WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 5, 616-629. Review Article ISSN 2277– 7105

DRUG TARGETS IN LEPROSY

Thirupathy Kumaresan Paraman, Thiruppathi Murugesen, Vijay Nagendiran Perumal*

Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankovil. Srivilliputhur, Virudhunagar (Dt).

Article Received on
08 March 2016,
Revised on 29 March 2016,
Accepted on 20 April 2016
DOI: 10.20959/wjpr20165-6178

***Corresponding Author**
Vijay Nagendiran Perumal
Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankovil. Srivilliputhur, Virudhunagar (Dt).

ABSTRACT

Leprosy is contagious disease caused by mycobacterium leprae (Acid fast bacteria). It is the leading cost of mortality among all other infectious disease. The emergence of resistance form's of leprosy strong epidomological existence AIDS, due to expand treatment with chemical and associated side effect of the exisisting drug fundamentals new and more effective drug to treat the leprosy and tuberculosis. In this record the structural genomic's mycobacterium leprae provide very important information to identify the potential target for the development of newer anti-leporal agent's. In addition the genome of mycobacterium leprae encoded a serious of target's that are unique in mycobacterium leprae. But are absent in host cell's. This target can particularly in hibit the growth of mycobacterium leprae enhance to reduce side effect, inhibit resistance development and removal of latent disease. In this review a new target particularly those widely cited in literature with structure containing potential inhibitor (or) substrate (or) structure based design of drug's which can be development of drug's which can be development of anti-leprosy drug.

INTRODUCTION

Mycobacterium leprae also known as Hansen's coccus spirally, mostly found in warm tropical countries, is a Gram positive bacteria that causes leprosy (Hansen's disease). It is an intracellular pleomorphic, acid fast, pathogenic bacteria. M.Leprae is an aerobic bacillus (rod shaped) surrounded by the characteristic waxy coating unique to mucobacteria. In size and shape, closely resembles Mycobacterium tuberculosis[1] M.Leprae was discovered in 1873 by the Norwegian physician Gerhard Armauer Hansen, who was searching for the bacteria in the

skin nodules of patients with leprosy.[2] Genome. M. leprae that was originally purified from the skin lesions of a multibacillary leprosy patient from Tamil Nadu, India (TN strain), and subsequently expanded in and purified from the liver of a nine-banded armadillo provided the source of DNA for sequencing of the M. leprae genome.[3] M. leprae are spread person to person by nasal secretions or droplets. However, the disease is not highly contagious like the flu. They speculate that infected droplets reach other peoples' nasal passages and begin the infection there. Some investigators suggest the infected droplets can infect others by entering breaks in the skin. M. leprae apparently cannot infect intact skin.[4] recent year many drugs have been resistanced by M.leprae, now the human genome sequence can help in elimination the potential drug targets that have close the multiplication of M.Leprae, which very much need to reduce the side effects, prevent the resistance development.[5]

In this review, we have noticed the genomic and structural genomic studies, novel targets mostly cited in the journals with drug substrate containing potent inhibitors or target based drug design are discussed here which is useful in the development of novel anti–leprol agent.

CURRENT THERAPIES AND DRUG RESISTANCE

In the 1950s, dapsone (diaminodimethyl sulfone) was introduced nas standard chemotherapy for leprosy and was used worldwide for treatment of both multibacillary and paucibacillaryforms of the disease. Long-term monotherapy with dapsone resulted in poor compliance in many areas, ultimately leading to the emergence of dapsone-resistant leprosy, resulting in treatment failures and resistance levels reported to be as high as 40% in some areas of the world. Fortunately, additional antimicrobial agents such as rifampin and clofazimine were developed and introduced for the treatment of leprosy. Although rifampin proved to be a powerful antileprosy drug, use of rifampin alone or in combination with dapsone for the treatment of dapsone-resistant leprosy led to the rapid development of rifampin-resistant organisms. Other drugs with antileprosy activity were also evaluated. Clofazimine proved to be only weakly bactericidal against M. leprae and therefore was not suitable as monotherapy for leprosy. To overcome the problem of drug-resistant M. leprae and to improve treatment efficacy, the World Health Organization recommended multidrug therapy for leprosy in 1981. The initial recommendation for patients with multibacillary leprosy was to give daily dapsone and clofazimine with monthly rifampin and clofazimine for 2 years or until the skin smear was negative. These recommendations, as well as diagnostic criteria, have been modified several times since 1981. Currently the World Health

