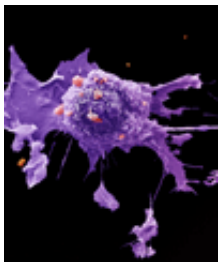
Breakthrough could make 'smart drugs' effective for many cancer patients

27 June 2011



(Medical Xpress) -- Newcastle and Harvard University reseachers have found that blocking a key component of the DNA repair process could extend the use of a new range of 'smart' cancer drugs called PARP inhibitors.

PARP inhibitors have been showing great promise in clinical trials for patients with breast, ovarian and prostate cancers caused by mutations in a gene called BRCA1. They work by blocking the action of PARP - a molecule involved in the repair of damaged DNA.

By themselves, PARP inhibitors are unable to kill cancer cells but when used to target cancer cells that lack a protein normally produced by the BRCA1 gene, which is also involved in DNA repair, the two factors act together to attack the cancer cell. They are no longer able to repair DNA damage, ultimately leading them to die.

But, BRCA deficient cancers only account for a small proportion of all cancers. To improve the effectiveness and range of PARP inhibitors the researchers looked at whether artificially recreating the effect of losing BRCA1 by blocking a key controller of the cell cycle, Cdk1, would have the same effect.

Cdk1 plays an important role in repairing DNA by switching on BRCA1 in response to DNA damage. So when the researchers blocked the action of Cdk1 and treated the cells with PARP inhibitors the same two-pronged effect was seen in cells not previously affected by PARP inhibitors. The research is published in Nature Medicine.

Professor Nicola Curtin from Newcastle University, whose early work, funded by Cancer Research UK, linked PARP inhibitors and BRCA mutations, said: "Our research shows how blocking Cdk1 compromises DNA repair in cancer cells, making them sensitive to PARP inhibitors. We were also able to show that this approach only targeted cancer cells, so if we are able to develop an effective Cdk1 drug we could have a more targeted treatment with fewer side effects.

"Now we need to take this research in the lab and develop an effective drug that can block Cdk1, so more patients can benefit from treatment with PARP inhibitors."

Dr Lesley Walker, director of cancer information at Cancer Research UK, said: "Cancer Research UK scientists have played a central role over the past two decades in developing PARP inhibitors. While they were originally designed to enhance the DNA damaging effects of chemotherapy and radiotherapy on cancer cells, where part of the DNA repair mechanism was already damaged, we are seeing they could be used to treat a wider range of cancers than previously thought. If the researchers are able to develop an effective drug to block Cdk1 we could have a powerful new tool to treat cancer patients."

More information: Johnson, N et al, Compromised CDK1 activity sensitizes BRCA-proficient cancers to PARP inhibition, *Nature Medicine* (2011)

Provided by Newcastle University