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Mycobacterium drug responses

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Abstract

Transcriptional analysis has been used to probe the biology of mycobacterial responses to antibiotics and to suggest new drug targets.

Significance and context

Mycobacterium tuberculosis is a bacterium of profound clinical interest, especially given the recent emergence of strains showing resistance to multiple drugs. The organism's complete genome has been sequenced, allowing the study of its complete transcriptional response to antibiotics. The response to small molecules in this, or any other, organism is of interest for a number of reasons: 'fingerprinting' responses to drugs may aid the identification of the mechanism of action of other molecules with interesting biological activities; the pattern of regulatory changes should reveal information about the basic biology of the organism; and genes for which regulatory changes are observed in response to a drug may themselves be promising drug targets. Wilson *et al.* use a cDNA microarray that includes "nearly every" predicted open reading frame from the *M. tuberculosis* genome to examine changes induced by isoniazid (INH) and ethionamide. These two medically important drugs block the synthesis of a component of the lipid barrier that coats the outside of the bacterium.

Key results

INH induces a significant increase in the transcription of 14 genes. These include a number of genes known, or indicated by homology, to be involved in fatty acid biosynthesis, a gene for a transporter protein of unknown substrate, and genes for four proteins of unknown function. The authors note that the transport protein, which is already known to be correlated with pathogenicity, might represent a particularly promising new candidate drug target. The same genes are upregulated in an INH-resistant strain in response to ethionamide, whereas other compounds toxic to the bacterium provoke different response profiles. The authors also observe similarities in the patterns of upregulation of a subset of the biosynthetic genes that are clustered in an operon-like fashion in the genome, and suggest roles for other genes on the basis of differences in the time-course of their induction.

Links

Information about the *M. tuberculosis* H37Rv genome project, along with some relevant links, is maintained at the Sanger Centre.

Reporter's comments

The idea that transcriptional arrays might be useful in drug target identification has been postulated for a while, and this paper may come to be viewed as an important proof-of-principle towards this end. Wilson *et al.* also highlight the ability of whole-genome analysis to bring otherwise obscure genes into the spotlight of potential therapeutic interest.

Table of links

Proceedings of the National Academy of Sciences of the United States of America

M. tuberculosis H37Rv genome project

References

1. Wilson M, DeRisi J, Kristensen H-H, Imboden P, Rane S, Brown PO, Schoolnik GK: Exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization. Proc Natl Acad Sci U S A. 1999, 96: 12833-12838. 0027-8424