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Cancer Stem Cell Hypothesis Meets Personalized Medicine in Lung Cancer
Cancer stem cells have enticed scientists because of the potential to provide more durable and widespread cancer cures by identifying and targeting the most voracious cells within a tumor.

Now, in the July 2 *Cell Stem Cell*, researchers at Children's Hospital Boston and their colleagues report they have identified cancer stem cells in a model of the most common form of human lung cancer and, more significantly, have found that the cancer stem cells may vary from tumor to tumor, depending upon the tumor's genetic signature. The findings connect personalized medicine and cancer stem cells.

Cancer stem cells are a subset of cancer cells believed to have the ability to both elude conventional treatments and to regenerate a tumor. Experimentally, they show up as cells that can be extracted from a tumor and transplanted to form a new tumor, from which the same tumor-propagating cells can again be extracted and transplanted with the same result. Kim's group was the first to perform this kind of serial transplantation study with lung cancers.

"Our study shows the cancer stem cell hypothesis is true in some lung cancers," said senior author Carla Kim, PhD, an Assistant Professor in the Stem Cell Program at Children's Hospital and the Department of Genetics at Harvard Medical School. "It also shows, from one lung cancer to another, the stem cells are not the same."

The paper's findings may help researchers identify potential cancer stem cells in patients' tumors carrying certain mutations and test them as new therapeutic targets, combining stem cell biology with genetic typing to determine what is driving the cancerous behavior of each patient's tumor.

In their study, Kim and her colleagues looked at mouse models of the three most commonly mutated genes in human lung cancer -- K-RAS and P53 (two genes predominantly mutated in adenocarcinomas of smokers) and one gene more often found mutated in non-smokers (EGFR). Led by HMS graduate student Stephen Curtis, the team identified cancer stem cells in a model that combined the K-Ras and p53 oncogenic mutations. When the researchers serially transplanted the cancer stem cells from this model into the lungs of mice, new tumors formed.

The cancer stem cells in the K-Ras/p53 mice sported one telltale molecule (Sca1), found on the surface of a tiny 1 percent of all the tumor cells. In the two other models of lung cancer used in the study, cells with that molecular marker were just as rare, but they failed to distinguish themselves as cancer stem cells. In the K-Ras model, all tumor cells were equally likely to propagate tumors. In the EGFR model, only the tumor cells lacking that molecule could propagate tumors.

"Our research indicates that the identity of the cancer stem cells could be different between one patient's tumor and another's," said Kim. "This will be crucial for researchers to consider as

therapies are designed to target specific cancer cell populations." While the team did not test any drug interventions or human lung cancer samples, these are the next important steps.

The study says lung cancers may have cancer stem cells, which are believed to elude conventional treatments. The study may help researchers find cancer stem cells in lung cancers and other tumors in people with the finding that different categories of tumors may have different cancer stem cells. For patients and researchers, it means that therapies targeting cancer stem cells may need to be well matched to the specific cancer stem cell and the specific mutations found in the patient's tumor. The findings validate the cancer stem cell hypothesis and may help cancer researchers.

"Our idea is that even though many patients' tumors may look similar, in order to offer truly personalized and effective targeted therapy, we need to know the genotype of a patient's tumor and successfully identify the cells that maintain that tumor," said Curtis. More work lies ahead of Kim's and other's teams in the search for new ways to attack tumors, yet they hope the most important next steps have now become much more clear.

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Citation:

Primary Tumor Genotype Is an Important Determinant
in Identification of Lung Cancer Propagating Cells
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