Malaria Factory

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'Malarial Key' to human cells

Atom by atom, scientists have discovered the shape of a key part of a protein that malaria parasites use to invade human red blood cells (RBC). The study, published by Nature, focused on Plasmodium knowlesi, a strain of malaria that usually infects monkeys rather than people.[1] However, these findings could help in the development of new drugs against Plasmodium vivax that infects 80 million people each year and attacks RBCs in the same way as P. knowlesi. This research may have fewer implications for tackling the more deadly strain, P. falciparum which kills over a million Africans, as it binds to different proteins on RBCs.

Malaria parasites replicate inside these RBCs. To get inside, they use a protein on their surface to latch onto a protein on the outside of the blood cell. The most important part of the parasite's protein is the 'Duffy-binding-like domain'. Until now, its structure was not clear. The researchers, from the India-based International Centre for Genetic Engineering and Biotechnology (ICGEB) and a French unit of the European Molecular Biology Laboratory, have now pinpointed the three-dimensional position of each of the domain's atoms using a technique called X-ray crystallography.

1. Singh SK, Hora R, Belrhali H, Chitnis CE, Sharma A. Structural basis for Duffy recognition by the malaria parasite Duffy-binding-like domain. Nature (21 Dec 2005) Letters to Editor: online

Promising malaria vaccine

Researchers have reported promising results from the first human trials of a malaria vaccine that mimics the natural immunity some people develop against the disease. If successful, the vaccine would provide much-needed protection against the disease, which kills up to three million people a year. The team at the Pasteur Institute in France published their results in the November edition of PLoS Medicine.[1]

Despite decades of effort, scientists have failed to make a malaria vaccine that works. The main reason is that once inside the human body, the parasite changes form several times. Vaccines usually work by stimulating the human immune system to make antibodies that attack antigens on infectious organisms. Although the malaria parasite has several antigens that a vaccine could target, they vary depending on what stage the parasite is at in its life cycle. This means that a vaccine might not work against all strains of the parasite. Druilhe and colleagues developed their vaccine against a protein (MSP3) made by the form of the parasite that enters human red blood cells- the most damaging stage of its life cycle.

This is also the form of the parasite that some people who are regularly exposed to the parasite develop immunity to. When the team tested the vaccine on 30 healthy people who had never had malaria, 23 of them produced antibodies in response. The researchers showed in laboratory tests that these antibodies helped to destroy the parasite.

For ethical reasons, the team could not infect the volunteers with malaria to see if the vaccine worked in people, but they now plan to test the vaccine in Burkina Faso on people who are already at risk from malaria.

1. Druilhe P, Spertini F, Soesoe D, Corradin G, Mejia P, Singh S, et al. A Malaria Vaccine That Elicits in Humans Antibodies Able to Kill Plasmodium falciparum. PLoS Medicine 2005, Vol 2, No. 11, e344.

Malaria's Networks

Recent malaria research - so intriguing that the scientists who conducted it did not initially believe their findings - could aid efforts to develop drugs or vaccines against the deadliest form of the disease.

The study, published in November in Nature revealed that the way proteins made by the parasite Plasmodium falciparum interact with each other is very different from the way proteins made by other organisms do.[1] The researchers had previously shown that species as distinct as fruit flies, microscopic worms and yeasts not only have hundreds of proteins in common, but also use them in similar ways. The research means that scientists might now have many more avenues to explore in their search for effective malaria vaccines or new drugs to combat the parasite, which is showing growing resistance to existing drugs such as chloroquine. P. falciparum causes more than 90 per cent of all human deaths from malaria, killing up to 2.7 million people every year, according to the World Health Organization.

This study characterized conserved patterns of interaction between the protein network of Plasmodium

falciparum and those of other species, and reported the specific network regions that are conserved. All of the examined networks contain dense complex structures of interactions, some of which are shared by yeast, worm and fly but not Plasmodium. These relationships are not clearly related to noise or bias in the Plasmodium interaction set. Some of the observed differences are almost certainly due to incomplete coverage in one or more networks: for instance, the present Plasmodium interaction set is focused on asexual life-cycle stages. Nevertheless, the comparison reflects the relative degree of similarity between the different networks. These differences are observed even when considering only those genes that are homologous across species.

It is generally expected that conserved genes will retain their functions and interactions. From this comparison, a different principle emerges: conservation of specific groups of related genes does not necessarily imply conservation of interaction among their encoded proteins. Further studies may distinguish the true differences from those related to network coverage and, ultimately, facilitate the discovery of new pharmaceuticals directed at the protein complexes unique to this parasite.

1. Suthram S, Sittler T, Ideker T. The Plasmodium protein network diverges from those of other eukaryotes. Nature 2005;438, 108-112.

