Double Whammy Starves Tumor Cells

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RESEARCH

An emerging strategy for treating cancer is targeting the so-called Achilles heel of tumor cells: their dependence on certain nutrient sources for survival. A new study by HMS researchers in the May 28 issue of *Molecular Cell* suggests a novel therapeutic method for killing these cells by selectively starving them of the energy they need to grow.

Traditional approaches to treating tumors focus on inhibiting the key mTORC1 pathway. When this pathway is hyperactivated, tumor cells can multiply unchecked. Though inhibiting mTORC1 slows this growth, it does not kill the cells, so tumors quickly reappear when treatment stops. But a potential Achilles heel of tumors with hyperactivated mTORC1 is that they constantly signal the cell to grow; the consequence, the authors of this study suggest, is that mTORC1 hyperactivation addicts tumors to certain nutrients to maintain this rapid growth rate.

“We feel that normally cells need to turn on and off the mTORC1 pathway to maintain a balance, especially in terms of energy and cell growth,” said John Blenis, HMS professor of cell biology and an author of the study. “Thus, when nutrient resources are limited, normal cells can preserve viability by decreasing demand.”

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—John Blenis

The researchers found that certain tumors with deregulated mTORC1 activity fail to maintain this balance. Inhibiting this pathway can therefore backfire by reducing a tumor’s energy consumption, allowing it to survive in a semi-dormant state until it can hijack the body’s vascular system to support further growth.

“Under conditions of energetic stress, tumor cells must respond by finding alternative sources of energy for survival,” said Blenis. Using cells that lacked tumor suppressor genes—cells in which mTORC1 was hyperactivated—Blenis, Andy Choo (a student in the HMS Biological and Biomedical Sciences program) and their colleagues applied stress to these cells by depriving them of glucose, their main energy source. Under these conditions, the cells became dependent on an alternative source for survival, glutamine.

The researchers then discovered how to deliver a double whammy against cancer: a naturally occuring small molecule that inhibits glutamine metabolism, combined with a chemotherapeutic agent that suppresses glucose metabolism, selectively killed cells with hyperactivated mTORC1. Cells in which this pathway was normally regulated were left unscathed.

The approach might lead to therapies that kill metabolically hyperactive cancer cells and leave healthy cells alone, Blenis said. “These findings reveal a possible therapy for treating cancers that depend on glucose and glutamine for energy production and cell survival,” he said. “Overall, we hope our work will encourage others to think about glutamine and glucose metabolism as an Achilles heel of tumors.”

—Mary Bates

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