Resistance, immunity and malaria vaccination

People who have survived a malaria infection often develop immunity to the disease. International malaria research is aimed at exploiting a person’s natural immunity in order to treat malaria effectively and avoid resistance to previously effective drugs. These new approaches also raise hopes that one day countries at high risk of malaria may be able to eradicate the devastating disease.

When the winners of the 2015 Nobel Prize in Physiology or Medicine were announced, it came as a surprise to the biomedical community. The three winning researchers appeared to have been awarded the prize for having developed relatively conventional medical drugs for treating diseases caused by tropical parasites. The biggest sensation was the awarding of the Nobel Prize to the 85-year old pharmacologist Tu Youyou from China who had spent decades isolating the anti-malaria drug artemisinin from an annual plant called sweet wormwood (Artemisia annua), which is widely used in traditional Chinese medicine. Tu was not only the first Chinese scientist to receive the Nobel Prize in Physiology and Medicine, but also one of only 12 women out of the 211 people (!) ever to receive this prestigious prize.

Resistance development

Artemisinin, and in recent years its semisynthetic derivatives, are considered to be the most effective drugs for treating malaria now that many Plasmodium falciparum (the causative agent of the dangerous malaria tropica) strains have become resistant to medicines such as quinine and chloroquine. The use of artemisinin preparations, as the Nobel committee highlighted at the 2015 award ceremony, has significantly reduced mortality rates for patients suffering from malaria, especially young children. The Nobel committee also said that Tu’s work saves more than 100,000 lives every year in Africa alone, which is the continent with the largest number of malaria cases worldwide.

Nevertheless, the disease is far from being eradicated. New artemisinin-resistant Plasmodium strains have already appeared. Fortunately, they are still limited to a small number of areas in Southeast Asia. The World Health Organisation recommends using artemisinin in combination with other malaria preparations (ATC, artemisinin-based combination therapies) to hold back the development of further resistances for as long as possible. Meanwhile, the search for effective malaria control strategies continues, with the body’s own immune defence system and vaccine development representing major research priorities.
Naturally acquired immunity as protection against malaria
In tropical Africa, it is mainly infants that contract and die from Plasmodium falciparum infection. The older the child, the fewer the malaria symptoms. Adults rarely develop malaria symptoms. This is a clear indication that repeated infection with Plasmodium falciparum leads to the development of natural immunity against the disease. “There is no doubt that infected people who have not yet developed the disease are an important transfer reservoir for the parasite,” explains Dr. Silvia Portugal, head of a group of researchers in the Department of Parasitology at the University Hospital of Heidelberg. Dr. Portugal has just received a European Research Council (ERC) Starting Grant totalling 1.5 million euros. Prof. Dr. Michael Lanzer, director of the Department of Parasitology, commented: “We are proud that Dr. Portugal, who is one of our outstanding young scientists, has decided to continue her research funded with a highly prestigious ERC Starting Grant here at the Heidelberg University Hospital rather than another top university.”

Silvia Portugal has carried out detailed field studies in Mali, a landlocked country in West Africa. Here, as well as in other countries in the Sahel zone, malaria outbreaks occur only during the rainy season when the Anopheles mosquitoes lay huge numbers of eggs. Virtually no malaria transmissions occur in the dry period. Portugal’s results suggest that the game of hide-and-seek played by Plasmodium falciparum has genetic causes and that the parasite adjusts its gene transcription to periods when no mosquitoes are available as intermediate hosts and the human immune system does not respond to the pathogen.

Over the next five years, the molecular biologist will use her ERC grant to find out which mechanisms the parasite uses to remain invisible to the immune system during the period when no mosquitoes are around, and how it resumes transmission during the subsequent rainy season. In addition to investigating the signalling pathways and metabolic profiles of the parasite, the researcher is particularly interested in the protein PfEMP1 that occurs in a number of different variants. This protein ensures that blood cells infected with Plasmodium falciparum adhere to the inner wall of blood vessels and are therefore unable to enter the spleen where diseased and old blood cells are normally removed. "We want to investigate which PfEMP1 variants are expressed by the parasite during the dry season, and how effectively these are recognised by the immune system,” says Silvia Portugal.

Vaccine candidates

One of the major goals of global malaria research is to develop an effective, preventive vaccine against the disease. Many approaches have not lived up to expectations. The vaccine RTS,S, which is the first and only vaccine approved by the European Medicines Agency for use against malaria, only showed limited efficacy, and the protection it gave declined rapidly over time. However, if the mechanisms underlying natural immunity are better understood, it should be possible to produce effective vaccines.

Faith H. A. Osier from Kenya, who was rewarded a Sofia-Kovalevskaja Award totalling 1.65 million euros from the Alexander von Humboldt Foundation in 2016 for her research, is working on the development of preventive vaccines. With her research group in the University Hospital of Heidelberg Department of Parasitology, Osier is looking for an antibody-based malaria vaccine that confers life-long protection against the parasite. Osier highlighted that the efficacy of IgG antibodies was proven more than 50 years ago when immunoglobulins isolated from the blood of
adults who had become immune to malaria, were administered to children with malaria.

It is still not clear which of the 5,400 proteins encoded by the Plasmodium falciparum genome induce the production of protective antibodies. Osier's goal is to develop a vaccine that is not targeted against individual proteins or protein fragments (as is the case with RTS,S and almost all other vaccine candidates currently being tested in clinical trials), but which is based on several antigens to which appropriate antibodies can attach so that the pathogen can be attacked by the human immune system at different stages of development. Osier is conducting a study to test the efficacy of the vaccine with volunteers in seven African countries.

Controlled vaccination with live parasites

Another strategy is being pursued by scientists led by Prof. Dr. Peter Kremsner, director of the Institute of Tropical Medicine at the University of Tübingen and coordinator of the “malaria” priority at the German Centre for Infection Research. The researchers conducted a clinical trial involving healthy volunteers never before infected with malaria, who were immunised with a vaccine produced by an American biotechnology company called Sanaria Inc. that contains viable, non-attenuated malaria parasites. The volunteers simultaneously received an anti-malaria drug. The group of volunteers that was given high doses of the Sanaria vaccine revealed full protection against malaria. Kremsner believes that the efficacy of the vaccine is down to the action of specific T lymphocytes in the human immune system and antibody responses against the parasites in the liver.
The scientists from Tübingen can now use this malaria vaccine to study naturally acquired immunity in Gabon in Central Africa. This investigation is being carried out in cooperation with colleagues from the Centre de Recherches Médicales in Lambaréné and with the vaccine producer Sanaria. Between 10 and 30 percent of the Central African population carry the sickle cell gene mutation, which has long been known to confer extensive resistance to malaria. In their study, the researchers compared infection rates and symptoms of people with and without sickle cell gene who were infected with malaria parasites in a controlled way. The results provide new insights into how the naturally acquired immunity against malaria works and will also prove important for the development of a malaria vaccine.

References:

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