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Lung cancer oncogene holds key to turning off cancer stem cells

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Scientists at the Mayo Clinic campus in Florida have found that the lung cancer oncogene PKCiota is necessary for the proliferation of lung cancer stem cells. These stem cells are rare and powerful master cells that manufacture the other cells that make up lung tumors and are resistant to chemotherapy treatment.

Their study, published in the Oct. 1 issue of *Cancer Research,* also shows that an agent, aurothiomalate, being tested at Mayo Clinic in a phase I clinical trial substantially inhibits growth of these cancer stem cells.

"Our data indicate that PKCiota is required for the earliest steps in the development of lung cancer, which is the expansion of tumor-initiating cells or cancer stem cells," says the study's senior author, Alan Fields, Ph.D., professor of pharmacology in the College of Medicine, Mayo Clinic, and chair of the Department of Cancer Biology at Mayo Clinic's campus in Florida.

"Lung cancer stem cells appear to be the major drivers in many common lung cancers, and in order for a therapeutic treatment to be effective, it has to disrupt these cancer stem cells," he says. "We show that aurothiomalate, the agent now being tested in lung cancer patients, can, in fact, target these cells."

Aurothiomalate was once used to treat rheumatoid arthritis, but the Mayo Clinic researchers discovered by screening thousands of Food and Drug Administration-approved drugs that it also can target PKCiota. The

agent is being tested in patients at Mayo Clinic's sites in Minnesota and Arizona and, based on this phase I trial, a phase II human clinical trial is planned to combine aurothiomalate with agents targeted at other molecules involved in cancer growth.

Dr. Fields and his colleagues were the first to discover that PKCiota is a human oncogene - an abnormal gene that cancer cells use to grow and/or survive. They found that PKCiota is genetically altered and over-expressed in a majority of lung cancers and that over-expression of the PKCiota gene in tumors predicts poor patient survival.

"We had previously shown that PKCiota is required to maintain tumor growth, but what this study sought to determine is whether PKCiota is involved in the initial steps of lung cancer development," Dr. Fields says.

Cancer stem cells are thought to hold the key not only to how lung tumors initially arise but also to how they are maintained and become resistant to treatment. Cancer stem cells are self-renewing and can also give rise to the cells that make up most of a tumor. In mice, an oncogene known as Kras is thought to transform normal lung stem cells into cancer stem cells, thereby initiating lung cancer, according to Dr. Fields. In the present study, the Mayo researchers established a strain of mice in which Kras can be activated at the same time that the PKCiota gene is inactivated. They found that when the PKCiota gene is inactivated, Kras was unable to cause errant growth and expansion of lung stem cells in mice, the process that initiates tumor formation.

"What this told us is that Kras requires PKCiota to transform the lung stem cells and make them proliferate," Dr. Fields says. "In other words, PKCiota is downstream from Kras, and is necessary for Kras to initiate lung tumor formation."

Because Dr. Fields and his colleagues had discovered that

aurothiomalate disables PKCiota, they tested whether this agent is effective against lung cancer that develops due to Kras mutation. "The drug showed potent inhibitory effects on the Kras-dependent proliferation of lung cancer stem cells both in cell culture and in animals," Dr. Fields says.

"That further suggests that a drug like aurothiomalate could have an effect on tumors that are dependent on either Kras or PKCiota for growth and survival, and that is potentially a lot of cancers," he says. "Aurothiomalate appears to be one of the few drugs available that can effectively target these critical cancer stem cells. In the clinic, however, it is likely that aurothiomalate will be most effective when combined with other agents designed to target other tumor survival pathways."

Source: Mayo Clinic (news : web)