Available online at www.sciencedirect.com
ScienceDirect
Archives of Biochemistry and Biophysics 464 (2007) 228–240
ABB
www.elsevier.com/locate/yabbi

Minireview

Structure, function and drug targeting in *Mycobacterium tuberculosis* cytochrome P450 systems

Kirsty J. McLean, Adrian J. Dunford, Rajasekhar Neeli, Max D. Driscoll, Andrew W. Munro *

Manchester Interdisciplinary Biocentre, Faculty of Life Sciences, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK

Received 12 February 2007, and in revised form 2 March 2007
Available online 10 April 2007

Abstract

The human pathogen *Mycobacterium tuberculosis* has made a dramatic resurgence in recent years. Drug resistant and multidrug resistant strains are prevalent, and novel antibiotic strategies are desperately needed to counter Mtb's global spread. The *M. tuberculosis* genome sequence revealed an unexpectedly high number of cytochrome P450 (P450) enzymes (20), and parallel studies indicated that P450-inhibiting azole drugs had potent anti-mycobacterial activity. This article reviews current knowledge of structure/function of P450s and redox partner systems in *M. tuberculosis*. Recent research has highlighted potential drug target Mtb P450s and provided evidence for roles of selected P450 isoforms in host lipid and sterol/steroid transformations. Structural analysis of key Mtb P450s has provided fundamental information on the nature of the heme binding site, P450 interactions with azole drugs, the biochemical nature of cytochrome P420, and novel mutational adaptations by which azole binding to P450s may be diminished to facilitate azole resistance.
© 2007 Elsevier Inc. All rights reserved.

Keywords: Tuberculosis; Cytochrome P450; Azole drugs; CYP121; CYP51; FprA; Ferredoxins; Cholesterol; Lipids

Tuberculosis (TB),[1] once referred to as the "white death" is a debilitating human disease caused by the bacterial pathogen *Mycobacterium tuberculosis* [1]. Once thought to be virtually eradicated in the western world, recent decades have seen a terrifying resurgence of the disease, with a major factor being its synergy with the HIV virus and the ease with which the bacterium can thrive in immunocompromised individuals [2,3]. It is now estimated that one third of the world's population is infected with *M. tuberculosis* (Mtb) and that an infected individual has an ~10% chance of developing TB in their lifetime [4], although this number is substantially elevated for HIV-infected individuals and in the elderly or poorly nourished. The infection is spread as exhaled droplets in coughs or sneezes from infected individuals, and the contagion may be caused by even a single bacterium ingested [3]. A hallmark of the disease is the "tubercle" (or granuloma), a cellular formation which results from phagocytosis of the Mtb by lung macrophages and the subsequent recruitment of other mononuclear cells from nearby blood vessels. This leads to the containment of the Mtb bacteria in cellular masses in the lungs. The decay of the granuloma (as observed in immune system failure in HIV patients) enables the escape of numerous infective bacteria, and the further spread and progression of the disease [3].

The resurgence of TB has been accelerated by the development of strains of the Mtb bacterium that are resistant to leading antitubercular drugs [5]. The major (most effective) drugs in clinical use have been rifampicin (also known as rifampin) and isoniazid (INH). The former is an effective inhibitor of bacterial DNA-dependent RNA polymerase [6]. The latter's mechanism of action has been resolved only in recent years, and involves activation of the prodrug isoniazid (by the catalase–peroxidase enzyme KatG) to a reactive isonicotinoyl radical that reacts with NAD(P) and

* Corresponding author. Fax: +44 161 306 8919.
E-mail address: Andrew.Munro@Manchester.ac.uk (A.W. Munro).

[1] *Abbreviations used:* TB, tuberculosis; Mtb, *M. tuberculosis*; INH, isoniazid; ETH, ethionamide; PZA, pyrazinamide; EMB, ethambutol.

0003-9861/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.abb.2007.03.026

inhibits NAD(P)-dependent enzymes, notably InhA [7] Resistance to these agents can arise through mutations to the *rpoB* gene (that diminish rifampicin binding without destroying polymerase activity) or by drug efflux mechanisms (for rifampicin), or by mutations in the activator *katG* and/or the likely target enzymes enoyl ACP reductase and the NADH dehydrogenase [8,9]. Resistance is now also widespread to many other first line and second line TB drugs, such as ethionamide (ETH), pyrazinamide (PZA) and ethambutol (EMB) [10]. INH, ETH and PZA are all prodrugs activated intracellularly by Mtb enzymes (Fig. 1). Multidrug resistant (MDR) Mtb is defined as a strain resistant to at least the two most effective drugs (isoniazid and rifampicin), and is now prevalent across the globe [11]. A more recent and frightening development has been the emergence and characterization of XDR Mtb (eXtreme or eXtensively drug resistant TB). XDR Mtb is not only MDR (*i.e.* isoniazid- and rifampicin-resistant), but is also resistant to at least three of the six major classes of second line antitubercular drugs [12]. The World Health Organization some time ago recognized this developing situation as one with potential to cause a ''global catastrophe'', and made an urgent call for research into development of new drugs and other strategies to halt the resurgence of what is one of man's oldest and most deadly pathogens [3,13]. An important and unexpected link between Mtb, cytochrome P450 and possible drug targeting only became evident as a consequence of the determination of the genome sequence of the bacterium in 1998, as explained below [14].

