Antibody slows tumor growth and metastasis in mice

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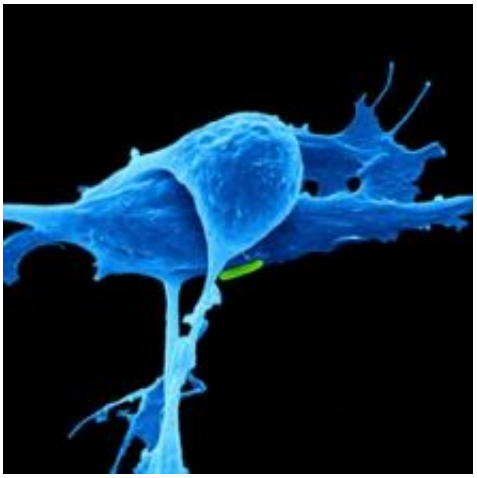

Johns Hopkins scientists report they have developed an antibody against a specific cellular gateway that suppresses lung tumor cell growth and breast cancer metastasis in transplanted tumor experiments in mice, according to a new study published in the February issue of *Nature Communications*.

The antibody, which they dubbed Y4, targets a potassium channel called KCNK9. Most commonly found in brain tissue and overabundant in lung, breast and other tumor cells, KCNK9 is among many gate like proteins that work to establish an electrical gradient that controls the flow of essential chemical ions, such as potassium in and out of cells that

need them to function. KCNK9's exact role in cancer is unclear, but scientists believe it helps tumor cells survive, grow and invade normal tissue.

"Our experiments do not predict how well the antibody would perform in cancer patients," says John Laterra, M.D., Ph.D., co-director of the Brain Cancer Program at the Johns Hopkins Kimmel Cancer Center and professor of neurology at the Johns Hopkins University School of Medicine. "But," he added, "the study points the way toward targeting this key channel in human cancers, particularly since KCNK9 is overexpressed in about 40 percent of breast and lung cancers."

Y4 was developed in the laboratory by Min Li, Ph.D., a study co-author formerly of the Johns Hopkins University School of Medicine and now at GlaxoSmithKline, by injecting mice with a human version of the KCNK9 protein to generate specialized cells that produce the KCNK9-specific antibodies. The antibody's ability to target KCNK9 attracted the attention of Laterra, who worked on the study with Li's doctoral student Han Sun, Ph.D.

When the researchers added Y4 to KCNK9-expressing human breast and lung cancer cells grown in the laboratory, the antibody reduced the cells' growth by between 25 to 65 percent, and triggered cell death in three of the cancer cell lines by between 5 and 30 percent. In further tests of the antibody, the scientists found that Y4 could slow the growth of human lung cancer cells transplanted into mice by up to 70 percent. The antibody did not shrink the lung cancer tumors or completely halt their growth. The drug also decreased the number of lung metastases in mice injected with mouse breast cancer cells, from an average of 30 metastases to an average of five after 25 days of treatment.

Laterra and colleagues also say they observed that the more KCNK9 is expressed in a tumor, the poorer the survival rates for lung and breast

cancer patients. They found that two-year survival rates for 35 people with squamous cell lung cancer with low levels of KCNK9 were 58 percent higher than 18 people with high levels. Ten-year survival rates for people with breast cancer were 10 percent higher in 175 patients with low KCNK9 levels, compared with 116 people with high levels of the channel.

Laterra says KCNK9 expression is not routinely measured in cancer patients, but if his study results are confirmed, he believes such testing should be considered. "We've generated a fair amount of evidence that targeting this channel alone can have antitumor effects," says Laterra. "We are now establishing more data on other common tumor types to find out what percentage are expressing this channel at levels that we feel would be sufficient to propose blocking the channel therapeutically one day."

Because ion channels control so many cellular activities, they often are targeted in other disorders by drug companies, such as the common topical anesthetic lidocaine and epilepsy drug phenytoin. But their similarities make them difficult to find drugs or small molecules that can strongly aim at and block a single channel such as KCNK9. "There have been drugs developed to inhibit these channels, but they've been inherently nonspecific," says Sun, the study's first author, who is now at City of Hope in California.

The researchers say Y4's antitumor potential will most likely be due to its ability to block the potassium channel, but there were also intriguing hints in their experiments with metastatic breast cancer in mice bred with normal immune systems that the antibody can also boost immune response against the tumors. It is possible, Laterra says, "that if you decorate cells that express this channel with our antibody, it may help activate immune T cells to kill the tumor cells."

Laterra says it might also be possible in the future to modify the antibody to improve its apparent antitumor immune response or to deliver the antibody in combination with other immune-stimulating drugs, such as checkpoint inhibitors that block proteins that shield cancer cells from immune system attacks.

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