Séminaire externe

Role of the human DNA repair and redox signalling protein APE1/ Ref-1 in the regulation of DNA transcription and replication.

APE1 participates in both: repair of oxidative DNA damage and redox-dependent transcriptional regulation of oncogenes which may be linked to cellular proliferation. Number of transcription factors (TFs) contain redox-sensitive cysteine residues at their DNA-binding sites. Hence oxygen radicals induced thiol oxidation of these TFs strongly inhibits their DNA binding activities and transcription of target genes. In human cells APE1 stimulates the DNA binding activities of the oxidized TFs that regulate cell growth, differentiation, survival, and death including AP-1, NF-κB, HIF-1a, p53, Egr-1, c-Myb et cetera.At present, the molecular mechanism underlying the non-DNA repair functions of APE1 remains unclear. Previously, we showed that the N-terminal redox domain of APE1 is essential for nucleotide incision repair (NIR) suggesting that these two functions share a common mechanism. In this work, we found that APE1 can bind to both regular and damaged DNA duplexes and induce specific conformational changes over entire length of DNA fragment. This APE1-induced DNA conformational change facilitates assembly of TFs on their DNA sites. We propose that APE1 acts as a DNA chaperone that binds to DNA in cooperative manner to introduce changes in helix conformation, this in turn enables DNA cleavage and facilitates binding of the sequence-specific nuclear proteins. Potential role of the APE1-catalyzed redox function in the organization of DNA/chromatin domains and the regulation of DNA transcription and replication in proliferating cells are discussed.

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CNRS UMR 8200

Université Paris Sud - Gustave Roussy Cancer Campus, Villejuif

Invité par Bertrand Castaing

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