MicroRNAs may be key to HIV's ability to hide, evade drugs

30 September 2007

Tiny pieces of genetic material called microRNA (miRNA), better known for its roles in cancer, could be a key to unlocking the secrets of how HIV, the AIDS virus, evades detection, hiding in the immune system. Researchers at Jefferson Medical College in Philadelphia have shown that when an individual infected with HIV receives a powerful cocktail of antiviral agents called HAART (highly active antiretroviral therapy), the virus calls on miRNAs to help it remain quiet and practically undetectable, temporarily shutting down its ability to replicate and infect.

The work, which appears September 30, 2007 in an early online edition of the journal *Nature Medicine*, may also have implications for new treatment strategies against the virus. According to Hui Zhang, M.D., Ph.D., associate professor of Medicine in the Division of Infectious Diseases at Jefferson Medical College of Thomas Jefferson University, who led the work, if researchers can learn to manipulate miRNA's inhibitory effect on HIV, they might be able to devise strategies to bring the virus out of hiding, or "latency," making it vulnerable to drugs and the body's immune system.

While HAART can drive the number of HIV particles in the blood to practically undetectable levels, the virus is not eliminated. It hides in "resting" immune system CD4 T cells in the body, including the testis, brain, and other places. The drug combination has to be taken the rest of the patient's life; if halted, the virus becomes active again.

"HIV latency and how to eliminate the replication-competent – and hidden – virus are big problems," Dr. Zhang explains, noting that the molecular mechanisms that are responsible for latency are unclear.

Dr. Zhang, post-doctoral fellow Jialing Huang, Ph.D., and their colleagues may have come across one possible explanation. HIV, they have found, recruits cellular miRNA – noncoding genetic material that has been shown to play a variety of roles in cancer and in biological regulation – in resting T cells to "control the translation of viral RNA into protein." This is the last step in the creation of HIV antigens, which make the virus visible to the immune system.

The team showed that a cluster of miRNAs bind to a certain location on the viral RNA, which in turn, blocks the creation of important proteins, and HIV replication. Resting CD4 T cells, they found, are "enriched" with more than the normal amount of these miRNAs compared to the activated T cells. When the researchers used antisense technology to block miRNA-caused viral inhibition, they found that the HIV again was active and able to replicate – proving miRNA's critical role in maintaining latency.

While Dr. Zhang and his team continue to study how cellular miRNA contributes to latency, he notes that using miRNA inhibitors "might become a kind of therapeutic approach to get the virus out of hiding, making it visible and a target" for the immune system. "That's the next step," he says.

Source: Thomas Jefferson University