Upside-down world: DNA protecting protein helps cancer drug to kill cells

April 28 2009

Some DNA repair enzymes can become double-edged swords - If they work too slowly, they can block necessary cell maintenance and contribute to cell death. This could explain the somewhat mysterious success of the widely used cancer drug 5-Fluorouracil (5FU) and help clinicians to predict patient's response to chemotherapy, according to new findings from the University of Basel, Switzerland.

The work, published in this week's issue of *PLoS Biology*, reports that 5FU keeps the DNA-repair enzyme TDG too busy to perform properly in cancer cells, thereby promoting tumor death.

5FU has been used in cancer therapy for more than four decades and remains a mainstay in the treatment of colorectal cancer. But precisely how the drug kills cancerous cells was not well understood. It was generally thought that as an inhibitor of thymidylate synthase the compound worked by starving cells of the thymidine needed to make DNA.

First author on the paper Christophe Kunz and his colleagues inactivated the TDG enzyme in different human and mouse cells and found that the cells became resistant to the cancer drug. They wondered how a DNA repair enzyme could change the tolerance of cells to chemotherapy. They found that, in addition to other effects, 5FU is incorporated into DNA, in the place of the normal DNA base Thymidine.

TDG identifies these 5FU insertions, and is tasked with removing the

5FU from the DNA. TDG depends on a chemical modification to leave DNA after doing its job, and its turnover is very slow. When large amounts of 5FU are present in DNA the slow turnover can overload the entire repair system. Under those circumstances, an abasic site (a site where a base is missing) is left unrepaired, and so the DNA damage response kicks in, and kills the cell. So TDG may cause the death of cells flooded with 5FU - a desirable goal in tumour therapy.

"These findings provide a better understanding of how 5-Fluorouracil kills cancer cells," says Dr. Kunz, "in the future this knowledge could provide clinicians with a prognostic tool to decide which chemotherapeutic treatment to use based on the patient's level of TDG expression in the tumor cells." To this end, future research should focus on determining whether TDG expression correlates with 5FU response rates in cancer patients.

More information: Kunz C, Focke F, Saito Y, Schuermann D, Lettieri T, et al. (2009) Base excision by thymine DNA glycosylase mediates DNA-directed cytotoxicity of 5-fluorouracil. PLoS Biol 7(4): e1000091.doi:10.1371/journal.pbio.1000091, biology.plosjournals.org/perls … journal.pbio.1000091

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