Uncovering the secrets of immune system invaders

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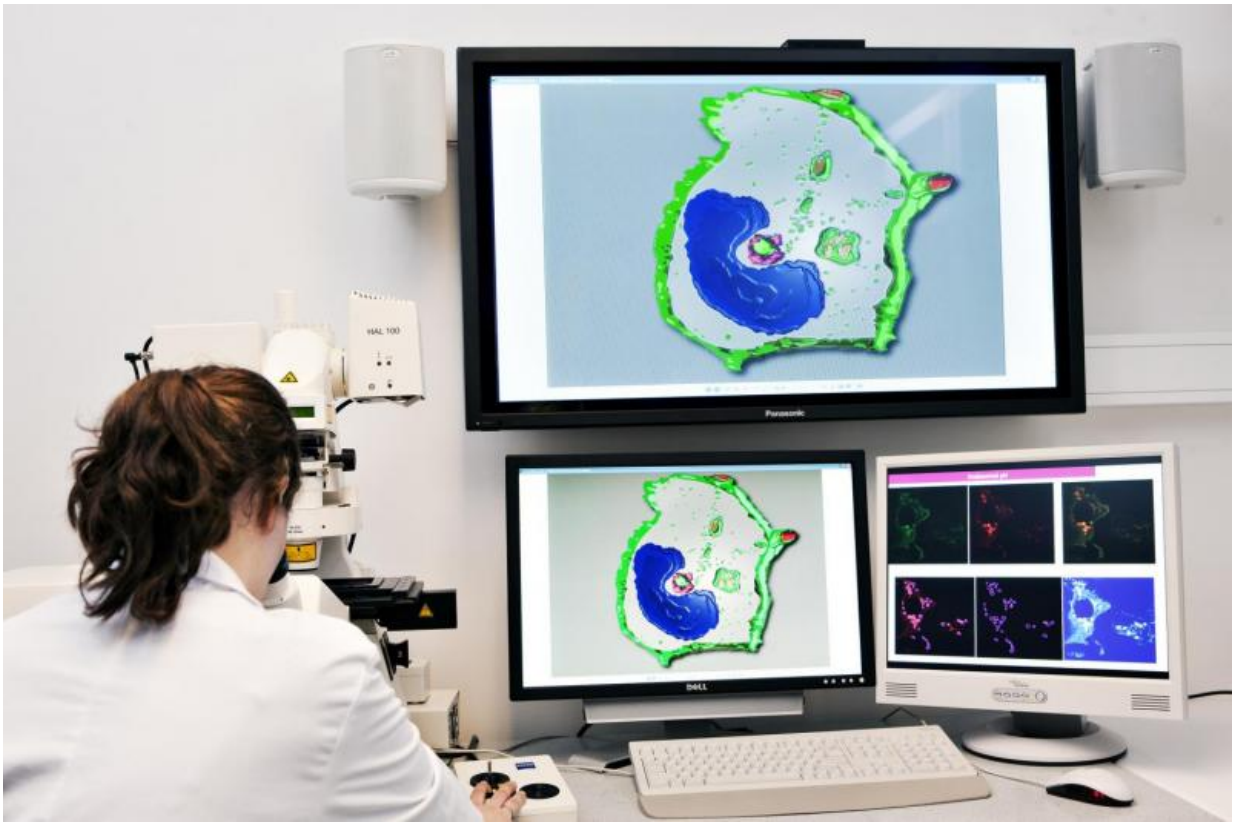

Researcher Marie Hjelmseth Aune at CEMIR, the Centre of Molecular Inflammation Research at the Norwegian University of Science and Technology, looks at a macrophage engulfing an invading bacterium. Credit: Photo: Geir Mogen, NTNU

The human immune system is a powerful and wonderful creation. If you

cut your skin, your body mobilizes a series of different proteins and cells to heal the cut. If you are infected by a virus or bacteria, your immune system responds with a series of cells that attack the invader and neutralize it.

But sometimes invaders find ways to exploit the very cells that are designed to protect us. Tuberculosis (*Mycobacterium tuberculosis*) and its lesser-known (and less virulent) relative *Mycobacterium avium* do exactly this, by hiding in immune cells called macrophages. A group of researchers from the Norwegian University of Science and Technology (NTNU) have now clarified one important step in the mechanism that allows these mycobacteria to trick the immune system so they can hide in macrophages. Their results are published in the 20-24 July online early edition of the *Proceedings of the National Academy of Sciences*.

