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Papillomavirus Oncogene Silences Innate Immune Response

Human papillomavirus type 16, the most common cause of cervical cancer, silences a key signaling molecule of immune response in its host cells. Once the body's own immune defense is missing, the pathogens are able to infect the cells of the cervical mucosa even more successfully. Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have found out that the viral E6 oncogene is responsible for this mechanism.

In the 1980s, Harald zur Hausen and his co-workers discovered that specific types of human papillomavirus (HPV) cause cervical cancer. Scientists soon found out how these pathogens cause cells to degenerate. It is known today that the main culprits are viral proteins E6 and E7. Both proteins switch off different cellular control functions, thus promoting cell growth.

Professor Dr. Frank Rösl and his co-workers at DKFZ have now discovered another mechanism by which the E6 oncoprotein of high-risk HPV16 promotes carcinogenesis. The oncogene silences production of an immune protein called interferon-kappa. Interferons are proteins which are part of our immune system and are responsible primarily for stimulating the immune response to viruses and tumors. Interferons are produced by white blood cells and other cell types. Interferon-kappa is relevant for HPV infections, because it is produced mainly in cells of the skin and mucosa (keratinocytes) which are the preferred hosts of the viruses. If interferon-kappa is not working in cells, other proteins involved in immune defense also cease to function properly.

Dr. Bladimiro Rincon-Orozco of Rösl's team has now shown for the first time that HPV16 switches off the interferon-kappa gene by biochemical modification of DNA. Such alterations of the genetic material are called epigenetic mutations. Studying HPV infected cells in a culture dish, the research team observed that interferon-kappa is epigenetically silenced. They were later able to confirm this result in cervical cancer tissue samples.

"Interferon-kappa is an important part of what is called innate immunity," Frank Rösl explains. Using this evolutionary old defense mechanism, the body can defend itself immediately after being infected with pathogenic agents, while formation of the specific "acquired" immune system may take some time. "By switching off the interferon production, the viruses prevent infected cells from being destroyed by this type of immune response," says Rösl, explaining the strategy of the virus that causes cancer. In the next step, the researchers are planning to investigate whether administering interferon-kappa can slow down the growth of cervical cancer cells and may thus support treatment of the disease.

A picture is available at:
http://www.dkfz.de/de/presse/pressemitteilungen/2009/images/HPV_1.jpg

Legend: Electron micrograph of human papilloma viruses

Credit: Hanswalter Zentgraf, German Cancer Research Center

Bladimiro Rincon-Orozco, Gordana Halec, Simone Rosenberger, Dorothea Muschik, Ingo Nindl, Anastasia Bachmann, Tina Maria Ritter, Bolormaa Dondog, Regina Ly, Franz X. Bosch, Rainer Zawatzky und Frank Rösl: Epigenetic Silencing of Interferon-κ in Human Papillomavirus Type 16–Positive Cells. Cancer Res 2009; 69: (22) November 15, 2009

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,000 staff members, including 850 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Württemberg (10%).

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