Chemistry and Biology of the Repair of (OG):A Mismatches by MutY enzymes

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DNA repair processes play an important role in maintaining the chemical integrity of DNA and preserving its informational content. The damaged base 8-oxoguanine (OG) is particularly sinister due to its subtle structural change that evades detection during replication and results in incorrect insertion of adenine to form OG:A mismatches. The MutY glycosylase is a unique iron-sulfur protein that prevents mutations by excising adenine from OG:A mismatches. MutY has captured the spotlight due to a direct correlation between inherited defects in the human MutY homologue (MUTYH) and colorectal cancer,[1] referred to as MUTYH-associated polyposis (MAP). Our research laboratory provided support for the discovery of MAP by providing functional analysis of the two most common variants in MUTYH revealing a hampered ability to recognize OG. We have also used a combination of synthesis of modified substrates, enzymology and X-ray crystallography to reveal features associated with damage recognition and adenine excision by MutY. Recently, using an azaribose transition state we have determined several crystal structures that provide intriguing new insight into the adenine excision mechanism by MutY. In addition, in order to correlate how defects in various aspects of the enzyme action impact repair, cellular repair assays on modified DNA substrates or with modified enzymes have also been performed. Taken together, our work highlights the importance of OG recognition in selecting and positioning adenine for excision. This work also illustrates the importance of both recognition and catalytic "check-points" to ensure proper excision of only inappropriate adenine residues by MutY and MUTYH.

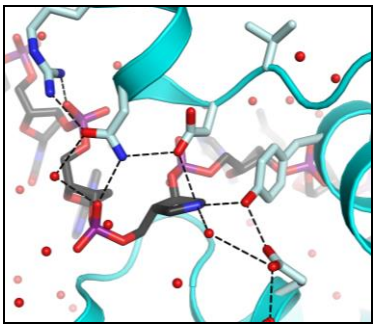

Fig. 1 Close-up view of transition-state analog in MutY active site

Keywords： DNA damage, DNA repair, transition state analogs, crystallography, enzymology

References

[1]David, S. S., O'Shea, V. L., Kundu, S., *Nature*, 2007, 447, 941-958.