Although the finding itself does not have immediate clinical implications, it adds to a greater understanding of the general mechanisms of how the immune system works, says corresponding author Trude Helen Flo, a professor of cell biology and co-director of NTNU's Centre of Molecular Inflammation Research (CEMIR).

"We think this is more of a general mechanism," and not just limited to mycobacteria, she said. And because certain cancers, such as lung cancer, are linked to the inflammation that the body mounts as a first step in the immune response, the finding adds an important piece to the puzzle of understanding what regulates inflammation and how this regulation can go wrong, she said.

Lady Windermere syndrome

Flo and her colleagues are interested in knowing more about how mycobacteria are able to persist in the human body because one variant, tuberculosis, remains a problem in lesser-developed countries and is

becoming more of a problem in developed countries as antibiotic-resistant strains of tuberculosis spread.

Mycobacterium avium is less likely to cause illness in healthy people, but is an organism that is found everywhere, which makes it easy to study. It can, however, cause major health problems in people with compromised immune systems, such as in diabetes or AIDS, in children, or people with lung defects, Flo said.

In fact, she said, during the 18th and 19th centuries, when it was considered impolite for well-to-do women to cough or spit, it was not uncommon for wealthier women to be afflicted by *Mycobacterium avium*. Infection by *Mycobacterium avium* is sometimes called "Lady Windermere syndrome," in reference to an 1892 Oscar Wilde play that pokes fun at manners and morals in upper class Victorian society.

Turning the immune system on and off

The researchers used *Mycobacterium avium* infections of human cells to study the role of a poorly understood protein called Kelch-like ECH-associated protein, also called Keap1.

When *Mycobacterium avium* invades a macrophage, the normal response of the macrophage is to send a signal - a call for help - for other cells to come help. This signal, in the form of something called inflammatory cytokines, causes inflammation in the body.

"But once this inflammatory mechanism is turned on, it is so strong, the body reacts very promptly to turn down the reaction," Flo said. "Otherwise, if the reaction is uncontrolled, you can have septic shock."

The researchers found that Keap1 helps to quickly turn down the immune system reaction when a macrophage is invaded by

Mycobacterium avium - which aids the mycobacteria in persisting in the macrophage, Flo said.

"Keap1 is a negative mechanism for controlling inflammation," she said. "But this negative reaction is also what makes us susceptible to *Mycobacterium avium*. The balance (in the immune system response) has to be perfect for mycobacteria to survive."

Flo said the study underscores the importance of balancing the inflammatory response.

In addition to the risk of septic shock from an uncontrolled immune system reaction, if the immune reaction "is prolonged and not terminated, it can cause chronic inflammatory diseases," she said.

However, if the immune system response "is dampened or weak, susceptibility to infections increases," she added. "Our study shows that in absence of Keap1, inflammatory responses increases and the growth of mycobacteria inside macrophages is hampered."

Immune cells from healthy donors

One distinct feature of the study was that the researchers used cells from blood donors as part of their research, rather than "cultured" immortalized cell lines that have been grown in the laboratory for decades and whose responses may be very different from primary cell isolated directly from humans.

Flo said that while using human cells from blood donors made the research more difficult and time-consuming, it also made the findings more valuable in terms of eventual clinical applications.

"We chose to isolate immune cells from healthy donors for our

experiments," she said. "These more closely reflect what is going on in real humans, and - although they are tricky to work with - can give us findings we believe should be more relevant for real disease."

Keap1 mutations and cancer

Flo said that one reason that Keap1 was of interest to her research group was because mutations in the Keap1 gene have been found in cancers that are associated with inflammation, such as lung cancer.

That means that Flo or other researchers could look for mutations in Keap1 in blood samples from biobanks, such as NTNU's Nord-Trøndelag Health Study (HUNT), which has collected health and biological information and material from 120,000 individuals over the last 30 years.

"We can look at patients' genes and see if they have accumulations of mutations in Keap1, which is at the core of regulating inflammation," she said. Biobanks such as HUNT that have collected data over decades allow researchers to see how different mutations are associated with different cancers, for example.

More information: Keap1 regulates inflammatory signaling in Mycobacterium avium-infected human macrophages. Jane Atesoh Awuh, Markus Haug, Jennifer Mildenberger, Anne Marstad, Chau Phuc Ngoc Do, Claire Louet, Jørgen Stenvik, Magnus Steigedal, Jan Kristian Damås, Øyvind Halaas and Trude Helen Flo. 20 July 2015 *PNAS*. www.pnas.org/cgi/doi/10.1073/pnas.1423449112

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