Structural and Biochemical Evaluation of the Catalytic Mechanism of a DNA Repair Enzyme, Human Oxoguanine DNA Glycosylase

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Genomic DNA is continuously exposed to reactive oxygen species originated from aerobic respiration, drugs, or other oxidative environments resulting in its oxidative lesion. An oxidation product of guanine base on DNA, 8-oxoguanine (oxoG) pairs with ATP as well as TTP during the replication leading T→A transversion mutation of the DNA, which is the second most common somatic mutation found in the p53 gene of human cancers. Human 8-oxoguanine DNA glycosylase (hOgg1) initiates the repair of oxoG in the genome, by catalyzing excision of oxoG and nicking of the lesion-containing DNA strand. We have studied the catalytic mechanism of the enzyme including the role of a key active site residue Asp 268 of hOgg1 by biochemical and structural analyses. Mutational studies allowed us to understand Asp 268 as an evolutionarily optimized residue for the catalysis and structural stability of the enzyme. We also crystallized and structurally characterized the end-product resulting from complete DNA processing by a catalytically active mutant form of human 8-oxoguanine DNA glycosylase (D268E hOgg1). The resulting structure is consistent with the currently accepted catalytic mechanism for the protein.