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Formation and processing of DNA damage substrates for the hNEIL enzymes

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A B S T R A C T

Reactive oxygen species (ROS) are harnessed by the cell for signaling at the same time as being detrimental to cellular components such as DNA. The genome and transcriptome contain instructions that can alter cellular processes when oxidized. The guanine (G) heterocycle in the nucleotide pool, DNA, or RNA is the base most prone to oxidation. The oxidatively-derived products of G consistently observed in high yields from hydroxyl radical, carbonate radical, or singlet oxygen oxidations under conditions modeling the cellular reducing environment are discussed. The major G base oxidation products are 8-oxo-7,8-dihydroguanine (OG), 5-carboxamido-5-formamido-2-iminohydantoin (2Ih), spiroiminodihydantoin (Sp), and 5-guanidinohydantoin (Gh). The yields of these products show dependency on the oxidant and the reaction context that includes nucleoside, single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), and G-quadruplex DNA (G4-DNA) structures. Upon formation of these products in cells, they are recognized by the DNA glycosylases in the base excision repair (BER) pathway. This review focuses on initiation of BER by the mammalian Nei-like1-3 (NEIL1-3) glycosylases for removal of 2Ih, Sp, and Gh. The unique ability of the human NEILs to initiate removal of the hydantoins in ssDNA, bulge-DNA, bubble-DNA, dsDNA, and G4-DNA is outlined. Additionally, when Gh exists in a G4 DNA found in a gene promoter, NEIL-mediated repair is modulated by the plasticity of the G4-DNA structure provided by additional G-runs flanking the sequence. On the basis of these observations and cellular studies from the literature, the interplay between DNA oxidation and BER to alter gene expression is discussed.

1. Introduction

Reactive oxygen species (ROS) are electron deficient and readily oxidize most biomolecules. At low concentrations, the ROS hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) are signaling agents harnessed by the cell to guide biological processes [1,2]. In contrast, when the concentration of H_2O_2 or $ONOO^-$ surpasses their signaling threshold, they promote oxidation of biomolecules, such as proteins, lipids, and particularly, nucleic acids [1,3]. High levels of ROS released under control in phagocytes provide protection from invading bacteria and viruses [4]; however, uncontrolled and high levels of ROS break-down cellular components leading to cancer, neurological disorders, and cardiovascular disease, to name a few [5–7]. Oxidation of the genome represents a critical location in which oxidatively-derived damage under high levels of ROS can lead to these diseases.

The guanine heterocycle (G) is the most electron rich of the four bases, and as a consequence, it has the lowest reduction potential resulting in G nucleotides as major sites of ROS-mediated oxidations [8]. Scientists have unearthed detailed information concerning the ROS-dependent pathways for oxidizing G leading to many products of varying stability [9–27]. On the basis of this information, the G oxidation products can be placed into groups dependent on whether the oxidation occurs at the sugar or heterocyclic base [12]. A product observed in nearly all studies conducted under biologically relevant

