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# Host genetics can contribute to lung damage in severe tuberculosis

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A third of the global population is infected with the bacterial pathogen, a mycobacterium, that causes tuberculosis (TB). Most carriers control the infection and are asymptomatic, but severe forms of the disease (more common in children and immune-compromised adults, and often caused by particularly aggressive—or hypervirulent—mycobacterial strains) kill over a million people every year. An article published on July 3rd in *PLOS Pathogens* now identifies a factor made by the host that exacerbates lung damage in severe TB. The results also suggest why gene mutations that render the factor inactive are common.

To understand the mechanisms underlying aggressive TB, Elena Lasunskaia from the Universidade Estadual do Norte Fluminense, Rio de Janeiro, Maria Regina D'Império-Lima from the Universidade de São Paulo, Brazil, and colleagues studied mouse models which recapitulate the symptoms of severe pulmonary TB in humans. Like human patients, mice infected with two different hypervirulent mycobacterial strains develop necrotic lesions in the lung, that is, areas of dead cells that break open and release their contents. The necrotic debris contains molecules that promote an influx of immune cells from the host, and the resulting local inflammation causes further damage to the lung tissue.

One of the contents of necrotic debris is the energy-storage molecule ATP, and when it is found outside cells, it is known to stimulate immune cells through the binding to the P2X7 receptor (P2X7R). The researchers asked whether this molecular pathway plays a role in the severe forms of TB that are associated with lung necrosis. They studied

mice that were lacking P2X7R and found that those mice survived otherwise deadly infections with either of the two hypervirulent mycobacterial strains.

A more detailed analysis suggested that P2X7R has a dual role in the development of aggressive TB. First, it appears to facilitate the dissemination of hypervirulent mycobacteria by killing infected immune cells but releasing their content, namely viable mycobacteria that have survived the process. Second, P2X7R also seems to contribute to lung inflammation and damage by promoting widespread tissue destruction.

The better outcomes in mice without P2X7R were only seen after infection with hypervirulent mycobacteria. When the researchers infected mice with a less aggressive TB strain, they found that P2X7R actually helped to control this infection. In this case, P2X7R-mediated stimulation of infected immune cells did not result in the cell death and release of viable mycobacteria, and so actually contained the infection rather than spreading it.

The observed opposite effects of P2X7R on lung infection with hypervirulent and less aggressive mycobacterial strains, respectively, could explain an epidemiological puzzle: P2X7R loss-of-function alleles (that is defective variants of the P2X7R gene) are common in humans despite the fact that they are linked to a higher risk of developing pulmonary TB. Based on their results, the researchers suggest that such variants might increase the risk of mild TB but reduce the risk of severe TB. This, they say "could explain why evolutionary pressure has maintained these gene polymorphisms at high rates in the human population."

They also state that their study "provides a perspective for the development of new therapeutic approaches in which drugs designed to inhibit P2X7R are used to ameliorate the outcomes of aggressive forms

of TB".

**More information:** Amaral EP, Ribeiro SCM, Lanes VR, Almeida FM, de Andrade MRM, et al. (2014) Pulmonary Infection with Hypervirulent Mycobacteria Reveals a Crucial Role for the P2X7 Receptor in Aggressive Forms of Tuberculosis. *PLoS Pathog* 10(7): e1004188. DOI: 10.1371/journal.ppat.1004188

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