New organoids facilitate faster study of early lung cancer, potential treatments

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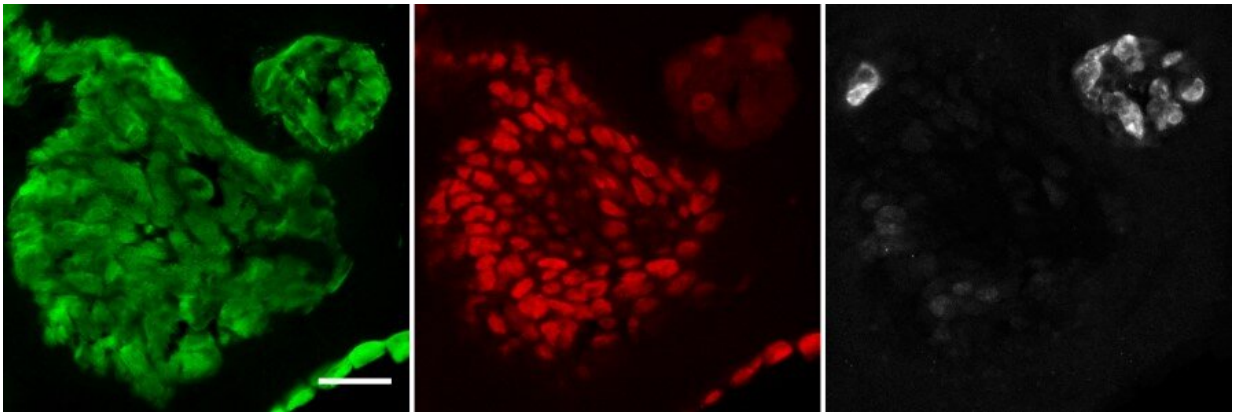

Two lung organoids made from mouse lung cells: a large one and a small one at upper right in each panel. Seven days after turning on the KRAS oncogene, indicated in green, some organoid cells lost molecular markers of mature, differentiated lung cells—see areas of decreased red staining in the middle panel. Some cells also gained markers of early lung development, shown in white, indicative of cancer progression. Credit: Antonella Dost

New research from Harvard Medical School and Boston Children's Hospital, in collaboration with Boston University and the University of California, Los Angeles, provides an accelerated platform for studying early-stage lung cancer and identifying and testing potential treatments: "organoids" created from lung cells.

The researchers reported Sept. 4 in *Cell Stem Cell* that the organoids allowed them to track one common, hard-to-treat lung tumor —adenocarcinoma driven by mutation in the KRAS gene—from its origins, capturing the molecular changes that took place as it progressed.

Lung cancer is the leading cancer killer in the U.S. It is often missed in its earlier stages, and while recent imaging advances have enabled earlier detection, there are still no targeted treatments for early-stage lung cancers.

The research team, led by Carla Kim, professor of genetics at HMS and professor of pediatrics at Boston Children's, used four parallel models of early lung cancer: tumor samples from patients with early (stage 1A) lung cancer, genetically engineered mouse models, and lung organoids derived from either mouse lung stem cells or lung cells created from human induced pluripotent stem cells.

"We know very little about the early events that transform a normal lung epithelial cell into a cancer cell," said Kim, co-senior author of the paper with Jane Yanagawa of UCLA and Darrell Kotton of the Boston University School of Medicine.

"In this study, we were able to use early-stage samples from lung cancer patients to show that our organoids truly mimic what happens in patients at the very early stages," said Kim. "We can see changes in the organoids within seven days that can take months to see in mice and even longer, probably years, in patients."

Tracking an early lung cancer

The researchers introduced the cancer-initiating KRAS mutation into the lung organoids' alveolar progenitor cells. They then used single-cell RNA sequencing to see what genes turned on, or expressed, as a result.

These studies revealed reduced expression of genes that are markers of mature lung alveolar cells and increased expression of genes involved in early lung development—known markers of cancer progression.

Studies in mice and in the patient tumor samples mirrored findings in the organoids.

"KRAS-mutant tumors are usually already resistant to therapy by the time they are diagnosed," noted Kim. "These studies lay a groundwork for finding new therapeutic avenues in the future when an early-stage lung cancer is detected."

Although this study looked at KRAS-driven lung cancer, the researchers believe that the organoid approach could facilitate the study of other kinds of cancer, including testing of candidate drugs.

"The collaborating teams really made progress together in understanding a stage of lung cancer that has been very tough to study in humans," said Kotton. "We hope these new human and lung organoid models of early lung cancer formation will now serve as powerful drug development platforms."

More information: Antonella F.M. Dost et al. Organoids Model Transcriptional Hallmarks of Oncogenic KRAS Activation in Lung Epithelial Progenitor Cells, *Cell Stem Cell* (2020). DOI: 10.1016/j.stem.2020.07.022

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