Archives of Biochemistry and Biophysics xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

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

Oxidatively generated base damage to cellular DNA by hydroxyl radical and one-electron oxidants: Similarities and differences

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ARTICLE INFO

Article history:
Received 24 February 2014
and in revised form 23 April 2014
Available online xxxx

Keywords:
Oxidized nucleobases
Radical cations
Tandem base lesions
Intrastrand cross-links
Interstrand cross-links
DNA–protein cross-links
Clustered DNA damage

ABSTRACT

Hydroxyl radical (·OH) and one-electron oxidants that may be endogenously formed through oxidative metabolism, phagocytosis, inflammation and pathological conditions constitute the main sources of oxidatively generated damage to cellular DNA. It is worth mentioning that exposure of cells to exogenous physical agents (UV light, high intensity UV laser, ionizing radiation) and chemicals may also induce oxidatively generated damage to DNA. Emphasis is placed in this short review article on the mechanistic aspects of ·OH and one-electron oxidant-mediated formation of single and more complex damage (tandem lesions, intra- and interstrand cross-links, DNA–protein cross-links) in cellular DNA arising from one radical hit. This concerns DNA modifications that have been accurately measured using suitable analytical methods such as high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry. Evidence is provided that ·OH and one-electron oxidants after generating neutral radicals and base radical cations respectively may partly induce common degradation pathways. In addition, selective oxidative reactions giving rise to specific degradation products of ·OH and one-electron oxidation reactions that can be used as representative biomarkers of these oxidants have been identified.
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Introduction

Major attention has been given during the last four decades to the elucidation of the mechanisms of oxidation of nucleic acids because of its implication in aging [1,2] and several pathologies including cancers [3–5], atherosclerosis [6] and neurological diseases [7,8]. Comprehensive oxidative pathways are now available concerning the formation of several classes of DNA lesions including single oxidized nucleobases, tandem base modifications, intra- and inter-strand cross-links [9–16] together with oligonucleotide single strand breaks and 2-deoxyribose oxidation products [17–19]. Reliable information on both the qualitative and quantitative aspects of generation of several oxidatively produced lesions in cellular DNA has been gained from the development of accurate biochemical and chemical methods including the modified comet assay [20,21] and high performance liquid chromatography coupled with electrospray tandem mass spectrometry (HPLC/ESI-MS/MS) or eventually MS^3 detection [22–24]. The availability of these powerful analytical tools also allows for the assessment of the kinetics of repair of dedicated modifications [21,25] and studies toward the protection against oxidative reactions to DNA afforded by exogenous compounds [26]. Another relevant feature of HPLC–ESI-MS/MS measurements deals with the unambiguous identification of oxidatively generated base damage to cellular DNA. As striking findings, it was found that several DNA degradation products detected in cells [27–35] are identical to those previously characterized in model studies involving hydroxyl radical (·OH),[1] singlet oxygen ($^1O_2$) or one-electron oxidants in aerated aqueous solutions [9–13,16,36–38]. The latter conditions where molecular oxygen (O_2) is able to react efficiently with most base radicals generated by either ·OH or one-electron oxidants appear to constitute suitable model systems for mimicking the cellular environment. This applies to the reactivity of oxidants towards DNA components and subsequent chemical reactions thus initiated that give rise to final decomposition products. The present review article is aimed at rationalizing the formation of oxidatively generated damage unambiguously detected in cellular DNA as the result of one initial radical hit. It appears that ·OH and one-electron oxidants exhibit similarities and also differences in the way they trigger the decomposition of nuclear DNA in cells. This survey does not include oxidation studies of cellular DNA by $^1O_2$, a ROS produced by either

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[1] *Abbreviations used:* ·OH, hydroxyl radical; $^1O_2$, singlet oxygen; HOCl, hypochlorous acid; ·NO, nitric oxide.

http://dx.doi.org/10.1016/j.abb.2014.05.001
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type II photosensitization mechanism [39,40] or the reaction of hypochlorous acid (HOCl) reaction with H_2O_2 [41], both of which have been shown to predominantly generate 8-oxo-7,8-dihydroguanine (8-oxoGua) [12,27,42,43]. In addition, we will not discuss the reactions of HOCl, resulting from the oxidation of chloride ion with H_2O_2 catalyzed by myeloperoxidase in activated neutrophils [44], which leads to the highly specific chlorination of bases in cellular DNA with the following decreasing order of efficiency: cytosine > guanine > adenine [45,46]. The formation of oxidatively generated clustered lesions to DNA including double strand breaks are considered as hallmarks of radiation-induced damage that arise from several radical hits and excitation events within one or two DNA helix turns [47,48] are also excluded in the present review.

Hydroxyl radical and one-electron oxidants in cells

The two main oxidative pathways of cellular DNA considered in the present survey are those induced by ·OH and several exogenous one-electron oxidants including type I photosensitizers and high intensity UV laser pulses.

