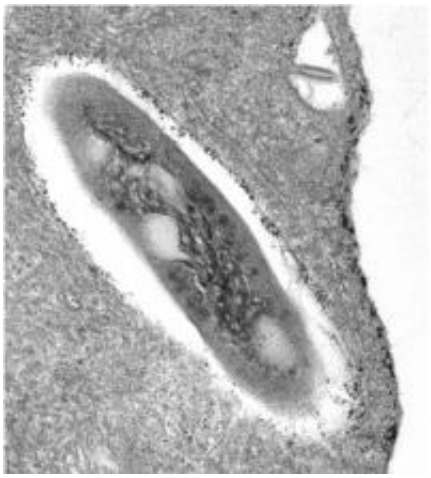
Heavy metals boost immunity

September 21 2011



This figure shows a tuberculosis bacillus (M. tuberculosis) in a macrophage. The compartment in which the bacillus resides (a vacuole known as a phagosome) is rich in zinc, which can be seen in the form of small black deposits (zinc sulfate) by electron microscopy after specific treatment. Credit: Chantal de Chastellier

A new natural defense mechanism against infections has been evidenced by an international team led by researchers from CNRS, Inserm, the Institut Pasteur and the Universite Paul Sabatier – Toulouse III. Zinc, a heavy metal that is toxic at high doses, is used by the cells of the immune system to destroy microbes such as the tuberculosis bacillus or E. coli. Published in the journal *Cell Host & Microbe* on 14 September 2011, this discovery makes it possible to envisage new therapeutic strategies and test new vaccine candidates.

One of the well-known strategies employed by our immune system to

destroy microbes consists in depriving them of essential nutrients such as heavy metals, particularly iron.

For the first time, an international study headed by researchers from the Institut de Pharmacologie et de Biologie Structurale, the Centre d'Immunologie de Marseille Luminy and the Institut Pasteur has shown that the reverse is also true: the immune cells are capable of mobilizing reserves of heavy metals, especially zinc, to poison microbes.

This phenomenon has been demonstrated for Mycobacterium tuberculosis, the agent responsible for tuberculosis in humans, which accounts for nearly 2 million deaths worldwide each year, and for Escherichia coli, of which certain strains can cause serious infections of the digestive and urinary systems.

In immune system cells (macrophages) that have ingested M. tuberculosis or E. coli, the researchers observed a rapid and persistent accumulation of zinc.

They also observed the production, on the surface of the microbes, of numerous proteins whose role is to “pump out”, in other words eliminate, heavy metals.

In macrophages, the microbes are thus exposed to potentially toxic quantities of zinc and they try to protect themselves against intoxication by synthesizing these pumps. Inhibiting the pumps through genetic engineering provides proof of evidence: M. tuberculosis and E. coli become even more sensitive to destruction by macrophages.

Zinc, although toxic when ingested in too high quantities, is therefore beneficial for the immune system, particularly because it is used by macrophages to poison microbes. Equivalent mechanisms could exist for other heavy metals such as copper. These results have very concrete

clinical implications. In particular, they re-open the debate on dietary supplementation (e.g. with zinc) and they may also lead to new antibiotics that would block the action of microbial pumps on metals or to new attenuated vaccine strains, which have already been tested as vaccine candidates.

More information: P1-type ATPases mediate microbial resistance to zinc poisoning in human macrophages. Botella H, et al., *Cell Host & Microbe*, 14 September 2011

Provided by CNRS