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Cancer drug target is promising lead for new TB treatments

Posted on Wednesday 17th November 2010

A key enzyme in Mycobacterium tuberculosis that enables the microbe to reproduce rapidly could be a golden target for new drugs against tuberculosis (TB), according to a study published in Microbiology on 17 November by scientists at the University of Birmingham.

The human equivalent of this enzyme has been targeted in some cancer treatments as well as in immunosuppressive chemotherapies. Scientists at the University's School of Biosciences have now shown that inhibiting the same enzyme in M. tuberculosis effectively kills the bacterial cells.

The enzyme called IMPDH is crucial for the survival of both human and bacterial cells. It is involved in the first stage of producing guanine nucleotides – the raw materials needed for DNA synthesis - as well as many other housekeeping processes that keep the cell alive and functioning.

The researchers identified the three genes in M. tuberculosis that encode IMPDH and then screened a library of 16 compounds that were likely to impede its function to some extent. Of the 16 diphenyl urea (DPU) compounds, 3 were able to inhibit IMPDH by more than 90%, killing M. tuberculosis cells.

Project leader Professor Gurdyal Besra from the University of Birmingham's School of Biosciences explained why IMPDH is a promising target to tackle TB. 'IMPDH is essential for cells to proliferate rapidly, which is one of the characteristics of microbial infection as well as human cancers. IMPDH has been used as a target in some anti-cancer drugs, as blocking the enzyme can prevent proliferation of the cell and induce cell death. Our findings show that inhibiting the bacterial version of IMPDH is a strategy that could be exploited for anti-TB drugs,' he said. 'The DPU compounds we tested have selective activity against Mycobacterium species meaning that any future drugs based on these would be specific and would not affect human cells.'

Nine million people are newly diagnosed with TB each year with increasing incidences of multi-drug resistant (MDR)-TB and extensively drug resistant (XDR)-TB. 'In the face of growing resistance to current therapies we desperately need new treatments for TB that are safe and effective,' stressed Professor Besra. 'We are tapping the potential of a so far unexploited target which could lead to the synthesis of a novel anti-tubercular drug and our findings, so far, are extremely encouraging,' he said.

Notes for Editors

Ref: mic/2010/042549
DOI: 10.1099/mic.0.042549-0

1. Professor Besra's paper, "Identification of novel diphenyl urea inhibitors of Mt-Guab2 active against M. tuberculosis" will be published in Microbiology and will appear online ahead of print on 17 November 2010. The original paper is available on request.

2. The Society for General Microbiology is the largest microbiology society in Europe, and has 5000 members worldwide. The Society provides a common meeting ground for scientists working in research and in fields with applications in microbiology including medicine, veterinary medicine, pharmaceuticals, industry, agriculture, food, the environment and education.

3. The Society publishes four distinguished journals of international repute: International Journal of Systematic and Evolutionary Microbiology, Journal of General Virology, Microbiology and Journal of Medical Microbiology (all monthly). The journals contain high-quality research papers and topical review articles. The online versions are published with the assistance of HighWire Press, with many added features and functions to aid the reader, and can be accessed via www.sgm.ac.uk/pubs.

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