Organization recommends counting lesions to distinguish paucibacillary from multibacillary disease, less than five lesions being classified as paucibacillary and five or more lesions as multibacillary. Since 1998 they have also recommended treating multibacillary patients for only 12 months and paucibacillary patients for only 6 months (reviewed in reference). In addition, a World Health Organization committee recommended that patients with a single lesion be treated with a single combination dose of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) (312; www.who.int/lep/romfaq3.htm), but this regimen remains very controversial. These recommendations arise from efforts to reduce the resources allocated to leprosy in developing countries and are the subject of considerable debate. Optimal diagnostic evaluation employing skin smears or biopsies, classifying the lesions on the Ridley-Jopling scale, and conservative, longer duration of treatment with multiple antimicrobials are recommended in the United States and most developed countries. Multidrug therapy has been very practical and successful for treatment of both multibacillary and paucibacillary leprosy and the overall number of registered cases worldwide has fallen dramatically. However, even with these powerful drug combinations, the number of newly registered cases has not fallen consistently, and drug resistance still occurs. A recent report demonstrated that 19% of 265 M. leprae isolates from biopsied samples of leprosy patients were resistant to various concentrations of dapsone, rifampin, or clofazimine and 6.23% were resistant to more than one drug in the mouse footpad susceptibility assay. In addition, several investigators have identified multidrug-resistant strains of M.leprae.

TARGETING WALL BIOSYNTHESIS

The cell wall of Mycobacterium leprae is essential for its growth and survival in infected host, and thus, contributes to the resistance to most commonly-used antibiotics and chemotherapeutic agents. The mycobacterial cell wall is comprised of three covalently linked macromolecules, peptidoglycan, arabinogalactan, and mycolic acid. The Cell wall is characterized as a preferred source of molecular targets because the biosynthetic enzymes do not have homologues in mammalianSystems.[6,7] currently used anti leprotic drugs acting on cell wall include dapsone (it is an sulfonamide derivatives inhibit bacterial folate synthase), clofazimine (it is a dye with leprostatic and its act interference with template fuctions of DNA), rifampin it inhibits the DNA dependent RNA polymerase.[8]

Fatty acid synthase

Fatty acid synthase is a multi enzyme protein that catalyses fatty acid synthesis.[9] This fatty acid biosynthesis is responsible for the production of the precursors of mycolic acids. Three different structural classes of mycolic acids, they are alpha mycolic acid, methoxymycolic acid andketomycolicacid.[6] The alpha mycolic acid is the most abundant form (70%), whereas the methoxymycolic acid and ketomycolic acid are the minor components (10 to 15%). Fatty acid bio synthesis conducted through the fatty acid synthase (FAS) system, which is divided in to two distinct forms i.e., fatty acid synthase I (FAS-I) and fatty acid synthase II (FAS- II). The enzyme FAS-I is responsible for the denova synthesis of C16-C26 fatty acids.[10] The FAS II system extents these fatty acids upto C56 to make precursors of mycolic acids, which is hall mark of the mycobacteria and essential for growth. Unlike FAS I, FAS II is not present in human beings and hence, inhibition of this enzyme, leadsto inhibit the mycolic acid biosynthesis. It is always considered as the most selective and attractive target design of antimycobacterial agents.

