Crucial gene activator in slow-killing parasite identified

5 January 2012

In the complicated life cycle of ancient flatworms that cause schistosomiasis, Case Western Reserve University researchers have identified a gene activator crucial to development of the parasites within humans - a potential target for a vaccine.

A description of the activator, which turns on rapid growth, is in the online journal *PLoS Neglected Tropical Diseases*.

Schistosomiasis, which causes organ damage and failure, afflicts more than 200 million people worldwide, killing 280,000 annually. Another 400 million people are at risk for the disease.

For decades, a single drug, praziquantel, has been used to kill the worms, and scientists are concerned the drug may become useless. The worms, called schistosomes, have shown they can develop resistance to praziquantel in the lab and there is currently no other drug to treat the disease.

Beyond that concern, the lack of a vaccine leaves human hosts in a cycle of their own: becoming infected, taking praziquantel, becoming reinfected - multiple times - due to the prevalence and ease of contracting the parasite in rivers and ponds in Asia, Africa and South America. Repeated exposure can add up to illness and death.

"This is really a disease of poor people," said Emmitt Jolly, professor of biology at Case Western Reserve and senior author of the paper. "The strategy to combat the disease cannot be expensive."

Jolly and John Milligan, a technician in Jolly's lab and lead author, spent two years studying, identifying and characterizing the protein, and gene activator, myocyte enhancer factor 2, commonly referred to at Mef2, in the flatworm's life cycle.

Depending on the phase of development, the schistosome lives in snails, in freshwater or in humans. From the snail, it becomes a tiny free swimmer that penetrates human skin. The parasite enters blood vessels and feeds on blood cells.

Sexually mature schistosomes congregate in blood vessels in a part of the abdomen called the mesentery. They mate and lay 300 to 1,000 eggs per day that migrate through the liver. About half the eggs are passed outside with urine and feces, depending on the species, and half get stuck in the body.

Upon reaching fresh water, the half excreted hatch into free swimmers that enter and grow in snails.

The half that remain in the body build up and cause an immune response. The eggs become encapsulated in granulomas, immune cells that wall off the foreign material. The result is significant organ damage, particularly in the liver, spleen, and intestine, but also other organs. Schistosomes can live and lay eggs for decades, the build-up of the granulomas slowly sickening and killing the host.

Mef2 is found in plants and yeast on up to humans. The activator is essential to muscle, nerve and bone development in humans, but how it works in flatworms was unknown.

Jolly and Milligan found, by homology, the protein appeared similar to Mef2 in yeast. Mef2 has two parts that act independently: one part binds to DNA, the second part activates gene expression.

When the researchers combined the schistosome gene activator with the DNA binder of yeast, the combination switched on the same yeast gene as the pure yeast gene activator.

They found that in the Schistosome, Mef2 expression is turned up right after the swimmer enters the human host. During this time, the

parasites grow from 100 micrometers in length to 10 to 16-millimeter worms.

Praziquantel is most effective when schistosomes start producing eggs inside human hosts. A vaccine could prevent the parasite from reaching sexual maturity and laying eggs inside of hosts - thereby preventing schistosomiasis, the researchers say.

Although Mef2 is present in humans, the portion of schistosome Mef2 that switches on gene activity is so different from human Mef2 that "We can target that part, and not affect the host," Jolly said.

Milligan and Jolly are working with other researchers to further understand schistosome Mef2 and are hopeful the work will lead to an alternative to praziquantel or a complimentary drug.

Provided by Case Western Reserve University