

Oxidative Mechanisms of DNA-Protein Cross-Linking

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»Oxidation of DNA by reactive oxygen species (hydroxyl radical, singlet oxygen, superoxide and electron transfer) compromise the genome by introducing base mutations and interrupting enzymatic processing. DNA damage has been linked to cancer, aging and neurological disease.

» The reaction mechanisms underlying DNA oxidation at guanine (G) are the focus of this study including the further oxidation of 8-oxoguanine (OG), a key biomarker of DNA oxidation. The reactive intermediate OG^{ox} is sensitive to nucleophilic attack by solvent water leading to Sp and Gh lesions that are highly mutagenic in cells.

»Under cellular conditions, DNA is surrounded by proteins, and their lysine-rich binding motifs provide amine nucleophiles that can intercept OG^{ox} leading to covalent cross-links. In the present study, cross-linking to single-stranded binding protein (SSB) tetramer was investigated to ascertain the oxidation conditions under which cross-links are formed, the sites of DNA-protein cross-linking, and structures of amino acids adducted to oxidized guanine sites. Understanding the structure and mechanism of DNA-protein cross-link formation builds our foundation for unraveling the molecular basis of mutagenesis.

