MedicalXpress

TB discovery paves the way for drugs that prevent lung destruction

April 25 2011

Scientists have identified a key enzyme responsible for destroying lung tissue in tuberculosis (TB), they report today in the *Journal of Clinical Investigation*. Drugs that inhibit this enzyme are already available, meaning that the finding could lead quickly to new treatments.

TB is caused by the bacterium Mycobacterium tuberculosis. The infection destroys patients' lung tissue, causing them to cough up the bacteria, which then spread through the air and can be inhaled by others. The mechanism behind this lung damage is poorly understood, and no treatments currently used prevent it from occurring. Patients require at least six months of antibiotic treatment, but drug-resistant strains of the bacterium are becoming increasingly common.

The new research shows that in patients with TB, there is an increase in levels of an enzyme called MMP-1 in their lungs. When the researchers infected human immune cells with TB in the lab, they found that the cells greatly increased production of this enzyme.

Since the mouse version of MMP-1 is not expressed in the lung, the researchers developed a transgenic mouse with human MMP-1 to investigate whether the enzyme causes lung damage in TB. When these mice were infected with TB, MMP-1 levels increased significantly and the infection led to lung damage similar to that seen in humans with TB.

The scientists also found that a drug proven to be safe in humans was effective at suppressing MMP-1 activity driven by TB infection in

human cells.

The findings suggest that similar drugs might prevent lung damage in TB patients and help limit the spread of the disease.

The study was done by researchers at Imperial College London with collaborators at Columbia University in New York and the University of East Anglia, and it was supported by the National Institute for Health Research (who funded the work on human cells), the Scadding Morriston Davies Travel Fellowship and the US National Institutes of Health.

Dr Paul Elkington, from the Department of Infectious Diseases and Immunity at Imperial College London, said:

"A third of the world's population is infected with tuberculosis, and almost 2 million people die from the disease every year.

"Standard TB treatment has remained unchanged for 35 years, and no current treatments prevent the lung destruction that TB causes. These findings suggest that drugs available now might be able to reduce deaths from TB."

Many MMP inhibitor drugs were developed in the 1990s because they showed initial promise for treating cancer. The researchers now plan to carry out further studies to see whether these drugs can prevent lung destruction in patients with TB.

Professor Jon Friedland, senior author of the study from the Department of Infectious Diseases and Immunity at Imperial College London, said:

"Until now, we haven't had a convincing explanation of how lung destruction is caused by TB. We hypothesised that protease enzymes

must be involved, since nothing else could break down the strong collagen fibres that make up the scaffold of the lung. The results of this study provide strong evidence to support that idea."

Dr Elkington and his colleagues first put forward their hypothesis that MMP enzymes play a key role in TB in a review article published earlier this year in the journal *Science Translational Medicine*.

More information: P. Elkington et al. "Matrix metalloproteinase-1 causes immunopathology in human tuberculosis and transgenic mice" *Journal of Clinical Investigation,* published online 25 April 2011

P. Elkington et al. "Tuberculosis Immunopathology: The Neglected Role of Extracellular Matrix Destruction" Sci Transl Med, 23 February 2011: Vol. 3, Issue 71, p. 71ps6 DOI: 10.1126/scitranslmed.3001847

Provided by Imperial College London