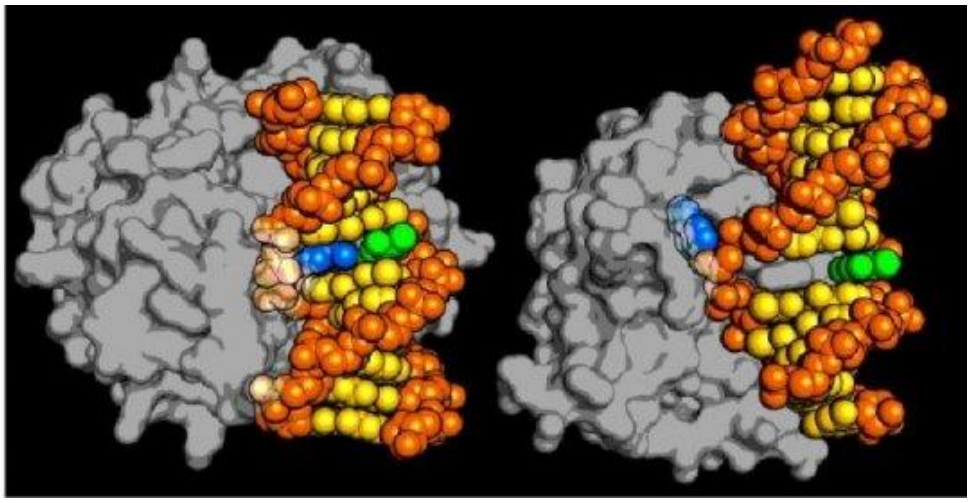
AlkD - A New DNA repair enzyme discovered

Ever since the discovery of the structure of DNA, biologists have learned that the double helix is in fact a highly reactive molecule that is constantly being damaged and that cells must make unceasing repair efforts to protect the genetic information that it contains.

A new class of DNA repair enzyme has been discovered which demonstrates that a much broader range of damage can be removed from the double helix in ways that biologists did not think were possible. Dr. Brandt Eichman who headed the research team that made the new discovery stated that if DNA were too reactive then it wouldn't be capable of storing genetic information. But, if it were too stable, then it wouldn't allow organisms to evolve.



The new type of DNA repair enzyme, AlkD on the left, can identify and remove a damaged DNA base without forcing it to physically "flip" to the outside of the DNA backbone, which is how all the other DNA repair enzymes in its family work, as illustrated by the human AAG enzyme on the right. The enzymes are shown in grey, the DNA backbone is orange, normal DNA base pairs are yellow, the damaged base is blue and its pair base is green.

The DNA double-helix has a spiral staircase structure with the outer edges made from sugar and phosphate molecules joined by stair steps composed of pairs of four nucleotide bases (adenine, cytosine, guanine and thymine) that serve as the basic letters in the genetic code.

There are two basic sources of DNA damage or lesions: environmental sources including ultraviolet light, toxic chemicals and ionizing radiation and internal sources, including a number of the cell's own metabolites (the chemicals it produces during normal metabolism), reactive oxygen species and even water.

They highlighted the fact that more than 10,000 DNA damage events occur each day in every cell in the human body that must be repaired for DNA to function properly. The newly discovered DNA repair enzyme is a DNA glycosylase, a family of enzymes discovered by Tomas Lindahl, who received this year's Nobel prize for recognizing that these enzymes removed damaged DNA bases through a process called base-excision repair. In base-excision repair, a specific glycosylase molecule binds to DNA at the location of a lesion and bends the double-helix in a way that causes the damaged base to flip from the inside of the helix to the outside.

Eichman and his collaborators discovered that a glycosylase called AlkD found in Bacillus cereus -- a soil-dwelling bacterium responsible for a type of food poisoning called the "fried rice syndrome" -- works in a totally different fashion. It does not require base flipping to recognize damaged DNA or repair it.

Seven years ago, Eichman's group discovered that AlkD had a structure unlike any of the other glycosylases. The researchers determined that the enzyme was able to locate damaged DNA that has a positive electrical charge. Positively charged alkylated bases are among the most abundant and detrimental forms of DNA damage.

The researchers have determined that AlkD excises alkylation damage by a series of interactions with the DNA backbone at and around the lesion while the lesion is still stacked in the double helix. Several of these interactions are contributed by three amino acids in the enzyme that catalyze excision of the damaged base.

The discovery shows that we still have a lot to learn about DNA repair, and that there may be alternative repair pathways yet to be discovered. It certainly shows us that a much broader range of DNA damage can be

removed in ways that we didn't think were possible. Bacteria are using this to their advantage to protect themselves against the antibacterial agents they produce. Humans may even have DNA-repair enzymes that operate in a similar fashion to remove complex types of DNA damage. This could have clinical relevance because these enzymes, if they exist, could be reducing the effectiveness of drugs designed to kill cancer cells by shutting down their ability to replicate.

Journal Reference:

Elwood A. Mullins, Rongxin Shi, Zachary D. Parsons, Philip K. Yuen, Sheila S. David, Yasuhiro Igarashi, Brandt F. Eichman. The DNA glycosylase AlkD uses a non-base-flipping mechanism to excise bulky lesions. Nature, 2015; DOI: 10.1038/nature15728.