Cold war - Fighting the threat of latent TB (w/ Podcast)

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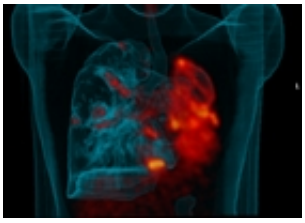

A combined FDG-PET/CT scan of latent TB infection in human lungs. Credit: NIH/NIAID

(PhysOrg.com) -- Scientists are making breakthroughs in studying the latent form of Mycobacterium tuberculosis. This work could revolutionise the treatment of TB.

One-third of the world's population is infected with 'Mycobacterium tuberculosis'. Our limited understanding and inability to effectively treat the latent form of the bacteria threatens efforts to eradicate the disease. But scientists are now making breakthroughs that could revolutionise the treatment of tuberculosis.

Tuberculosis is one of the biggest global health threats. The World Health Organization (WHO) estimates that two billion people - one-third of the world's population - are infected with the 'Mycobacterium tuberculosis'. But with the vast majority, you wouldn't know it.

What they have is latent TB. A person does not fall ill unless the bacteria develop into the active form, which happens to 1 in 10 infected people.

"Ninety per cent of infected people don’t progress to active TB," says Professor Douglas Young of the Tuberculosis Research Group at Imperial College London. "But at least some of those retain a lifetime risk of doing so at a later time. That leaves a problem in that you can generally control the infection but you can't eliminate it."

It is this lingering level of infection that could thwart the WHO's goals of halving the prevalence of TB by 2015, and eliminating it as a public health threat by 2050.

"To really control the disease what we need is a way to prevent people with latent TB going on to develop the active disease," says Professor Young. "If we can combine that with treatment for active TB then that would really control the disease."

Grey area

Professor Young is the principal investigator of a Grand Challenges in Global Health Project studying latent TB. In the audio clip below he discusses attempts to reduce the chances of those infected going on to develop active TB.

One of Professor Young's group's primary aims is uncovering the differences between the active and latent forms of 'M. tuberculosis'. And one major step forward was the discovery that TB is not a simple two-state affair.

Like many before them, they originally thought that the two TB states were easily distinguishable: in active TB the bacteria divide, causing damage and disease; while in latent TB the bacteria lie dormant.

What they found instead was a spectrum, a range of greys rather than black and white.

"When you look at a tissue sample from someone with active TB, not all the bacteria are active. Some lesions contain actively replicating bacteria, but others are quiet with no replication. There's a spectrum that diffuses into each other, not a clear break."

This led to the realisation that the non-replicating bacteria pose part of the problem in treating active TB.

"We think the reason TB treatments take so long [a typical drug regime takes an arduous six to nine months] is that in the first month you kill all the actively replicating bacteria, but you have to extend it in order to kill the non-replicating bacteria," says Professor Young.

"We know that 'M. tuberculosis' is only vulnerable when it is dividing and they only do that now and again. If the drug happens to be there when it does divide, then it can be killed."

The upside is that finding a way to kill the latent bacteria would also shorten the time needed for active TB treatments. But to date such methods have proved elusive.

New targets

Discovering a new drug that can kill bacteria is more complicated than simply targeting a single part of the organism. Often it is several targets, or a whole mechanism, needing to be knocked out for the drug to work.

The goal is to find systems that are essential for the bacteria's survival while in the latent state. One approach is to target the ability to survive in a low-oxygen environment. This is often the case when TB lesions break down as the tissue around them starts to decay, which is fairly common

in human TB infections. The body's immune cells also create low-oxygen conditions when they wall off the bacteria in an attempt to kill them.

Dr Clifton Barry, of the National Institute of Allergy and Infectious Diseases in the USA and another member of the Grand Challenges team, has been looking for new compounds that kill the bacteria in low-oxygen conditions.

Early in 2009 his team discovered that PA-824, a compound that kills latent TB bacteria, works by releasing nitric oxide. This is produced naturally by immune system cells after they engulf bacteria inside the cell, but the researchers found that the drug requires two factors from the bacteria to work. The drug has the added bonus of being harmless to humans, who don't have these factors.

"Now that we know how the compound kills the bacteria, we're developing versions that are 10 to 100 times better at killing it in anaerobic conditions than PA-824," says Professor Young.

"We have several candidate molecules that are going forward for evaluation that we hope will be entering clinical trials within the next one to two years," says Dr Barry.

Another approach is to target the bacteria's level of adenosine triphosphate. A high level of these energy molecules is required when 'M. tuberculosis' is actively replicating. But when latent, the bacterium requires lower levels of ATP to power its basic functions.

"If you can reduce that level even a bit that kills the organism. This looks like an Achilles heel for the non-replicating bacteria as maintaining ATP levels for their core metabolism is vital," says Professor Young. Pharmaceutical company Johnson & Johnson already has one compound

targeting this in clinical trials for multidrug-resistant TB.

Live imaging
As vital as new drugs are, it is just as important to identify the patients most at risk.

Part of the reason why latent TB is a relatively neglected area of research is that it is difficult to characterise. Early studies of latent TB were based on tissue samples from the lungs of dead patients and gave confusing results, differing greatly from one study to the next.

Modern methods, which rely on skin tests, aren't much more accurate.

"When someone gets exposed to TB, they usually produce immune cells (T-cells) specific to the bacteria," says Professor Young. "So if you do a skin test, you can say, yes they have this type of T-cell. But you don't know whether they are still carrying the infection or whether their immune system has got rid of it."

Live imaging is a particularly exciting development, using CT (computerised tomography) and PET (positron emission tomography) scanners to look directly at TB lesions developing in the lungs of patients. PET scans illuminate areas of inflammation using radiolabelled tracers, while CT takes high-resolution X-ray images of the body, allowing the 3D structure of the scanned region to be reconstructed.

"These are widely used in cancer therapy, but have not been applied previously to infectious diseases such as TB," says Dr Barry.

Working with lung surgeons in Korea, Dr Barry is developing these techniques to provide not only a useful diagnostic tool but also a way to directly measure the effect of drugs on the disease.

"Using this combination of CT and PET imaging we're seeing how dynamic TB is," says Professor Young.

"We can see every single lesion in a patient, we can measure it, look at its functional status, and then treat the patient with drugs and see if the lesions heal or get worse. It is profoundly changing our way of looking at TB."

Revolution

These developments could revolutionise our approach to tuberculosis treatment. Rather than try to treat everyone infected with latent TB, we could instead target the smaller one in ten most at risk.

Says Professor Young, "We estimate that two billion people around the world have latent TB, but are all of them at risk of developing active TB? We assume not."

"Ideally we want a way to identify the people who are really at risk of active TB and target those for treatment. At the same time, we need to gain a better understanding of the biology of latent TB and develop drugs that work in a few weeks rather than six to nine months."

"If we can do that, then the WHO's elimination goal becomes possible because you're applying a feasible treatment to a realistic population."

More information: R Singh et al. Bicyclic nitroimidazoles are intracellular NO donors and kill non-replicating Mycobacterium tuberculosis. *Science* 2008 28 November [Epub ahead of print].

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