Retrovirus in the human genome is active in pluripotent stem cells

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A retrovirus called HERV-H, which inserted itself into the human genome millions of years ago, may play an important role in pluripotent stem cells, according to a new study published in the journal *Retrovirology* by scientists at UMass Medical School. Pluripotent stem cells are capable of generating all tissue types, including blood cells, brain cells and heart cells. The discovery, which may help explain how these cells maintain a state of pluripotency and are able to differentiate into many types of cells, could have profound implications for therapies that would use pluripotent stem cells to treat a range of human diseases.

"What we've observed is that a group of endogenous retroviruses called HERV-H is extremely busy in human embryonic stem cells," said Jeremy Luban, MD, the David L. Freelander Memorial Professor in HIV/AIDS Research, professor of molecular medicine and lead author of the study. "In fact, HERV-H is one of the most abundantly expressed genes in pluripotent stem cells and it isn't found in any other cell types."

In the study, Dr. Luban and colleagues describe how RNA from the HERV-H sequence makes up as much as 2 percent of the total RNA found in pluripotent stem cells. The HERV-H sequence is controlled by the same factors that are used to reprogram skin cells into induced pluripotent stem (iPS) cells, a discovery that garnered the 2012 Nobel Prize in Physiology or Medicine. "In other words, HERV-H is a new marker for pluripotency in humans that has the potential to aid in the development of iPS cells and transform current stem cell technology," said Luban.

When a retrovirus infects a cell, it inserts its own genes into the chromosomal DNA of the host cell. As a result, the host cell treats the viral genome as part of its own DNA sequence and begins making the proteins required to assemble new copies of the virus. And because the retrovirus is now part of the host cell's genome, when the cell divides, the virus is inherited by all daughter cells.

In rare cases, it's believed that retroviruses can infect human sperm or egg cells. If this happens, and if the resulting embryo survives, the retrovirus can become a permanent part of the human genome, and be passed down from generation to generation. Scientists estimate that as much as 8 percent of the human genome may be comprised of extinct retroviruses left over from infections that occurred millions of years ago. Yet these sequences of fossilized retrovirus were thought to have no discernible functional value.

"The human genome is filled with retrovirus DNA thought to be no more than fossilized junk," said Luban. "Increasingly, there are indications that these sequences might not be junk. They might play a role in gene expression after all."

An expert in HIV and other retroviruses, Luban and his colleagues were seeking to understand if there was a rationale behind where, in the expansive human genome, retroviruses inserted themselves. Knowing where along the chromosomal DNA retroviruses might attack could potentially lead to the development of drugs that protect against infection; better gene therapy treatments; or novel biomarkers that would predict where a retrovirus would insert itself in the genome, said Luban.

Turning these same techniques on the retrovirus sequences already in the human genome, they discovered a sequence, HERV-H, that appeared to be active. "The sequences weren't making proteins because they had been so disrupted over millions of years, but they were making these

long, noncoding RNAs," said Luban.

Specifically, the HERV-H sequence was making abundant amounts of RNA in human embryonic stem cells—and only stem cells. In total, there are more than 1,000 HERV-H retrovirus genomes scattered throughout the human genome. The Luban lab also found high levels of HERV-H RNA in some iPS cells. Other iPS cells, perhaps those lines that were not sufficiently reprogrammed to pluripotency, had lower levels of the HERV-H RNA, another indication that HERV-H may be an important marker for pluripotency.

Interestingly, the HERV-H genes that were expressed in human pluripotent stem cells are only found in the human and chimpanzee genomes, indicating that HERV-H infected a relatively recent ancestor to humans, said Luban.

"Once upon a time HERV-H was an invader to our genome and perhaps caused diseases like AIDS or cancer," said Luban. "Now it seems that a kind of détente has been reached. Not only that, but this ancient invader may one day be exploited by clinicians to cure people of a wide range of diseases using stem cell therapies."

Luban and colleagues will next try to determine the specific mechanisms by which HERV-H contributes to pluripotency.

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