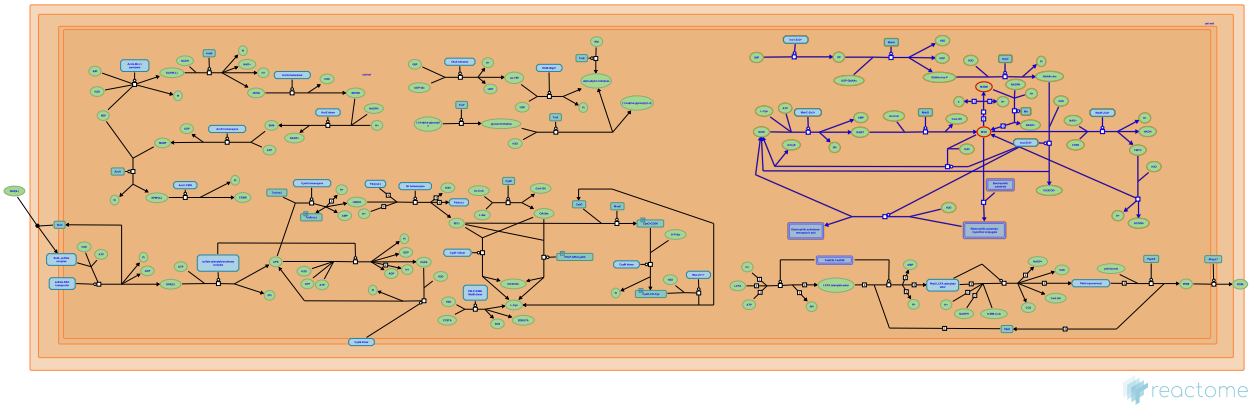
Mycothiol metabolism



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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.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

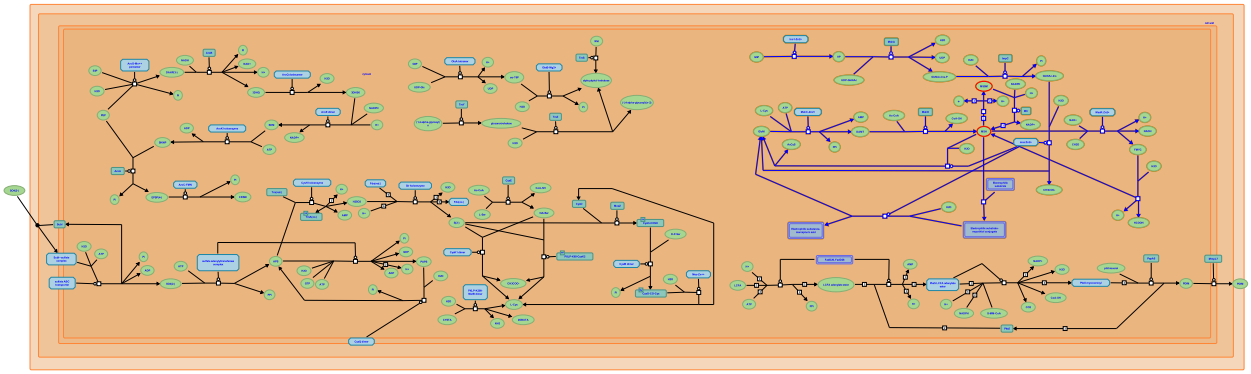
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Mycothiol metabolism ↗

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

Newton, GL., Buchmeier, N., Fahey, RC. (2008). Biosynthesis and functions of mycothiol, the unique protective thiol of Actinobacteria. *Microbiol Mol Biol Rev, 72*, 471-94. ↗

Rawat, M., Av-Gay, Y. (2007). Mycothiol-dependent proteins in actinomycetes. *FEMS Microbiol Rev, 31*, 278-92. ↗

