

Cancer protein discovery may aid radiation therapy

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Scientists at Dana-Farber Cancer Institute have uncovered a new role for a key cancer protein, a finding that could pave the way for more-effective radiation treatment of a variety of tumors.

Many cancers are driven in part by elevated levels of cyclin D1, which allow the cells to escape growth controls and proliferate abnormally. In the new research, reported in the June 9 issue of *Nature*, researchers discovered that cyclin D1 also helps cancer cells to quickly repair DNA damage caused by radiation treatments, making the tumors resistant to the therapy.

Based on this finding, the researchers made cancer cells more sensitive to several [cancer drugs](#) and to radiation by using a molecular tool to lower the cancer cells' cyclin D1 levels, said Peter Sicinski, MD, PhD, senior author of the report and a professor of genetics at Dana-Farber.

"This is the first time a cell cycle [protein](#) has been shown to be directly involved in DNA repair," said Siwanon Jirawatnotai, PhD, the lead author of the paper. "If we could come up with a strategy to inhibit cyclin D1, it might be very useful in treating a variety of cancers."

The gene for cyclin D1 is the second most-overexpressed gene found in human cancers, including [breast cancer](#), [colon cancer](#), lymphoma, melanoma, and [prostate cancer](#). Cyclin D1's normal function in cellular growth control is to temporarily remove a molecular brake, allowing the cell to manufacture more DNA in preparation for cell division. When

cyclin D1 is mutated or is overactivated by external growth signals, the cell may run out of control and proliferate in a malignant fashion.

The findings came in a series of experiments by Jirawatnotai, a post-doctoral fellow in the Sicinski lab. With the goal of uncovering details of cyclin D1's function in human cancer cells, Jirawatnotai broke open four types of cancer cells, isolated the cyclin D1 protein, and searched for other proteins with which it interacted.

The experiment netted more than 132 partner proteins, most of them part of the cell cycle protein mechanism in which cyclin D1 is a major player. But unexpectedly, the scientists also observed that the cyclin D1 protein was binding to a cluster of DNA repair proteins, most importantly RAD51. The RAD51 protein is an enzyme that rushes to broken parts of the cancer cell's DNA instructions and repairs the damage, including damage caused by radiation therapy administered to stop cancer cells' division and growth. In another experiment, it was observed that cyclin D1 was recruited along with RAD51 to the [DNA damage](#) site.

"This was a surprise," said Jirawatnotai. "This finding showed that cyclin D1 has an unexpected function in repairing broken DNA." In additional experiments, he used a molecular tool, RNA interference (RNAi) to drastically reduce the level of cyclin D1 in the cancer cells. "When you lower D1 levels, you get poorer repair," he said.

When [cancer cells](#) with reduced cyclin D1 protein levels were administered to mice, the resulting tumor proved to be more sensitive to radiation than those grown from cells with overexpressed cyclin D1.

Currently, cyclin D1 is thought to be responsible for driving cancer cell proliferation. Agents that target cyclin D1 are currently in clinical trials, with the goal of reducing cancer cell growth. The new findings strongly

suggest that targeting cyclin D1 may increase susceptibility of human cancers to radiation, said the scientists, and this discovery may encourage targeting cyclin D1 even in these cancers whose cells do not depend on cyclin D1 for proliferation.

"Our results potentially change the way we think about cyclin D1 and cancer and may encourage targeting cyclin D1 in a very large pool of human cancers which do not need cyclin D1 for proliferation, but may still depend on cyclin D1 for [DNA repair](#)," said Jirawatnotai, who also holds a faculty position at the Mahidol University in Bangkok, Thailand.

Provided by Dana-Farber Cancer Institute

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