MedicalXpress

Findings suggest how cancer cells can become resistant to DNA damage-inducing treatments

October 23 2011

An international team of scientists led by UC Davis researchers has discovered that DNA repair in cancer cells is not a one-way street as previously believed. Their findings show instead that recombination, an important DNA repair process, has a self-correcting mechanism that allows DNA to make a virtual u-turn and start over.

The study's findings, which appear in the Oct. 23 online issue of the journal *Nature*, not only contribute new understanding to the field of basic cancer biology, but also have important implications for potentially improving the efficacy of cancer treatments.

"What we discovered is that the DNA repair pathway called recombination is able to reverse itself," said Wolf-Dietrich Heyer, UC Davis professor of microbiology and of molecular and cellular biology and co-leader of Molecular Oncology at UC Davis Cancer Center. "That makes it a very robust process, allowing cancer cells to deal with DNA damage in many different ways. This repair mechanism may have something to do with why some cancer cells become resistant to radiation and chemotherapy treatments that work by inducing DNA damage."

Heyer likens this self-correcting ability of the DNA repair system to driving in a modern city where u-turns and two-way streets make it easy to rectify a wrong turn. "How much harder would it be to re-trace your

path if you were in a medieval Italian city with only one-way streets," he said.

In the current study, Heyer and his colleagues used yeast as a model system to elucidate the mechanisms of DNA repair. They expect their findings, like most that come out of work on yeast, will be confirmed in humans. "Whether in yeast or humans, the pathways that repair DNA are the same," Heyer said.

The research team used electron microscopy to observe repair proteins in action on strands of DNA. They saw a presynaptic filament called Rad51 regulating the balance between one enzyme (Rad55-Rad57) that favors recombination repair and another (Srs2) that inhibits recombination repair. By controlling the balance between the two enzymes, Rad51 can initiate genetic repair - or the u-turn - as needed.

"It is a tug-of-war that has important implications for the cell because, if recombination occurs at the wrong time in the wrong place, the cell may die as a consequence." The ability of the repair system to abort ill-fated repair attempts, gives the cell a second shot, improving cellular survival after its DNA is damaged. This is exactly what is dreaded in cancer treatment.

"There are a lot of hints in the scientific literature suggesting that DNA repair contributes to resistance to treatments that are based on inducing DNA damage such as radiation or certain types of chemotherapy," Heyer said. "The ability of cancer cells to withstand DNA damage directly affects treatment outcome, and understanding the fundamental mechanisms of the DNA repair systems will enable new approaches to overcome treatment resistance."

Heyer said the team's next step is to look at the enzyme system in humans and see whether they find the same principles at work. This

work has received funding and has already begun. One application of this work will be to target the self-correcting mechanism in cancer cells as a way of sensitizing them to radiation and/or chemotherapy treatments.

"If we can confirm that these types of mechanisms exist in human cells, then we will have an approach for making cancer cells more sensitive to DNA damage-inducing treatments."

Provided by University of California - Davis