Mycobacterium tuberculosis biological processes

Jassal, B., Koile, I., Pardo, AM., Stephan, R., Warner, D.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

03/05/2019
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 68

This document contains 6 pathways (see Table of Contents)
Mycobacterium tuberculosis biological processes

Stable identifier: R-MTU-870392

*Mycobacterium tuberculosis* H37Rv is the laboratory strain most widely used of the pathogen *M. tuberculosis*, an actinobacterium that carries many properties of its family to the extreme. It is not only interesting as one of the top three bacterial killers, with one third of the world having a dormant infection, but also as a model for other mycobacteria regarding the processes of slow growing, dormancy, host interaction, very long chain fatty acid biosynthesis, outer cell wall assembly, as well as sulfolipid, siderophore, and mycothiol biosynthesis.

*M. tuberculosis* produces mycolic and phthioceranic acids, the fatty acids with the longest carbon atom chains known. With up to 20 hours, it has the longest reproduction time in mycobacteria. In human macrophages in dormant state, it spends decades without reproduction. Consequently, to fully investigate these properties new methods will have to be invented.

While the treatment of an *M. tuberculosis* infection appears standard in Western countries, it still involves six months of a regime of three antibiotics that have been known for a long time. Not unexpectedly, acceptance and adherence to such a prolonged therapy are less than desired, and this contributes to spontaneous resistance from an already higher than average mutation rate of *M. tuberculosis* due to replication errors. Fueled by the HIV advance, strains of this bacterium are on the rise with resistance to all used antibiotics. For this reason, *M. tuberculosis* is the testbed of new antibiotics development, and it offers the opportunity of many unique and essential biochemical pathways. (Camus et al. 2002; Leibert and Rom, 2010)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-06-08</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2010-11-25</td>
<td>Reviewed</td>
<td>Warner, D.</td>
</tr>
<tr>
<td>2011-02-16</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Mycothiol metabolism

Location: Mycobacterium tuberculosis biological processes

Stable identifier: R-MTU-870331

Mycothiol (MSH), a conjugate of glucosamine, cysteine and inositol, is the Actinobacteria equivalent of glutathione. It serves as a pool for both the unstable cysteine and reduction equivalents. Mycothiol takes part in enzymatic reactions including detoxification of electrophilic compounds, inactivation of reactive oxygen and nitrogen species, reductions, and isomerizations.

*M. smegmatis* mutants devoid of MSH are sensitive to oxidative and nitrosative stress, and antibiotics. In *M. tuberculosis*, however, mycothiol synthesis is essential, no null mutants are known. Results from MshD mutants, which have about 1 per cent of MSH, show the importance of mycothiol in environments where antimicrobial factors, including reactive oxygen and reactive nitrogen intermediates, are formed, such as within macrophages (Newton et al, 2008; Rawat and Av-Gay, 2007)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-06-07</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2010-11-25</td>
<td>Reviewed</td>
<td>Warner, D.</td>
</tr>
<tr>
<td>2011-02-16</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Trehalose biosynthesis

**Location:** Mycobacterium tuberculosis biological processes

**Stable identifier:** R-MTU-868688

**Compartments:** cytosol

The non-reducing disaccharide trehalose is found in insects, plants, and microorganisms. In bacteria, it is a storage energy source and is essential for the survival of many stress conditions. In mycobacteria, trehalose is also part of the cell wall and of the 'cord factor' which is important for entry into the host (Elbein et al, 2003; Tropis et al, 2005; Jain & Roy, 2009)

*M. tuberculosis* has three ways to synthesize trehalose: from UDP-glucose and glucose phosphate (the OtsAB pathway), from maltose (the TreS pathway), and from glycogen (TreYZ pathway). The OtsAB pathway was shown to be essential for the organism. It is not known, however, whether or not the essentiality of trehalose for the mycobacterial growth is directly connected to the biosynthesis of cell wall mycolates (De Smet et al, 2000; Murphy et al, 2005)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-29</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2010-11-25</td>
<td>Reviewed</td>
<td>Warner, D.</td>
</tr>
<tr>
<td>2011-02-16</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Sulfur compound metabolism

Location: Mycobacterium tuberculosis biological processes

Stable identifier: R-MTU-936621

Unique small sulfur compounds, as well as unique pathways to sulfur amino acids are known in Mycobacteria. Sulfoglycolipids and mycothiols are an important part of the hardy pathogen nature of these organisms. Their pathways make interesting targets for drug designers (Bhave et al, 2007).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-06-17</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2010-11-25</td>
<td>Reviewed</td>
<td>Warner, D.</td>
</tr>
<tr>
<td>2011-02-16</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
The shikimate pathway leads to the biosynthesis of chorismate, which, in mycobacteria, is a precursor of aromatic amino acids, naphthoquinones, menaquinones and siderophores. The enzymes of this pathway are attractive pharmaceutical targets, as the pathway is absent from mammals, and there are no redundancies in it (Herrmann and Weaver, 1999).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-09-13</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2010-11-25</td>
<td>Reviewed</td>
<td>Warner, D.</td>
</tr>
<tr>
<td>2011-02-16</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Dimycocersyl phthiocerol biosynthesis

Location: Mycobacterium tuberculosis biological processes

Stable identifier: R-MTU-9635470

The survival of Mtb, depends on its ability to invade the host, replicate, and transmit infection. At its initial peripheral infection Mtb infects macrophages, and part of the immune evasion is accomplished by using cell-surface-associated phthiocerol dimycoceroserate (PDIM) (Siegrist M S & Bertozzi C R, 2013). In nature, fatty acids must be activated before they can be assimilated into various metabolic pathways. The universal mechanism of n-fatty acid activation involves conversion of fatty acids by a family of omnipresent fatty acyl-CoA ligases (FACLs). The biosynthesis of PDIM, an alternate mechanism of fatty acid activation, catalyzed by fatty acyl-AMP ligases (FAALs) was established in Mtb (Arora P, 2008).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-02-13</td>
<td>Authored, Edited</td>
<td>Pardo, AM., Koile, I.</td>
</tr>
<tr>
<td>2019-02-13</td>
<td>Reviewed</td>
<td>Stephan, R.</td>
</tr>
</tbody>
</table>
# Table of Contents

Introduction .......................... 1
- Mycobacterium tuberculosis biological processes .......................... 2
  - Mycothiol metabolism .............................................. 3
  - Trehalose biosynthesis .............................................. 4
  - Sulfur compound metabolism ....................................... 5
  - Chorismate via Shikimate Pathway .................................. 6
  - Dimycocersyl phthiocerol biosynthesis .................................. 7

Table of Contents .................................. 8