Insights into Light-driven DNA Repair by Photolyases

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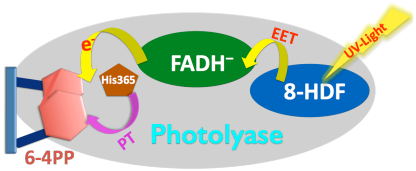
UV radiation triggers various chemical reactions in DNA such as intra-strand cross-linking between adjacent pyrimidines, causing genetic mutations. In fact, pyrimidine dimers are supposed to be the major players in the formation of skin cancer. DNA photolyases are enzymes initiating cleavage of mutagenic pyrimidine (6-4) pyrimidone photolesions by a photo-induced electron transfer from flavin adenine dinucleotide to the lesion.



Using hybrid quantum mechanical/molecular mechanical (QM/MM) dynamics, we have carried out series of simulations to completely map out the entire evolution of functional processes involved in the molecular mechanism of this important biological system. We have demonstrated that the electron catalyzing the repair is generated via an intermolecular Coulombic decay (ICD) process [1]. In fact, this is the first example for ICD as operating mechanism in a real biological system. We have presented the most energetically feasible electron-induced splitting mechanism in which the initial step is electron-coupled proton transfer from the protonated Histidine to the lesion, which proceeds simultaneously with intramolecular OH transfer along an oxetane-like transition state [2]. Our theoretical findings are in agreement with experimental time-resolved measurements [3]. The experimental spectroscopic signature of the detected 6-4PP intermediate is assigned theoretically to a specific molecular structure determining the operating molecular mechanism of the electron-induced restoration of (6-4) photolesions. Thereby, all pieces of the (6-4) photolesion repair puzzle are finally put together [4].

[1] P. Harbach , M. Schneider, S. Faraji, A. Dreuw, *J. Phys. Chem. Lett.* 4, 943 (2013).

[2] S. Faraji and A. Dreuw, *J. Phys. Chem. Lett. 3*, 227 (2012), S. Faraji, G. Groenhof and A. Dreuw, *J. Phys. Chem. B.* 117, 10071 (2013)

[3] J. Li et al, Nature 466, 887 (2010). S. Faraji and A. Dreuw, *Ann. Rev. Phys. Chem.* 64, (2014).

[4] S. Faraji, D. Zhong, and A. Dreuw, *Angew. Chem. Int. Ed. Engl*, 55, 5175 (2016). S. Faraji, A. Dreuw. *Photochem. Photobiol*, 93, 37 (2017).