3 QUESTIONS ON . . .
How Tumor Cells Grow

With Maria Fomicheva of Vanderbilt University

BY SARAH DIGIULIO

MARIA FOMICHEVA

CRISPR (which stands for "clustered regularly interspaced short palindromic repeats") is a genome screening tool that allows researchers to edit or delete individual genes—as well as identify the specific genes in the body responsible for certain traits. Now researchers have used the technology to identify a genetic switch that may induce cancer cell division (and thus, tumor growth). The protein they identified, TRAF3, may play a role in 80-90 percent of cancers. Further research is needed to better understand what causes TRAF3 to be disrupted, but the current findings could play an important role in better understanding the mechanisms of cancer cell behavior.

"It is important for us to understand the mechanisms that control this kind of cell behavior," noted the study's lead author, Maria Fomicheva, who is a graduate student in the lab of Ian Macara, PhD, the Louise B. McGavock Chair and Professor of Cell and Developmental Biology at Vanderbilt University.

The research was conducted at the Vanderbilt-Ingram Cancer Center and additionally funded by the National Cancer Institute. The study was published in the journal *eLife* (2020; doi: 10.7554/eLife.63603). In an interview with *Oncology Times*, Fomicheva shared her thoughts about the research.

1 What are the key findings from your research and what's new about these findings?

"It is known that normal cells divide only until they reach a certain density, then they stop and become quiescent. In contrast, cancer cells ignore density restraints and keep dividing endlessly. It is very important to understand these processes, but the mechanisms have not yet been fully explained.

"To find new, unknown regulators of density-dependent proliferation, we designed and developed a whole-genome CRISPR KO screening approach. We found a novel protein important for this control, TRAF3. We studied the mechanisms of TRAF3-dependent density control and found that acts as an 'off' switch for a cell process called non-canonical NF-κB signaling. The loss of TRAF3 keeps this pathway 'on,' which prevents cells from entering a non-dividing quiescence state. TRAF3 had been previously studied in immune cells, but very little was known about its function in epithelia, and it had not been linked to cell proliferation.

"We were led to study TRAF3 because it was a top hit from our genome-wide CRISPR knockout screen, which was designed to identify genes that normally maintain the correct cell density.

"We are generally interested in the collective behavior of epithelial tissues, and how this is disrupted in cancer, specifically in breast cancer. Epithelial cells make collective decisions about whether to continue dividing (so the tissue grows) or to stop division, but the underlying mechanisms that determine these behaviors are not fully understood. Cancer cells lose this collective decision-making ability. They behave selfishly, not responding to neighboring cells."

2 Could you explain how CRISPR technology allowed you to conduct this research?

"CRISPR is an immensely powerful technology that enables us to precisely and fully wipe out individual genes, which is extremely helpful for studying the functions of those genes.

"Whole-genome CRISPR screening allows us to target mutations to every gene in the genome, and select only those mutations that disrupt the processes we are interested in. In our case, our design allowed us to screen through thousands of genes and find one novel regulator of cell density—TRAF3."

3 What are the implications of your work? How might it one day improve treatment and outcomes for patients with cancer?

"It is known from previous studies that TRAF3 is important for the development of blood malignancies. It was also shown that TRAF3 is mutated in 4-5 percent of head and neck, lung, cervical, uterine, and some other cancers. In addition, low TRAF3 levels are associated with poor survival in lung and gastric cancer. However, prior to our work, there was no known causal connection of TRAF3 to epithelial cancer progression (carcinomas).

"CRISPR screens are very powerful tools for discovery in cancer research. Because a key hallmark of cancer is unregulated cell proliferation, the identification of new pathways that control proliferation will provide novel therapeutic targets.

"Our research suggests that inhibiting the signaling pathways downstream of TRAF3 will block hyperplasia and might suppress cancer growth. We hope to test this hypothesis in the future.

"Our novel approach to CRISPR screening can help other scientists to perform similar screens, with the possibility of discovering additional regulators of tissue growth." OT

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