Tuberculosis: Discovery of a critical stage in the evolution of the bacillus towards pathogenicity

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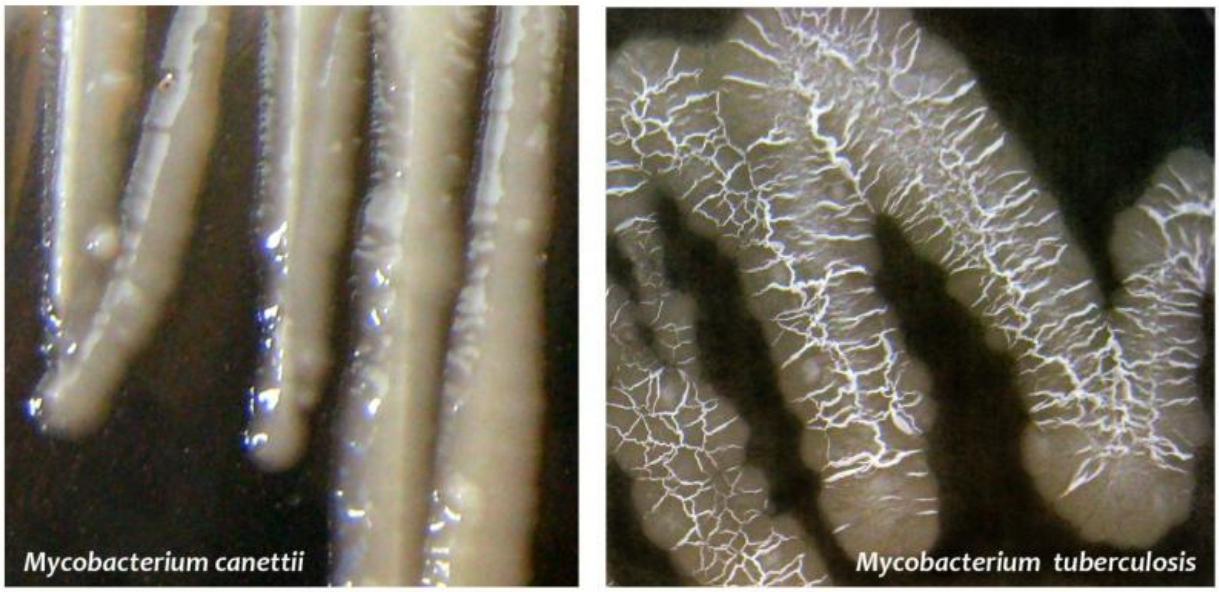

On a solid culture medium, the colonies of M. canettii are smooth and sticky while those of M. tuberculosis are dry, rough and wrinkled Credit: © Roland Brosch, Institut Pasteur.

It is the disappearance of a glycolipid from the bacterial cell envelope during evolution that may have considerably increased the virulence of tuberculosis bacilli in humans. Scientists from the CNRS, the Institut Pasteur and the Université Toulouse III – Paul Sabatier have shown that

this disappearance modified the surface properties of Mycobacterium tuberculosis, favoring its aggregation in "cords" and increasing its pathogenicity. These findings, which enable a better understanding of the mechanisms linked to the evolution and emergence of tuberculosis bacilli, constitute a major advance in our knowledge on this disease. They are published in *Nature Microbiology* on 27 January 2016.

Tuberculosis is a chronic bacterial disease caused by the infective agent Mycobacterium tuberculosis. In 2014, 9.6 million cases of tuberculosis and 1.5 million deaths were recorded throughout the world, meaning that this disease ranks second among causes of death from a single infective agent (WHO, 2015). To fight this disease, it is necessary to better understand the factors and mechanisms that favor its emergence and spread.

The evolutionary stages and their associated genetic adaptations that enabled the tuberculosis bacillus to colonize humans are still little understood, unlike those of other infectious diseases such as plague or typhus. To address this issue, the scientists focused on another bacillus, Mycobacterium canettii, which is known to cause rare cases of tuberculosis and to be genetically close to the ancestor of M. tuberculosis. The team observed that colonies of these bacteria differed markedly from those of tuberculosis bacilli. While on solid media the M. tuberculosis colonies were dry, rough and wrinkled, those of M. canettii were smooth and viscous. In liquid culture, the former were markedly aggregated and formed cords while the latter were completely dispersed.

By studying spontaneous mutants of M. canettii forming rough colonies, the scientists found that the change in appearance of these colonies was caused by a recombination between two genes involved in the production of a bacterial cell wall glycolipid. By focusing specifically on the genetic organization of this region in tuberculosis bacilli, they were able to demonstrate that a similar recombination had occurred in the ancestor of

M. tuberculosis. This recombination led to inactivation of the biosynthetic pathway for the glycolipid and hence its disappearance from the surface of the bacilli. The scientists showed that in M. canettii, this disappearance modified the surface properties and thus favored its aggregation in "cords," in the same way as observed for M. tuberculosis. Finally, by using different animal and cellular models of infection, the team established that this modification of the bacterial cell envelope triggered a change in the interaction with host defense cells and an increase in the virulence of M. canettii.

This discovery constitutes an essential stage in understanding the origin and emergence of the tuberculosis bacillus. The scientists will now continue studying M. canettii and M. tuberculosis in order to determine the bacterial factors, and the immune responses induced by these factors, which have contributed to the success of M. tuberculosis as a major human pathogen.

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