Nanotweezers Unlock Anticancer Drug Secrets

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The annoying bulges of an overwound telephone cord that shorten its reach and limit a caller's motion help explain why drugs called camptothecins are so effective in killing cancer cells, according to investigators led by Mary-Ann Bjornsti, Ph.D., at St. Jude Children's Research Hospital, and Nynke Dekker, Ph.D., at Delft Technology University.

Using nanoscale magnetic tweezers (nanotweezers), the researchers showed that a camptothecin drug called topotecan kills cancer cells by preventing an enzyme called DNA topoisomerase I from uncoiling double-stranded DNA in those cells. Instead, the DNA becomes locked in tight twists called supercoils, which bulge out from the side of the overwound DNA molecule much like the bulges in an overwound telephone cord. If these supercoils accumulate and persist while the cell is trying to separate the two strands of DNA to make exact copies of the chromosomes during cell division, the cells will die.

In this first-of-its-kind study, researchers used the nanotweezers to monitor changes in the length of an individual DNA molecule caused by the action of a single topoisomerase I enzyme. They also used the nanotweezers to study how the binding of a single topotecan molecule to this enzyme-DNA complex alters DNA uncoiling.

Based on the results of those studies, the researchers developed the supercoil theory to explain the drug's ability to kill cancer cells and then tested that theory in yeast cells. They concluded that the accumulation of

DNA supercoiling kills the cells using a newly discovered biophysical mechanism. Their findings also provide insights into the drug's action that could help scientists in the clinical development of these agents. This work appears in the journal Nature.

"This is the first time that the tools of nanotechnology have helped scientists develop a biological hypothesis that was subsequently tested by followup experiments in a living organism," said Bjornsti, a member of the St. Jude Department of Molecular Pharmacology.

Dekker and her colleagues at Delft Technology University developed the magnetic tweezers for studies in biophysics and adapted the technique to the current study of the effect of topotecan on topoisomerase I in cooperation with Bjornsti's research group.

The researchers made their discovery using the magnetic tweezers technique to attach one end of a double-stranded DNA molecule from a magnetic bead while securing the other end to a glass surface. They then rotated a tiny magnet over the top of the magnetic bead, which in turn rotated the bead holding the DNA, twisting the DNA into supercoils and shortening it to about one-seventh of its original length.

When the team added topoisomerase I to the DNA, the strand uncoiled to its original length within a few seconds. This suggested that the enzyme had nicked the supercoils, relieving tension and allowing the DNA to expand to its previous length. But in the presence of topotecan, the rate of DNA uncoiling due to topoisomerase I was reduced twentyfold compared with uncoiling without topotecan. However, the surprising finding was that drug binding slowed topoisomerase I uncoiling of overwound DNA (positive supercoils) more than the rewinding of the strands of DNA that was underwound (negative supercoils).

This work, which was supported in part by the NCI, is detailed in the paper “Antitumour drugs impede DNA uncoiling by topoisomerase I.” An abstract of this paper is available through PubMed.

Source: National Cancer Institute