Base Excision Repair by TDG: A Possible Role of Extrahelical Imino-Tautomers?

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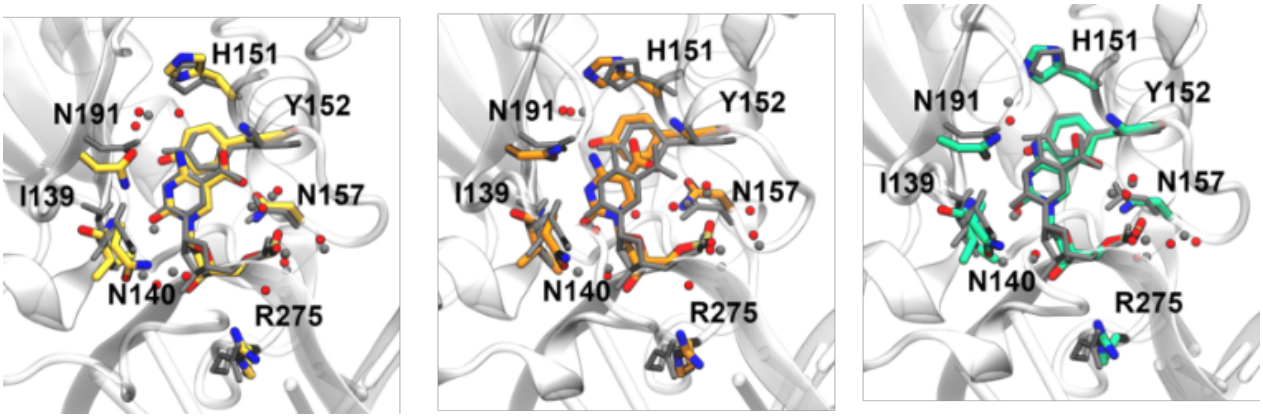

Thymine DNA glycosylase (TDG) is an important enzyme involved in DNA repair, which removes mispaired or modified DNA bases and thus ensures genetic integrity. We previously investigated possible reasons for its substrate specificity, both in the intrahelical (flipped-in) and in the extrahelical (flipped-out) state of the damaged bases 5-carboxylcytosine, 5-formylcytosine, 5-hydroxymethylcytosine and 5-methylcytosine. We showed that imino tautomers probably do not contribute to recognition in the intrahelical state, and that recognition most likely takes place once the bases are flipped out into the TDG binding pocket (extrahelical complexes). Here, only amino tautomers of the bases of interest were investigated.

We have now extended the range of possible forms of the substrates to achieve a deeper understanding of the situation in the protein substrate complex prior to the chemical reaction. For this reason, we investigated the role of imino-tautomeric forms of the damaged DNA bases flipped out into the enzyme active site as well as the effect of different protonation states of the substrate bases and an important histidine residue in the binding pocket.

The results obtained agree well with our previous work and the experimental data, and also indicate that imino tautomers might play a role in extrahelical recognition and as a starting point in the actual chemical reaction. We plan to investigate this in more detail.

[1] F. Beierlein, S. Volkenandt, P. Imhof, *J. Phys. Chem. B* **2022**, *126,* 1188. (DOI: 10.1021/acs.jpcb.1c09896)

[2] S. Volkenandt, F. Beierlein, P. Imhof, *Molecules* **2021**, *26,* 5728. (DOI: 10.3390/molecules26195728)