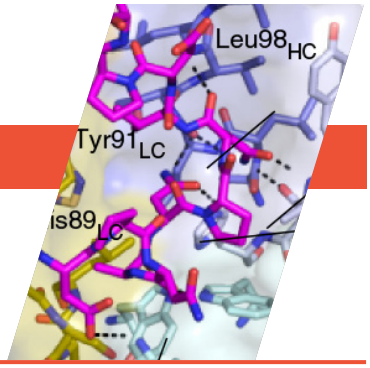
BIOLOGICAL SCIENCES

Structures Reveal New Target for Malaria Vaccine



Computer simulations show how two antibodies—CIS43 (yellow-purple) and CIS42 (gold-green)—interact with peptide 21, a protein fragment from the malaria parasite. In CIS43, peptide 21 stayed buried in a groove between the antibody's two parts. This strong affinity helps explain why CIS43 is so effective in preventing malaria. In CIS42, peptide 21 detached from its initial binding pocket and lost most of its electrostatic interactions.

Scientific Achievement

Researchers isolated human-derived antibodies that protect against malaria, and protein-structure studies revealed the antibodies' site of attack.

Significance and Impact

The discovery paves the way for the development of a more effective and practical human vaccine for malaria, a disease responsible for half a million deaths worldwide each year.

The need for a malaria vaccine

Malaria kills about 445,000 people a year, mostly young children in sub-Saharan Africa, and sickens more than 200 million. It's caused by a parasite, *Plasmodium falciparum* (Pf), and is spread to humans through the bite of an infected *Anopheles* mosquito.

The parasite's complex life cycle and rapid mutations have long challenged vaccine developers. Only one experimental vaccine, known as RTS,S, has progressed to a Phase 3 clinical trial (testing on large groups of people for efficacy and safety). To elicit an immune response, this vaccine uses a fragment of circumsporozoite protein (CSP), which covers the malaria parasite in its native conformation. However, the trial results showed that RTS,S is only moderately effective, protecting about one-third of the young children who received it over a period of four years.

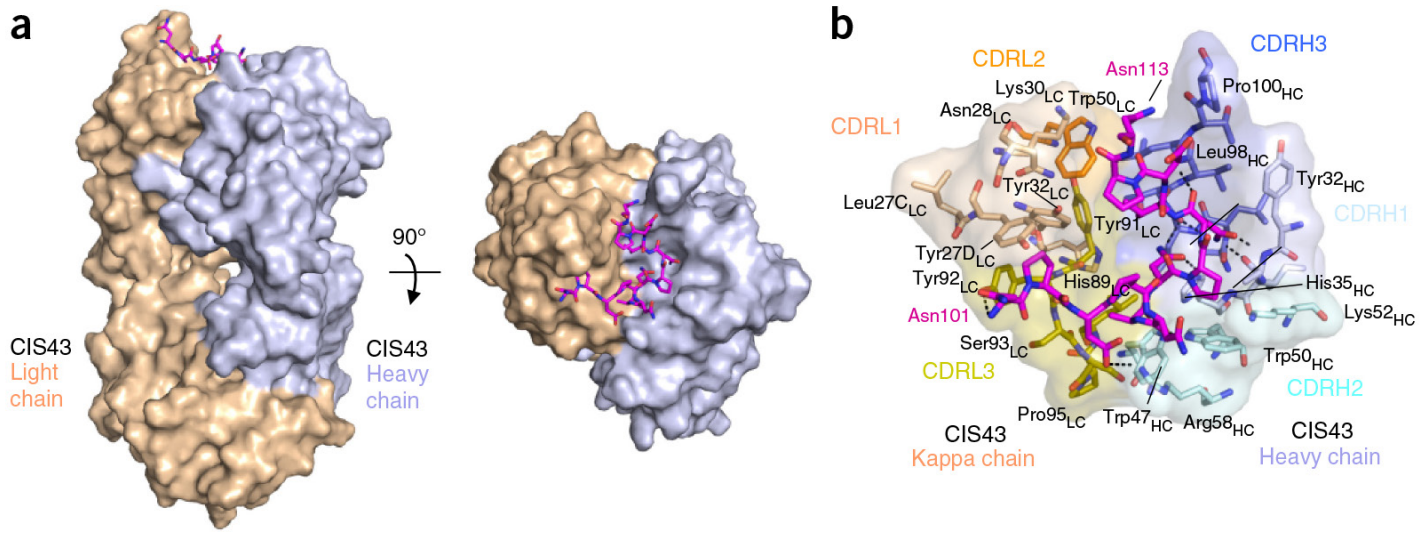
A new antibody is isolated

In the work described here, researchers isolated a new antibody, CIS43, from the blood of a human volunteer who received an experimental vaccine made from whole, weakened malaria parasites. The use of a whole-parasite vaccine allowed the isolation of antibodies against CSP. The CIS43 antibody in particular proved to be highly effective at preventing malaria infection following transfer into mice prior to exposure.

The researchers showed that CIS43 strongly binds to a novel site at the junction of CSP's N-terminus and repeat region (the "junctional epitope"). The antibody and the junctional epitope were subjected to a number of biophysical and structural analyses, with the ultimate goal of rationally designing a vaccine with improved efficacy and practicality.

In the groove

For structural studies, the researchers co-crystallized CIS43 with various peptides (amino-acid sequences) from CSP, including the junctional epitope. Protein crystallography at ALS Beamlines 5.0.1 and 5.0.2 revealed that the peptides fit into a groove formed between two parts of the antibody (the heavy chain and the light chain), along with details of the interactions. For comparison, the researchers also co-crystallized the peptides with antibody



(a) Left: Surface representation of CIS43 (light chain in tan and heavy chain in light blue), with peptide 21 shown as sticks (purple). Right: A 90° rotation of the representation. (b) Details of the interactions between peptide 21 (purple sticks) and the CIS43 epitope (colored sticks).

CIS42, which also showed specificity to the junctional epitope but had limited neutralizing function in vivo. Of note, CIS43's angle of binding to the junctional epitope differed from CIS42's.

Target acquired

In general, it was found that CIS43 binds strongly to a specific epitope of CSP—peptide 21—that occurs only once along the length of the protein. This CIS43-binding epitope is conserved across 99.8 percent of all known strains of Pf, making CIS43 potentially useful as a preventive antibody against all Pf strains. Moreover, peptide 21 provides a conserved target for next-generation experimental malaria vaccines.

The researchers plan to assess the safety and protective efficacy of CIS43 next year in controlled human malaria infection challenge trials. If the tests go well, CIS43 could be developed as a prophylactic measure to prevent infection for several months after administration. Such a prophylactic antibody could be useful for tourists, health-care workers, military personnel, or others who travel to areas where malaria is common. Moreover, if the antibody prevents malaria infection for up to six months, it might be combined with antimalarial drugs and be deployed as part of mass drug administration efforts that potentially could eliminate the disease in malaria-endemic regions.

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