Sickle cell anemia as malaria defense

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Sickle cell anemia causes pain, fatigue and delayed growth, all because of a lack of enough healthy red blood cells. And yet genetic mutations that cause it - recessive genes for the oxygen-carrying hemoglobin protein - have survived natural selection because they also seem to provide a natural defense against malaria. Scientists have long known this, and they have long wondered how it worked.

In a paper published this month in the journal *Science*, researchers describe their look into how mutated hemoglobin genes defend their cells against attacks by the malaria parasite Plasmodium falciparum. Study lead author Marek Cyrklaff, an electron microscopist and molecular biologist at Heidelberg University in Germany, explained the results.

Q: How dangerous is this malaria parasite?

A: There are a large number of casualties every year - something like 500 million new infections and approximately 1 (million) to 2 million people who die every year. Of the various malaria parasites, Plasmodium falciparum is the most virulent of all.

When infected or damaged, red blood cells are normally supposed to be removed by the spleen or the liver. But the parasite inside the infected red blood cell sends molecules called adhesins to the cell's surface to make the red blood cell adhere to the blood capillaries, to make it sticky. So the infected cells do not get cleaned out of the blood circulation because they stay in the microvasculature, in the capillaries of the other

organs. This is the strategy of the pathogen to survive and multiply.

The invaded red blood cells stick to the epithelium, to the capillaries, and block blood circulation to vital organs like the brain, or the placenta in pregnant women. Very often, this leads to death.

Q: How does the parasite achieve this?

A: For the first time, we observed the role of what is known as the actin cytoskeleton in the process. Actin is a protein that is one of the skeletal elements in every cell; normally, among other tasks, these actin networks are responsible for maintaining the shape of the cell.

When the malaria parasite invades the red blood cells it hijacks the actin cytoskeleton and uses it to build a cable system out of actin filaments to carry the adhesins to the cell's surface.

Until now, the role of this actin cytoskeleton was not really proven. Our work is the first to show that actin is involved.

Q: Where does sickle cell disease come in?

A: Some part of the human population has a mutation to their hemoglobin, which is the protein in the red blood cell that carries oxygen. Often, people of sub-Saharan African origins have two copies of this mutated gene, which leads to severe sickle cell disease.

Individuals with that disease suffer a lot, because their abnormally shaped, nonflexible blood cells block blood circulation and deliver less oxygen to the body. But, on the other hand, this trait is beneficial to humans because it prevents the most severe symptoms of malaria, including death. So throughout history, during endemic times of malaria, people who carried such mutations to the hemoglobin code had much

better chances of survival.

For people with one normal gene and one mutated gene, the Plasmodium parasite makes itself very comfortable in the cells that they have. These patients also get the typical symptoms of malaria - the recurring fever, anemia and so on - but they do not die. This is an advantage from carrying the sickle cell gene - which is why the mutation has survived in the population.

This has been known for a relatively long time, but the mechanism of this protection has not been understood. So we took sickle cells from sickle cell anemia patients; we infected them with Plasmodium parasites, put them in an electron microscope and studied this actin cytoskeleton.

Rather than the long cables of actin you would see in a normal infected red blood cell, in sickle cells we see actin filaments that are shorter, that are somehow not fully developed. In sickle cells, for some reason, the parasite is not able to form the fully functional actin network in the host cell.

Q: Can we use these findings to defend against the parasite?

A: This is still in the area of basic science. However, our findings shed light on new and hitherto uncharted territory in the complex interactions between the malaria pathogen and its host. The logical step now is to identify the factors involved in this natural protection, and future studies will aim to develop inhibitors. But before we succeed in an efficient antimalarial strategy, it will take more years of work.