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Team identifies a switch that may help target dormant cancer cells

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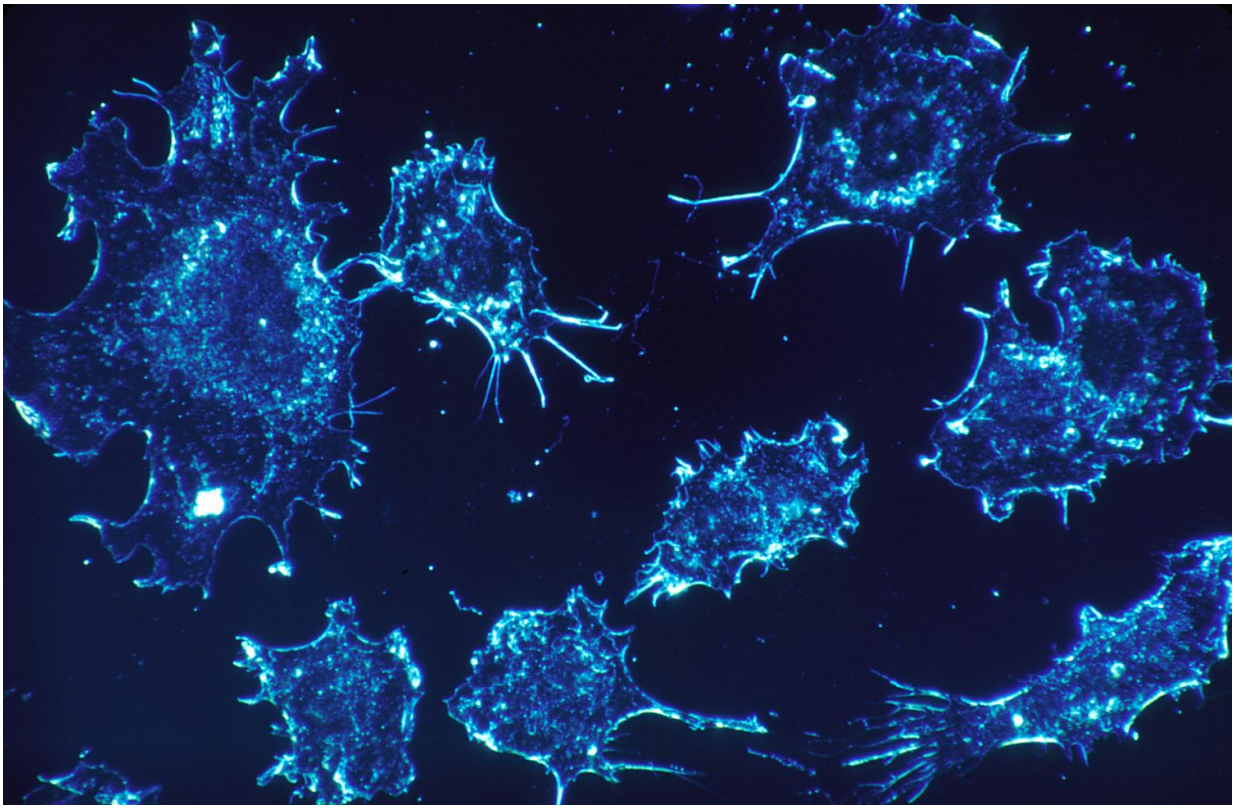

Cancer cells. Credit: Dr. Cecil Fox, National Cancer Institute

A study by scientists at the University of Arizona and the University of Pittsburgh may hold the key to targeting dormant—or inactive —cancer cells, which are resistant to chemotherapy and other treatments. The results were published today in the journal *Cell Reports*.

Cells can enter a sleeplike state known as quiescence, during which they stop growing and dividing. Just as sleep can be deep or shallow, a cell's quiescence also can vary in depth. Altering this depth can make it easier or more difficult for a cell to "wake up" and start dividing again.

Because cancer therapies target cells that are awake and actively dividing, quiescent cancer cells often evade treatment. Metastatic cells, those that have left the primary tumor site and spread to distant organs, are especially good at evading treatment by entering quiescence. After cancer therapy has ended, these cells eventually may wake up and begin dividing again, often very aggressively, leading to cancer recurrence.

The UA Cancer Center's Guang Yao, PhD, UA assistant professor of molecular and cellular biology, is the senior coauthor of the study. His lab investigated ways to use a genetic "dimmer switch" to regulate the dormancy of normal cells and tumor cells. This strategy may be key to targeting metastatic tumors.

According to Dr. Yao, this research could lead to ways to "make quiescence shallower so that those cells cannot be hidden from therapeutic treatment." Dormant cancer cells that are roused from their slumber and begin multiplying would once again be vulnerable to chemotherapies.

Alternately, learning how to regulate cancer cells' dormancy could allow scientists to turn the dimmer switch in the other direction. Inducing a deep slumber in cancer cells could prevent them from waking up to cause cancer recurrence.

Previous research identified a network of genes called Retinoblastoma (Rb)-E2F that plays a pivotal role in normal cell division and quiescence. Disruption of the Rb-E2F gene network often leads to uncontrolled cell division and cancer formation.

Dr. Yao's lab constructed a computer model to simulate how changing the expression of different genes in the Rb-E2F network affects the depth of quiescence. The computer model made predictions that investigators then were able to test in a rat-cell model. They increased the expression of various target genes in live cells and observed changes in the depth of quiescence, reflected in how easily cells could be roused from their "sleep."

Not all genes in the network affect the quiescence depth to the same degree. "Different components of the Rb-E2F network can be experimentally altered to change quiescence depth to different levels, like adjusting a dimmer switch," said Dr. Yao. For example, higher expression of one gene (Myc) in the network reduces the depth of quiescence in small increments, whereas higher expression of another gene (Cyclin D) reduces depth of quiescence in larger increments, making it much easier to wake the cells from their quiescent "slumber."

"The advantage of understanding this 'dimmer switch' mechanism is that we can more accurately adjust the dormant level of cells so that we may specifically target dormant cancer cells, whose quiescent state is likely less stable than that of normal cells," Dr. Yao commented.

The Yao lab is at the forefront of research into the control of quiescence depth. Earlier this year, in an article published in *Nature Communications*, the lab demonstrated that prior cell growth affects the Rb-E2F switch in quiescent cells, leading to variations of quiescent depth. In another report in *Oncotarget*, they identified natural compounds derived from a mushroom that can reduce the quiescence depth of dormant cancer cells, sensitizing them to chemotherapy drugs.

With respect to future studies, Dr. Yao added, "We are investigating how the Rb-E2F switch interacts with other quiescence regulatory pathways to control quiescence depth in different cell types under

different conditions, which may help future development of therapies against dormant cancer cells."

Provided by University of Arizona