

New strategy in the fight against TB?

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A new approach to combating the tubercle bacillus, the microorganism that kills some 1.5 million people in the world each year, has been developed by a French-British team including scientists from CNRS, Inserm, the Institut Curie and Université Toulouse III - Paul Sabatier. The researchers have discovered that an amino acid, aspartate, is essential for the development of the bacillus because it acts as its main source of nitrogen. They have also succeeded in establishing the mechanism by which the bacterium extracts aspartate from its host. These results, published online on 29 September 2013 in the journal *Nature Chemical Biology*, could make it possible to develop new antibiotics and new vaccines derived from attenuated strains of the bacillus, incapable of supplying themselves with aspartate.

Tuberculosis, an infectious disease that generally affects the lungs and kills more than 1.5 million people each year throughout the world, is caused by a bacterium known as *Mycobacterium tuberculosis*. A vaccine, BCG, is available against the bacillus but its efficacy is variable. Antibiotic treatments also exist, but doctors are increasingly confronted with strains that are resistant to several antibiotics, hence the need to develop new therapeutic and preventive strategies.

The researchers from the Institut de Pharmacologie et de Biologie Structurale (CNRS/Université Toulouse III - Paul Sabatier) who coordinated this work focused on the mechanisms whereby *M. tuberculosis* supplies itself with nitrogen, an essential element in the synthesis of a large number of biomolecules, proteins, nucleic acids and vitamins for example. They studied an amino acid transporter known as

AnsP1 and showed that this transmembrane protein is responsible for capturing aspartate, an amino acid, and then introducing it into the bacterium. In fact, a mutant of the genetically inactivated bacillus in this transporter proved incapable of growing in a medium containing aspartate as unique nitrogen source. The researchers then tried to determine whether aspartate really is an important source of nitrogen for the bacillus. To do so, they used a technique that makes it possible to map all the metabolites present in a cell. The team fed the bacilli with aspartate containing a heavy isotope of nitrogen and showed that *M. tuberculosis* in fact assimilates nitrogen from aspartate, which is then found in numerous molecules synthesized by the microorganism.

Using a small-molecule imaging technique, the researchers showed that when macrophages (cells of the immune system present in large quantities in the pulmonary tract) infected by the bacillus were placed in contact with aspartate containing heavy nitrogen, the heavy isotope ended up in the pathogen. In other words, AnsP1 allows the bacillus to capture [nitrogen](#) from its host cell. In in vivo experiments, the researchers infected mice with a bacillus in which AnsP1 was inactivated. Surprisingly, this bacillus strain proved to be highly attenuated: it multiplied more slowly and caused much less damage than normal strains to the lungs of the mice models. This highlights the unsuspected role of this aspartate transporter in the virulence of the mycobacterium.

AnsP1 and the other molecules involved in the metabolism of aspartate could therefore be potential targets for [new antibiotics](#). Furthermore, this mutant strain in which AnsP1 has been inactivated could turn out to be a good candidate for the development of novel vaccines capable of providing better and longer protection than BCG.

More information: Mycobacterium tuberculosis nitrogen assimilation and host colonization require aspartate, Alexandre Gouzy, Gérald

Larrouy-Maumus, Ting-Di Wu, Antonio Peixoto, Florence Levillain, Geanncarlo Lugo-Villarino, Jean-Luc Gerquin-Kern, Luiz Pedro Sório de Carvalho, Yannick Poquet & Olivier Neyrolles. *Nature Chemical Biology*.

Provided by CNRS

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