

Tobacco use makes precancerous cells that fertilize cancer growth

April 1 2019, by Garth Sundem

Tobacco use causes a field of precancerous cells, increasing the risk of developing head & neck cancer. But exactly how this precancerous field influences cancer has been often overlooked. Now a University of Colorado Cancer Center study presented at the American Association for Cancer Research (AACR) Annual Meeting 2019 offers an exciting idea: Maybe these precancerous cells "fertilize" nearby cells with cancerous changes to grow and resist therapy.

"We wanted to understand how these [precancerous cells](#) may impact neighboring cancer," says Christian Young, Ph.D., research instructor at CU Cancer Center and the study's senior author. The current study explores this communication between precancerous and cancer cells in the context of an enzyme called PI3K.

The enzyme PI3K is activated in many or even most cancers, with some researchers considering PI3K over-activation an essential feature driving the disease. Attractively, PI3K is a "kinase" and the class of drugs known as [kinase inhibitors](#) has proven effective against a host of cancer types, for example erlotinib against EGFR+ cancers and crizotinib against ALK+ cancers. Kinase inhibitors have been developed against PI3K as well, and by and large they do a lovely job of killing cancer cells in dishes. The ongoing question has been why PI3K inhibitors do not necessarily work in patients—what are cancer cells doing to resist this therapy that should kill them?

The current study offers an intriguing hint: "These [cancer cell lines](#) in

culture are sensitive to PI3K inhibition, but when you put them next to precancerous cells, they become resistant," Young says.

To explore this observation, Young and colleagues including first author Khoa Nguyen, an undergraduate student at CU Boulder, grew head and [neck cancer](#) cells in the same dish as precancerous cells (called NOK cells), and then hit the cells, alone and together, with PI3K inhibitors. Cancer cells grown with NOK cells grew faster and resisted PI3K inhibition compared with cancer cells grown alone. When the researchers grew NOK cells alone, then removed the cells, and "fertilized" cancer cells with the culture medium in which NOK cells had grown, they saw similar cancer cell growth and PI3K inhibitor resistance.

Additionally, the NOK cells were stimulating cancer stem cell-like features in the recipient cancer cells. This means that in addition to resisting PI3K therapy, cancer cells that sit alongside precancerous cells may themselves become more dangerous, for example, more able to restart the disease.

"What this means is that some properties of cancer cells may not necessarily be intrinsic. In our study, cancer cells were given some of their cancer-like and stem cell-like properties by nearby, precancerous cells," Young says.

Continuing the line of study, Young and his team asked what these precancerous cells were giving to head and neck cancer cells that allowed them to resist PI3K therapy and gain cancer stem cell-like traits. Using the SomaScan proteomics platform at the CU Cancer Center Microarray Shared Resource, the team was able to analyze more than 1,300 proteins found in dishes in which NOK cells were grown. What they found is a dramatic increase in EGFR ligands—think of PI3K like an engine driving cancer growth. EGFR is another engine that can work alongside

PI3K. In this analogy, EGFR ligands are like fuel, allowing cancer cells, in the absence of PI3K, to power their growth and survival through the engine of EGFR instead.

"It was the precancerous cells that were providing this fuel," Young says.

Continuing work is moving Young's basic science into mouse models of head and neck cancer. Eventually, the goal may be to inhibit EGFR along with PI3K, perhaps negating the EGFR escape route that precancerous [cells](#) seem to be providing to [cancer cells](#).

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