Free Radical Biology and Medicine 107 (2017) 266–277

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Aberrant base excision repair pathway of oxidatively damaged DNA: Implications for degenerative diseases☆

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ARTICLE INFO

Keywords:
Oxidatively damaged DNA
8-oxo-7,8-dihydroguanine, purine 8,5′-cyclo-2′-deoxyribonucleosides, base excision repair
DNA glycosylase, nucleotide incision repair
AP endonuclease
Nucleotide excision repair, trinucleotide expansion
Mismatch repair

ABSTRACT

In cellular organisms composition of DNA is constrained to only four nucleobases A, G, T and C, except for minor DNA base modifications such as methylation which serves for defence against foreign DNA or gene expression regulation. Interestingly, this severe evolutionary constraint among other things demands DNA repair systems to discriminate between regular and modified bases. DNA glycosylases specifically recognize and excise damaged bases among vast majority of regular bases in the base excision repair (BER) pathway. However, the mismatched base pairs in DNA can occur from a spontaneous conversion of 5-methylcytosine to thymine and DNA polymerase errors during replication. To counteract these mutagenic threats to genome stability, cells evolved special DNA repair systems that target the non-damaged DNA strand in a duplex to remove mismatched regular DNA bases. Mismatch-specific adenine- and thymine-DNA glycosylases (MutY/MUTYH and TDG/MBD4, respectively) initiated BER and mismatch repair (MMR) pathways can recognize and remove normal DNA bases in mismatched DNA duplexes. Importantly, in DNA repair deficient cells bacterial MutY, human TDG and mammalian MMR can act in the aberrant manner: MutY and TDG removes adenine and thymine opposite misincorporated 8-oxoguanine and damaged adenine, respectively, whereas MMR removes thymine opposite to O^6-methylguanine. These unusual activities lead either to mutations or futile DNA repair, thus indicating that the DNA repair pathways which target non-damaged DNA strand can act in aberrant manner and introduce genome instability in the presence of unrepaired DNA lesions. Evidences accumulated showing that in addition to the accumulation of oxidatively damaged DNA in cells, the aberrant DNA repair can also contribute to cancer, brain disorders and premature senescence. For example, the aberrant BER and MMR pathways for oxidized guanine residues can lead to trinucleotide expansion that underlies Huntington's disease, a severe hereditary neurodegenerative syndrome. This review summarises the present knowledge about the aberrant DNA repair pathways for oxidized base modifications and their possible role in age-related diseases.

Abbreviations: ROS, reactive oxygen species; AP, apurinic/apyrimidinic site; 8-oxoG, 8-oxo-7,8-dihydroguanine; 8-oxoA, 8-oxo-7,8-dihydroadenine; Fapy, formamidopyrimidines; 2-oxoA, 2-hydroxyadenine; Thymine glycol, 5,6-dihydroxy-5,6-dihydrothymine; Hx, hypoxanthine; εA, 1,N^6-ethenoadenine; 5ohC, 5-hydroxycytosine; εC, 3,N^4-ethenocytosine; 5′*S*-cdA and 5′*R*-cdA, diastereoisomeric (5′*S*)- and (5′*R*)-8,5′-*cyclo*-2′-deoxyadenosines; cdG, 8,5′-*cyclo*-2′-deoxyguanosine; DB[*a*,*l*]P-N^2-dG and DB[*a*,*l*]P-N^2-dA, dibenzo[*a*,*l*]pyrene adduct linked to N^2 atom of dG and dA nucleotides, respectively; AL-dA, 7-(deoxyadenosin-N^6-yl)aristolactam; AL-dG, 7-(deoxyguanosin- N^2-yl)aristolactam; BER, base excision repair; ab-BER, aberrant BER; NIR, nucleotide incision repair; MMR, mismatch repair; NER, nucleotide excision repair; GG-NER, global genomic NER; TC-NER, transcription coupled NER; APE1/APEX1, major human AP endonuclease 1; MPG/AAG/ANPG, human alkyl-purine DNA glycosylase; OGG1, human 8-oxoG-DNA glycosylase; AlkA, *E. coli* alkyl-purine DNA glycosylase; Fpg, *E. coli* 8-oxoG-DNA glycosylase; MutY, *E. coli* mismatch-specific adenine-DNA glycosylase; MUTYH, human mismatch-specific adenine-DNA glycosylases; TDG, human mismatch-specific thymine-DNA glycosylase; MBD4, human methyl-binding domain protein 4; HD, Huntington's disease; SASP, Senescence Associated Secretory Phenotype; DDR, DNA damage response

☆ This article is one of a series of papers on the subject of oxidative DNA damage & repair that have been published as a special issue of Free Radical Biology & Medicine to commemorate the Nobel Prize won by Prof. Tomas Lindahl. A detailed introduction and synopsis of all the articles in the special issue can be found in the following paper by Cadet & Davies [183].

