

Repairing DNA damage: Researchers discover critical process in cancer treatment

6 November 2008

(PhysOrg.com) -- From the sun's UVA rays to tobacco smoke, our environment is chock-full of DNA-damaging agents that can lead to cancer. Thanks to our body's DNA repair mechanisms, however, the effects of many carcinogens can be reversed thereby preventing the formation of tumours.

Now, according to a new study published in the early online edition of *Proceedings of the National Academy of Sciences* of the USA (PNAS), scientists from the Université de Montréal and the Maisonneuve-Rosemont Hospital Research Centre have identified a new biochemical pathway which controls DNA repair.

"Our study is the first to identify a regulatory role for the ATR protein in a specific DNA repair system, which is called nucleotide excision repair or NER," says Elliot Drobetsky, senior author and associate professor of immunology and oncology at the Université de Montréal.

"NER is a critical DNA repair system that removes pieces of damaged DNA before these pieces can be converted into genetic mutations that destroy the function of tumour-preventing proteins in the body. Characterizing how the NER system is turned on or off is critical to understanding how tumours develop. In this system, ATR is the key that turns on the repair machinery."

ATR-mediated NER often defective in tumour cells

The scientific team used cultured lung cells to investigate the role of ATR in NER function. They found that inhibiting ATR resulted in a dysfunctional NER system and, during a very critical period of the cell's growth cycle, damaged DNA was not repaired at all.

What's more, they discovered that some tumour cell lines are completely deficient in ATR-mediated

NER, which provides solid evidence that the DNA repair function of ATR may be pivotal in cancer development. "Our study reveals an original mechanism to explain how exposure to environmental carcinogens initiate and promote cancer," adds Dr. Drobetsky.

Chemotherapy implications

The goal of conventional chemotherapy is to kill tumour cells – leaving normal cells relatively unaffected – by damaging their DNA. As such, in what may seem paradoxical, many chemotherapeutic drugs which are used to cure cancer are themselves powerful carcinogens that can also cause cancer.

"As shown in the current study, a non-functional ATR pathway resulting in limited DNA repair may be characteristic of many tumour cell types, but not of normal noncancerous cells. Determining if the NER system is working in patient tumours may therefore be an important first step to chemotherapy prescribing practices," says Yannick Auclair, the study's lead author and a PhD student at the Université de Montréal.

Any tumours identified as defective in ATR-mediated repair are expected to respond extremely well to chemotherapy, because the cells in these tumours would be extremely hypersensitive to certain anti-cancer drugs unlike normal cells in the rest of the body.

"These findings open a whole new area of research," says Dr. Drobetsky. "Our data harbour critical implications not only for understanding how cancer develops but also for devising new strategies to greatly improve cancer treatment."

Provided by University of Montreal

APA citation: Repairing DNA damage: Researchers discover critical process in cancer treatment (2008, November 6) retrieved 18 November 2022 from <https://medicalxpress.com/news/2008-11-dna-critical-cancer-treatment.html>

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