African parasite makes component of fat differently from all other organisms

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Studying the parasite that causes African sleeping sickness, scientists at Johns Hopkins have discovered a previously unknown way of making fatty acids, a component of fat and the outer layer of all cells. The find unveils more about the biology of this hard-to-kill parasite and could lead to a target for designing new drugs to fight the illness that infects a half-million people and kills 50,000 a year worldwide.

Results of the study, in the Aug. 25 issue of *Cell*, "show that this is a completely new biochemical pathway for making fatty acids," says Soo Hee Lee, Ph.D., a postdoctoral fellow in the Department of Biological Chemistry at the Institute for Basic Biomedical Sciences at Hopkins. "It may be that the enzymes in the pathway could be good targets for designing drugs to treat sleeping sickness."

The single-celled trypanosome that causes African sleeping sickness, transmitted between humans and animals by bloodsucking tsetse flies, goes through several different stages in its life cycle. One such form is harbored by the insect and the other multiplies in a host's bloodstream.

There, the parasite avoids detection by the human immune system by replacing each of the 10 million proteins on its outer layer - known as the cell membrane - with different proteins that are not recognized by immune cells. These proteins are attached to the cell membrane by an anchor composed in part of a fatty acid only 14 units long - dubbed myristate -- whereas typically, in other organisms, these types of anchors contain longer fatty acids, generally 16 or 18 units long.

"For many years we thought the parasite had to get the myristate from its human host because we never could see any evidence that it could make the fatty acid itself," says Paul Englund, Ph.D., a professor of biological chemistry in the Institute of Basic Biomedical Sciences at Hopkins. "Several years ago we found that it does actually make myristate as well as other fatty acids, and now we found that it uses a biochemical pathway we never knew to look for."

They learned about this new fatty acid-making pathway by hunting the trypanosome genome for stretches of DNA known to be involved in fatty acid synthesis in other organisms, like animals and plants.

The researchers reasoned that knocking out the fatty acid-making genes would prevent the parasite from making myristate and other fatty acids.

But when one member of the research team, Jennifer Stephens, knocked out a single gene in the trypanosome known to make fatty acids in other organisms, there was no change in the parasite's ability to make myristate. Surprised, the researchers then examined the trypanosome genome more carefully and discovered enzymes that in other organisms are known to increase the size of a fatty acid molecule - dubbed elongases, for making fatty acids longer - but never have been shown to actually make a new fatty acid molecule.

Lee knocked out these elongases to see if the parasite might have difficulty making fatty acids. To the researchers' surprise, the parasites lacking elongases were unable to make the 14-unit myristate or other fatty acids.

"A novel feature of the elongase pathway is that it contains four different enzymes that take turns in elongating fatty acids," says Lee. "This modular pathway allows the parasite to control the size of the fatty acids it makes."

"It turns out that trypanosomes use an entirely unique mechanism of making fatty acids. No other organism ever studied uses elongases to make them," says Englund, suggesting that attacking biochemical pathways that make fatty acids could be a way to treat sleeping sickness. According to the researchers, the research community is extremely interested in developing drugs that target bacterial enzymes involved in fatty acid synthesis. An example of one is called isoniazid, which currently is used to treat tuberculosis.

"Trypanosomes cause significant health problems in remote areas of Africa with poor health care," says Englund. "There is tremendous need for new drugs to cure these diseases."

Source: Johns Hopkins Medical Institutions