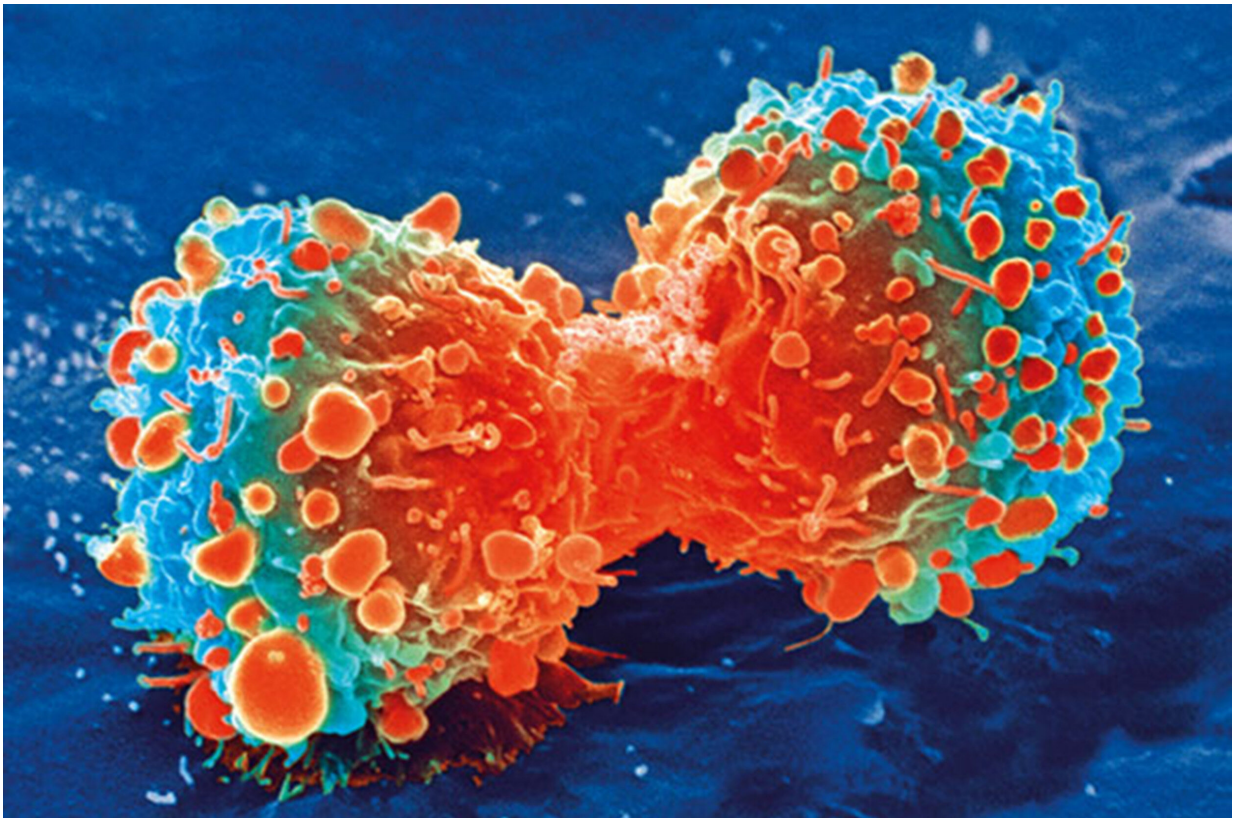
Medical Xpress

Scientists discover reasons why targeted immuno-oncology drugs sometimes fail

October 23 2019



Cancer cell during cell division. Credit: National Institutes of Health

Researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) report a discovery that helps

scientists understand why some tumors lack immune cell infiltration and are therefore unresponsive to newer PD-1 targeted therapies.

PD-1 is a checkpoint protein on T cells, a type of immune cell that helps the body recognize abnormal cells and disease in the body. PD-1 normally acts as an "off switch" that helps keep T cells from attacking other cells. PD-1 inhibitors are part of a class of drugs known as monoclonal antibodies that are used in oncology to selectively block this protein and boost immune response to attack cancer cells.

Previously reported data has shown that a primary reason some cancer patients do not respond to the PD-1 therapy is the inability of the fighter T cells (known as CD8 T cells) to invade the tumor microenvironment, a state also known as "cold tumors."

In this new study, Yiping Yang, MD, Ph.D., and colleagues report data showing the specific cellular mechanisms that limit the ability of CD8 T cells to infiltrate the tumor microenvironment. They show that Hedgehog signaling shut down chemokine secretion by tumor-associated macrophages—which is critical to CD8 T-cell infiltration. By blocking (inhibiting) the hedgehog pathway, the researchers were able to reverse the process and promote CD8 T-cell infiltration into the tumor microenvironment.

"Our data shows that hedgehog inhibitors given in combination with a PD-1 blockade were more effective in killing cancer cells than a single agent alone in preclinical models of both liver and lung cancer," says Yang, director of the Division of Hematology at Ohio State and member of the Leukemia Research Program at the OSUCCC—James. "This is an important discovery with the potential to significantly enhance the efficacy of PD-1 therapy and guide new immunotherapeutic strategies in cancer."

Yang and his colleagues report their findings in the *Journal of Clinical Investigation*.

The current study was conducted in preclinical models of liver and lung cancer. The goal of Yang and colleagues at the OSUCCC—James is to translate this important discovery from the laboratory to the bedside to benefit cancer patients. The researchers are planning to conduct phase I clinical trials using combination strategies in PD-1 and hedgehog inhibitors for treating patients with lung and liver cancers.

More information: Amy J. Petty et al, Hedgehog signaling promotes tumor-associated macrophage polarization to suppress intratumoral CD8+ T cell recruitment, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI128644

Provided by Ohio State University Medical Center