Mycobacterial enoyl acyl carrier protein reductase (InhA)

InhA, the enoyl acyl carrier protein reductase (ENR) from Mycobacterium leprae, is one of the key enzymes involved in the type II fatty acid biosynthesis pathway of M.lepre. InhAcatalyses the final enzymatic step in the elongation cycle of the FAS II pathway. Inhibition of InhA disrupts the biosynthesis of the mycolic acids and induces cell lysis. InhA represents the superb drug target. The enzyme is the target of antimicrobial drugs. Seveal co-crystallized structures of InhA (PDB code: 2NSD, 1ZID) are available, which can be explored in development of anti leprotic drugs.

Mycobacterial beta- ketoacyl carrier protein synthase III enzymes, Fabh(PDB code: 2Q01)[11,12] and MabA (PDB code:1UZN)[11] are other key condensing enzymes responsible for initiation of FAS II pathway, and have emerged as attractive new targets for novel antileprotic drugs in recent years.

Polyketide synthases (PKSs) and fatty acyl-AMP ligases (FAALs) also play an important role in mycolic acid biosynthesis.[17,18]Polyketide synthase Pks13, which is crucial for mycobacterial growth, catalyzes the final condensation step in mycolic acid synthesis in FAS-II pathway. However, the fulllength structure of Pks13 protein is still unavailable. Nevertheless, several crystal structures of Pks13 homologues or active domain provide valuable insights about the mechanism of Pks13 enzyme activity.Nevertheless, several crystal

structures of Pks13 homologues or active domain provide valuable insights about the mechanism of Pks13 enzyme activity. Acyl-AMP ligase, FadD32 andthe AccD4-containing acyl-coenzyme A (CoA) carboxylaseare also proved to be essential formycobacterial growth.[9,10,11] the FAALs activate fatty acids acyl adenylates and transfer them onto the PKSs which then produce unusual acyl chains that are the components of mycobacterial lipids. The FAALs,FaD32 and the AccD4-6[14,17] containing acyl coenzyme A (CoA) carboxylase are essential for virulence and intracellular growth of the pathogen. Therefore these enzymes are explored can be design of newer anti leprotic drugs.

Peptidoglycan biosynthesis

Peptidoglycan consists of alternating units of N-acetylglucosamine and N-gycolylmuramic acid and forms the backbone of the mycolyl-arabinogalactan-peptidoglycan (mAGP). The side chains of peptide are attached to muramic acid, and thus, crosslinked to arabinogalactan (AG) via a phosphodiester line to the position 6 of a proportion of muramic acid residues, In 2005, LeMagueres and colleagues reported the 1.9-Å crystal structure of alanine racemase from M.leprae (Alr (Mtb)) and identified a conserved entryway into the active site (PDB code: 1XFC) These knowledge of detailed structural investigation and related biochemical analysis made thisenzyme a challenging but important target for drug design against leprosy; furthermore, the related studies provided valuable insights about the precise mechanism of D-cycloserine inhibition against drug-resistant leprosy.

Arabinogalactan andlipoarabinomannan biosynthesis

Arabinogalactan polymer is composed exclusively of D-galactofuranosesand D-arabinofuranoses, which are extremely rare in nature, while other crucial components of mycobacterial cell wall are known to be embedded into the framework of mAGP.[6] In addition to the essential role in mycrobacterial cell wall, lipoarabinomannan(LAM) also exhibits a wide spectrum of immunomodulatoryactivity.[6] These observations suggest the possibilities to target arabinogalactan and LAM biosynthesis pathways to treat leprosy. For example, ribosyltransferase is key to catalyze decaprenyl-phosphoryl-D-atabinosesynthesis.[22] UDP-galactopyranosemutase[21], galactofuranosyltransferase[24], dTDP-6-deoxy-L-lyxo-4-hexulose reductase (RmID)[25], RmlBand RmlC are also essential for mycobacterial growth.[23] These enzymes can be the potential targets for anti-M.leprosydrug discovery. The D-arbinan containing polymers, AG and LAM, are essential components of the unique cell envelope of the pathogen leprosy.

