

Antimicrobial action and antimicrobial

resistance in Mtb



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the <u>Reactome Textbook</u>.

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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

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This document contains 1 pathway and 3 reactions (see Table of Contents)

Antimicrobial action and antimicrobial resistance in Mtb 🛪

Stable identifier: R-HSA-9639775

Diseases: tuberculosis



Antimicrobial compounds kill microorganisms or inhibit their growth, either in the host, outside on the skin (antiseptics), or in the environment (disinfectants). In the host they are named after the target symbiont, for example antibiotics, antifungals, and antiparasitics. It suffices to permanently stop an essential pathway in the symbiont to kill it. Broad spectrum antimicrobials usually target a conserved pathway like protein synthesis or cell wall construction, in order to affect a whole taxonomic group (Arenz & Wilson 2016, Barry et al. 2007, Green 2002).

Resistance of microorganisms (bacteria, viruses, parasites) to antimicrobials is one of the most important public health problems. Many mechanisms exist, and they are either acquired by mutation, by horizontal gene transfer, or are already intrinsic to the organism. The main mechanisms are modification of the antimicrobial, or its removal from the place of action, modification of its binding partner in the affected pathway, or usage of a back-up pathway. Participation of the organism in a consortium (like in biofilms) enables additional resistance mechanisms (Aminov & Mackie 2007, Peterson & Kaur 2018, van Acker et al. 2014, van Acker & Coenye 2016).

The events described here are specific to Mtb infection.

Literature references

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RNAP transcribes Mtb RNA polyanion *オ*

Location: Antimicrobial action and antimicrobial resistance in Mtb

Stable identifier: R-HSA-9697085

Type: transition

Compartments: cytosol

Diseases: tuberculosis



The Mtb RNA polymerase core complex consists of 5 subunits $(2\alpha:\beta:\beta':\omega)$ and elongates transcribed RNA polyanion by the step-wise attachment of ribonucleoside triphosphates, according to the DNA template (Hu et al. 2012).

Literature references

Morichaud, Z., Hu, Y., Brodolin, K., Leonetti, JP., Chen, S. (2012). Mycobacterium tuberculosis RbpA protein is a new type of transcriptional activator that stabilizes the σ A-containing RNA polymerase holoenzyme. *Nucleic Acids Res.*, 40, 6547-57. *¬*

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Rifampicin binds Mtb RNAP 7

Location: Antimicrobial action and antimicrobial resistance in Mtb

Stable identifier: R-HSA-9697086

Type: binding

Compartments: cytosol

Diseases: tuberculosis



The core of the bacterial RNA polymerase (RNAP) consists of 5 subunits and is highly conserved across the kingdom. The antimycobacterial drug rifampicin binds to the rpoB subunit and inhibits transcription (Wehrli et al. 1968, Heil & Zillig 1970).

Literature references

Knüsel, F., Staehelin, M., Wehrli, W., Schmid, K. (1968). Interaction of rifamycin with bacterial RNA polymerase. Proc. Natl. Acad. Sci. U.S.A., 61, 667-73. ↗

Zillig, W., Heil, A. (1970). Reconstitution of bacterial DNA-dependent RNA-polymerase from isolated subunits as a tool for the elucidation of the role of the subunits in transcription. *FEBS Lett.*, *11*, 165-168. 7

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Defective rpoB in Mtb RNAP transcribes RNA polyanion 🛪

Location: Antimicrobial action and antimicrobial resistance in Mtb

Stable identifier: R-HSA-9697084

Type: transition

Compartments: cytosol

Diseases: tuberculosis



Mutations in several regions of bacterial RNA polymerase (RNAP) subunit rpoB disable binding of rifampicin, and recover enzymatic activity (Jin & Gross 1988, Telenti et al. 1993). The most clinically prevalent mutation associated with rifamycin resistance is S456L which accounts for 40-75% of all rifamycin resistant mutants (Stefan et al. 2018).

Literature references

- Jin, DJ., Gross, CA. (1988). Mapping and sequencing of mutations in the Escherichia coli rpoB gene that lead to rifampicin resistance. J. Mol. Biol., 202, 45-58. 7
- Marchesi, F., Imboden, P., Telenti, A., Matter, L., Colston, MJ., Cole, S. et al. (1993). Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. *Lancet*, 341, 647-50. 7
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