The silence of the genes

April 22 2010

Viruses have evolved a broad range of strategies that enable them to evade the immune systems of their hosts. A team of researchers led by LMU virologist Professor Jürgen Haas has been studying a novel, recently discovered mechanism that pathogenic viruses exploit for this purpose, and their latest results could point the way to new antiviral therapies. The mechanism is based on the production of short RNA molecules, called microRNAs, by the virus.

RNA is chemically related to the genetic material DNA, and full-length RNA copies of gene sequences specify the structures of all cell proteins. MicroRNAs (miRNAs), on the other hand, play a crucial role in regulating gene expression.

"Viruses use them to regulate the expression not only of their own genes, but also of host genes", says Haas. "Because human cells also produce regulatory miRNAs, the viral molecules do not provoke an immune response". Haas and his team, in cooperation with several other groups in Germany and abroad, have now identified 158 human genes that are targeted by miRNAs synthesized by two types of herpesvirus that can cause cancer in humans. "Our findings provide fundamental insights into the functions of viral miRNAs", according to Haas. "The viral genes that encode miRNAs could offer points of attack for targeted, and urgently needed, antiviral agents." (*Cell Host and Microbe* online, 22 April 2010)

Gene regulation, the biological process by which genes are turned on and off, is a fundamental element of cell function. A gene is a defined segment of the double-stranded genomic DNA. When a gene is active,

the sequence of such a segment is transcribed from one DNA strand into RNA copies. The RNAs known as messenger RNAs (mRNAs) specify the sequences of all the proteins required by a given cell type by a second process known as translation. The proteins made by a cell determine its structure and function, so the appropriate proteins must be produced in the correct amounts and at the right time. Gene expression is therefore strictly controlled. In recent years it has become clear that short RNAs known as microRNAs (miRNAs) play a crucial role in this process in most organisms. The sequences of miRNAs are "complementary" to parts of mRNAs, and bind to them to form partially double-stranded structures. This prevents synthesis of the corresponding proteins and may lead to the degradation of the mRNAs. It is estimated that the expression of 20-30% of all human genes is regulated in this way. "The system acts as a sensitive regulator for fine tuning of many cell functions", says Professor Jürgen Haas of the Max von Pettenkofer Institute at LMU Munich. "It is also essential for proper tissue development."

Viruses too use miRNAs to regulate expression of their genes. But some viral miRNAs do double duty by intervening in the regulation of the host's genes. Viruses consist only of a DNA or RNA genome wrapped in a protein coat, and they must infiltrate into cells in order to reproduce. Having invaded a suitable cell, a virus essentially reprograms it to produce new viral particles. "The battle between virus and host begins as soon as the first cell has been infected", reports Haas. "In principle, the immune system is capable of recognizing infected cells and inducing them to undergo programmed cell death or apoptosis. Apoptosis involves the orderly destruction of cells -- and any viruses they may contain -- but viruses have developed multiple ways of preventing it. Indeed, to enhance their own replication, some viruses even cause their host cells to enter a state of uncontrolled proliferation, and this can ultimately lead to cancers, as is the case with certain herpesviruses that infect humans."

Two of these, Epstein-Barr Virus (EBV) and Kaposi Sarcoma-Associated Herpes Virus (KSHV), cause chronic infections of B cells (the antibody-producing cells of the immune system) and both can provoke the development of malignancies. It was already known that herpesviruses carry genetic information for the synthesis of miRNAs. Haas and his collaborators set out to identify the host mRNAs on which these inhibitory molecules might act. They first isolated the molecular complex that brings the snippets of viral RNA and their targets together. Microarray analysis of the associated host mRNAs then allowed the investigators to identify the corresponding cellular genes affected. "We were able to identify 158 genes in this way", says Haas. "Many of them code for proteins involved in antiviral defence, so it makes sense that the virus should try to turn such genes off. Our work not only shows how viruses control host gene expression, it identifies viral miRNA genes as possible targets for innovative antiviral agents. If we could design and deliver therapeutic miRNAs tailored to bind to viral miRNAs, we might be able to defeat the virus by turning its own weapons against it."

More information: "Systematic Analysis of Viral and Cellular MicroRNA Targets in Cells Latently Infected with Human γ-Herpesviruses by RISC Immunoprecipitation Assay"; Lars Dölken et.al., Cell Host and Microbe online, 22. April 2010
Doi:10.1016/j.chom.2010.03.008

Provided by Ludwig-Maximilians-Universität München