Cell cycle-blocking drugs can shrink tumors by enlisting immune system in attack on cancer

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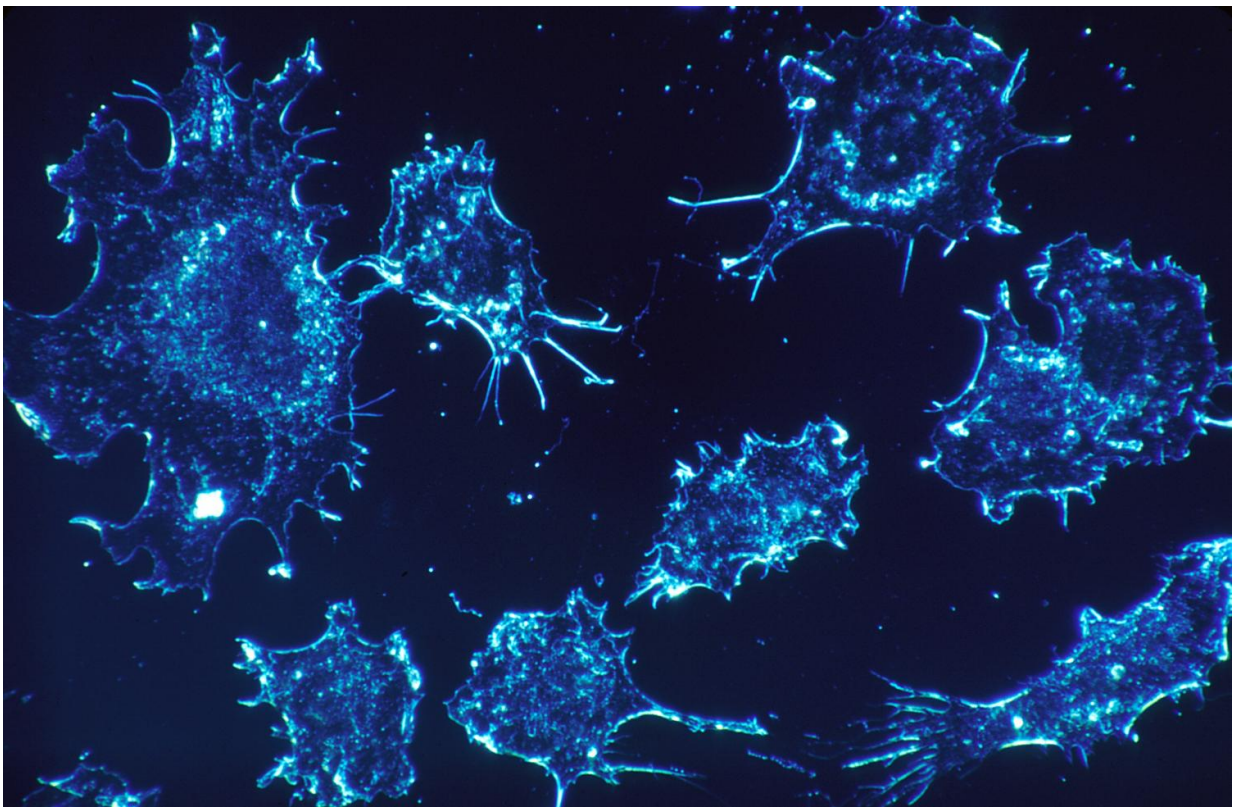

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In the brief time that drugs known as CDK4/6 inhibitors have been approved for the treatment of metastatic breast cancer, doctors have

made a startling observation: in certain patients, the drugs—designed to halt cancer cell division—do not just stop tumors from growing but can cause them to shrink, in some cases markedly.

New research by scientists at Dana-Farber Cancer Institute (Dana-Farber) and Brigham and Women's Hospital (BWH) reveals an unexpected mechanism behind these tumor regressions. In a study published online today by the journal *Nature*, the investigators show that CDK4/6 inhibitors not only stymie the division of cancer cells but can also spur the immune system to attack and kill the cells. When the drugs were coupled with other immunotherapy agents, the anti-cancer effect can be even greater, they report.

The findings, which follow Dana-Farber scientists' recent discovery that CDK4/6 inhibitors can slow the growth of cancer cells carrying a surplus of a certain protein, suggest that the drugs' potential in cancer treatment has only begun to be tapped. If their effectiveness increases in combination with immunotherapies, as early evidence indicates, that potential may be greater than is even now apparent.

"The CDK4 and 6 proteins are critical drivers of the cell-division cycle and are required for the formation and growth of various types of solid tumors," says Dana-Farber's Shom Goel, MD, PhD, co-first author of the study with Molly DeCristo of the Hematology Division at BWH.

"Agents that block the proteins - CDK4/6 inhibitors—have received Food and Drug administration approval for some patients with metastatic breast cancer, but they've also shown promise against others types of tumors in clinical trials. In early clinical trials of these drugs, we noticed that in some breast cancer patients the tumors didn't just remain the same size—as would be expected with drugs that interfere with cell division—but began to recede, sometimes quite dramatically, said Goel."

To understand why this occurs, they examined the effect of a CDK4/6 inhibitor called abemaciclib in mice with breast or other solid tumors. They found the agent not only stalled the tumor cell cycle but also caused the immune system to mount an attack on the tumors. They confirmed the finding by analyzing tissue samples from women participating in a clinical trial of a CDK4/6 inhibitor for breast cancer.

The drugs trigger an anti-tumor immune response in two ways, the researchers discovered. In cancer cells, the drugs produce a substantial increase in the display of abnormal proteins on the cells' surface. These proteins, called antigens, serve as a signal to the immune system that a diseased or cancerous cell is present and needs to be eliminated. At the same time, the drugs can spark a reduction in immune system cells known as T regulatory cells (Tregs), which usually tamp down the immune response to disease or infection. Fewer Tregs results in a fiercer immune system attack. The cumulative effect of these processes is a halting or reversal of tumor growth.

"The anti-tumor immune response with CDK4/6 inhibition was somewhat unexpected—some had previously thought that CDK4/6 inhibitors would block anti-tumor immunity, due to effects on T cell proliferation, but our findings demonstrate quite the opposite," DeCristo states. "This surprising finding opens the door for combining immunotherapy with CDK4/6 inhibitors."

In clinical trials, about 20 percent of breast cancer patients treated with abemaciclib by itself have a significant response to the drug and another 20 to 30 percent have stabilizations of tumor growth, the authors explained. The responses have tended to appear within four months of starting the therapy, they added.

In the current research, even better results have been obtained in mice when the drugs are used in combination with immunotherapy agents

known as checkpoint inhibitors, which can foil cancer's ability to evade an immune system attack. "It appears that the CDK4/6 inhibitors might be able to sensitize some patients' cancers to the anti-tumor effects of immune checkpoint inhibitors," the authors state. "The result might be especially encouraging for breast cancer patients, who have derived little benefit from immunotherapy in trials conducted to date."

Further research is needed to understand why some patients receive the full spectrum of benefits from CDK4/6 inhibitors while others don't, and to seek ways to expand these benefits to more patients. The results also should spur future studies of combined regimens of CDK4/6 inhibitors and different types of immunotherapy, the authors state.

More information: Shom Goel et al. CDK4/6 inhibition triggers anti-tumour immunity, *Nature* (2017). DOI: 10.1038/nature23465

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