Blocking molecular target could make more cancers treatable with PARP inhibitors

29 June 2011

BOSTON--Researchers at Dana-Farber Cancer Institute have demonstrated a molecular strategy they say could make a much larger variety of tumors treatable with PARP inhibitors, a promising new class of cancer drugs.

Currently, the role of PARP inhibitors has mainly been restricted to cancers whose cells lack functioning versions of the damage-repair proteins BRCA1 or BRCA2 -- chiefly certain breast and ovarian cancers.

In a paper published online by Nature Medicine, Geoffrey Shapiro, MD, and colleagues report that the BRCA1 repair protein is dependent on another protein, CDK1, known primarily as a regulator of the cell division cycle. When the scientists blocked CDK1 in cancer cell lines and in a mouse model of lung cancer, BRCA1 function was disrupted, making them susceptible to being killed by a PARP inhibitor.

Because most types of tumors don't have a mutated BRCA1 protein, they are less likely to be affected by PARP inhibitor treatment. The new findings, said Shapiro, "suggest that by blocking CDK1, we can disable BRCA1 in many types of cancers and make them sensitive to a PARP inhibitor. It could extend the use of these drugs to a much larger group of patients."

Shapiro, who heads Dana-Farber's Early Drug Development Center, said a clinical trial combining a CDK1 blocker and a PARP inhibitor in a variety of solid tumors is being planned.

Cells are equipped to heal damage to their DNA strands, which are constantly being nicked or broken by exposure to environmental contaminants or randomly during cell division. Cancer cells, in addition, become adept at repairing potentially lethal DNA damage caused by radiation and chemotherapy drugs, and use their DNA repair machinery to survive and grow uncontrollably.

A major thrust in cancer research currently is developing ways to disable tumor cells' repair toolkits to make them more vulnerable to DNA-damaging agents. PARP inhibitor drugs prevent tumor cells from repairing less-serious damage to the DNA strands of cancer cells; if those cells happen to lack a normal BRCA protein, the damage becomes more serious and the cells can't repair it, and then the cells die.

Most types of cancer cells, however, have normal BRCA proteins, making PARP inhibitors less effective. The Dana-Farber scientists sought a way to get around this and convert "BRCA-competent" tumor cells to "BRCA-less" cells that would be sensitive to anti-PARP drugs. Their studies revealed that BRCA1 molecules depend on the cell-cycle protein CDK1 to activate them.

CDK1 was previously identified as a regulator of the cell division cycle that can be overactive in many types of cancers, leading to unchecked growth. Currently several CDK1 inhibitors are in clinical trials as potential weapons against cancer. Shapiro and his colleagues implicated CDK1 for the first time as a control point in the DNA repair circuit that contains BRCA1. This suggested that blocking CDK1 activity might prevent BRCA1 from rescuing cancer cells from life-threatening DNA damage.

In a study involving lung cancer cells in the laboratory and implanted in mice, the researchers "found that if we deplete cancer cells of CDK1, we disrupt DNA repair and the cells become very sensitive to PARP inhibitors," said Shapiro, the senior author of the report. The researchers obtained their results using an existing CDK1-blocking drug along with a PARP inhibitor.

As a more stringent test, they tried the same strategy in mice genetically engineered with an oncogene, KRAS, that drives the most aggressive lung cancers in humans.

"We achieved tremendous responses in this mouse model," Shapiro said. "The survival curve of the animals nearly doubled."

In addition, he said, his team collaborated with pathologists at Brigham and Women's Hospital to show that the CDK1-PARP inhibiting strategy is selective for cancer cells -- normal cells were unaffected. Accordingly, Shapiro said, they did not observe significant toxicity from the drug treatment.

"We're quite excited about this and looking forward to evaluating this combination in clinical trials," said Shapiro.

Provided by Dana-Farber Cancer Institute