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Review

Role of oxidatively induced DNA lesions in human pathogenesis

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ABSTRACT

Genome stability is essential for maintaining cellular and organismal homeostasis, but it is subject to many threats. One ubiquitous threat is from a class of compounds known as reactive oxygen species (ROS), which can indiscriminately react with many cellular biomolecules including proteins, lipids, and DNA to produce a variety of oxidative lesions. These DNA oxidation products are a direct risk to genome stability, and of particular importance are oxidative clustered DNA lesions (OCDLs), defined as two or more oxidative lesions present within 10 bp of each other. ROS can be produced by exposure of cells to exogenous environmental agents including ionizing radiation, light, chemicals, and metals. In addition, they are produced by cellular metabolism including mitochondrial ATP generation. However, ROS also serve a variety of critical cellular functions and optimal ROS levels are maintained by multiple cellular antioxidant defenses. Oxidative DNA lesions can be efficiently repaired by base excision repair or nucleotide excision repair. If ROS levels increase beyond the capacity of its antioxidant defenses, the cell's DNA repair capacity can become overwhelmed, leading to the accumulation of oxidative DNA damage products including OCDLs, which are more difficult to repair than individual isolated DNA damage products. Here we focus on the induction and repair of OCDLs and other oxidatively induced DNA lesions. If unrepaired, these lesions can lead to the formation of mutations, DNA DSBs, and chromosome abnormalities. We discuss the roles of these lesions in human pathologies including aging and cancer, and in bystander effects.

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Contents

1. Induction and processing of oxidative DNA lesions in human cells and tissues

Elevated ROS levels can create oxidative stress in a cell and chronic exposure to this stress can result in permanent changes in the genome [1,2]. It is generally accepted that the accumulation of oxidative DNA lesions may promote mutagenesis, human pathogenesis and loss of homeostasis. These oxidative lesions can be induced not only by ROS generated by exposure to exogenous agents including ionizing or non-ionizing radiation (IR), drugs, and

Abbreviations: 8-oxo-dG, 8-oxo-2′-deoxyguanosine; BER, base excision repair; DEANO, diethylamine NONOate; DSB, double-strand break; FISH, fluorescent in situ hybridization; Mbp, mega base pair; mtDNA, mitochondrial DNA; NO, nitric oxide; OCDL, oxidative clustered DNA lesions; ROS, reactive oxygen species; SSB, single-strand break; Topo, topoisomerase.

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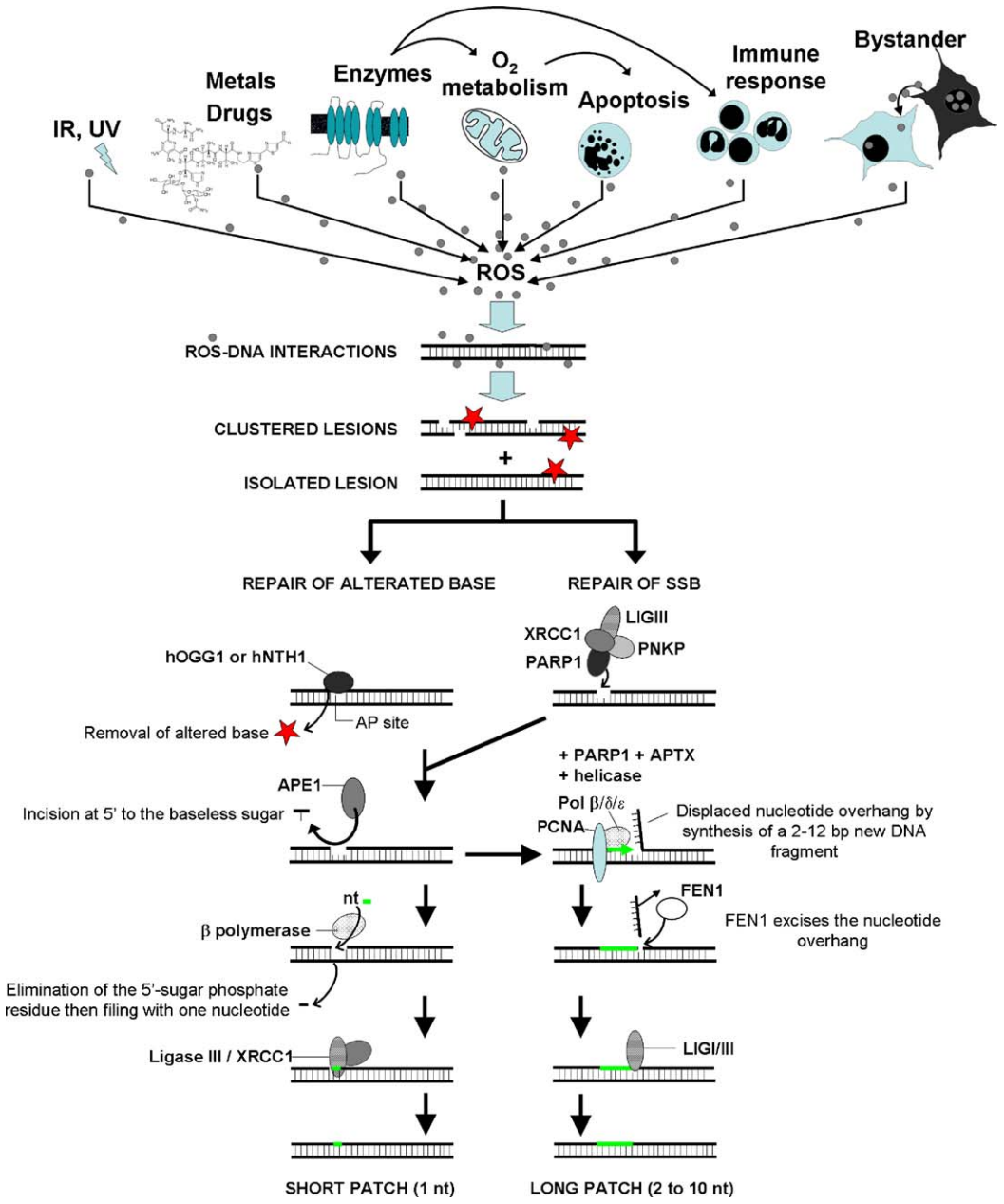

