

## Abstract

Proper repair of damaged DNA bases is important for genomic stability and cancer prevention. One pathway that has evolved to remove oxidative DNA damages is called the base excision repair pathway. The first step in this pathway utilizes enzymes called DNA glycosylases, which are responsible for finding, recognizing, and removing damaged bases. Mutations in one glycosylase, MUTYH, have been found to be responsible for a particular type of colon cancer in humans. One of these mutations is a single amino acid substitution in a “wedge” residue that crystal structures show insert into the DNA adjacent to the damage. Determining the DNA scanning behavior of the wedge variant will elucidate mechanism behind this particular tumorigenesis. In this project, we have examined the DNA scanning behavior of the wedge variant using single molecule analysis on an E. coli homolog, MutY. We show that the MutY wedge variant (Y82C) exhibits faster and more randomized scanning motion along the DNA indicating a decrease in intrahelical interrogation due to the lack of the wedge residue responsible for recognizing, removing, and ultimately repair of the damaged DNA. Additionally, the wedge variant displays a decreased binding lifetime to the DNA, further reducing the ability of the variant to repair the damaged DNA. Overall, this gives a better understanding of the mechanism behind DNA repair and the importance of the wedge residue to this process. Furthermore, this may lead to better treatments for MUTYH related cancers.