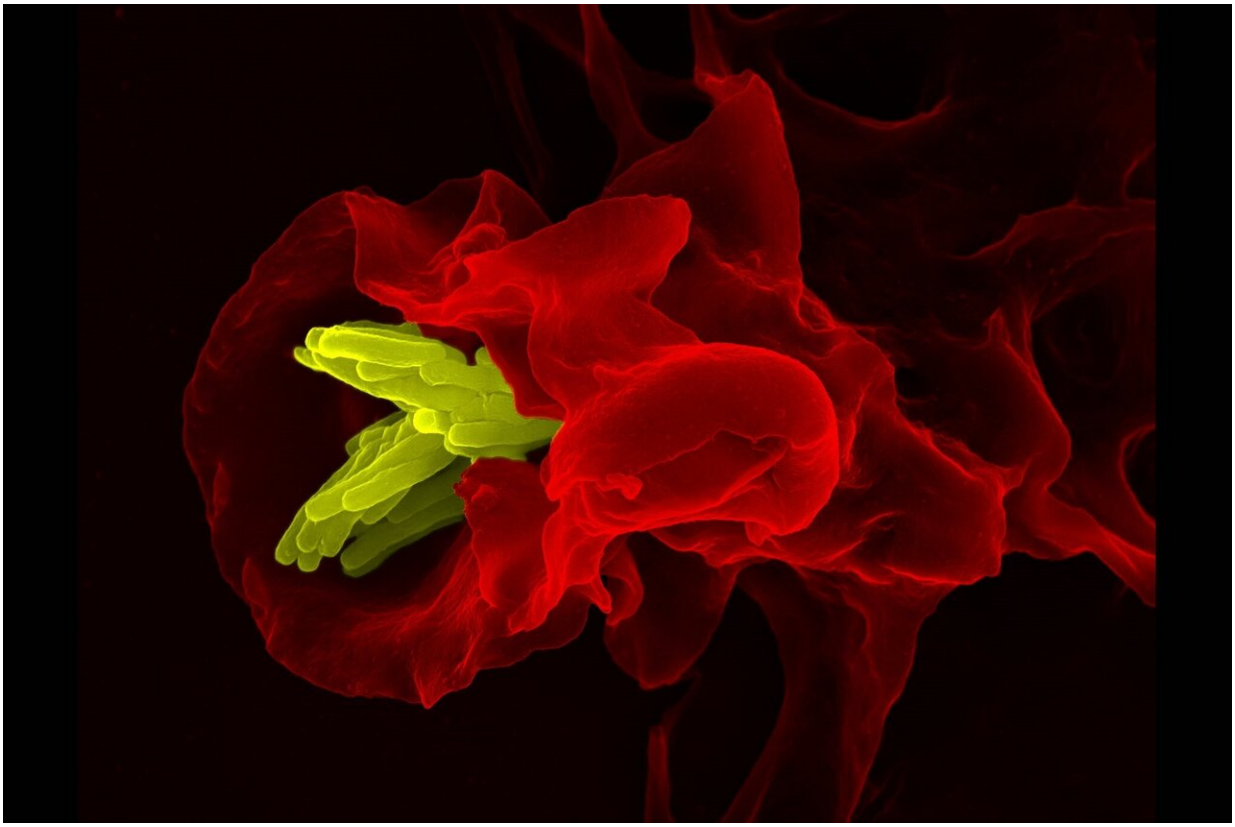
Disrupted movement makes macrophages more lethal to tuberculosis bacteria

April 14 2021, by Bryce Benda



Macrophages are white blood cells that play an important role in our immune system. They search out, eat and break down broken cells and pathogens. Because of their function they can be found all over our body. The image pictures a macrophage (red) engulfing tuberculosis bacteria (yellow), taken with ZEISS FE-SEM. Credit: Dr. Volker Brinkmann, Max Planck Institute for Infection Biology, Berlin/Germany.

Macrophages—the front line of our immune system—protect us from infections. But in the case of the tuberculosis bacteria, this often goes wrong. The group of Annemarie Meijer from the Leiden Institute of Biology has now discovered that macrophages in zebrafish are better able to eliminate tuberculosis bacteria if they lack a certain receptor. The research, published in the journal *Cell Reports*, may contribute to new treatment strategies for tuberculosis.

Tuberculosis is the world's most lethal bacterial infection: ten million people die from the disease every year. No good vaccine against tuberculosis yet exists. Moreover, the treatment of the disease is increasingly endangered by the emergence of antibiotic resistance. "To find leads for new treatment strategies, it's important to better understand how tuberculosis bacteria circumvent the immune system," says Professor of Immunobiology Annemarie Meijer.

Marcophages: friend or foe?

The first immune cells that tuberculosis bacteria come into contact with are the macrophages (see text frame below). These moving cells can quickly detect an infection, but in tuberculosis they play a dual role, says Meijer. "On the one hand, they provide a barrier, because they engulf and break down bacteria. But on the other hand, they contribute to the disease process: some tuberculosis bacteria can survive in the macrophages, spreading the infection through the body."

Receptor forces action

Meijer's group studies the role of macrophages in a zebrafish model for tuberculosis. "The transparent larvae of zebrafish are very suitable for visualizing the moving macrophages with a microscope." In the article in *Cell Reports*, the group investigates a mutant of the zebrafish that is more

resistant to infection. Meijer: "This zebrafish mutant lacks a Cxcr3 receptor, which also exists in humans. The receptor recognizes signaling substances, so-called chemokines, which are released during infections. This chemokine receptor causes the macrophages to jump into action and move in the direction of these signals."

Better defense

But why are zebrafish without this chemokine receptor better able to clear away tuberculosis bacteria? Meijer and her colleagues discovered that there are two reasons for this. "First of all, the bacteria are spread less quickly because the macrophages move less. This makes the course of the disease milder."

The second explanation is an increased degrading capacity of the poorly moving macrophages. "They contain large accumulations of breakdown vesicles, or lysosomes. The lack of the chemokine receptor causes that genes involved in the production and function of lysosomes are regulated differently. As a result, the macrophages are programmed to be better able to eliminate an infection with tuberculosis bacteria."

Meijer suggests that inhibiting this receptor is therefore an interesting possibility for future immunotherapy of tuberculosis. "By using a drug to block the action of the chemokine receptor, the macrophages will be better able to fight off the tuberculosis bacteria."

More information: Disruption of Cxcr3 chemotactic signaling alters lysosomal function and renders macrophages more microbicidal. *Cell Reports*. DOI:doi.org/10.1016/j.celrep.2021.109000

Provided by Leiden University