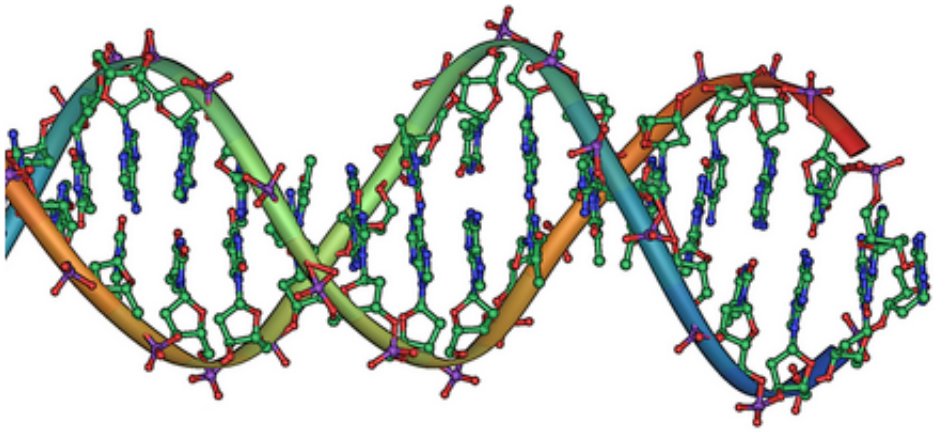
New DNA insights may lead to cancer therapy

October 23 2015, by Heather Lindsey



DNA double helix. Credit: public domain

Researchers at Weill Cornell Medicine have developed a better understanding of a complex mechanism that contributes to the growth of telomeres, the repetitive sequences of DNA that protect the end of a cell's chromosomes. Their study, published Oct. 22 in *PLOS Genetics*, may one day allow scientists to develop new, targeted cancer drugs.

Each time a normal cell divides, its telomeres shorten, a process that eventually leads to cell death. To avoid this fate, cancer cells maintain

their telomere length and continue to divide uncontrollably. The majority of cancer cells use the enzyme telomerase to add DNA to their telomeres. However, about 10 to 15 percent of cancer cells use a different process, or pathway, to maintain their telomere length.

This pathway, called ALT, for alternative lengthening of telomeres, exchanges pieces of DNA from one chromosome to another or copies DNA from one portion of a chromosome to another portion. The team discovered vulnerabilities in ALT that investigators could harness for new cancer therapies.

"By understanding what factors, or mechanisms, are required for the ALT pathway to function, we will be able to better develop drugs that block these factors in cancer cells," said senior author Dr. Neal Lue, a professor of microbiology and immunology and a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. Other study investigators include lead author Dr. Eun Young Yu and Dr. William K. Holloman, also of the Department of Microbiology and Immunology and a member of the Meyer Cancer Center – which helped support the research – and Dr. Jose Perez-Martin of the Institute of Biology and Functional Genomics in Salamanca, Spain.

To learn more about the ALT pathway, the researchers used Ustilago maydis, a yeastlike fungus containing telomeres that share many of the same features as human telomeres. By genetically manipulating the fungus, they triggered the ALT pathway, and then showed that eliminating a specific gene prevented the pathway from working. The gene, BLM, encodes an enzyme that separates DNA strands, a process that appears to be important for starting the recombination process, Lue said.

"We knocked out BLM and showed that the ALT pathway is completely dead and that these cells can no longer add DNA to their telomeres," he

said. "If we can design an inhibitor against BLM, it would probably be effective in reducing the growth of some cancer cells."

Additionally, deleting the gene MRE11, which plays a role in maintaining telomere length and repairing DNA, decreased ALT pathway activity by about 20-fold, said Lue. Consequently, MRE11 appears to be another promising drug target.

Lue and his colleagues are now growing ALT cancer cells and knocking out BLM and MRE11 to confirm their study results.

"We're trying to translate our findings from the fungal model to actual cancer cells," he said, adding that researchers are also trying to determine if any other factors play an important role in the ALT pathway.

Provided by Cornell University