Abbreviations: AP, abasic site; APE1, apurinic/apyrimidinic endonuclease; Asc, ascorbate; BER, base excision repair; DHT, 5,6-dihydro-2′-deoxythymidine; DHU, 5,6-dihydro-2′-deoxyuridine; dsDNA, double-stranded DNA; ESCODD, European Standards Committee on Oxidative DNA Damage; Fapy-A, 4,6-diamino-5-formamidopyrimidine; Fapy-G, 2,6-diamino-4-hydroxy-5-formamidopyrimidine; FEN1, flap endonuclease 1; Fpg and EcFpg, formamidopyrimidine DNA glycosylase; G, guanine; $G^{\cdot+}$, guanine radical cation; $G^{\cdot}$, guanine radical; G4, G-quadruplex; Gh, 5-guanidinohydantoin; Gh^{ox}, oxidized 5-guanidinohydantoin; hmU, 5-hydroxymethyl-2′-deoxyuridine; GSH, glutathione; hnRNP-U, heterogeneous nuclear ribonucleoprotein-U; 5-HOC, 5-hydroxy-2′-deoxycytidine; 5-HO-G, 5-hydroxy-guanine; 5-HOO-G, 5-hydroperoxy-guanine; 8-HOO-G, 8-hydroperoxy-guanine; 8-HO-G, 8-hydroxy-guanine; 5-HOU, 5-hydroxy-2′-deoxyuridine; hTelo, human telomere sequence; Ia, iminoallantoin; Ia^{ox}, oxidized iminoallantoin; I, inosine; 2Ih, 5-carboxamido-5-formamido-2-iminohydantoin; Iz, 2,5-diaminoimidazolone; LCMS, liquid chromatography mass spectrometer; meFapyG, 2,6-diamino-4-hydroxy-5-*N*-methylformamidopyrimdine; NAC, *N*-acetylcysteine; Nei and EcoNei, endonuclease VIII; Neil1 and NEIL1, endonuclease VIII like-1; Neil2 and NEIL2, endonuclease VIII like-2; Neil3 and NEIL3, endonuclease VIII like-3; NER, nucleotide excision repair; Nth, endonuclease III; OG, 8-oxo-7,8-dihydroguanine; OG^{ox}, oxidized 8-oxo-7,8-dihydroguanine; PCNA, proliferating cell nuclear antigen; PNK, polynucleotide kinase; POLβ, polymerase beta; REAP, restriction endonuclease and post-labeling; RPA, replication protein A; ROS, reactive oxygen species; ssDNA, single-stranded DNA; Sp, spiroiminodihydantoin; Tg, thymine glycol; *VEGF*, vascular endothelial growth factor; WRN, Werner syndrome protein; YB-1, Y-box protein 1; Z, 2,2,4-triamino-2*H*-oxazol-5-one

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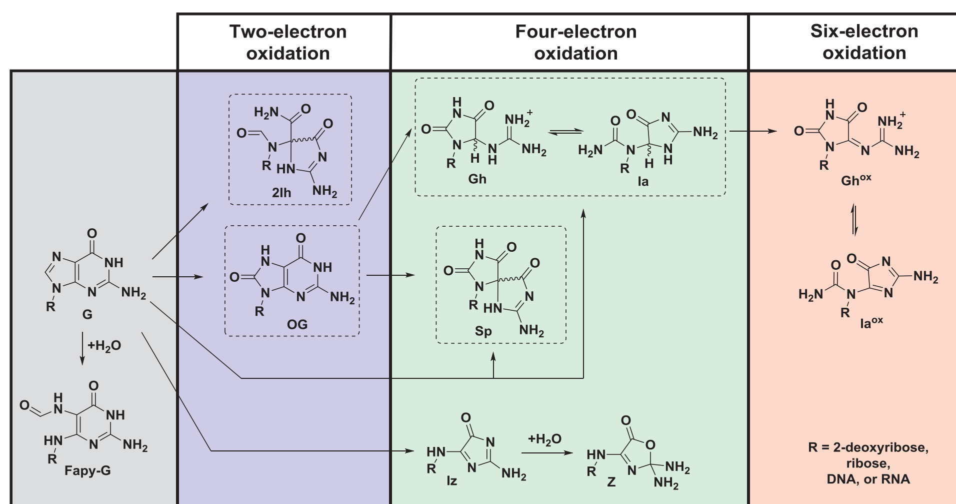

Scheme 1. Overview of G oxidation products and the extent to which each was oxidized leading to their formation. The products inside the dashed boxes are the main focus of this review because they are the best substrates for the hNEIL glycosylases (2Ih, Sp, or Gh) or a key precursor to these products (OG).

reaction conditions is the base oxidation product 8-oxo-7,8-dihydroguanine (OG; Scheme 1) [9–25]. Furthermore, OG is found in cell extracts and has been identified as a biomarker for monitoring the extent of cellular oxidative stress [28]. Lastly, OG is dramatically more sensitive toward oxidation than is G [29] yielding the hydantoin products spiroiminodihydantoin (Sp) and 5-guanidinohydantoin (Gh) [30–32], and these products also result from direct 4-electron oxidation of G [33,34]. The present review will briefly summarize the reaction conditions leading to OG, Sp, and Gh. Additionally, work to establish the possible importance of 5-carboxamido-5-formamido-2-iminohydantoin (2Ih) in cellular oxidations will be described. A detailed analysis of the mechanisms and intermediates leading to these products will not be provided and can be found in other reviews [9–24].