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http://dx.doi.org/10.1016/j.freeradbiomed.2016.11.040
Received 30 June 2016; Received in revised form 22 November 2016; Accepted 23 November 2016
Available online 24 November 2016

1. DNA damage and DNA excision repair systems

1.1. Endogenous and exogenous DNA damage

Cellular DNA is constantly challenged by various endogenous and exogenous genotoxic factors that inevitably lead to DNA damage: structural and chemical modifications of primary DNA sequence. Generation of reactive oxygen species (ROS) hydroxyl radical (˙OH), superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) supported by aerobic respiration is a major source of endogenous DNA damage. About 80 different types of base and sugar lesions induced by ROS have been identified [1] (Fig. 1). Free radicals can damage nucleobases and sugar moieties in DNA either directly or indirectly. Hydroxyl radicals preferentially react with C8 atom of purines in DNA to generate 8-oxo-7,8-dihydroguanine (8-oxoG), 8-oxo-7,8-dihydroadenine (8-oxoA) and formamidopyrimidines (Fapy) [2,3], and with C5-C6 double bond of pyrimidines to form glycols [4,5] (Fig. 1). Importantly, the major endogenous oxidized bases 8-oxoG, 5-hydroxyuracil (5ohU) and 5-hydroxycytosine (5ohC) are miscoding and, if not repaired, lead to mutation upon replication [6–8]. Oxidation of adenine residues in DNA results in the formation of 2-hydroxyadenine (2-oxoA) [9]. It should be noted that the formation of oxidatively induced adenine modifications including 8-oxoA and FapyA is about 10-fold lower than that of related guanine degradation products upon exposure of cellular DNA to either hydroxyl radical or one-electron oxidants [10–12]. Damage to the free nucleotide pool is also common and generates a similar spectrum of lesions [2,13].

Metabolic activation of organic peroxides leads to the formation of methyl radicals which react with DNA and produce 8-methylguanine (8meG), a highly mutagenic DNA adduct [14,15]. In addition to small base modifications, ROS can also generate bulky diastereoisomeric (5′*S*)- and (5′*R*)-8,5′-*cyclo*-2′-deoxyadenosine (cdA) and 8,5′-*cyclo*-2′-deoxyguanosine (cdG) adducts (Fig. 1). Purine 5′,8-*cyclo*-2′-deoxyribonucleosides (cdPu) are generated by hydroxyl radical attack at C5′ with H-abstraction resulting in formation of the C5′-centered sugar radical, which, in the absence of oxygen, reacts with the C8 of the purine. Subsequent oxidation of the resulting N7-centered radical leads to intramolecular cyclization with the formation of a covalent bond between the C5′ and C8 positions of the purine nucleoside. When present in DNA duplex, cdA causes large changes in backbone torsion angles, which leads to weakening of base pair hydrogen bonds and strong perturbations of the helix conformation near the lesion for both diastereoisomers. These properties of cdA adducts make them strong blocks for both DNA replication and transcription. The *S*-cdA diastereoisomer is removed in the NER pathway much less efficiently than 5′*R*-cdA [16] and is also present at a higher background level in mouse organs [17]. These latter data are conflicting with previously reported findings showing that 5′*R*-cdA is barely detectable in cellular DNA upon exposure to 2 kGy of ionizing radiation [18]. Although cdPu are minor oxidation products, since they are produced with an about 2 orders of magnitude lower efficiency than 8-oxoG by hydroxyl radical [12], accumulation of these bulky adduct in genomic DNA in absence of repair could have deleterious biological consequences for the cells. Indirectly, ROS can generate reactive aldehydes as products of membrane lipid peroxidation (LPO), which can react with DNA bases forming exocyclic etheno (ε) adducts 1,N^6-ethenoadenine (εA) and 3,N^4-ethenocytosine (εC) [19]. Etheno adducts are ubiquitous and have been found in DNA isolated from tissues of untreated rodents and humans [20]. Importantly, εA and εC levels are significantly increased by cancer risk factors related to oxidative stress/LPO, such as dietary ω-6 fatty acids intake, chronic infections and inflammatory conditions [21]. The εA and εC residues in DNA are highly mutagenic, especially in mammalian cells. Therefore the repair processes eliminating ε-adducts and cdPu from DNA should play a crucial role in maintaining the stability of the genetic information.

