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Press information

Tuberculosis: newly discovered molecule in the immunity system plays a vital role in combating mycobacteria

Only 10% of individuals infected by *Mycobacterium tuberculosis*, which causes tuberculosis, go on to develop the disease. Why this should be is one of the questions Jean-Laurent Casanova and his team at Inserm Unit 980, "Human genetics of infectious diseases"/Université Paris Descartes, and their fellow researchers at New York's Rockefeller University, asked themselves. To try and find an answer to this question, they set about studying the genetic components of human susceptibility to mycobacteria. The results of the study, published in this week's issue of *Science*, reveal the key role played by a specific protein called ISG15 in immunity against mycobacteria

Tuberculosis is caused by a mycobacterium, chiefly *Mycobacterium tuberculosis*, also known as Koch's bacillus. An estimated 25% of the world's population is infected by tuberculosis. Of this number, 233 million men, women and children (10%) will develop clinical signs of the disease. Tuberculosis is currently responsible for 1.4 million deaths a year. Existing antibiotic treatments are becoming less effective and many vaccination campaigns end in failure. At least 50% of people who have been vaccinated do not develop any immunity. New strategies are therefore needed to combat tuberculosis effectively.

The question Jean-Laurent Casanova and his team have been trying to answer for more than 15 years is why all infected individuals do not go on to develop the disease. It was demonstrated a hundred years ago that identical twins, who share the same genetic material and an identical environment, are far more likely to both develop the disease than fraternal twins who are living in the same environment. That's why the research team set out to prove that the likelihood of an infected individual developing the disease was determined by genetic factors.

The latest complete human genome sequencing techniques, combined with all the material resources at Rockefeller University, were put to work to identify these genetic components in children suffering from mycobacterial infections.

In 2010, the team identified the genetic etiology behind the illness in three children from two separate families. Two mutations in the ISG15 gene, resulting in a total loss of function, were observed.

Until then, the role played by ISG15 had primarily been described in vitro and in vivo in mice in antiviral immunity studies. ISG15-deficient laboratory mice were more likely to be infected by *M. tuberculosis* than wild mice.

In the article published in Science on 2 August, Jean-Laurent Casanova's team explain how the ISG515 protein works. They show that it is a molecule secreted in response to the mycobacterial infection which induces the production of IFN-**γ**[1]. This research puts the spotlight on ISG15, a new player in the fight against mycobacterial diseases.

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[1] A "messenger" produced by the immunity system in response to a viral or bacterial attack. The crucial role of this messenger in combating mycobacteria has already been demonstrated.

The new discovery opens up many new possibilities. From the medical angle, screening for new patients is underway and IFN-**γ** injections could provide an alternative therapeutic approach. From the scientific research point of view, gaining detailed insight into ISG15's action mechanism and regulations will definitely teach us more about immunity against mycobacteria, which is a vital step forward in the fight against tuberculosis.

Sources

Mycobacterial disease and impaired IFN-γ immunity in humans with inherited ISG15 deficiency

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