

Antifungal drug kills TB bug

Scientists hoping to find new treatments for one of the world's most deadly infectious diseases say drugs used to treat common fungal infections may provide the answer.

Tuberculosis, or TB, is a highly contagious disease of the lungs that was thought to have been virtually eliminated by the 1960s, but is now resurgent and kills nearly two million people worldwide every year. New infections are occurring at a rate of one per second.

Of equal concern is the dramatic rise in the incidence of new strains of TB that are resistant to traditional antibiotics. As a result, the World Health Organisation, the Bill Gates Foundation and the European Union have all launched initiatives to tackle the problem.

Now, biologists at The University of Manchester have shown that chemicals called azoles – the active agent in many antifungal drugs – kill the TB bacteria, and could be effective in tackling the emerging drug-resistant strains.

"TB is back with a vengeance with a third of the world's population currently infected," said Professor Andrew Munro, who led the research in Manchester's Faculty of Life Sciences.

"The bacterium survives the initial attack by the body's immune system and then lies dormant, usually in the lungs, waiting for any sign of weakness, such as a secondary infection. Its resurgence over the last 20 years has been closely associated with the AIDS epidemic, which destroys the human immune system and has allowed TB to get a grip once again."

London is the TB capital of Europe, although most large cities here and in North America have seen rapid increases in the number of TB infections. However, the problem is most acute in Africa and Asia where HIV/AIDS is also most prolific and a shortage of traditional TB medicines and problems with patient compliance has led to the emergence of drug-resistant strains of the disease.

"There were only ever a limited number of drugs that were effective against TB anyway," said Professor Munro, who is based in the University's £38 million Manchester Interdisciplinary Biocentre.

"People in places like India or Africa would be given antibiotics but often not in sufficient quantities to kill the bug completely; this is how resistant strains develop and these regions have become huge breeding grounds for these 'super strains'."

Funded by the EU's NM4TB (new medicines for tuberculosis) project, the Manchester team set about trying to find alternative drugs that could be used to treat these multi-drug resistant varieties of TB, known as MDR-TB.

"We knew that the TB bacterium was a clever organism, able to evade the human immune system and to survive long-term, sometimes unnoticed, in the body. We also realised that these peculiar features of the TB bacterium must mean that there are 'unusual' aspects of its composition and biochemistry that set it apart from most other bacteria and that could provide new targets for antibiotic drugs.

"When we began looking at the bug and its DNA content in more detail, we noticed it had some unusual characteristics. In particular, we noted the presence of a very large number of enzymes called P450s, which are usually associated with more complex organisms.

"In humans, P450s oxygenate molecules in the body and are essential for steroid metabolism; they are also prevalent in the liver where they help us detoxify and dispose of countless chemicals and toxins that enter

our system. Most bacteria have few, if any, P450s but we discovered that the TB bacterium has 20 different types."

Even more exciting for the team was the knowledge that existing anti-fungal drugs already target P450s as a way to treat, for example, systemic and more superficial infections caused by fungi such as *Candida albicans* (the causative agent of thrush).

"The class of drugs called azoles are able to kill off fungal infections by blocking the actions of one of its P450s that is essential for maintaining the cell structure," said Professor Munro. "We were able to show in laboratory experiments that various types of these azole drugs were also very good at killing the TB bacterium, and also that they bind very tightly to a number of the TB P450 enzymes that we have isolated – inactivating their function."

Source: University of Manchester

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