Researchers reveal genetic secrets of devastating human parasite

September 20 2007

An international team of researchers has revealed the genetic secrets of one of the world's most debilitating human parasites, Brugia malayi (B. malayi), which the World Health Organization estimates has seriously incapacitated and disfigured more than 40 million people around the globe.

The study, which appears in the September 21 issue of the journal *Science*, reveals dozens of potential new targets for drugs or vaccines and should provide new opportunities for understanding, treating and preventing elephantiasis, the disfiguring disease caused by the B. malayi parasite. In addition, understanding how this particular parasite has adapted to humans may help organ transplant researchers, according to the authors.

More than 150 million people worldwide are infected with filarial parasites—long, thread-like microscopic worms that can live for years inside the human body and cause severe, debilitating diseases. The female B. malayi worms can live up to eight years in the human body, eventually leading to a ghastly, disfiguring disease known as elephantiasis, which is characterized by excessive buildup of lymphatic fluid in the body and extreme swelling in limbs, trunk or head. People can be affected when bitten by infected insects or spiders.

The longevity of this parasite complicates treatment because existing drugs target the larvae and, thus, do not completely kill the worms. The drugs often must be taken periodically for years, and the worm can cause

a massive immune reaction when it dies and releases foreign molecules in the body.

According to first author, Elodie Ghedin, Ph.D., assistant professor of infectious diseases, University of Pittsburgh School of Medicine, having a complete genetic blueprint of the organism will undoubtedly lead to the development of much better therapies. “The genomic information gives us a better understanding of what genes are important for different processes in the parasite’s life cycle. So, it will now be possible to target these genes more specifically and interrupt its life cycle,” explained Dr. Ghedin, who led the sequencing project while at The Institute for Genome Research, which is now part of the J. Craig Venter Institute, a not-for-profit research organization in Bethesda, Md.

Dr. Ghedin led a team of scientists from research institutions around the globe in analyzing the 90 million base pair genome of B. malayi. From the sequence analysis, they predicted approximately 14,500 to 17,800 protein coding regions, or genes, in the B. malayi genome, which was in agreement with previous estimates. Comparative analysis of the B. malayi genome with that of another nematode, Caenorhabditis elegans, revealed that more than 20 percent of the predicted proteins in B. malayi are specific to the parasite.

Based on this finding, Dr. Ghedin and her colleagues suggested that these B. malayi-specific genes—almost 2,000 in all— constitute an “interesting list” of initial candidates for functional studies of the gene products. In addition, from the genome sequence, Dr. Ghedin and her co-investigators identified several metabolic pathways containing dozens of gene products that they believe are likely to be helpful for the discovery of more targeted and effective drug therapies. These include pathways involved in molting, nuclear receptor responses, collagen processing, neuronal signaling, protein phosphorylation (i.e., protein kinases) and host and endosymbiont metabolism.

“Insights into the gene activation pathways of B. malayi will undoubtedly speed the pace of discovery of new treatments. And any new interventions to reduce the burden of disfiguring elephantiasis around the world will indeed be welcome,” said Donald Burke, M.D., dean of the University of Pittsburgh Graduate School of Public Health.

In addition, when the researchers compared the sequences of predicted gene products (proteins) of B. malayi to that of interleukins, chemokines and other immune signaling molecules from humans, they identified a number of candidates they believe are responsible for allowing the nematode to evade immune detection. According to the investigators, these proteins may be immune modulators that promote the survival of the parasite or allow its development.

Understanding how this particular parasite has adapted to humans may yield medical benefits far beyond treating elephantiasis, says collaborator Alan L. Scott, Ph.D., of the Bloomberg School of Public Health at Johns Hopkins University. “Parasitic worms are a lot like foreign tissue that has been transplanted into the human body. But unlike baboon hearts or pig kidneys, which the immune system quickly recognizes as foreign and rejects, worms can survive for years in the body. Discovering how they do so may someday benefit transplant surgery,” explained Dr. Scott.

Source: University of Pittsburgh