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First evidence of new 'druggable' DNA repair target to destroy cancer cells

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(Medical Xpress) -- Blocking a key DNA damage repair enzyme, called APE1, could provide a new way to kill cancer cells containing faulty BRCA genes, according to research presented at the National Cancer Research Institute (NCRI) Cancer Conference in Liverpool, today.

Researchers at The University of Nottingham have developed small molecules that block APE1. They tested the ability of these molecules to stop the enzyme from repairing DNA damage in breast, pancreatic and cervical cancer cells containing faults in BRCA1 or BRCA2 genes.

The BRCA genes control a separate, major DNA repair pathway. Cells with damaged BRCA1 or BRCA2 have a faulty 'repair kit'. This allows damaged cells to accumulate faults and multiply out of control – which increases the risk of developing cancer, especially ovarian and breast cancer.

But too much damage can lead to cell death. Blocking APE1 in these BRCA-deficient cells effectively blocks two repair routes at once, killing the cancer cells.

This technique of blocking two repair routes is already being used with a new class of drugs called PARP inhibitors. These prevent cells fixing faults in BRCA-deficient cells by blocking PARP, a key enzyme in the same repair pathway as APE1.

APE1, like PARP, is essential for carrying out a type of DNA damage

repair – removing and correcting faulty DNA components – but has a more specific role in this repair process compared to the PARP enzymes.

The research suggests that APE1 could provide an additional drug target to PARP.

Dr Srinivasan Madhusudan, clinical senior lecturer and consultant in medical oncology, who is leading the APE1 drug discovery research programme at The University of Nottingham, said: “This important study provides the first evidence that APE1 is an important new target for personalised cancer treatment.

“Not only could these molecules provide a basis for new drugs to treat cancers with faulty BRCA genes – especially breast and ovarian cancer – but they could help ‘soften up’ cells from many cancer types to boost the effect of radiotherapy and chemotherapy.”

Professor Steve Jackson, a DNA damage repair expert, said: “Destroying cancer cells by knocking out two repair mechanisms simultaneously is emerging as an important way to treat the disease. We’ve already made strides in developing treatments that do this, and this new research builds on that work.

“This promising new target may lead to even more specific drugs capable of delivering a knock-out double blow to cancer cells, leaving healthy cells unharmed - so potentially causing fewer side effects.

“It also brings fresh hope for the development of new drugs which can be prescribed when patients become resistant to conventional treatments. We’ll look forward to further development of potential new drugs to block this very specific target with great interest.”

Baroness Delyth Morgan, Chief Executive of Breast Cancer Campaign, which part-funded the research, said: "With up to ten per cent of all breast cancers thought to result from faulty BRCA1 and/or 2 genes, new treatments for these patients could possibly help up to 4,800 of the women diagnosed with the disease in the UK each year. Currently there are limited options available to them and this potential new treatment, although at an early stage could provide a real lifeline and a better chance of survival, which can only be good news."

More information: www.ncri.org.uk/ncriconference … /abstracts/A186.html

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