

MARCH 01, 2006

A Case of Mistaken Molecular Identity

Researchers in Argentina have determined that night blindness is a new clinical symptom of Chagas disease. A team led by Howard Hughes Medical Institute (HHMI) international research scholar Mariano Jorge Levin and Cristina Paveto of the Institute for Genetic Engineering and Molecular Biology (INGEBI), National Council of Scientific Research and Technology in Buenos Aires, found that the immune system of individuals with the tropical disease can shut down a key reaction in the retina, causing night blindness.

“This is a new observation, a new clinical symptom of Chagas disease,” said Levin, head of the Laboratory of the Molecular Biology of Chagas Disease at the University of Buenos Aires, Argentina. Levin and colleagues report their findings in the March 2006, issue of the *FASEB Journal*.

"This is a new observation, a new clinical symptom of Chagas disease."

- Mariano Jorge Levin

Chagas disease affects people living in regions of Latin America where insects carrying the parasite *Trypanosoma cruzi* thrive in crowded and substandard housing. At night, the insects emerge and bite, transferring the Chagas parasite into a new host. Their victims are often children. After an acute infection characterized by swollen eyelids, those infected usually feel better. But the parasite remains active inside them, in a chronic phase of infection, quietly invading cells and stimulating the immune system. As a result, people can develop heart and gastrointestinal problems months or years after being infected. Some 30,000 people die each year from Chagas disease, according to the World Health Organization, but the number of people who are carrying latent infections is unknown.

“We now know that Chagas patients may have trouble seeing at night,” said Levin. “And this gives us additional motivation to improve conditions for people living in areas where Chagas disease is common.”

Silvia Matsumoto, a physician from the Dr. Teodoro Alvarez Hospital in Buenos Aires and first author of the paper, launched the investigation after noticing Chagas patients complaining about vision problems. “This was her idea, that the same antibodies that touch the heart cells might also block rhodopsin,” said Levin.

Matsumoto conducted thorough eye examinations of 45 Chagas disease patients with heart problems. She found that under bright conditions, the Chagas patients performed comparably to 50 healthy control individuals. But in the dark, 37 of 45 (82 percent) Chagas patients had trouble seeing with at least one eye, and 19 of 45 (42 percent) had trouble with both eyes. Matsumoto then approached Paveto, and both contacted Levin, whose laboratory was well-stocked with antibodies from Chagas patients and who had already developed the tests needed to study molecular mimicry.

In previous research, Levin and colleagues showed that the immune systems of patients infected by *T. cruzi* generate antibodies that attack the parasite but also cause damage to heart cells. Levin suspected “molecular mimicry” as the cause of the misguided attack. Molecular mimicry occurs when a molecule that is part of an infectious agent resembles a molecule native to the body. Eventually, the immune system begins to mistake the native molecule for the invader. Levin's investigations revealed that an intra-cellular *T. cruzi* protein resembles the beta1-adrenergic receptor on the surface of heart cells, a finding that helped explain why Chagas patients develop certain heart problems.

Now, it turns out, molecular mimicry can also upset the delicate machinery inside retinal cells. Levin and his team found that antibodies geared to attack *T. cruzi* also block rhodopsin, a molecule that converts light into electrical impulses sent to the brain. “Rhodopsin takes light and transforms it - that's its function,” said Levin.

To demonstrate molecular mimicry in the retina, Paveto extracted rhodopsin from cow's eyes. Through a series of tests, the team showed that cow rhodopsin, which is similar to the human protein, reacts with antibodies produced by Chagas patients.

“We showed that the same antibodies that attack heart cells can also interfere with rhodopsin,” Levin said. “This is important, because it enlarges the concept of molecular mimicry in Chagas disease.” Rhodopsin and beta1-adrenergic receptors in heart cells belong to the same class of molecules, a subfamily of the G-protein-coupled receptors, he pointed out.

Paveto, an independent researcher at INGEBI—an institute that is home to three HHMI international research scholars—conducted much of the painstaking work on the project by developing an original method to test rhodopsin function, said Levin.

Levin said that Chagas patients' vision problems are caused exclusively by the antibodies that block rhodopsin, and not by inflammation. “In the hearts of Chagas patients, we see scarring because there is a complex reaction that causes inflammation,” he said. “But there are no such scars in the eyes of Chagas patients with reduced vision.”

“No one knew about the night blindness, so we don't know, for instance, if Chagas patients have more accidents at night,” Levin added. “That's one of many ideas to explore now. The research also points out that we need new drugs or vaccines to stop the parasite, and at a social level, it stresses the need to improve living conditions of Chagas patients, particularly those living in rural areas.”