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New understanding of DNA repair could eventually lead to cancer therapy

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A research group in the Faculty of Medicine & Dentistry at the University of Alberta is hoping its latest discovery could one day be used to develop new therapies that target certain types of cancers.

The discovery by Mark Glover, his graduate student Zahra Havali-Shahriari and post-doctoral fellow Nicolas Coquelle has shed light on what happens in cells when DNA is damaged. They solved the structure of a DNA repair enzyme called polynucleotide kinase/phosphatase, or PNKP. This allows them to see what is happening when this enzyme is repairing DNA.

Their findings have been published in the *Proceedings of the National Academy of Sciences*, a high-impact scientific journal.

In normal cells damaged DNA can lead to the breakdown of chromosomes and, ultimately, cancers. On the other hand, damaging DNA in cancer cells is a useful way to kill them. A long-term goal of this research is to find ways to specifically block PNKP from doing its repair work in cancer cells as a possible new cancer therapy.

"We can finally visualize it bound to the damaged ends of DNA," said Glover, a professor in the Department of Biochemistry. "We've trapped the enzyme bound to the damaged DNA before it actually repairs the damage. One of the surprising things that comes out of this study is that we also see that the enzyme has to unwind the DNA double helix."

Work over the last 10 years, pioneered in large part in the Faculty of Medicine & Dentistry, revealed that the enzyme PNKP plays a critical role in the repair of broken DNA ends produced by radiation and other agents. Until now, though, no one knew how it finds and repairs the damage.

"It breaks base pairs [of DNA] apart, peels off the broken end and then PNKP inserts that broken end into the enzyme," explains Glover. "It then performs a chemical reaction on the damaged DNA end, reversing the damage and releasing it so that the broken DNA strand can be welded together with the rest of the double helix. We now understand more about how this thing works; an enzyme that is protecting us from getting cancers."

However, the same enzyme also protects cancer cells. "We find a lot of tumours become resistant to these therapies [radiation and chemotherapy]," said Glover. "The holy grail of cancer therapy is to find drugs that we could give to people that would sensitize their tumours to these therapies.

"One way you could sensitize tumours is to target what they're using to repair damaged DNA. One of the ideas is that we could specifically inhibit this PNKP enzyme."

Sensitizing the tumours to therapies could also lower side effects, adds Glover.

The lab is already starting to test some compounds that could act as inhibitors for PNKP in tumours and they've seen some positive early results.

Because radiation is proven effective in some but not all cancers, new treatment avenues are necessary. Glover is playing a vital role in moving

potential new treatment forward.

"It requires a lot of basic research to find out what's going on in all these different cancers," he said.

Provided by University of Alberta