



Review

The dimycocerosate ester polyketide virulence factors of mycobacteria

Kenolisa C. Onwueme^{a,b,*}, Cheryl J. Vos^b, Juan Zurita^b,
Julian A. Ferreras^b, Luis E.N. Quadri^{b,*}

^a *Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD-PhD Program, New York, NY 10021, USA*

^b *Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA*

Abstract

Recent advances in the study of mycobacterial lipids indicate that the class of outer membrane lipids known as dimycocerosate esters (DIMs) are major virulence factors of clinically relevant mycobacteria including *Mycobacterium tuberculosis* and *Mycobacterium leprae*. DIMs are a structurally intriguing class of polyketide synthase-derived wax esters discovered over seventy years ago, yet, little was known until recently about their biosynthesis. Availability of several mycobacterial genomes has accelerated progress toward clarifying steps in the DIM biosynthetic pathway and it is our belief that reviewing the bases of our current knowledge will clarify outstanding issues and help direct future endeavors.

© 2005 Elsevier Ltd. All rights reserved.

Abbreviations: ACP, acyl carrier protein; AT, acyltransferase; CFU, colony forming unit; dextro, dextrorotatory; DIM, dimycocerosate ester; dPGL, deacylated phenolic glycolipid; DH, dehydratase; ER, enoyl-ACP reductase; hyg, hygromycin; km, kanamycin; KR, ketoreductase; KS, keto-acyl ACP synthase; levo, levorotatory; MalCoA, malonyl CoA; MeMalCoA, methyl malonyl CoA; Mbov, *Mycobacterium bovis*; Mgas, *M. gastri*; Mhae, *M. haemophilum*; Mkan, *M. kansasii*; Mlep, *M. leprae*; Mmar, *M. marinum*; Mtb, *M. tuberculosis*; Mulc, *M. ulcerans*; MYCS, mycocerosic acids; PDIM, phthiocerol dimycocerosate; PGL, phenolic glycolipid; PCOL, phthiocerol; ϕ PCOL, phenolphthiocerol; PDON, phthiodiolone; PTOL, phthiotriol; SAM, S-adenosyl methionine; STM, signature tagged mutagenesis; wt, wild-type.

* Corresponding authors. Tel.: +1 212 396 1100; fax: +1 212 746 8678 (K.C. Onwueme), Tel.: +1 212 746 4497; fax: +1 212 746 4028 (L.E.N. Quadri).

E-mail addresses: kco2001@med.cornell.edu (K.C. Onwueme), leq2001@med.cornell.edu (L.E.N. Quadri).

Contents

1.	Introduction	261
2.	The polyketide synthase genes in <i>M. tuberculosis</i>	261
2.1.	Polyketides and virulence	261
2.2.	Comparative domain analysis	264
2.3.	Classification of <i>M. tuberculosis</i> pks'	264
3.	Characterization of DIMs	264
3.1.	Discovery and structural studies	264
3.1.1.	Phthiocerol	264
3.1.2.	Phthiocerol wax esters and mycocerosic acids	266
3.1.3.	Mycosides	266
3.1.4.	Structural refinements	266
3.2.	Stereochemical studies	267
3.2.1.	Relative stereoconfiguration of the 9,11-diol	267
3.2.2.	Absolute configuration of the C4 center	267
3.2.3.	Absolute configuration of phthiocerol	267
3.2.4.	Stereoconfiguration of mycocerosic acids	268
3.3.	Species distribution	269
3.3.1.	<i>M. tuberculosis</i>	270
3.3.2.	<i>M. bovis</i>	270
3.3.3.	<i>M. leprae</i>	271
3.3.4.	<i>M. kansasii</i>	271
3.3.5.	<i>M. gastri</i>	272
3.3.6.	<i>M. marinum</i>	272
3.3.7.	<i>M. ulcerans</i>	272
3.3.8.	<i>M. haemophilum</i>	273
3.4.	The dextrorotatory methyl-branched fatty acids	273
4.	DIM biosynthesis	273
4.1.	Early chemical approaches	274
4.1.1.	Studies on phthiocerol biosynthesis	274
4.1.2.	Studies on mycocerosic acid biosynthesis	274
4.1.3.	Studies on mycoside biosynthesis	275
4.2.	Genetic and biochemical approaches	275
4.2.1.	Mycocerosic acid synthase	276
4.2.2.	The DIM glycol linear PKS system	278
4.3.	Tailoring steps	282
4.3.1.	The DIM glycol C3 ketoreductase	282
4.3.2.	DIM glycol C3-O-methyltransferase	283
4.3.3.	Phenolic DIM <i>p</i> -glycosylation	283
4.4.	The DIM wax synthase	284
4.4.1.	PapA5 activity and crystal structure	284
4.5.	DIM transporters	286
4.6.	Other genes implicated in DIM synthesis	286
4.7.	Sequence and/or timing of events	288
4.8.	Outstanding issues and further insights	289
4.8.1.	Variations in glycol stereoconfiguration	289
4.8.2.	Variations in the DIM glycol C4 center and acyl chain configurations	292
5.	Physiological functions	293
5.1.	Oxidative stress	294
5.2.	Immune responses	294

Download English Version:

<https://daneshyari.com/en/article/10842974>

Download Persian Version:

<https://daneshyari.com/article/10842974>

[Daneshyari.com](https://daneshyari.com)