'Goldilocks' gene could determine best treatment for tuberculosis patients

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Tuberculosis patients may receive treatments in the future according to what version they have of a single 'Goldilocks' gene, says an international research team from Oxford University, King's College London, Vietnam and the USA.

This is one of the first examples in infectious disease of where an individual's genetic profile can determine which drug will work best for them – the idea of personalised medicine that is gradually becoming familiar in cancer medicine.

The scientists found that people generate an immune response to tuberculosis that is 'too much', 'too little' or 'just right', according to what versions they have of the LTA4H gene.

The findings indicate that patients are likely to benefit from different drug treatments depending on their LTA4H gene profile.

Furthermore, the researchers show that steroids used as part of the standard treatment for the most severe form of tuberculosis, TB meningitis, only benefit some patients.

The results of the study, part-funded by the Wellcome Trust, are published in the journal *Cell*.

Tuberculosis is a major cause of death worldwide, with an estimated 9.4 million cases and 1.7 million deaths in 2009. The disease is caused by

Mycobacterium tuberculosis bacteria and differs according to where the infection takes hold. Most TB affects the lungs, but around 40% of cases involve disease elsewhere. In perhaps 1% of cases, TB affects the brain. This form of the disease, TB meningitis, is the most serious. It is hard to diagnose and treat, and even with treatment it is often fatal.

The standard treatment for TB meningitis involves a range of antibiotics to try and kill the bacteria, and the steroid dexamethasone to dampen inflammation – the body's response to tuberculosis infection that can be almost as much of a problem.

The new study combines work in zebrafish at the University of Washington, Seattle to identify genes and biological pathways involved in the immune response to TB, with clinical research work in collaboration with Pham Ngoc Thach Hospital, the Hospital for Tropical Diseases and the Oxford University Clinical Research Unit in Vietnam.

The scientists identified a gene in zebrafish associated with susceptibility to tuberculosis, which controlled the balance of the inflammatory response. Variations in the DNA code in this gene could alter different biological pathways, leading either to too much inflammation or too little. Both too much and too little inflammation were problems, allowing the tuberculosis bacteria to thrive and multiply.

The researchers showed that blocking the appropriate biological pathway with drugs could restore just the right level of inflammatory response.

The researchers based in Vietnam then went back to samples from a previous clinical trial in over 500 patients with TB meningitis. They showed changes at a single position in the human LTA4H gene were associated with treatment response.

Only those having LTA4H genes that led to too much inflammation

benefitted from the use of the steroid dexamethasone.

There is some suggestion that the steroid could have an adverse effect for those whose LTA4H genes already lead them to have a reduced inflammatory response, though the result is not statistically significant.

'It's like a "Goldilocks" gene. Depending on what versions of the LTA4H gene you have inherited, you could see an inflammatory response to tuberculosis that is "too much", "too little", or "just right",' explains Dr Sarah Dunstan Head of Human Genetics of Oxford University Vietnam. 'You are likely to benefit most from a treatment tailored to your own genes.'

Dr Guy Thwaites of King's College London and who lead the clinical study in Vietnam on a Wellcome Trust Fellowship says: 'This is a fundamental discovery. It is now possible to think about the use of simple but rapid genetic tests to determine how people will respond to tuberculosis infection and whether they would benefit from steroids.'

'The findings could apply much more widely than just in TB meningitis, or other forms of tuberculosis,' adds Dr Thwaites. 'Since the inflammation pathways governed by the LTA4H gene are central to many infections, there could be implications for many diseases.'

'This study highlights the power of really good clinical research supported through Wellcome Trust Fellowships and linked with some of the very best scientists in the world in Vietnam and the USA, which can bring immediate benefits to patients and also point the way to develop better, more targeted drugs to treat people with tuberculosis in the future,' says Professor Jeremy Farrar who leads the Oxford University Clinical Research Unit in Vietnam. 'The idea that a patient's genes can determine what treatment they will benefit from is pretty novel outside of cancer. Nothing like this has been seen before in infectious disease.

Now we need to see if we can use this to help patients with this devastating disease'

More information: 'Host genotype-specific therapies can optimise the inflammatory response to mycobacterial infections', by David Tobin et al., *Cell* (2012).

Provided by King's College London