Editions

2010-06-07	Authored	Stephan, R.
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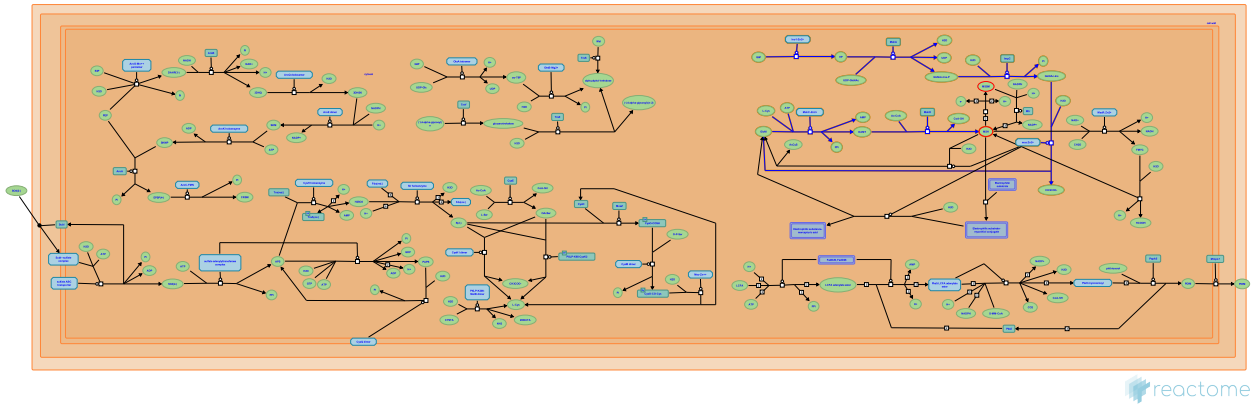
Mycothiol biosynthesis ↗

Location: Mycothiol metabolism

Stable identifier: R-MTU-879299

Compartments: cytosol



Biosynthesis of mycothiol starts from glucose-6-phosphate and proceeds directly to *myo*-inositol-1-phosphate, contrary to phosphatidylinositol synthesis. One of the following steps, the removal of the phosphate group, is catalyzed by a still unknown phosphatase. The pathway is essential in *M. tuberculosis* (Newton et al, 2006; Sareen et al., 2003)

Literature references

Sareen, D., Newton, GL., Fahey, RC., Buchmeier, NA. (2003). Mycothiol is essential for growth of Mycobacterium tuberculosis Erdman. *J Bacteriol, 185*, 6736-40. ↗

Newton, GL., Ta, P., Bzymek, KP., Fahey, RC. (2006). Biochemistry of the initial steps of mycothiol biosynthesis. *J Biol Chem, 281*, 33910-20. ↗

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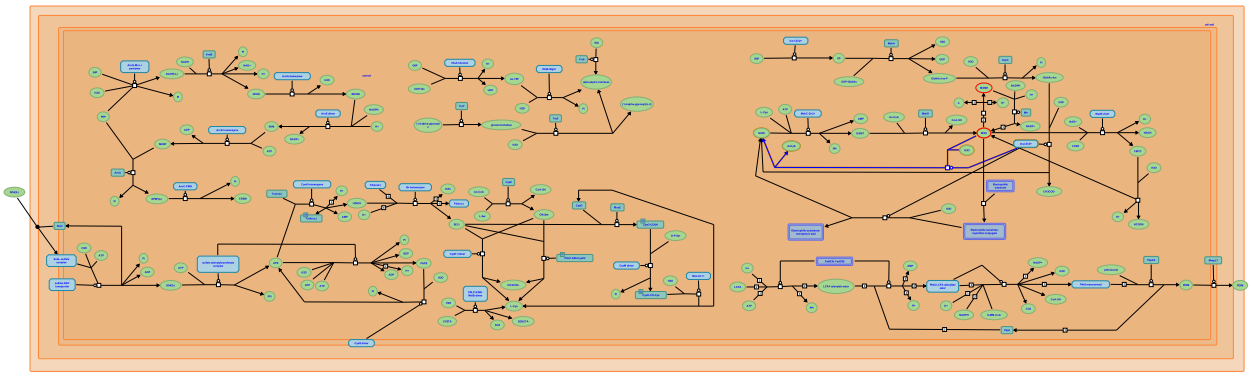
Mycothiol catabolism ↗

Location: Mycothiol metabolism

Stable identifier: R-MTU-879325



Mycothiol and its adducts that result from detoxification can be readily cleaved into smaller molecules. The mycothiol pool therefore serves as storage for unstable cysteine and sugars. (Rawat and Av-Gay, 2007; Newton et al, 2008)

Literature references

Rawat, M., Av-Gay, Y. (2007). Mycothiol-dependent proteins in actinomycetes. *FEMS Microbiol Rev, 31*, 278-92. ↗

Newton, GL., Buchmeier, N., Fahey, RC. (2008). Biosynthesis and functions of mycothiol, the unique protective thiol of Actinobacteria. *Microbiol Mol Biol Rev, 72*, 471-94. ↗

