Master switch found to stop tumor cell growth by inducing dormancy

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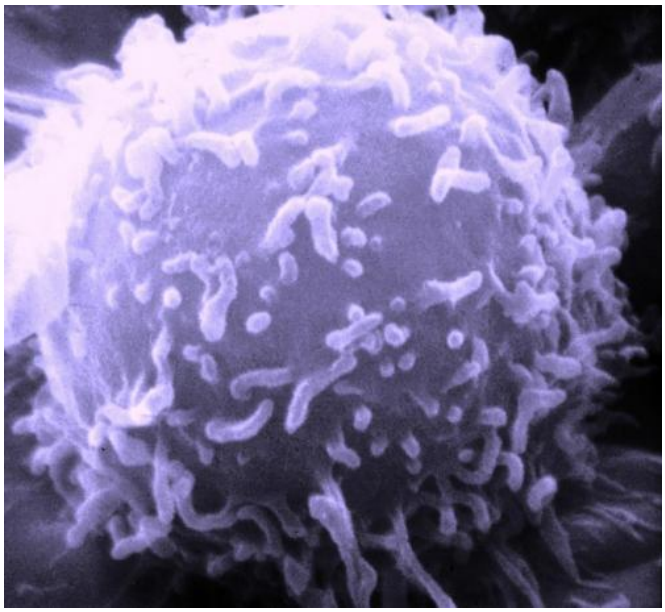

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Two existing cancer drugs turn on a gene that tells tumor cells to remain inactive, according to a study led by researchers at the Icahn School of Medicine at Mount Sinai and published today in *Nature Communications*.

Researchers discovered that the gene NR2F1, when switched on, programs tumor cells to stay dormant. When the gene is switched off, tumor cells divide and multiply as part of abnormal growth, potentially allowing dormant cells to grow into tumors throughout the body (metastasis). Combining the anticancer drugs azacytidine and retinoic acid significantly increased the amount of active NR2F1 in tumor cells. These patterns were found in mouse models of several cancers, and confirmed in prostate cancer cells from human patients.

Results suggest that NR2F1 is a "master regulator" of tumor cell growth, influencing several genes that determine whether cells remain inactive, or quiescent in medical terms. According to the study, NR2F1 exerts control over long lasting programs in stem cells in the human embryo, where it directs cells to stop growing and become specialized cells (neurons) for life. This function suggests that NR2F1 may exert a long-lasting effect on tumor cells, keeping them dormant after they have broken off from an original tumor.

"Our results explain why some tumor cells scattered through the body are committed to remaining harmless for years, while others cause active disease," said Julio A. Aguirre-Ghiso, PhD, Professor of Medicine, Hematology and Medical Oncology, and Otolaryngology at the Icahn School of Medicine. "In finding this master switch we found a way to analyze tumor cells before treatment to determine the risk of a cancer recurrence or metastasis."

"Azacytidine and retinoic acid, the latter a form of vitamin A, prevented tumor cells from rapidly multiplying, restored normal cell function, and activated several tumor suppressor genes that are often turned off in tumors," said study co-leader Maria Soledad Sosa, PhD, a postdoctoral fellow in Hematology at the Icahn School of Medicine. "We now have strong evidence that combining these well-known drugs may have a profound, long-lasting therapeutic effect."

The current study builds on the research team's earlier finding that lowering amounts of tumor suppressor genes TGF?2 and p38 awakened dormant tumor cells, fueling metastatic tumor growth. Azacytidine and retinoic acid restored TGF?2 expression and p38 activation to drive tumor cell dormancy.

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