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Cancer stem cells are not one size fits all, lung cancer models show

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Cancer stem cells have enticed scientists because of the potential to provide more durable and widespread cancer cures by identifying and targeting the tumor's most voracious cells. Now, researchers at Children's Hospital Boston and their colleagues 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.

"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 Boston and the department of genetics at Harvard Medical School (HMS). "It also shows, from one lung cancer to another, the cancer stem cells are not the same."

Cancer stem cells are a subset of cancer cells believed to elude conventional treatments and eventually 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. According to Kim, this is the first serial transplantation study to identify lung cancer tumor-propagating cells.

The findings, published in the July 2 *Cell Stem Cell*, connect the cancer stem cell hypothesis with molecular profiling of tumors (sometimes called personalized medicine). The results may allow researchers to combine stem cell biology with genetic typing to identify what drives the

cancerous behavior of each patient's tumor and to develop new therapeutic targets.

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 combining 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 two other models of lung cancer, 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 paper says the identity of the cancer stem cells could be different between one patient's lung tumor and another's," said Kim. "This will be crucial for researchers to consider as they design therapies to target specific cancer cell populations." The team did not test any drug interventions or human lung cancer samples. These are the next important steps, she said.

The findings may also help other researchers identify cancer stem cells by taking into account the cancer's genetic signature. For patients, optimal treatment may rely on a combination of the tumor genotype and its tumor-propagating cell phenotype.

"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.

Provided by Children's Hospital Boston

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