A Cancer Story: How do cells release their 'brakes' to allow division?

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In a new study, researchers at UNC Lineberger Comprehensive Cancer Center have discovered details of how cells release their brakes to allow replication and division to proceed. The findings, published in the journal *Cell Reports*, could help scientists develop a possible therapeutic strategy for halting cancerous growth.

Typically, there is a lock on cells that prevents tumor growth, said senior author Michael J. Emanuele, PhD, an assistant professor of pharmacology in the UNC School of Medicine. This lock keeps cells from erroneously entering their 'S phase,' or the DNA replication phase, and starting cell division. "Here, we show how a common growth signaling pathway in cells can destroy one of the brakes on cell division to allow cell division to move forward," Emanuele said.

In the study, researchers described how a common signaling pathway in cancer cells – the PI3-kinase signaling pathway – helps to turn off one of the natural brakes on cell division. Specifically, PI3-kinase signals activate the AKT enzyme, which then passes a series of messages telling cells to move forward with division. AKT binds to another molecule, called Cyclin F, to allow it to destroy the cdh1 molecule, which then releases a "brake" on cell division. That brake is controlled by a large, multi-subunit enzyme termed the Anaphase Promoting Complex/Cyclosome, or APC/C.

Emanuele said cancer cells could hijack this naturally occurring pathway to release the brakes on division.

"The cancer cell is leveraging a normally functioning pathway in the cell, but aberrantly turning it on, taking advantage of something built into the circuitry of the cell to allow cell division to occur and promote tumor proliferation," he said.

Their findings could lead to a potential new area of cancer drug discovery. Blocking Cyclin F could potentially prevent the degradation of cdh1, and keep the APC/C brake on cell division in place. Emanuele said they believe this strategy could be less toxic than other strategies to prevent cell division.

More information: Rajarshi Choudhury et al. The E3 Ubiquitin Ligase SCF(Cyclin F) Transmits AKT Signaling to the Cell-Cycle Machinery, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.08.099

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