TARGETS IN DNA METABOLISM

In M.leprae, there are two classes of ribonucleotidereductases (RNRs), which are currently named as Class Iband Class II, respectively, and are responsible for catalyzing the formation of deoxyribonucleotides from ribonucleotides. Class Ia is found in mammalian cells and certain bacteria, such as E. coli.[26] Due to their essential roles, RNRs are characterized as the potential targets for antibacterial drug discovery. Class I enzymes are composed ofthe two homodimericproteins, R1 and R2. Protein R1contains substrate binding site, whereas R2 has a stable free radical on a tyrosine residue, neighboring antiferromagneticallycoupled high spin Fe(III)-Fe(III) site in each polypeptide of the R2 dimer, which is crucial for the enzyme activity.[27] Although two genes encode RNR subunit in M. leprae, R2-2 is generally believed to be the enzymatically active form[28]. Uppsten and colleagues reported the crystal structure for the small subunit of M. Leprae RNR andidentified the clear active center, which helps elucidate the mechanism of its activity (PDB code: 1UZR).[29] As the small subunit of M.leprae RNR was reported to be hypersensitive to the class I RNR inhibitor hydroxyurea[30], the structural knowledge provides a new direction to discover anti-M. leprotic inhibitors.

DNA ligase can link together two DNA strands that have double-strand break. DNA ligases are classified as either NAD+- or ATP-dependent, depending upon their specific cofactor.[31] Comparing to the universal ATP-dependent ligases, NAD+-dependent ligases (LigA) are only found in certain viruses and bacteria, including M. Leprae. Srivastava and colleagues recently reported thecrystal structure of M. Leprae LigA with bound AMP and provided it as a novel target for anti-M. Lepraedrug discovery. Moreover, it is found that several nucleoside analogue and other compounds are effectively LigA inhibitors.[32] In particular, glycofuranosylateddiamine-based inhibitors could distinguish between the two types of ligases, and showed anti-leprotic activity[33]

Thymidine kinase (TK), also known as a phosphotransferase, is found in most living cells. There are two forms of TKs inmammalian cells (TK1 and TK2), while several bacteria express their own TKs. As TKs have key functions in DNA synthesis, and therefore, in cell division, they are the targets of many anti-bacteria drugs. Recently, Li de la Sierra and colleagues reported the crystal structure of the M. Leprae TMP kinase (PDB code: 1G3U). They also identified a magnesium-binding site and a characteristic LID region. Comparing to the homologues in E. coli and yeast, the binding site of TMP in M.leprae shows distinct differences. The observations about the interaction network, involving highly conserved side-

chains of the protein, the magnesium ion, a sulphate ion and TMP itself, present M. leprae TK as a good target to design selective inhibitors[34]. Based on this work, a serial of M.leprae TK inhibitors were identified, among which 30- azido deoxy thymidine monophosphate is a special one—it is a competitive inhibitor of M.leprae TK, but is a substrate for TKs in human and other species.[35]

TARGET IN BIOSYNTHESIS OF AMINO ACIDS AND CO-FACTORS

Aminoacid and co-factor's which are very much needed for the multiplication of M.leprae bacteria, because they are nutrition to survival of the M.leprae. Therefore, by inhiniting (or) altereting the biosynthesis pathway these essential aminoacids and co-factor's are the unique and effective target to control the growth of mycobacteria.

The shikimate pathway

The shikimate pathway consists of seven enzymatic reactions (through seven enzymes, AroB, AroC, AroE, AroG, Arok, ArokΔ and AroQ) by which phosphoenolpyruvate and erythose 4-phosphate are converted to chorismate. The absence of this pathway in mammals makes them potential targets for development of antilepral drugs.[36,37]

Acyl CoA Synthetase

Most of the genes are involved in biosynthetic and metabolic pathways, so the product of these genes can be aimed for the novel drug target. Acyl CoA Synthetase is an enzyme that participates in fatty acid biosynthesis. The activation of fatty acids by Acyl-CoA Synthetase is the need of de novo lipid biosynthesis, fatty acid catabolism and remodeling of biological membranes. Therefore by emphasizing this protein as a drug target can help in the identification of novel drugs to cure leprosy.[38]

Pantothenate kinase (PanK)

Panthothenate (vitamin B5) is involve in coenzyme A(CoA) biosynthesis of fatty acid by attaching to acyl carrier proteins [CATALYTIC ACTIVITY : ATP + PANTOTHENATE = ADP + D-4'- PHOSPHOPANTOTHENATE][39] by inhibiting this biosynthesis which give new drug target for anti-lepral drugs.

