of first-line and/or second line drugs. In this section we review the strategies employed and analyze structure-activity relationships (SAR), which have led to the development of new anti-TB agents. In addition, we review new pharmacophore groups. One problem that must be considered in the design of anti-TB compounds is that there is a subpopulation of bacteria in a persistent non-replicating state. This is considered a major contributing factor to long drug treatments for TB. For this reason, it is important to determine if compounds have potential activity against these bacteria at the onset of design. We should also consider the physicochemical properties that directly affect the pharmacokinetics and pharmacodynamics of drugs (Imramovsky, et al., 2007; Izumizono, et al., 2011; Jadhav et al., 2009; Karthikeyan, et al., 2010). An example of this is the influence of stereoisomers on biological activity, because individual enantiomers have significant differences in activity, although sometimes the activity of some enantiomers cannot be explained.

Future perspective

The unremitting and steady rise in tuberculosis together with the emergence of resistance against traditional antitubercular drug regimen and the pathogenic synergy with HIV has put enormous pressure on public health systems to introduce new treatments. In drugresistant tuberculosis it is important to understand how the resistance emerges.

Consequently, great efforts have been made in the area of Mtb genomics, proteomics and target identification via advanced technologies and therefore several welcome developments come in the light having novel target with newer mode of action. In this concern, Linezolid a class of oxazolidinone antibiotics is under study and was approved for the treatment of MDR tuberculosis (D´Oca, et al., 2010; Delaine, et al., 2010; Eoh, et al., 2009; Goncalves, et al., 2010; Hearn et al., 2009; Heath et al., 2001; Khoje, et al., 2010; Mao, et al., 2010; Sankar, and Pandiarajan. 2010). A remarkable series of diarylquinolines, TMC207, have a very good level of in vitro activity against *M. tuberculosis*. Moreover, further research led to a series of structurally related nitroimidazo [2,1-b]oxazoles that is: OPC-67683. Remarkably, the mechanisms of action of these new arrivals are well-understood with new and novel target. Also, in the field of preclinical research, well-established classes of compounds and molecular targets are still interesting, however, in some of the cases when similar target molecules are present in humans; future development has to ensure a high degree of selectivity (Meganathan, 2001; Meng, et al., 2009; Nava-Zuazo, et al., 2010; Odell et al., 2009; Rivers, and Mancera, 2008; Sainath, et al., 2009). Further investment in developing fundamental genetic systems and more accurate models of human disease would significantly facilitate TB drug discovery efforts in the long term, in particular enabling robust validation of novel targets. However, all these possibilities require RandD activities and therefore, there is a demand in continuing research in this direction and more financial assistance from developed nations and industrial houses to achieve the goal of eradicating *Mycobacterium tuberculosis* from the world in coming years (Shi, and Sugawara. 2010; Shiradkar, et al., 2007; Singh, et al., 2011; Vanheusden, et al., 2002; Yoya, et al., 2009).

Executive summary

Tuberculosis (TB) is a chronic infectious disease caused by *M. tuberculosis*. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs. Treatment regimen of tuberculosis comprises five first line antiTB drugs namely isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol followed by second line antiTB drugs namely fluoroquinolones and one of the injectable aminoglycosides. Besides the traditional antitubercular drugs available commercially, several new heterocycles were synthesized in recent past. The new potential antitubercular agents have been classified according to their chemical entities (Eswaran, et al., 2010; Ferriz, et al., 2009; Gasse, et al., 2008; Gill, et al., 2008). In an effort to develop new and more effective therapies, molecules that can also effective against MTB and MDR-TB. Natural products play a major role in drug discovery, as a unique source of original structures, which can provide models for future drug design. In the field of antitubercular agents, the lichen dibenzofuran derived secondary metabolite: usnic acid has been shown to display an interesting activity, but its weak potency did not permit its further development as an antimycobacterial drug (Betts, et al., 2003; Bocanegra-García, 2010; Correia et al., 2009; Cunico, et al., 2011).

Discussion

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a remarkably successful pathogen that has latently infected a third of the world population (Zhang et al., 2006). Infection occurs via aerosol, and inhalation of a few droplets containing *M. tuberculosis* bacilli is enough for lung infection. After infection, *M. tuberculosis* pathogenesis occurs in two stages. The first is an asymptomatic state that can persist for many years in the host, called latent TB. The second stage requires only a weakened immune response to become activated (Zhang, 2004), then the bacteria begins replicating and causing characteristic symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death. The emergence of Human Immunodeficiency Virus (HIV) and the resultant Acquired Immune Deficiency Syndrome (AIDS) pandemic underlined the importance of reactivation of the disease and its potentially catastrophic outcome since over 50% of deaths among HIVinfected patients results from co-infection with *M. tuberculosis* with the two pathogens inducing each other's replication, thus accelerating the collapse of the immune system (Cole and Alzari, 2007). While it is impossible to determine the exact number of cases, the latest World Health Organization (WHO) survey estimates that close to 2 million deaths occur every year, that there are approximately 8 million new cases annually, and that every third individual on the planet has been exposed to or infected by *M. tuberculosis* (Dye, 2006; Cole and Alzari, 2007).

Although TB can be treated and even cured with chemotherapy, treatment is exceedingly lengthy and takes 6-9 months (Blumberg, et al., 2003). In addition to significant toxicity, lengthy therapy also causes poor patient compliance, which is a frequent cause for

selection of drug resistant and often deadly multidrug resistant TB (MDR-TB) bacteria (Zang et al., 2006). Currently, TB chemotherapy is made up of a cocktail of first-line drugs, isoniazid (INH), Rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), which are given for six months (Blumberg et al., 2003). If this treatment fails as a result of bacterial drug resistance or intolerance to one or more drugs, second-line drugs are used, such as *para*-aminosalicilate (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine. These are generally less effective or more toxic with serious side effects (Blumberg et al., 2003). This second-line treatment can also result ineffective since MDR-strains that exhibit resistance to these second-line drugs are currently on the rise (Zhang and Amzel, 2002) Treatment is also made quite difficult by the presence of metabolically silent, persistent or dormant bacteria within host lesions. These are not susceptible to the anti-mycobacterial drugs that usually kill growing but not persistent bacteria (Zhang, 2004). While there are many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, and ineffective drugs, duration of lengthy treatments is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid heath improvement, thereby favoring the emergence of drug-resistant strains (Cole and Alzari, 2007)

Conclusion

Tuberculosis remains the leading infectious disease worldwide, despite the availability of TB chemotherapy and the BCG vaccine. This is further demonstrated by the fact that half a year of treatment with multiple drugs is needed. Recent genetic and genomic tools as well as high-throughput screening, and structure-based drug design strategies have allowed the discovery of new anti-TB drugs. These are increasingly receiving more attention, and a large number of new compounds or derivatives from existing drugs are under investigation. With this and a better understanding of the unique biology of TB, more targets will be validated, and hopefully a pattern will emerge that will help us reach the goals of more potent compounds that allow multiple stages and drug targets to be addressed.

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