Malaria: Cooperating antibodies enhance immune response

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Malaria is one of the most infectious diseases worldwide. Scientists from

the German Cancer Research Center (DKFZ) in Heidelberg, Germany, and from the Hospital for Sick Children (SickKids) in Toronto, Canada, have studied how the human immune system combats malaria infections. In this study, the researchers discovered a previously unnoticed characteristic of antibodies against the malaria parasite: They can cooperate with each other, thus binding even stronger to the pathogens and improving the immune response. The results, now published in *Science*, are expected to develop a more effective vaccine against the disease.

Each year, an estimated 200 million people contract malaria and approximately 440,000 people succumb to the infectious disease. Although regarded as a tropical disease, malaria can occur in both tropical and subtropical regions. There are malaria cases in Germany as well, with 500 to 600 patients annually. Most of these cases are travelers returning from malaria-endemic regions in Africa or Asia.

"How severe the course of malaria gets, depends on the body's immune response," explains Hedda Wardemann from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). "Immune cells can destroy the pathogens that have invaded the body after a mosquito bite."

In regions where malaria is widespread, people often exhibit a certain immunity that prevents a severe course of the disease. As a result of repeated exposure to the malaria parasite, their bodies have been able to improve their immune responses to the disease. A vaccine is supposed to provide the same kind of immunity but without having to go through an infection.

"Studying the immune response of people who have been exposed to malaria parasites can provide clues about how we can make a malaria vaccine," explains Jean-Philippe Julien, Scientist from SickKids, with

whom Wardemann and her team investigated antibodies against the malaria pathogen. The antibodies were obtained from study participants who have had repeated contact with the parasite in the past.

Antibodies are actors of the immune system. They attach to specific targets on the surface of pathogens so they can block their development and tag them for destruction. For an antibody to prevent infection effectively, its affinity (the strength of its interaction with the pathogen) is pivotal. The immune system specifically multiplies antibodies with high affinity to ensure they are present if the body gets infected with the same pathogen again.

Among the antibodies studied, the DKFZ and the SickKids scientists found a group that displayed a previously unnoticed characteristic that appears to be valuable for the immune system: They interact directly with each other. The antibodies can do so because the target structure where the antibodies attach on the malaria pathogen's surface has a special feature. "The protein contains a short sequence of four motifs that repeats itself many times," explained Wardemann, an immunologist.

An antibody can attach to each of the sequence repeats. Neighbouring antibodies can then interact directly among each other. "This type of cooperation between antibodies has been unknown so far in humans," Julien said. "In an indirect way, it enhances the affinity of the antibodies to the pathogen, explaining why our immune system selects for these antibodies."

The human immune system stores these protective antibodies in order to mount a better response in case of a new infection with the same pathogen. Subsequent diseases may then take a milder course—or be prevented altogether. This mimics the immunization effect from vaccines.

Next, the scientists plan to investigate how their results may be used to improve immunization protection against malaria and bring them one step closer to a malaria vaccine. In addition, they will explore whether these observations can be transferred to other repetitive molecules that are present on other pathogens.

More information: "Antihomotypic affinity maturation improves human B cell responses against a repetitive epitope" *Science* (2018). science.sciencemag.org/lookup/ … 1126/science.aar5304

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