

Solving the Case of the Shape-Shifting Tumor in Lung Cancer

Some cancer cells change behavior when they develop resistance. Researchers identified a new driver in small-cell lung cancer — and a potential new drug target.

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Some cancer cells, such as those in lung tumors, change drastically in appearance and behavior when they develop resistance to targeted therapies. The result of these changes, collectively known as histological transformation (HT), is a more aggressive tumor type. HT necessitates a new therapeutic strategy, since the original oncogene is no longer driving the tumor's spread. But first, researchers have to find out which genes have assumed control.

To this end, former Damon Runyon Fellow Eric E. Gardner, PharmD, PhD, and his colleagues at Weill Cornell Medicine have developed a model to recreate the molecular events that drive the transformation of EGFR-mutant lung cancer, treatable with an EGFR inhibitor, to small cell lung cancer, a much more aggressive disease. The team found that, during this process of HT, the small number of lung cancer cells that remain after treatment take on the characteristics of neuroendocrine cells, which release hormones into the bloodstream in response to nerve signals. Significantly, neuroendocrine cells, unlike most lung cells, are sensitive to mutations in the Myc gene family. The team had identified the new cancer driver—and a potential new drug target.

As evidenced by this finding, this model enables researchers to study histological transformation in slow-motion detail, illuminating other oncogenes besides the original target and highlighting strategies for treating aggressive cancers such as small cell lung cancer.

“We feel the work represents a significant advancement in understanding how lung cancers develop and acquire resistance to certain oncogene targeted therapies,” Dr. Gardner said.

“Not every oncogene acts like an oncogene—context is key,” added his co-author, Ashley M. Laughney, PhD, in a [tweet](#).

1/ Not every [#oncogene](#) acts like an oncogene – context is key. Here, with the Varmus Lab [@WCM](#)

[@WCM_MeyerCancer](#), we demonstrate an ‘oncogene’ in the wrong cell type doesn’t act like an oncogene anymore. <https://t.co/yFaDT2TFVV>
— Ashley Laughney (@LaughneyLab) [February 9, 2024](#)

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