Researchers Discover Virus Using Same Tools as Host Cell

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Duke University Medical Center researchers have discovered that the virus which causes Kaposi's Sarcoma encodes a molecule for controlling gene regulation nearly identical to one found normally in human cells. Both versions of the molecule, known as a microRNA, appear to play a role in the development of cancer.

In normal cells, microRNAs are able to slow and stop a cell's production of a particular protein. However, within the past several years, scientists have discovered that many microRNAs are also implicated in the development of cancers. One in particular, called miR-155, has been linked to lymphoma, cancerous white blood cells.

Certain viruses also encode their own microRNAs, but their function has been unclear. One such virus is Kaposi's Sarcoma Associated Herpesvirus (KSHV) which causes a rare skin cancer that disproportionately affects HIV-infected individuals.

Duke University Medical Center researchers report in the Dec. 13 issue of the journal *Nature* that a microRNA expressed by KSHV has evolved to exploit the same cancer-causing pathway as miR-155. This may represent the first example of a viral microRNA cancer-causing gene.

"The viral microRNA expressed by Kaposi's Sarcoma Associated Herpesvirus (KSHV), is remarkably similar in both structure and function to miR-155, which has previously been associated with lymphoma," said Bryan R. Cullen, Ph.D., professor in the Department of

Molecular Genetics and Microbiology and senior author on the paper. "This microRNA may represent one mechanism behind KSHV-induced cancers."

The researchers demonstrated that the viral microRNA and miR-155 normally found in cells regulate the same genes, including several associated with B cell function and cell cycle regulation. KSHV infection may promote B cell tumors by repressing one or more of these genes, Cullen explained. Therefore, turning off viral microRNAs, "could be a step toward a treatment for virus-induced cancers," he said.

Cullen investigated that possibility with help from technology developed by Regulus Therapeutics, a biopharmaceutical company formed by a joint venture between Alynlam Pharmaceuticals and Isis Pharmaceuticals. The company was the first to develop chemically engineered molecules, called antagomirs, which can be used to turn off specific microRNAs.

The researchers were able to use an antagomir targeted to the viral microRNA to reactivate the expression of a protein it suppressed. Using this method, they hoped to nullify the cancer-promoting effects of the viral miRNA.

Antagomirs could be used to permanently treat other viruses that make microRNAs, like herpes simplex virus, possibly through a topical application, Cullen said.
Eventually, other cancer-causing viral microRNAs could be blocked with specifically targeted antagomirs.

Other herpes viruses, such as Epstein-Barr virus, contain microRNAs that are not similar in structure or function to miR-155. However, Epstein-Barr virus appears to promote cancer via a different route: by activating the expression of naturally occurring miR-155 in infected B-

cells, the researchers note. Though miR-155's role is unclear, it appears to push white blood cells toward growth as part of the immune response. These findings may reveal an interesting evolutionary technique through which viruses hijack the machinery of their host cells in order to replicate.

Source: Duke University Medical Center