The Mtb genome sequence—a plethora of P450s

The Mtb gene sequence was first determined in the laboratory of Stewart Cole at the Institut Pasteur in 1998, and revealed some unusual phenomena [14]. The large proportion of genes involved in lipid metabolism was not unexpected, given the complexity of lipids in Mtb. The bacterium has a dense, lipid-rich cell envelope that is critical for infection and for persistence in the host (Fig. 2). Of particular note in this envelope are the abundant mycolipids, which are very long chain (C60–C90) α-branched, β-hydroxylated fatty acids [15]. However, an unexpected finding was the presence of twenty different genes encoding various cytochrome P450 (P450) isoforms [16]. At the time of determination of the genome sequence, this was an

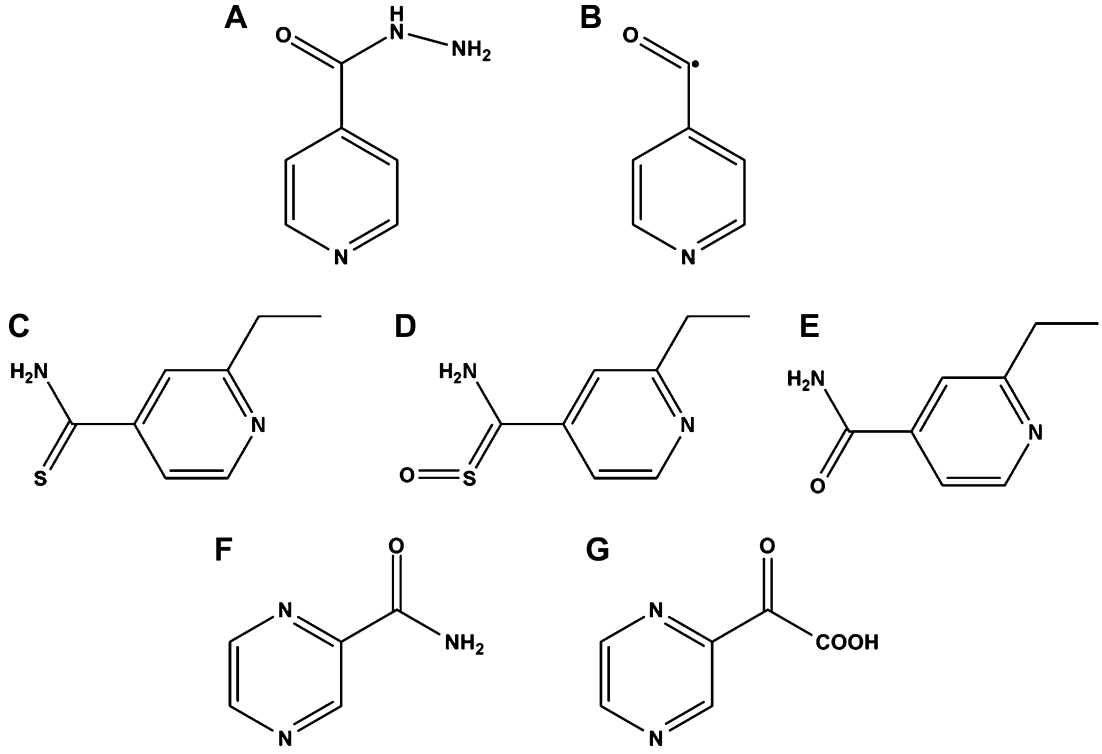

Fig. 1. Antitubercular prodrugs and their activation by Mtb enzymes. A number of current antitubercular drugs acquire bacteriotoxicity through activation by Mtb enzymes (*i.e.* they are really prodrugs). Isoniazid (INH) (A) is oxidatively activated by Mtb catalase/peroxidase KatG to form the reactive isonicotinoyl radical (B) which forms adducts with NAD^+ and $NADP^+$ (and with other acyl radicals). INH is an inhibitor of cell wall mycolic acid synthesis, and has multiple other effects on DNA, lipid, carbohydrate and NAD metabolism [7,10]. Ethionamide (ETH) (C) is oxidatively activated by the FAD-containing monooxygenase EthA to form the S-oxide form (D). This is further oxidised by EthA to form 2-ethyl-4-amidopyridine (E) via a postulated sulfinic acid intermediate, which has been suggested to be the key reactive ETH derivative. ETH inhibits the same target as INH (InhA). EthA also activates related thiacetazone and thiobenzimide prodrugs [79,80]. Pyrazinamide (PZA) (F) is converted to its active form pyrazinoic acid (POA) (G) by the nicotinamidase/pyrazinamidase PZase (encoded by the *pncA* gene). PZA has no defined target of action, but protonated POA (HPOA) accumulates under acid conditions within the bacilli and causes cellular damage [81].

Download English Version:

https://daneshyari.com/en/article/8292136

Download Persian Version:

https://daneshyari.com/article/8292136

Daneshyari.com