Potential treatment for TB solves puzzle

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Scientists have uncovered a new target for the potential treatment of TB, finally resolving a long-running debate about how the bacterial cell wall is built. The research, published in the July issue of *Microbiology* reveals several molecules that could be developed into drugs to treat tuberculosis.

Multi drug-resistant strains of Mycobacterium tuberculosis, the bacterium that causes TB, sparked concern but the recent emergence of extensively drug-resistant strains (XDR-TB) means the search for new treatments is imperative.

Unlike human cells, bacteria have cell walls. Molecules called mycolic acids form a vital part of these walls. To produce them, bacteria carry out several processes but until recently, scientists were unsure of the genes that control each step. One vital step is dehydration - the removal of a water molecule to lengthen the acid chain. Researchers from the University of Birmingham have shown that the gene Rv0636 controls this step, which provides new avenues for the development of treatments for TB.

"FAS-II is a group of enzymes that work together to carry out dehydration," said Professor Gurdyal Besra from the University of Birmingham. "We know that the molecules NAS-21 and NAS-91 can stop these enzymes from building cell walls, so we looked at their effect on Mycobacteria. We also wanted to find out if one of the enzymes is coded for by the gene Rv0636."

Professor Besra and his colleagues made modifications to NAS-21 and NAS-91, making several analogues based on the original molecules. They then tested these analogues to see if they stopped the enzymes from working. "Both series of compounds demonstrated activity against the FAS-II enzymes alone," said Professor Besra. "When we tested them against live bacterial cells we noticed that some of the analogues stopped the cells from building mycolic acids, which effectively killed them.

"We also tested them on bacteria that were overexpressing Rv0636, which meant they were producing extra enzymes. These cells were resistant to NAS-21 and NAS-91, suggesting that the gene Rv0636 does code for an enzyme in the FAS-II complex," said Professor Besra. "So we have solved the mystery.

The researchers have also identified a new class of compounds that could be developed into successful treatments for tuberculosis that are urgently required in the future. "The emergence of drug-resistant strains of Mycobacterium tuberculosis has highlighted the need for new TB drugs. We hope our discovery will lead to a new rationale for the design of treatments," said Professor Besra.

Source: Society for General Microbiology