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Vaporized viral vector shows promise in anti-cancer gene therapy

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A new lung cancer therapy employing a vaporized viral vector to deliver a cancer-inhibiting molecule directly to lung tissue shows early promise in mouse trials, according to researchers at the Ministry of Education, Science and Technology in Korea.

Gene therapy is an area of great promise, but delivery mechanisms, which have included intravenous injection and intratracheal instillation, have proven problematic for effective delivery of genetic therapy to lung tissues.

"Aerosol delivery targets the lungs specifically and represents a noninvasive alternative for targeting genes to the lung," wrote Myung-Haing Cho, D.V.M., Ph.D., professor at Seoul National University and principal investigator of the study. "The delivery of genes via aerosol holds promise for the treatment of a broad spectrum of pulmonary disorders and offers numerous advantages over more invasive modes of delivery."

The results of Dr. Cho's promising research will be published in the June 15 issue of the *American Journal of Respiratory and Critical Care Medicine*.

Lung cancer is the most common cause of cancer deaths worldwide, killing more people each year than breast, prostate and colon cancers combined. It costs the U.S. alone more than $9 billion a year, according to the Centers for Disease Control and Prevention. Most available

therapies—surgery, radiation and chemotherapy—offer transient relief at best and are typically ineffective in advanced stages of the disease. For this reason, novel therapies for lung cancer are of great interest.

Dr. Cho and colleagues targeted the Akt signaling pathway, which has been shown to be an important regulator of cell proliferation and cancer progression. A recent report found that 90 percent of non-small cell lung carcinomas were associated with the activation of the Akt signaling pathway. They chose a lentiviral vector, derived from a retrovirus and known for its ability to infect nondividing cells and effect persistent genetic changes. They transfected the lentiviral vector with a negative regulator of Akt signaling, carboxyl-terminal modulator protein (CTMP), which would theoretically inhibit Akt signaling, thus suppressing cancer cell proliferation and tumor growth.

Using a mouse model of lung cancer, the researchers designed a double-control study, exposing one-third of the mice to the aerosolized CTMP vector, one-third to the vector alone and one third were untreated.

"In this study, our main purpose was to determine if viral delivery of CTMP can provide useful tool for designing lung tumor treatment," said Dr. Cho. "We would like to demonstrate that CTMP can suppress lung tumor mass in the lungs and lentivirus may act as an effective carrier of CTMP."

After four weeks of twice-weekly treatments, the researchers found exactly that: both pathological and histological examination of the mice revealed that CTMP delivery suppressed lung tumor mass in the lungs of the mice. Furthermore, the number and volume of tumors were significantly decreased in CTMP-treated mice.

The researchers also found that CTMP increased apoptosis, inhibited angiogenesis and suppressed production of several proteins, such as

cyclin D1, CDK4 and CDK2, which are important in cancer cell growth.

"Our results demonstrated that lentivirus-mediated CTMP overexpression suppressed Akt activity and inhibited tumor progression," wrote Dr. Cho. "Repeated aerosol gene delivery may provide an effective noninvasive model of gene delivery and understanding the role of CTMP in the multistage lung tumorigenesis may be essential in developing effective therapeutics for lung cancer."

Source: American Thoracic Society (news : web)