Fig. 1. ROS have different origins. ROS can arise following exposure to ionizing radiation or light (IR, UV), drugs and other chemicals such as metals. Enzymes, oxygen metabolism and apoptosis also account for ROS production. Finally, the inflammatory responses involving the immune system and bystander signaling also utilize ROS. When ROS enter the nuclear cell compartment, they interact with DNA creating lesions ranging from base or sugar modifications to abasic sites (represented by red stars) and SSBs. ROS-induced DNA lesions can appear in an isolated or clustered form and they are primarily repaired by two BER subpathways: the short-patch and the long-patch pathways. The short-patch or single-nucleotide pathway is initiated by a DNA glycosylase (hOGG1 or hNTH1) that cleaves and removes the altered base, giving an abasic site. This abasic site is then processed by an endonuclease (APE1) allowing DNA polymerase β to process the next step, catalyzing the elimination of the 5′-sugar phosphate residue and filling the gap with a nucleotide. Finally, the nick is sealed by the ligase III/XRCC1 complex. To simplify, only the branch of the short-pathway utilizing a monofunctional glycosylase is represented. SSBs can be repaired by the long-patch pathway (replacing approximately 2–12 nucleotides). This subpathway is dependant on PCNA and FEN1. It contains many of the same factors as the short-patch pathway but in contrast to the short-patch subpathway, DNA synthesis is thought to be mediated by several DNA polymerases including polymerases β, δ and ε. nt: nucleotide.

other chemicals such as metals [3–7] but also from endogenous sources including oxygen metabolism, apoptosis, and inflammatory responses involving the immune system [2,8–13] (Fig. 1).

Among these oxidative DNA lesions are abasic sites, single strand DNA breaks (SSBs), sugar moiety modifications, and deaminated and adducted bases [2,14,15]. Various studies have estimated that anywhere from 0.1 to 100 oxidative DNA lesions per Mbp may exist in normal cells and tissues [16–19]. One of the more common oxidative DNA lesions, 8-oxo-2′-deoxyguanosine (8-oxo-dG), is estimated to be present at approximately 1 per Mbp [20–22]. When two or more oxidative DNA lesions are present within 10 base pairs of each other, it is considered an oxidative clustered DNA lesion (OCDL). These OCDLs have been variously estimated to be present at levels between 0.02 and 0.8 clusters per Mbp in normal human primary cells as well as in tumor cells [23–25].

While individual DNA lesions are generally repaired efficiently, some OCDLs may be more difficult to resolve [26–31]. In some circumstances oxidative lesions can lead to DNA double-strand break (DSB) formation (Fig. 2) [32]. A DSB can arise when two SSBs form close to each other on opposite strands, when topoisomerases