Lumazine synthase

The enzymes involved in the biosynthesis of riboflavin represent attractive targets for the development of drugs against bacterial pathogens, because the inhibitors of these enzyme are

not likely to interfere with enzymes of the mammalian metabolism. Lumazine synthase (PDB code: 2C92, 2C9D)[40] catalyzes the penultimate step in the riboflavin biosynthesis pathway.

TARGETS IN GLYOXYLATE BYPASS

Glyoxylate shunt pathway is a carbon assimilatory pathway that allows the net synthesis of C4 dicarboxylic acids from C2 compounds. The first step of glyoxylate shunt is catalyzed by isocitrate lyase (ICL). There are two M. tuberculosis ICL proteins, a smaller one ICL1 and a larger one ICL2, which will cause complete impairment of M. tuberculosis replication and rapid elimination from infected lungs.[41,42] The structure of M. tuberculosis ICL was reported by Sharma and colleagues, and presents the precise inhibitory mechanism of the potent anti-M. tuberculosis 3-nitropropionate and 3-bromopyruvate.[43]

EXPLORING NEW TARGETS

ATP bio synthesis

The effect of trifluoperazine (TFP), a calmodulin antagonist, which was investigated on in vitro ATP levels of human derived Mycobacterium leprae. M. leprae were obtained from biopsies from multi-bacillary forms of leprosy and were incubated in a modified Dubos medium system which supports limited in vitro synthesis of M. leprae, where different concentration of trifluoperazine was incubated. Samples for estimation of bacillary ATP levels were taken at day 0 and at 14 days of incubation. TFP inhibited ATP levels in M. leprae and this inhibitory effect was marginal at 2.5 Wg ml31 (35% inhibition), highly significant at 5 Wg ml31 (87% inhibition) and almost total at 10 Wg ml31 (98.5% inhibition). This compound appears to have potential as an anti-leprotic drug.[44]

Inositol-1-phosphate synthase

Inositol and its metabolites are widely found in eukaryotes but are uncommon in prokaryotes. As a consequence, prokaryotic ionsitol metabolism remains poorly understood. The first know enzymatic step in the de novo biosynthesis of inositol is mediated by the ino1gene, which encodes 1-L-myo-inositol-1-phosphate synthase (I-1-P synthase)[45]. In mycobacteria several important metabolites such as Phosphatidylinositol (PI) is an abundant phospholipid in the cytoplasmic membrane of mycobacteria and the precursor for more complex glycolipids, such as the PI mannosides (PIMs) and lipoarabinomannan (LAM) and glycosylphosphatidyliositol (GPI) are derived from ionositol. Thus denovo biosynthesis of inositol might be a useful pathway to intercept for the drug development.[46,47,48]

Regulatory proteins

The regulatory protein, such as ArgP[49], GInD, GInE[50, 51] and IdeR[52]s could act as transcription factors, regulators for other proteins, and cofactors, etc., and are essential for Mycobacterium leprae and tuberculosis growth. By inhibition of the regulatory proteins would have additive effects of disrupting a whole network of M.Leprae lifecycle and thus, prevent the growth in infected host. Thus the reported structural investigation is still very limited till now, and current drug discovery strategy to target these proteins is mainly based on biochemical assay.

CONCLUSION

Structural and functional information determined to this structural genomics effort will enable use of this information to development of new drug's and treatment for leprosy.

Many novel targets which are involved in the many no of step's in mycobacterium leprae life cycle. It could be vital role for anti-leprosy drug discovery have been reported.

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