The catalytic mechanism of hOGG1 base-excision repair enzyme; the theoretical modeling of reaction channels and substrate activation

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The 8-oxo-2'-deoxyguanosine (OxoG) lesions occurring in human genome are repaired by human OxoG glycosylase 1 (hOGG1) base-excision repair enzyme. The actual catalytic mechanism of hOGG1 is unknown although several mechanisms were suggested based on available x-ray structures, biochemical data and theoretical modelling. We proposed the reaction mechanism of hOGG1 that is initiated via enforced pyramidalization of glycosidic nitrogen (N9) of OxoG [1]. The N9-pyramidalization allows direct proton addition to glycosidic nitrogen during base excision via deprotonation of hOGG1 residue Lys 249. Pyramidal geometries of the glycosidic nitrogen found in x-ray structures of normal nucleic acids [2] were explained theoretically [3]. The N9-pyramidalization activates specifically the damaged nucleobase and initiates efficient base excision pathway [4]. Concept of the experimental validation of hOGG1 base-excision mechanism will be presented along with preliminary data.

[1] Šebera, Trantirek, Tanaka, Sychrovský, JPC B, **2012**, 116, 12535-12544.

[2] Sychrovský, Foldynova-Trantírkova, Spackova, van Meervelt, Blankenfeld, Vokacova, Sponer, Trantírek, NAR, **2009**, 37, 21, 7321-7331.

[3] Sychrovský, Vokacova, Trantírek, JPC A, **2012**, 116, 4144-4151.

[4] Šebera, Trantírek, Tanaka, Nencka, Fukal, Sychrovský, RSC Adv., **2014**, 4, 44043–44051.