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Molecular model of DNA glycosylase stimulation by human apurinic/apyrimidinic endonuclease 1

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Motivation and Aim: The base excision repair (BER) pathway consists of sequential action of DNA glycosylase and apurinic/apyrimidinic (AP) endonuclease necessary to remove a damaged base and generate a single-strand break in duplex DNA. Human multifunctional AP endonuclease 1 (APE1) plays essential roles in BER by acting downstream of DNA glycosylases to incise a DNA duplex at AP sites and remove 3′-blocking sugar moieties at DNA strand breaks. Human 8-oxoguanine-DNA glycosylase (OGG1), methyl-CpG-binding domain 4 (MBD4), and alkyl-N-purine-DNA glycosylase (ANPG) excise a variety of damaged bases from DNA. The major human apurinic/apyrimidinic (AP) endonuclease, APE1, stimulates DNA glycosylases by increasing their turnover rate on duplex DNA substrates. At present, the mechanism of the stimulation remains unclear.
Methods and Algorithms: Electron microscopy (EM) indicated that APE1 can oligomerize onto a DNA fragment. Atomic force microscopy (AFM) revealed that APE1 oligomerization induces a kink in the DNA backbone to detect an abasic site. To elucidate the molecular mechanism of the APE1-catalyzed stimulation, we employed the stopped-flow fluorescence analyses of the interaction of APE1 with human DNA glycosylases OGG1, MBD4^{cat}, and ANPG^{cat} bound to their DNA-substrates.
Results: TEM and AFM imaging of APE1-DNA complexes showed that polymerization of APE1 on DNA proceeds in an apparently sequence-independent manner. Full-length APE1 oligomerization along DNA induces helix distortions, which in turn enable stimulation of DNA glycosylases. It was shown that truncated APE1 protein lacking the first N-terminal 61 amino acid residues (APE1-NΔ61) cannot stimulate DNA glycosylase activities of OGG1, MBD4, and ANPG^{cat} on duplex DNA substrates. Altogether, these results suggest that the first 61 N-terminal residues of APE1 participate in protein polymerization along DNA and in formation of oligomerlike complexes by binding to undamaged DNA.
Conclusion: We propose that APE1 oligomers on DNA induce helix distortions thereby enhancing molecular recognition of DNA lesions by DNA glycosylases *via* a conformational proofreading/selection mechanism. APE1-mediated structural deformations of the DNA helix stabilize the enzyme–substrate catalytic complex and promote dissociation of human DNA glycosylases from the product AP-site with a subsequent increase in their turnover rate.
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