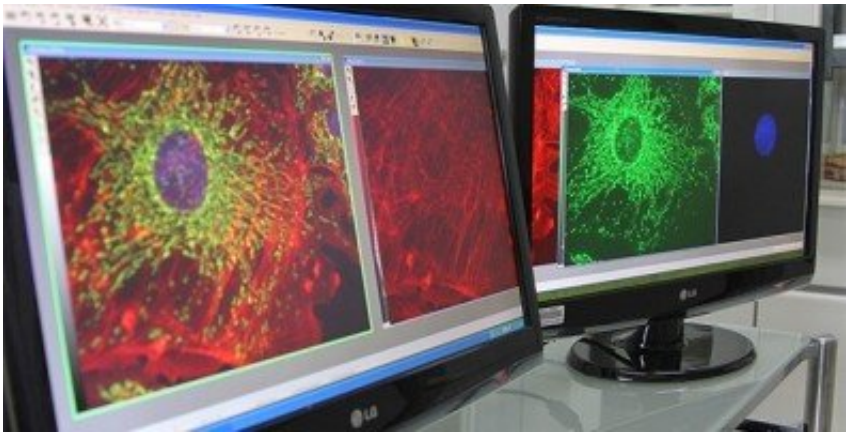
Genetically modified virus combats prostate cancer

June 27 2019



In a study with mice, a gene therapy developed in Brazil kills cancer cells and avoids adverse side effects when combined with chemotherapy. Credit: Marcos Santos / USP Imagens

Researchers at the São Paulo State Cancer Institute (ICESP) in Brazil have used a genetically manipulated virus to destroy tumor cells upon injection into mice with prostate cancer. The virus also made tumor cells more sensitive to chemotherapy drugs, halting tumor progression and almost eliminating tumors in some cases.

The results were obtained by a team led by Bryan Eric Strauss, head of the Viral Vector Laboratory at ICESP's Center for Translational Research in Oncology (CTO), and are described in an article in *Gene Therapy*.

"We used a combination of gene therapy and chemotherapy to combat prostate cancer in mice," said Strauss. "We chose the weapon we considered most likely to work as a tumor suppressant," he said, referring to p53, a gene that controls important aspects of cell death and is present in both rodents and humans.

In the laboratory, the gene was inserted into the genetic code of an adenovirus. The modified virus was then injected directly into tumors in mice.

"First, we implanted human prostate cancer cells in the mice and waited for tumors to grow. We then injected the virus directly into the tumors. We repeated this procedure several times. On two of these occasions, we also systemically administered cabazitaxel, a drug commonly used in chemotherapy. After that, we observed the mice to see if the tumors developed," Strauss said.

The experiments used several groups of mice, all of which were inoculated with prostate tumor cells. To verify the efficacy of the gene therapy, the researchers administered an unrelated virus to one of the groups as a control.

The second group received only the virus with p53. The third group received only cabazitaxel. The fourth group, corresponding to 25% of the mice, received a combination of the drug and the virus.

When the tumor cells were infected by the modified virus, it penetrated the cell nucleus—where genes act—and triggered cell death. The p53 gene was particularly effective at inducing cell death in prostate cancer.

"Individual treatments with p53 or cabazitaxel alone had an intermediate effect in terms of controlling tumor growth, but the combination had the most striking result, totally inhibiting tumors," Strauss said.

The experiments proved that the modified virus caused the death of the tumor cells it infected. "The association of the drug with gene therapy resulted in full control of tumor growth. In other words, we observed an additive or even synergistic effect. It can also be assumed that the virus with p53 made tumor cells more sensitive to the action of the chemotherapy drug," he said.

According to Strauss, the virus cannot be injected into the bloodstream. "For the therapy to work, we need to inject the virus directly into tumor cells," he said.

Tumors can evidently be controlled using chemotherapy drugs alone, he recalled, but the high doses required can have significant side effects. One is leukopenia, or loss of white blood cells, a constraint for this type of chemotherapy because it impairs the immune system.

"In our study, we used a subtherapeutic dose, which was not sufficient to control the tumor. This was done to avoid leukopenia," Strauss said.

Immune system

Destroying tumor cells with p53 does not guarantee that all cancer cells will be eliminated, including metastases. Stimulation of the organism's immune response was the answer found by the researchers.

According to Strauss, if the combination of p53 and cabazitaxel is not sufficient to activate the immune system, the use of a second gene in addition to p53 can be considered.

The interferon-beta gene was chosen for its key role in the immune system. Interferons are proteins produced by leukocytes (white blood cells) and fibroblasts that interfere with the replication of fungi, viruses, bacteria and tumor cells while also stimulating the defense activities of

other cells.

"Both p53 and interferon-beta can kill tumor cells. We wanted to combine them for cell death to wake up the immune system. This is known as immunogenic cell death," Strauss said.

Previous studies by the group served as a basis for the idea. When a combination of ARF (a functional partner of p53) and interferon-beta was inserted into the tumor cell nucleus, the mouse's immune system ceased recognizing the tumor cell as part of its organism and identified it as an external agent to be combated.

"When this happens, the immune system combats tumor cells both at the treatment site and in tumors located elsewhere," Strauss said.

"Our goal now is to refine these approaches. We're engaged in experiments to find out whether they deserve to advance to the stage of clinical trials in human patients."

More information: Rodrigo Esaki Tamura et al, Combination of cabazitaxel and p53 gene therapy abolishes prostate carcinoma tumor growth, *Gene Therapy* (2019). DOI: 10.1038/s41434-019-0071-x

Provided by FAPESP