Endogenous sources

The two main endogenous sources of oxidative radical reactions having the ability to damage cellular DNA consist of ·OH and one-electron oxidants. In contrast superoxide radical ($O_2^{\cdot -}$) and H_2O_2 that are major ROS generated by respiratory burst and phagocytes [49] show very low reactivity with the nucleobases and 2-deoxyribose moiety [50]. The only known reaction mediated by $O_2^{\cdot -}$ involves the one-electron reduction and addition to C5 of highly oxidizing guanine radical Gua(–H)· that arises from deprotonation of the guanine radical cation [10,51]. It has also been reported that H_2O_2 is able to undergo electrophilic addition to N1 of adenine giving rise to the formation of adenine N1-oxide with however a very low efficiency [52]. Therefore H_2O_2 is likely involved in the formation of ·OH by Fenton type reactions with either ferrous ion and copper ions as the reducing agents, although in the latter case $^1O_2$ oxidation and one-electron oxidation of guanine have also been suggested to occur at least in model studies [53]. It may also be pointed out that ·OH reacts essentially at the site of its generation without any significant migration within the cells. Another relevant endogenous one-electron oxidant is inorganic carbonate radical anion ($CO_3^{\cdot -}$) [54,55] that arises from the decomposition of nitrosoperoxycarbonate, the product of the reaction of peroxynitrite and carbonates [49,56]. It is also well-documented that $ONOO^-$ is generated by radical coupling of nitric oxide (·NO) and $O_2^{\cdot -}$, two poorly reactive species, during inflammation processes in tissues [55].

Exogenous radical oxidizing agents

Ionizing radiation is one of the most commonly used exogenous oxidizing agents even if the molecular mechanism of action is complex involving several possible radical events in the formation of damage [57]. The indirect effect of X- and gamma-rays that predominates in aqueous solutions gives rise to ·OH through the radiolysis of water [17]. In addition, there is a contribution of ionization processes with the transient formation of organic radical cations through the direct interactions of high energy photons with target biomolecules such a DNA. A suitable way of generating DNA radical cations consists of exposing targets to high-intensity nanosecond UVC laser pulses leading to one-electron oxidation of purine and pyrimidine bases by a bi-photonic process [58,59]. One-electron oxidation of the guanine base is also possible upon incubation of cells with bromate, a renal carcinogen, subsequent to thiol-mediated reduction into Br_2O [60]. A selective one-electron oxidation of the guanine base can also be achieved upon incubation of cells with 6-thioguanine and related analogs including azathioprine and 6-mercaptopurine that are incorporated into DNA before UVA excitation [61].

Similarities between hydroxyl radical and one-electron oxidants-mediated DNA damage

The two exogenous oxidizing systems which were applied to induce a significant increase in the yields of modified bases in cellular DNA with respect to steady-state levels include ionizing radiation through the predominant generation of ·OH and high intensity UV laser irradiation for one-electron oxidation of purine and pyrimidine bases.

Single oxidized bases

Several oxidized pyrimidine bases have been measured by HPLC–ESI-MS/MS as the corresponding 2′-deoxyribonucleosides after suitable extraction and enzymatic digestion of cellular DNA from either human monocytes [28,29] or Fischer F98 glioma cells [34] exposed to gamma rays of ^{137}Cs sources. These include as degradation products of thymidine (dT) the four diastereomers of *cis* and *trans* 5,6-dihydroxy-5,6-dihydrothymidine (dTGly), 5-(hydroxymethyl)-2′-deoxyuridine (HmdU) and 5-formyl-2′-deoxyuridine (5-FodU). More recently (5*R**) and (5*S**)-1-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-5-hydroxy-5-methylhydantoin (HydT), two diastereomeric pyrimidine ring rearrangement products have been detected as additional ·OH-mediated thymine oxidation products in cellular DNA [34]. In addition, 5-hydroxy-2′-deoxycytidine (5-OHdC), *cis* and *trans* diastereomers of 5,6-dihydroxy-5,6-dihydro-2′-deoxyuridine (dUGly) and 3-(1-carbamoyl-4,5-dihydroxy-2-oxoimidazolidine (ImidC) together with the (5*R**) and (5*S**)-1-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-5-hydroxyhydantoin (HydU) have been detected as cytosine decomposition products in the DNA of gamma-irradiated Fischer F98 glioma cells [34]. Several of these oxidized 2′-deoxyribonucleosides including dTGly, 5-HmdU, 5-FodU and 5-OHdC have also been shown to be generated in cellular DNA upon exposure to high intensity UVC nanosecond laser pulses [35]. The formation of dTGly may be rationalized in the initial steps by either ·OH addition across the 5,6-ethylenic bond with a strong preference for the C5 position or hydration of the thymine radical cation **1** giving rise to the 6-hydroxy-5,6-dihydrothymin-5-yl radical **2** [11,16,17]. Subsequently O_2 is able to efficiently react with the carbon centered radicals thus generated at diffusion controlled rates of reaction giving rise to the formation of hydroperoxyl radicals and in turn to intermediate 5(6)-hydroxy 6(5)hydroperoxides [11,16]. The peroxyl radicals or hydroperoxides can decompose to give dTGly (Fig. 1). It may be concluded that there are strong similarities between the two types of oxidation reactions leading to dTGly particularly when ·OH addition takes place at the C6 position of thymine. This applies as well to the oxidative formation of 5-HmdU and 5-FodU that may be generated from either the deprotonation reaction of **1** or the ·OH-mediated H–atom abstraction from the methyl group of thymine, both resulting in the formation of 5-(uracilyl)methyl radical **3** [11]. Another relevant example of similarities in the ·OH-mediated and one-electron oxidation of pyrimidine bases recently became apparent with the recent measurement of 5-OHdC in cellular DNA exposed to ionizing radiation and high intensity UVC irradiation [35]. The formation of 5-OHdC may be explained by the transient formation of cytosine radical cations upon one-electron oxidation followed by conversion of 6-hydroxy-5,

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