Nature's elegant solution to repairing DNA in cancer, other conditions

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A major discovery about an enzyme's structure has opened a window on understanding DNA repair. Scientists at Duke University Medical Center have determined the structure of a nuclease that will help scientists to understand several DNA repair pathways, a welcome development for cancer research.

DNA repair pathways are very important in the context of cancer biology and aging, but the tools the cell uses to do those repairs are not well understood.

"Until we saw the structure using X-ray crystallography, we didn't understand how it could recognize so many unusual DNA structures," said senior author Lorena Beese, Ph.D., James B. Duke Professor of Biochemistry. "The relative arrangement of the binding sites and of the active site itself for this enzyme is important for recognition during the repair process, and I don't think we could have imagined how it came together."

The study appears in this week's issue of *Cell* journal.

"We present the first structural information about these nucleases in humans, and that information is important for DNA substrate recognition and enzymatic mechanism," Beese said. "The discovery is important for understanding the mismatch repair pathway, and more generally, it will help us understand other pathways as well."

If mismatch repairs are not completed properly, this deficiency can have profound effects on human health, including genes that mutate spontaneously, forms of colorectal cancer, and the development of an estimated 15-25 percent of sporadic tumors, the authors noted.

"Scientists have been interested in obtaining a detailed picture of where the atoms are in this protein for a long time. We were able to determine the structure, because we put together the right experiments at the right time – good protein expression, good purification, and fortunately when we got crystals we had the right team to solve the structure and do the biochemical experiments," Beese said. "This was truly a team effort."

The next step is to study complexes of this molecule with other proteins in the repair pathway. "By understanding the interactions between proteins, we will get more insight into how it works and how the activities are regulated," Beese said. "In terms of future therapeutic strategies, these interfaces present exciting targets for new drugs."

Also to be published in the April 14 issue of *Cell*, a team lead by John Tainer at the Lawrence Berkeley labs reports that another nuclease in a related pathway has the same structural arrangements.

"It's remarkable how nature has solved complex topological puzzles in DNA substrate recognition with such elegant simplicity," Beese said.

Provided by Duke University Medical Center