Genetic variant offers protection against TB and leprosy

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A study into why some people are more resistant than others to diseases such as tuberculosis (TB) and leprosy has identified a new genetic variant which affects susceptibility to these diseases. The findings, published today in the journal *Cell*, may have implications for future treatments for the two conditions.

TB and leprosy, whilst seemingly very different diseases, are both caused by rod-shaped, aerobic bacteria known as mycobacteria; TB is caused by *M. tuberculosis*; leprosy by *M. leprae*. Exposure to the bacteria causes very varied outcomes amongst patients: for example, in the case of M. tuberculosis, some people will resist infection, others will carry the bacteria asymptomatically, and yet others may develop life-threatening symptoms.

Our immune system uses two broad strategies to defend us from infection: innate immunity and adaptive immunity. Innate immunity is the immune response that we are born with; it is the first line of defence, swift, but more generalised than adaptive immunity. The latter strategy enables the immune system to adapt its response to infection in order to better target itself towards specific invading pathogens.

To investigate how mycobacteria cause disease - and what protects some people but not others - researchers at the University of Washington in Seattle, together with researchers from the Wellcome Trust's South East Asia programme in Vietnam, studied zebrafish. As with mammals, the zebrafish relies on adaptive immunity - the immune response which

'learns' from invading pathogens - for maximal control of mycobacterial infection. The zebrafish's transparent larvae allow researchers to see how its innate immune response behaves before the adaptive immunity has chance to learn to recognise a pathogen.

The researchers infected the genetically-screened zebrafish with their own natural mycobacterial pathogen, M. marinum. By examining the effect that this had on the larvae, the researchers were able to see the early steps of mycobacterial infection and identify which was the key locus that increased susceptibility. They found this to be the lta4h locus, which has a human equivalent, LTA4H. The locus is responsible for regulating production of key chemicals involved in the inflammatory response to infection.

The researchers then turned their attention to case-control studies - comparisons of patients ('cases') against healthy volunteers ('controls') - to see whether genetic variants in the LTA4H region affected susceptibility to mycobacterial infection in humans, examining patients in Vietnam with a particularly dangerous form of TB known as meningeal TB, and patients in Nepal with leprosy.

"We found that carrying a particular genetic variant of LTA4H seems to offer protection against TB in the Vietnamese patients and leprosy in the Nepalese patients," says Dr Sarah Dunstan from the Oxford University Clinical Research in Ho Chi Minh City, part of the Wellcome Trust's South East Asia programme in Vietnam. "This is an interesting finding and opens up a potential new target for drugs against these diseases."

Effective treatment for TB has been available for over 50 years, however patients face 6 month long treatment schedules with numerous, potentially toxic drugs. Combating the global burden of TB will rely on new and improved drugs and findings such as these reveal new opportunities for drug development.

More information: Tobin DM, et al. The lta4h Locus Modulates Susceptibility to Mycobacterial Infection in Zebrafish and Humans. Cell; 4 March 2010

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