Researchers show host Mta1 gene is required for optimal survival of schistosome parasites

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By using mice lacking a crucial gene that controls the process of chromatin remodeling of cytokines including those responsible for inflammation and comparing them to normal wild type mice with the gene, researchers at the George Washington University School of Medicine and Health Sciences have shown that the gene, Mta1, is essential for the parasite Schistosoma haematobium to establish a productive infection and survival in the host.

Schistosomes are flukes (helminth worms) that can infect people when they come into contact with water carrying the parasite. They proliferate and cause chronic inflammation and fibrosis in the liver, and many migrate to the bladder, causing inflammation, granulomas, and eventually, bladder cancer. S. haematobium is responsible for two-thirds of the world's 200 to 400 million cases of human schistosomiasis, resulting in an estimated 280,000 deaths per year.

Publishing in the July issue of the journal *Hepatology*, the researchers demonstrated the role of Mta1, the metastasis-associated protein-1 (MTA1) gene, in the survival of schistosomes. They infected two strains of mice with schistosome cercariae, a larval stage of the parasite, by immersing their tails in water containing cercariae, from which the cercariae penetrated the skin. The wild type mice had the intact Mta1 gene, and Mta1-/- mice lacked the gene but were normal in other respects.

At various times after infection, blood was taken from the portal

circulatory system of the liver to look for worms, and parasite eggs were quantified from the liver tissue. "At the twelfth week of infection we found that the wild type mice, that is, the mice in which the gene was intact, had severe granulomatous lesions in the liver. The worm count was very high, and in the mice that did not have the gene, we did not have any worms. Neither did we have any eggs that we could collect from the portal perfusion," said lead author Sujit Nair, PhD, Assistant Research Professor in the department.

A total of 15 worms were recovered from the wild type mice but none from Mta1-/- mice. Similarly, wild type animals yielded 6556 eggs per gram of liver tissue while no eggs were evident in the Mta1-/- livers. The researchers confirmed that the Mta1-/- mice had been successfully infected with schistosomes by checking their serum antibody responses to the parasites. Both strains showed increasing antibody responses to antigen from the worms over the course of the infection. However, only the wild type mice made a strong antibody response to egg antigen, indicating a lack of egg production and full development to adulthood in the Mta1-/- mice.

The researchers concluded from these results that absence of the Mta1 gene does not compromise the mice's susceptibility to S. haematobium infection, but a lack of metastasis-associated protein-1 limits the survival and/or maturation of schistosomes in the host, and possibly egg release and deposition as well.

Senior author Rakesh Kumar, PhD, Professor and Chairman of the Department of Biochemistry and Molecular Biology in the School of Medicine and Health Sciences, explained that expression of MTA1, a nuclear protein, regulates the expression of inflammatory cytokines that are produced by Th1 and Th2 cells of the immune response. By increasing the expression of MTA1 in the wild type mice, the parasite "hijacks" MTA1, "which in turn will allow it to up-regulate pro-

inflammatory cytokines, and these pro-inflammatory cytokines in turn will provide a favorable atmosphere for the pathogens to grow and cause a persistent inflammation. And it's the persistent inflammation over time which we believe can lead to cancer," he said. "If we take out MTA1, the entire inflammatory cascade will be significantly reduced."

Dr. Kumar said previous studies have used mice lacking aspects of their immune systems to study parasitic infections, but this is the first study to show a relationship between the host MTA1 and the schistosome parasite and the first "to show, using immune competent mice... that there is a deregulation of Th1 and Th2 responses in the Mta1-/- mice following parasite infection."

Co-author Peter Hotez, MD, PhD, Chair of the Department of Microbiology, Immunology, and Tropical Medicine at the University and President of the Sabin Vaccine Institute, said S. haematobium is one of the most important causes of cancer in the world but is often neglected in the developed world because it affects "the poorest regions of sub-Saharan Africa."

By providing insight into the mechanism by which worms cause inflammation, the current study has implications beyond the major cancer-causing flukes, and the findings may potentially extend to all worm parasites.

Furthermore, Dr. Hotez said the Schistosomes also cause granulomatous lesions on the cervix, uterus, and lower female genital tract. "Now we're just beginning to realize that this is an important problem for girls and women," he said. "Those granulomas are associated with a three- to four-fold increase in the horizontal transmission rate of HIV/AIDS. So this parasite may be one of the most important co-factors in the transmission of AIDS."

"From the on-going work in the laboratory, it is clear that the significance of MTA1 master coregulator is not going to be limited to Schistosoma as MTA1 appears to be equally important for the survival of liver fluke" said Dr. Kumar. "It is now possible for the team to start develop strategies to target MTA1 to reduce the global burden of diseases caused by parasite-induced inflammation."

More information: To view this paper online on the journal Hepatology web site, visit: onlinelibrary.wiley.com/doi/10 … 2/hep.24354/abstract

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