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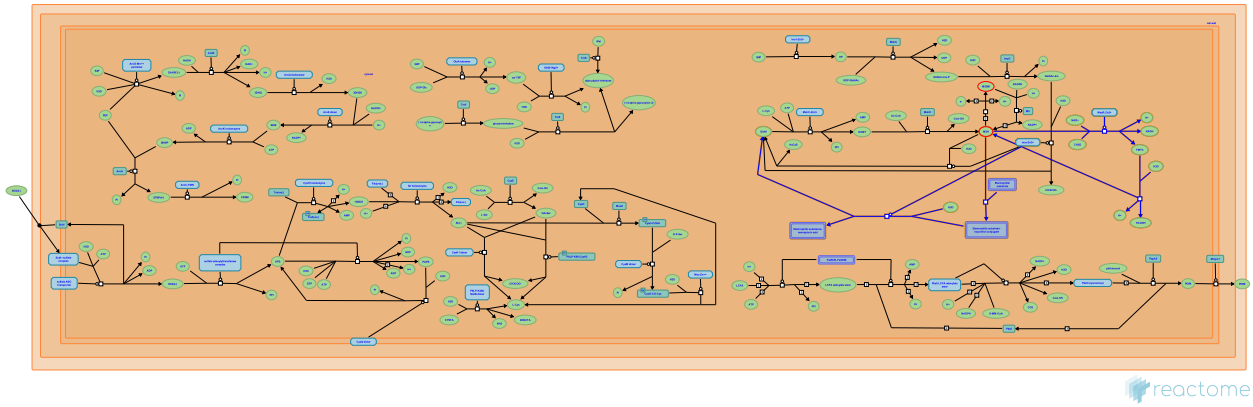
Mycothiol-dependent detoxification ↗

Location: Mycothiol metabolism

Stable identifier: R-MTU-879235

Compartments: cytosol



In analogy to glutathione, mycothiol is part of the detoxification machinery of the *M. tuberculosis* cell. The biotransformation of electrophilic toxins consists of creating an adduct with mycothiol, its cleavage into a "mercapturic acid" and glucosaminyl-inositol (with which mycothiol is recycled), and transport of the mercapturic acid through the membrane. The protein(s) catalyzing the transport are still unidentified.

Further molecules that are changed to less dangerous entities with the help of mycothiol are formaldehyde and the nitrosyl radical (Rawat and Av-Gay, 2007; Newton et al, 2008).

Literature references

Newton, GL., Buchmeier, N., Fahey, RC. (2008). Biosynthesis and functions of mycothiol, the unique protective thiol of Actinobacteria. *Microbiol Mol Biol Rev, 72*, 471-94. ↗

Rawat, M., Av-Gay, Y. (2007). Mycothiol-dependent proteins in actinomycetes. *FEMS Microbiol Rev, 31*, 278-92. ↗

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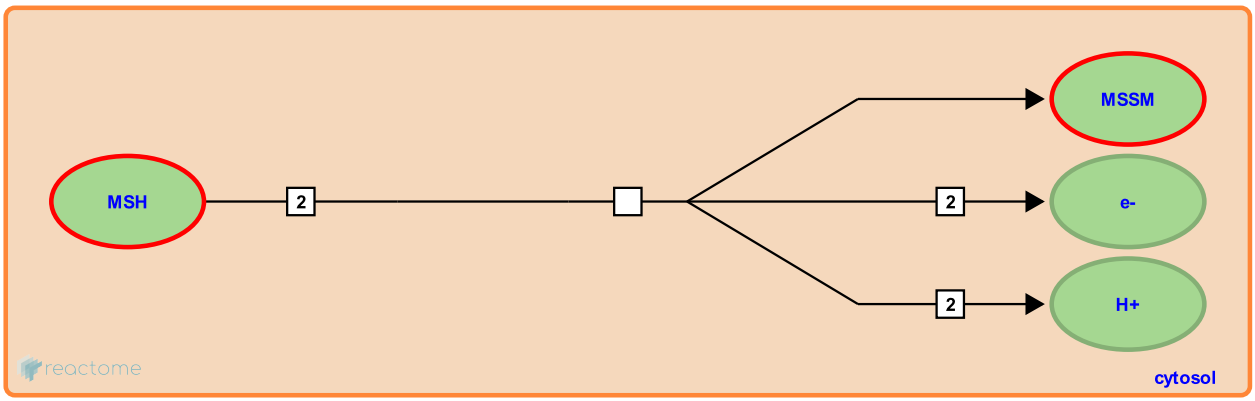
mycothiol is oxidized to mycothione ↗

