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[Medicine] Academia Sinica's Researchers Find Cancer-initiating Cells in KrasG12D-induced lung Adenocarcinoma

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Academia Sinica Newsletter (2012/01/02) Lung cancer is the leading cause of cancer-related mortality worldwide; it is one of the most commonly diagnosed malignancies in developed countries and is a growing problem in developing countries. In 2010, there were 41,000 patients who died of cancer in Taiwan; among them, 20% died of lung cancer. Especially for women in Taiwan, lung cancer has been the number one cause of death in the ten most common cancers during the last 20 years. A research team led by Dr. John YU, Distinguished Research Fellow at the Institute of Cellular and Organismic Biology (ICOB), Academia Sinica, has identified cancer-initiating cells in KrasG12D-induced lung adenocarcinoma. These findings, which contribute to the search for new strategies for treatments of lung cancer, were published in the journal, Cancer Research, on December 1.

There are two common types of lung cancer: small cell lung cancer (15%) and non-small cell lung cancer (85%). Activation of a gene called Kras oncogene was found in 20%~40% of non-small-cell lung cancers, about 80% of which occurred with a mutation at codon 12. Recently there has been a tremendous amount of interest in identifying the cancer stem cells responsible for these tumors, i.e., their exact cellular origin, which may offer new insight on new treatments. In this study, Dr. YU's group reports the establishment of a new mouse model of lung cancer in which the KrasG12D gene is under the control of a "molecular switch". This switch allowed them to turn the cancer gene on and off and thereby control the formation and progression of lung cancer.

Mr. Huan-Chieh CHO in Dr. YU's laboratory, a graduate student from Graduate Institute of Microbiology and Immunology, National Yang-Ming University, used this model to identify the specific cell types from which non-small cell lung cancer originate. This finding promises to contribute to the development of methods to detect human lung cancers earlier and treat them more effectively.

Dr. YU's group reported the generation and analysis of transgenic mice (CCSP-rtTA/TetO-Cre/LSL-KrasG12D) in which KrasG12D is under the control of an antibiotic. Activating this gene in mice by feeding them Doxycycline gives them lung tumors. The group then used FACS fractionation to highly enrich for two special subtypes of lung cells called bronchiolar Clara cells and alveolar type II cells. The most aggressive tumors arose from bronchiolar Clara cells. Activated bronchiolar Clara cells were capable of generating secondary tumors that spread widely in the lung; these secondary tumors also had the ability to differentiate into a wide variety of tissue types and contained not only bronchiolar epithelial markers such as panCK, but also the intracellular differentiation marker, proSPC. This finding was consistent with the notion that cancer-initiating cells do not only self-renew, but can also differentiate into heterogeneous tissue types.

Tumors were also found to arise from alveolar type II cells in this mouse model, due to the CCSP promoter activity in these cells; but secondary tumors that arose from these cells were less aggressive and did not differentiate as broadly. They remained restricted only in the same alveolar region where they first arose, and remained mostly negative for panCK staining, suggesting they lacked the ability to differentiate into heterogeneous tissue types, unlike the "cancer-initiating cells".

Analysis of tumors of bronchiolar origin also indicated that they upregulate genes that activate cell growth and downregulate genes that inhibit cell growth, consistent with their aggressive growth. These results therefore suggest that bronchiolar cells are likely to be the origin for the aggressive lung cancers. This mouse model might therefore provide an opportunity to examine signaling profiles of these aggressive tumors and to study the differential sensitivities of "cancer-initiating cells" to new investigational drugs.

Related Website:
http:// cancerres.aacrjournals.org/content/71/23/7250.full

Media Contacts:
Dr. John YU, Joint Appointment Distinguished Research Fellow, Institute of Cellular and Organismic Biology and Genomics Research Center, Academia Sinica, (Tel) +886-2-2789-9589
Mei-Hui LIN, Public Affairs Office, Central Office of Administration, Academia Sinica mhlin313@gate.sinica.edu.tw
(Tel) +886-2-2789-8821, (Fax) +886-2-2782-1551, (M) 0921-845-234
Pearl HUANG, Public Affairs Office, Central Office of Administration, Academia Sinica
pearlhuang@gate.sinica.edu.tw
(Tel) +886-2-2789-8820 (Fax) +886-2-2782-1551 (M) 0912-831-188

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