Resistance is emerging to antimalarial drug of choice

Malaria parasites found in West Africa are showing signs of resistance to what is thought to be the most powerful antimalarial drug. Artemisinin, which is extracted from a Chinese herb known as sweet wormwood, is the most potent and fastest-acting antimalarial. It was introduced in several African countries after the parasite developed resistance to chloroquine. Yet, in the December issue of The Lancet, researchers from Cambodia, France and Senegal show that some resistance to the drug is emerging in French Guiana and Senegal.[1]

It is believed that the parasite is less likely to develop resistance to a combination of drugs than to a single drug used in isolation and the parasite's resistance to artemisinin is a serious concern in need of careful monitoring. The team took blood samples from 530 malaria patients in Cambodia, French Guiana and Senegal, and tested the parasites for artemisinin resistance. No resistant parasites were found in the Cambodian samples, but samples from French Guiana and Senegal showed signs of resistance. The report suggests that the uncontrolled use of artemisinin might have created conditions favorable for the rise of resistant malaria - especially in French Guiana, where the local parasite population has undergone considerable genetic mutation over time.

They also predict that under the carefully controlled regimen of artemisinin use prevalent in Cambodia, resistance might be delayed or possibly even prevented. In response to the widespread emergence of malaria parasite strains that are resistant to several drugs, the World Health Organization (WHO) has recommended the use of artemisinin-based combination drug therapy as first-line treatment. So far, there has been no evidence of resistance to it in human cases of malaria, however, to prevent any widespread incidence of artemisinin-resistant malaria, monitoring and further research are important.

The study recommended that the drug should only be administered in approved artemisinin-based combination therapies (ACTs), and never alone. It is postulated that the Cambodian samples showed no sign of resistance because at the time they were taken, in 2001, artemisinin was only used in combination therapies there. According to the Cambodian health ministry, however, there is now an illegal market for artemisinin in the country.

1. Jambou R, Legrand E, Niang M, Khim N, Lim P, Volney B, et al. Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6. The Lancet - 2005,366:1960-63

Environment affects malaria risk as much as genes do

People's risk of getting malaria is determined as much by their environment as by their genes, say researchers. They say this means that increasing access to insecticide-treated bednets and healthcare is, in the short-term, an easier and more effective way of fighting the disease than trying to understand how people's genes affect it.

Margaret Mackinnon of the University of Edinburgh, United Kingdom, and colleagues spent five years recording new cases of malaria in more than 3,500 Kenyan children. The team published their findings online in the November edition of PLoS Medicine.[1]

They found that genetic factors explained about a quarter of the variation in the risk of getting malaria. Meanwhile, 29 per cent of this variation was determined by which houses the children lived in. Children in households with the most malaria cases got the disease twice as often as those living in houses with the fewest cases - even though the children played and ate together. Although the researchers have not yet identified what makes a household high risk, they say socio-economic factors could play an important part. For example, poor families often cannot

afford housing materials and insecticide-treated bednets that would protect them from mosquitoes.

Although studying whether human genes protect against malaria could lead to improved prevention and treatment in the long-term, the researchers say it is important that people use existing low-tech measures to control the disease. But other malaria experts believe this is easier said than done because although treated bednets are effective, their cost - even when heavily subsidised - is still too high for many of the world's poorest people.

Genetic and unidentified household factors each accounted for around one quarter of the total variability in malaria incidence in the study population. The genetic effect was well beyond that explained by the anticipated effects of the haemoglobinopathies alone, suggesting the existence of many protective genes, each individually resulting in small population effects. While studying these genes may well provide insights into pathogenesis and resistance in human malaria, identifying and tackling the household effects must be the more efficient route to reducing the burden of disease in malaria-endemic areas.

1. Mackinnon MJ, Mwangi TW, Snow RW, Marsh K, Williams TN. Heritability of Malaria in Africa, PLoS Medicine 2005;2:340.

Mosquitoes prefer to bite 'attractive' minority

Scientists have worked out how much people vary in their attractiveness to mosquitoes carrying malaria - 20 per cent of those at risk receive 80 per cent of infectious bites, they say.[1] Targeting public health interventions to those most at risk could lead to more effective malaria control. They warn, however, that more research is needed to identify what makes some people more attractive to mosquitoes than others. The study published in the November edition of Nature used data from about 5,000 children in 90 communities across Africa. It looked at how many bites the children got and the proportion that developed malaria. The study reports that some people get more bites than others because, chemically, they are more attractive to mosquitoes. Other factors such as living near mosquito habitats, being pregnant and living in poor-quality housing also raise the risk of being bitten. The study suggests that such a targeted approach could be more effective than using broader malaria control measures.

1. D. L. Smith, J. Dushoff, R. W. Snow and S. I. Hay. The entomological inoculation rate and Plasmodium falciparum infection in African children. Nature 2005;438,492-495.