The picture of a static B-form helical genome that simply holds the cellular blueprint has emerged as incomplete. Genomes are rich in regulatory chemical modifications, and DNA adopts other secondary structures beyond B-form helices. Mounting evidence supports hairpin [35], A-form [36], Z-form [37], triple helix [38], Holliday junction [39], i-motif [40], and G-quadruplex (G4) [41] structures having the capability to form in genomes. Therefore, this review will cover the current state of our knowledge regarding how some of these various structural contexts impact G oxidation, leading to a discussion of knowledge gaps in the literature on this topic.

Oxidatively-derived damage to DNA, if left unrepaired, would be detrimental to cellular survival because the distorted blueprint would be incapable of providing proper instructions to the cell. To maintain a complete set of instructions, biology has evolved a DNA repair system to fix damaged nucleotides. The importance of DNA repair mechanisms was highlighted in 2015 when Tomas Lindahl, Paul Modrich, and Aziz Sancar shared the Nobel Prize in Chemistry for their work on this topic. With regard to repair of G-base oxidation products, both the base excision repair (BER) and nucleotide excision repair (NER) pathways are invoked [42–45]. This review will focus on BER repair of G-base oxidation products by the three members of the NEIL DNA glycosylase family, ending with a focus on repair in structural contexts beyond B-form helices. The literature summary presented will guide a discussion on recent cellular studies hypothesizing how G oxidation and its repair may serve as a signaling pathway in cells, beyond constituting unwanted damage that must be removed and corrected.

2. ROS formed in the cellular context

Oxidative phosphorylation is a metabolic pathway for generation of energy that occurs in the mitochondria of eukaryotic organisms. This metabolic pathway represents a controlled redox chain for reduction of the strong oxidant O_2 by four electrons to H_2O, while generating a proton gradient to synthesize ATP. Under ideal conditions, O_2 is reduced to H_2O; however, partial reduction of O_2 yielding superoxide ($O_2^{\cdot-}$) occurs in a ~0.1–2% yield depending on the cellular state [46]. The $O_2^{\cdot-}$ formed exists in low picomolar concentrations and has a ~1 μs half-life [1]. The major pathway for removal of $O_2^{\cdot-}$ in cells is conversion to H_2O_2 by superoxide dismutase (SOD, Fig. 1**A** Reaction 1) [1]. The H_2O_2 formed upon dismutation has a cellular half-life of ~10 μs due to its removal by catalases and peroxidases [1]. The concentration of H_2O_2 is ~200 nM under normal conditions that increases to low micromolar concentrations under oxidative stress [1]. The half-life for H_2O_2 is sufficiently long to allow intracellular and intercellular diffusion because it readily passes through membranes. Neither $O_2^{\cdot-}$ (E_{red} = 0.94 V vs. NHE) nor H_2O_2 (E_{red} = 0.32 V

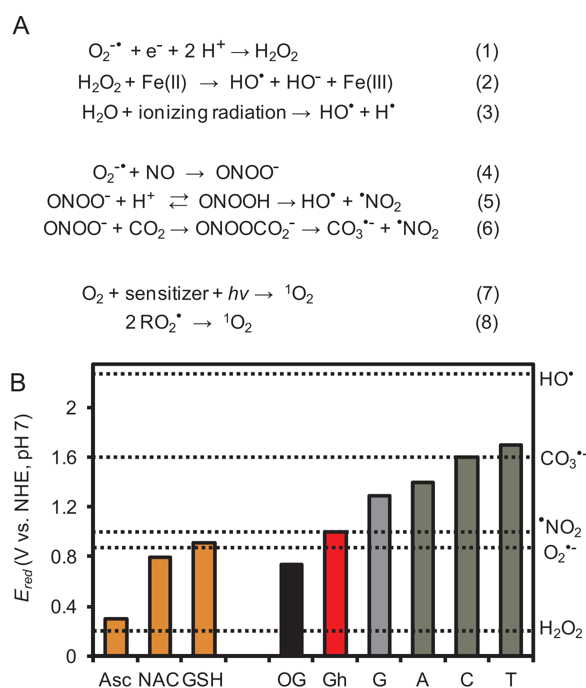

Fig. 1. Mechanisms for ROS formation, redox potentials for nucleosides, ROS, and reductants. (A) Reaction schemes for generation of ROS. (B) Plot of the redox potentials for nucleosides, reductants (Asc = ascorbate, NAC = *N*-acetylcysteine, GSH = glutathione), and various ROS.

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