Location: Mycothiol metabolism

Stable identifier: R-MTU-879266

Type: transition

Compartments: cytosol



The oxidation of mycothiol provides electrons for the maintenance of cell redox homeostasis. In which reactions exactly those electrons are used is unknown. A possibility is the existence of MSH-dependent peroxidases. (Rawat and Av-Gay, 2007)

Literature references

Rawat, M., Av-Gay, Y. (2007). Mycothiol-dependent proteins in actinomycetes. *FEMS Microbiol Rev, 31*, 278-92. ↗

Editions

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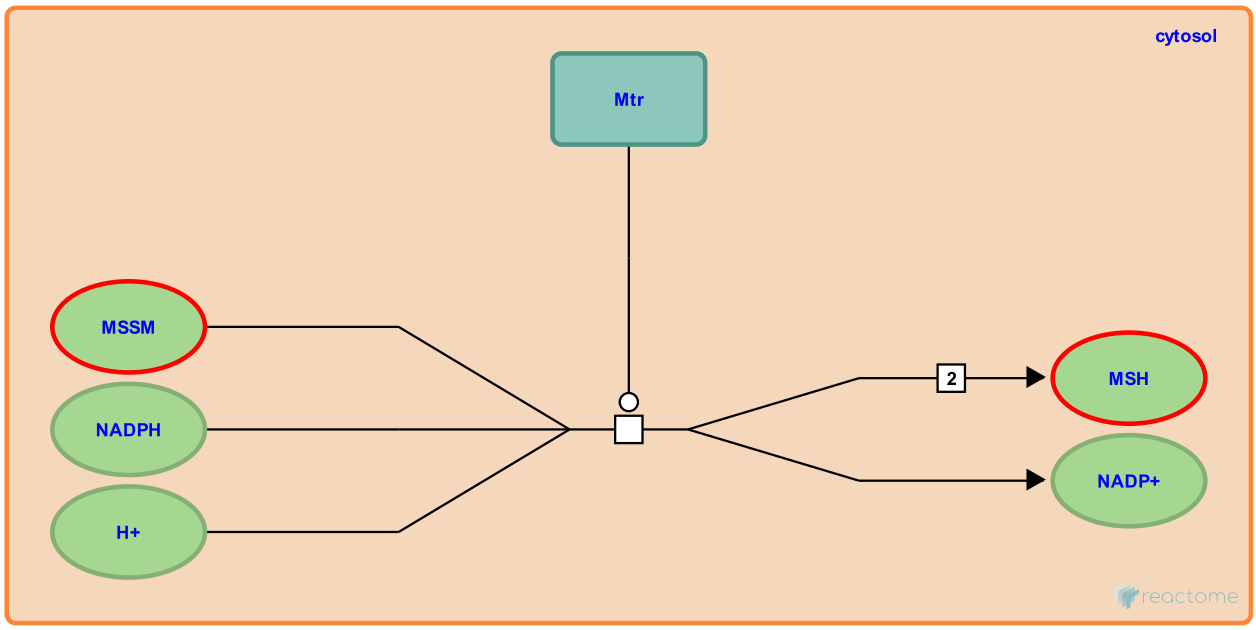
mycothione is reduced to mycothiol ↗

Location: Mycothiol metabolism

Stable identifier: R-MTU-879322

Type: transition

Compartments: cytosol



Mycothiol is recycled using a reduction equivalent (NADPH/H+) and the help of the mycothione reductase enzyme. Although a *mtr* null mutant was obtained by McAdam and coworkers in *M. tuberculosis*, another study by Sassetti suggests the enzyme is essential in the H37Rv strain. It appears possible that thioredoxin reductases can provide some enzymatic rest activity. (Patel and Blanchard, 1999; Rawat and Av-Gay, 2007)

Literature references

Patel, MP., Blanchard, JS. (1999). Expression, purification, and characterization of Mycobacterium tuberculosis mycothione reductase. *Biochemistry, 38*, 11827-33. ↗

Rawat, M., Av-Gay, Y. (2007). Mycothiol-dependent proteins in actinomycetes. *FEMS Microbiol Rev, 31*, 278-92. ↗

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