Killer immune cells that halt malaria could hold key to new vaccines

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Scientists have revealed that immune cells called natural killer (NK) cells

may play a key role in ridding the body of malaria-infected blood cells, a study in *eLife* reports.

The discovery adds to knowledge of how natural immunity to malaria develops in people living in areas where the parasite is common, and provides a new mechanism that could be exploited in the mission to create a malaria vaccine.

"One of the main objectives in malaria research is to define the mechanisms by which naturally acquired antibodies provide protection," says lead author Gunjan Arora, Postdoctoral Fellow at the National Institute of Allergy and Infectious Diseases (NIAID), US. "We know that NK cells kill virus-infected cells and cancer cells, but a clear role for them in contributing to protection from malaria is yet to be established. We wanted to investigate the effects of human NK cells on malaria-infected blood cells in the presence of different human antibodies."

They started by isolating NK cells from people in the US who had never been exposed to malaria and looking at the effects on malaria-infected red blood cells in the presence of different antibodies. When incubated with antibodies from people in Mali, who have a degree of natural immunity to malaria, the NK cells became active and produced immune-stimulating molecules.

Next, the team looked at whether NK cells could kill infected red blood cells without damaging uninfected ones. They labelled NK cells, along with infected and uninfected red blood cells, and incubated them together with different antibodies. In the presence of the Mali antibodies, but not those from people in the US, the NK cells killed the infected red blood cells but left uninfected cells intact.

This led the scientists to investigate whether NK cells could also halt the growth of malaria within red blood cells. They allowed the parasites

within red blood cells to go through one cycle of growth, and then counted the resulting number of newly infected cells. In the absence of antibodies, or with antibodies isolated from people in the US, NK cells blocked malaria growth by around 4-6%. When incubated with antibodies from people in Mali, the NK cells blocked growth by more than 60%. This showed that antibody-activated NK cells can stop malaria parasites from maturing into a form that can go on to infect other blood cells.

Finally, the team wanted to find the mechanism behind this antibody-driven attack by NK cells. Blood cells infected with malaria have molecules on their surface that antibodies recognize and use to attract immune cells. The team identified a molecule that was essential for activation of NK cells in response to malaria-infected blood cells. Although PfEMP1 was already known to be important in antibody recognition of malaria-infected cells, this study showed for the first time that it is crucial for activating NK cells in a manner dependent on antibodies.

"Considering the essential role of antibodies in granting clinical immunity to people living in areas of high malaria transmission, and the limited effectiveness of malaria vaccines tested so far, any immune responses that depend on antibodies warrant further investigation," says senior author Eric Long, Senior Investigator at NIAID. "Our discovery of antibody-mediated killing of malaria-infected blood cells by NK cells adds an additional immune mechanism to those already known."

More information: Gunjan Arora et al, NK cells inhibit Plasmodium falciparum growth in red blood cells via antibody-dependent cellular cytotoxicity, *eLife* (2018). DOI: 10.7554/eLife.36806

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