Endogenously generated DNA base oxidation products are not restricted to singular lesions produced by hydroxyl radical reactions. In fact one-electron oxidation of the DNA bases that can be mediated by peroxynitrite during inflammation constitutes a relevant degradation pathway that may give rise in addition to single oxidized bases to tandem modifications, interstrand DNA cross-links, DNA-protein cross-links [22–24]. In addition to endogenous oxidative stress, cells are also

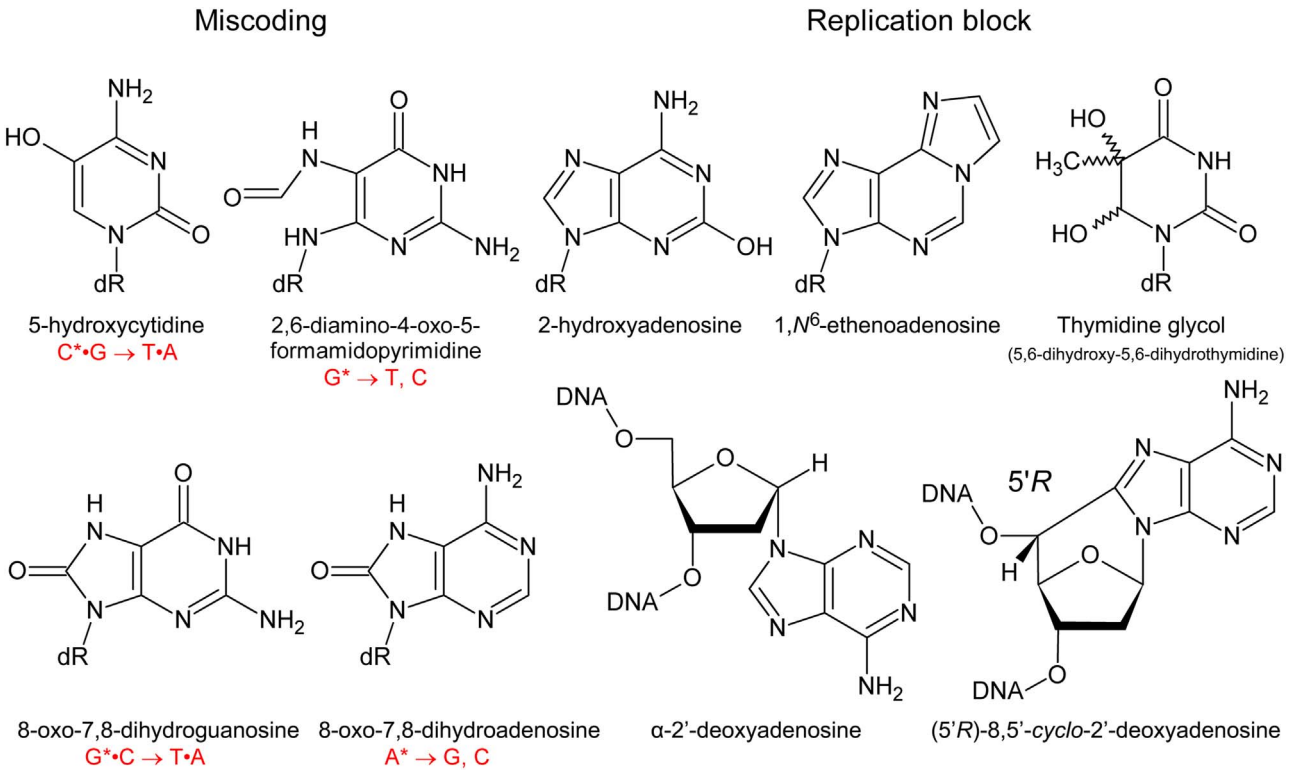

Fig. 1. Chemical structures of the major oxidative DNA lesions.