Study supports DNA repair-blocker research in cancer therapy

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Scientists at Dana-Farber Cancer Institute have uncovered the mechanism behind a promising new approach to cancer treatment: damaging cancer cells' DNA with potent drugs while simultaneously preventing the cells from repairing themselves.

The findings being reported in the Aug. 14 issue of *Molecular Cell* help explain the promising results being seen in clinical trials of compounds that force cancer cells with genetic damage to self-destruct instead of "resting" while their DNA undergoes repairs.

"What we have shown suggests that you can use these drugs to sensitize cancer cells to DNA-damaging chemotherapy," said Geoffrey Shapiro, MD, PhD, senior author of the report. "This is a mechanism by which these inhibitory drugs may be synergistic with DNA-damaging agents."

Interestingly, Shapiro said, when the same repair-blocking drugs were administered to normal, non-cancerous cells, the cells became less sensitive to DNA damage from a chemotherapy drug. This is an encouraging indication that repair-blocking drugs may selectively make cancer cells vulnerable to chemotherapy while protecting normal cells from DNA damage, the scientists said.

Cells' native capacity for fixing DNA damage is normally beneficial, but it can be problematic for cancer therapy as it enables tumor cells to become resistant to a number of standard drug agents. All cells progress through a series of phases -- called the cell cycle -- including quiescence,

or resting, growth, and cell division. The transition from one phase to the next is regulated by "checkpoint" proteins that, among other things, are designed to prevent damaged, potentially dangerous cells from reproducing.

The body deals with DNA-damaged cells in two ways. It can order them to self-destruct through "programmed cell death," also known as apoptosis. Or, it can issue signals from the checkpoint proteins to put the cells into "cell cycle arrest," causing them to remain quiescent while the broken DNA is fixed before they resume normal activity.

Repair-blocking drugs are designed to squelch the checkpoint proteins' signals, preventing the chemotherapy-damaged cancer cells from initiating the rest phase and undergoing repairs. Instead, they're forced to progress through the cell cycle and, because of their broken DNA, self-destruct through apoptosis. Accordingly, the tumor loses much of its power to develop resistance to drugs that attack DNA.

When a cell senses damage to its DNA, it triggers a series of events, called a "checkpoint cascade." Two major checkpoint proteins, cdk1 and cdk2, send signals that stop the cell cycle. At the same time, a flock of repair proteins are recruited to the site of the DNA damage.

In clinical trials aimed at disrupting the DNA-repair process, scientists are using inhibitor drugs to block cdk signaling. The drugs cause the damaged cells to bypass the checkpoint control and continue to grow and divide -- and ultimately die. Those trials are showing promising results, said Shapiro. He and his colleagues, in their new paper, demonstrate the molecular mechanism by which cdk inhibitors work, and they say that the explanation bodes well for continued research on the drugs.

Previously, it was known that cdk1 and cdk2 were virtually interchangeable in most cancer cells, and if one of the proteins

malfunctioned or was knocked out, the other could compensate for it.

To find out if this overlap might pose a problem for cdk-inhibitor therapy, the researchers disabled just one of the proteins -- cdk1 -- in cultured lung cancer cells and treated the cells with cisplatin, a DNA-damaging agent. Even though the partner cdk2 protein was still active, the cdk1-depleted cancer cells failed to stop, rest, and repair themselves; it was evident that they were now more vulnerable to death from the cisplatin.

But how did the loss of just the one checkpoint protein disrupt the repair process?

The investigators showed that a key player in DNA repair -- the BRCA1 protein best known in its mutated form as an inherited breast cancer risk factor -- couldn't fulfill its mission in lung cancer cells lacking cdk1.

Going a step further, the researchers administered a cdk-inhibiting drug to lung cancer cells that hadn't been stripped of their cdk1 protein. In these cells, BRCA1 activity was reduced, demonstrating that the cdk inhibitors work in large part by keeping BRCA1 on the sidelines, weakening the DNA repair team.

"These results explain the observations seen in clinical trials" currently being conducted at Dana-Farber and elsewhere, said Shapiro, who is also an associate professor of medicine at Harvard Medical School. "The data give us confidence to go ahead with testing of cdk inhibitors in combination with DNA-damaging chemotherapy."

Source: Dana-Farber Cancer Institute