In a bizarre twist, Cyclin D, long believed to promote cancer, actually activates tumor suppressor

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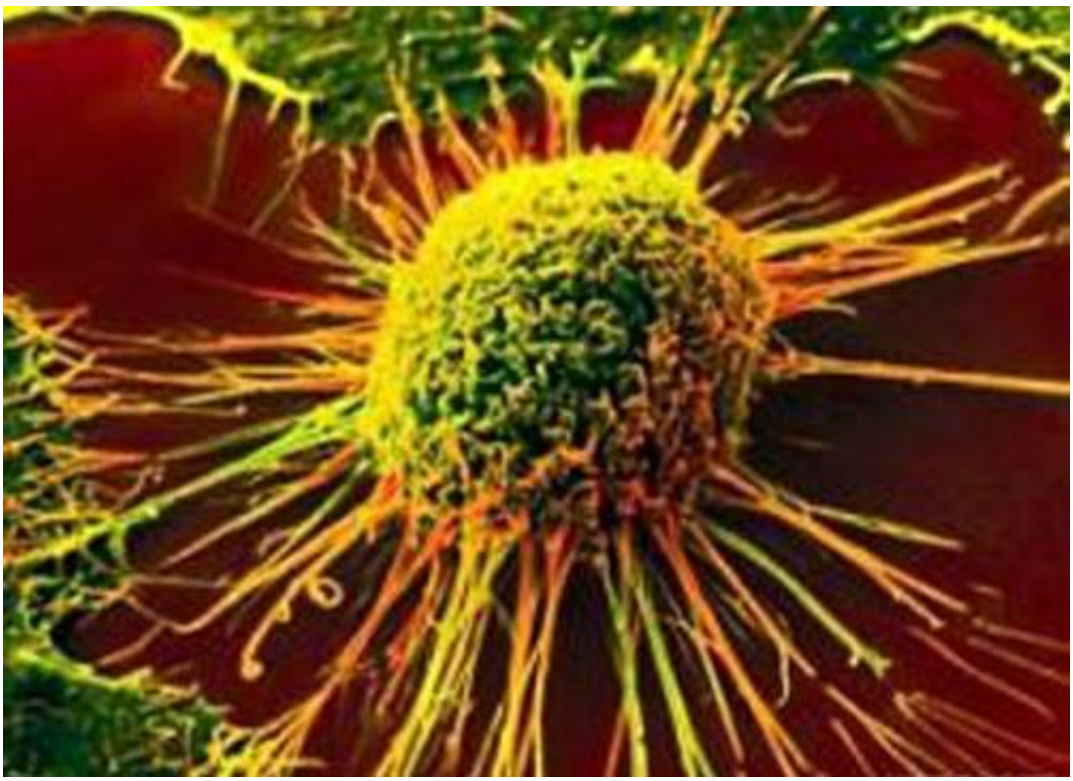

Researchers at the University of California, San Diego School of Medicine say a protein essential to regulating cell cycle progression – the process of cell division and replication – activates a key tumor suppressor, rather than inactivating it as previously thought.

"The finding is the result of literally 20 years of work in my lab," said Steven F. Dowdy, PhD, professor in the Department of Cellular and Molecular Medicine at UC San Diego. "It completely turns upside-down what was thought to be a fundamental aspect of cell cycle progression in all cancer cells driven by one of the most common genetic pathways mutated in cancer, namely the p16-cyclin D pathway."

The findings are published in the journal *eLife*.

Cyclin D is synthesized during the first stage of cell replication and is believed to help drive the complex, multi-stage process, including interaction with the retinoblastoma (Rb) protein, whose function is to prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide. Rb acts as a tumor suppressor.

But mutated or dysfunctional Rb is associated with several major cancers and Cyclin D has long been described as an oncogene that promotes cancer because it was believed to inactivate the Rb tumor suppressor function through a process called phosphorylation, which involves phosphate molecules being added to proteins, essentially turning them on or off.

Dowdy and colleagues painstakingly counted the number of phosphates added to Rb during cell cycle progression. There are as many as 14, but the scientists found that cyclin D adds just a single phosphate at one, and only one, of the 14 locations during the early G1 phase of cell cycle progression, essentially make 14 different versions of the Rb tumor suppressor. The single phosphate serves to activate Rb, not inactivate it as had been thought for over 20 years.

The researchers said the findings fundamentally change the understanding of G1 cell cycle regulation and the molecular origins of many associated cancers. It is critically important to understand how a

genetic pathway actually functions and the consequences of interrupting it, especially in this case where there are multiple drug inhibitors of cyclin D being tested in clinical trials for breast cancer.

Moreover, how the next cyclin, cyclin E, that actually does inactivate Rb becomes activated has not been heavily investigated because it was thought to be the less important second domino, whereas we now know it is the first domino, added Dowdy.

Provided by University of California - San Diego