

How Injured Lung Cells Are Reprogrammed to Drive Lung Cancer

Research sheds light on KRAS gene mutations and the early development (and possible treatment) of lung cancer.

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Lung cancer is the leading cause of cancer death in the United States, and nearly a third of these cancers are driven by mutations in the KRAS gene. Long considered an “undruggable” cancer target, mutant KRAS proteins are known to rewire alveolar type II progenitor (AT2) cells, which line the lung surface and are responsible for repairing lung tissue after injury. KRAS inhibitors are now making their way to the clinic, but as yet only a subset of patients respond, highlighting the need to better understand the role of mutant KRAS in the development of lung cancer.

A recent study from former Damon Runyon Fellow Aaron L. Moye, PhD, and colleagues at Boston Children’s Hospital sheds new light on the disease’s early stages. In three-dimensional organoid models, human data, and in vivo studies, Dr. Moye’s team observed that injured AT2 cells enter a temporary, highly plastic state before self-renewing or differentiating into another type of lung cell known as AT1 cells. This flexibility, while crucial for repair after injury, becomes a liability in the presence of a KRAS mutation.

The team found that mutant KRAS hijacks AT2 cells while they are in this injured transitional state, such that, rather than self-regenerate or differentiate into AT1 cells, they retain their plasticity. Consider a device that has been wiped in order to be recycled or sold to a new owner; mutant KRAS is like a hacker who takes advantage of the device’s blank slate to reprogram it. Having been rewired, KRAS-mutant AT2 cells express different genes than do normal AT2 cells, notably the tumor-promoting genes *ITGA3* and *SRC*.

“Our findings [...] highlight how oncogenic mutations and injury/inflammation can interact with terrible consequences,” wrote Dr. Moye, noting that the study “sheds light on a vulnerability that could be targeted for the treatment of early-stage lung adenocarcinoma.”

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