GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION
50 Years – Research for A Life Without Cancer

No. 13 March 11, 2015 (Koh)

Deadly to cancer cells only:
A molecular cause for selective effectiveness of parvovirus therapy discovered

Parvoviruses can destroy cancer cells and are currently being tested in a preliminary clinical trial to treat malignant brain cancer. For their replication, the viruses need a particular enzyme in the cell. Scientists from the German Cancer Research Center (DKFZ) have now discovered that in healthy human cells, parvoviruses are unable to activate this enzyme. In many cases of malignant brain cancer, however, the enzyme is permanently active. As a result, this enables the viruses to replicate and to destroy the cancer cells. It accounts not only for the viruses' natural selectivity for cancer cells but also helps identify cancer patients who might benefit from parvovirus therapy.

Parvoviruses are a class of viruses that normally infect rodents; in humans, they do not cause any disease symptoms. However, they are able to infect and kill cancer cells. The details behind this biological selectivity on the part of the viruses have not been understood until now. “Since the viruses might soon play a role in cancer medicine, it is important to know why they replicate exclusively in tumor cells in humans,” says virologist Dr. Jürg Nüesch from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ).

In order to complete their life cycle within the cell and to produce the next generation of viruses, the viruses depend on the activity of a specific cellular enzyme called PDK1 kinase. This kinase acts like a main switch for numerous cellular functions. Normally, it is activated from the outside by growth factors that attach to the cell.

Nüesch and his colleagues, Séverine Bär and Jean Rommelaere, have now discovered that in the cells of mice, which are natural hosts for parvovirus H1, the virus is able to activate PDK1 via an internal pathway that is independent of growth factors. An enzyme complex called PKCη/Rdx is involved in this process. This complex transfers a phosphate group to a specific protein building block of PDK1, leading to its activation.

In normal human cells, however, where the virus cannot replicate, it is unable to activate PDK1 using this alternative pathway. When the researchers equipped these normal cells in the Petri dish with permanently activated PDK1, the virus was successfully able to infect the cells and replicate inside of them.

The situation is different in cancer cells, especially in glioblastoma – the most malignant kind of brain tumor. Nüesch and his colleagues examined 70 glioblastoma tissue samples and discovered that in 36 percent of these samples, PDK1 was already phosphorylated from the start and, therefore, permanently activated.

“For the cancer cells, permanent activation of PDK1 is biologically useful because it allows them to be independent of growth factors,” Nüesch explains. “The parvoviruses, in turn, exploit this for their own purposes. Thus, we have found, for the first time, a molecular cause for the virus’s natural selectivity for cancer cells. Additionally, in PDK1 phosphorylation we have discovered a biomarker that enables us to predict whether therapy with parvoviruses can be effective in a particular tumor."

In the treatment of brain cancer, one approach currently being tested is the use of substances that block growth factor receptors on the cell surface. The detection of PDK1 phosphorylation also has predictive value in this regard. If PDK1 is activated via the alternative pathway, then the cancer cell is independent of growth factors; therefore, blocking them would not help the patient.

Under the leadership of Jean Rommelaere, scientists at the DKFZ have been studying parvoviruses since 1992. Their goal is to develop a viral therapy to attack glioblastoma. At Heidelberg Neurosurgical University Hospital, a preliminary clinical trial has been ongoing since 2011, where the safety of treatment with H1 virus is currently being evaluated.

Séverine Bär, Jean Rommelaere, and Jürg P.F. Nüesch: PKCη/Rdx-driven Phosphorylation of PDK1: A Novel Mechanism Promoting Cancer Cell Survival and Permissiveness for Parvovirus-induced Lysis. Plos Pathogen 2015, DOI: 10.1371/journal.ppat.1004703

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