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Acid test for *Mycobacterium tuberculosis*

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Summary

New *Mycobacterium tuberculosis* genes have been discovered that may have a role in the bacterium's survival in human phagosomes

Significance and context

The airborne, rod-shaped, Gram-positive pathogenic bacterium *Mycobacterium tuberculosis* causes human tuberculosis (TB), one of the world's most pressing health problems. According to the World Health Organization, every year more than 1.5 million TB cases occur in sub-Saharan Africa, nearly 3 million in Southeast Asia, and over 250,000 in Eastern Europe. AIDS with coexistent mycobacterial infection also directs our attention to TB in western cities. Because the symptoms of TB are easily confused with those of other diseases, it can be difficult to diagnose.

One of the first steps in human infection with *M. tuberculosis* is phagocytosis of bacteria by macrophages in the lung. Phagosomes that contain living mycobacteria rapidly acidify, reaching a pH of less than 6, rising again over several hours to 6.5. This is in contrast to phagosomes containing dead bacteria in which the pH drops to 5.5. These results suggest that living bacteria may actively inhibit phagosome acidification in a process initiated by sensing low pH. Using microarray analysis, Fisher *et al*. isolated a set of *M. tuberculosis* genes whose expression is altered after an acid shock.

Key results

In the microarray analyses, the chip used contained all open reading frames (ORFs) annotated in the *M. tuberculosis* H37Rv genome sequence. RNA of cultured *M. tuberculosis*, grown and subjected to an acid shock of pH 5.5 for 15 or 30 minutes, was prepared, and fluorescently labeled cDNAs were produced from this RNA by reverse transcription. The microarray analyses revealed a set of 23 ORFs whose expression was upregulated by at least 1.5-fold, with one group of genes having more than 3-fold greater expression. The latter group encodes a probable monooxygenase, a probable acetyl hydrolase, a short-chain alcohol dehydrogenase, an acyl-CoA synthase, and some conserved hypothetical proteins, most probably involved in nonribosomal peptide/polyketide synthesis. Other genes whose expression was induced by between 1.5- and 2-fold after a 15 minute acid shock encode, for example, an isocitrate lyase, a 3-hydroxyacyl-CoA dehydrogenase, and an alkyl hydroperoxide reductase. In addition, the

expression of 58 ORFs was repressed after acid shock. These include genes encoding, for instance, a β-ketoacyl-ACP synthase, a transcriptional regulator, possible membrane proteins, and phosphate permease. The expression results were confirmed by real-time PCR. The gene for isocitrate lyase (an enzyme involved in the glyoxylate pathway), was, for instance, induced by a factor of 2-2.5 after an acid shock of 15 or 30 minutes, but was induced to significantly higher levels after acid treatment for 18 hours. This suggests that low pH may stimulate fatty-acid metabolism, which may be required for survival under these new environmental conditions.

Links

The genome sequence of *Mycobacterium tuberculosis* H37Rv and links to other informative sites can be accessed at The Sanger Centre.

Reporter's comments

Inhibition of phagosomal acidification by live *M. tuberculosis* within phagosomes is one of the first features of *M. tuberculosis* infection in humans. Fisher *et al*. isolated a set of genes, the expression of which is altered on acid shock. Future work should be focused on the biochemical and functional analysis of these *M. tuberculosis* genes as this will contribute to our understanding of the initial steps leading to disease. Mutants should be constructed to test the importance of those genes for survival under acidifying conditions. New drugs that block the mechanisms that *M. tuberculosis* uses to inhibit phagosomal acidification, used alone or in combination with drugs that affect mycobacterial cell wall synthesis, might be effective treatments for tuberculosis.

Table of links

Journal of Bacteriology

Mycobacterium tuberculosis

References

1. Fisher MA, Plikaytis BB, Shinnick TM: Microarray analysis of the *Mycobacterium tuberculosis* transcriptional response to the acidic conditions found in phagosomes. J Bacteriol. 2002, 184: 4025-4032.