A gene for susceptibility to tuberculosis

The complex genetic nature of what makes some people more susceptible than others to tuberculosis (TB) may finally be revealing itself. The answer may lie in the genes that control cell-mediated immunity, specifically a newly discovered gene that governs how macrophages cope with infectious organisms such as Mycobacterium tuberculosis. The discovery sheds new light on the molecular basis of the pathogenesis of TB, a disease that kills more than 2 million people each year.

Searching for the genes

In an attempt to identify the responsible gene(s), Pan and colleagues replaced the sst1 region in the TB-susceptible mice with the same region from a normal mouse strain. They found that this “congenic” strain was more resistant to infection with M. tuberculosis and better able to control the replication and spread of M. tuberculosis.

In addition, the authors isolated a gene in the sst1 region that was expressed in macrophages from the congenic mice but not in macrophages from the susceptible mice. This gene — the Intracellular pathogen resistance 1 (Ipr1) gene — encodes a protein that appears to be linked to how the macrophages die upon infection.1 For example, in susceptible mice, infected macrophages died by necrosis, whereas in congenic mice, they underwent apoptosis (a tightly controlled form of cellular suicide). Therefore, it seems that the Ipr1 gene affects the choice of a cell-death pathway in infected macrophages. Interestingly, this effect also appears to be quite general, since mice expressing the protein could also suppress the growth of Listeria monocytogenes.

The protein that the Ipr1 gene encodes is similar to the human protein SP110b.2 Both of these proteins contain domains that suggest they regulate gene expression. In addition, they are both regulated by interferons. Intriguingly, changes in SP110b have been connected to susceptibility to hepatitis C.3 This suggests that Ipr1 is involved in how pathogens and host interact, potentially through the regulation of gene expression in macrophages.

References

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