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Hypothesis Paper

8-Oxo-7,8-dihydroguanine: Links to gene expression, aging, and defense against oxidative stress

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ABSTRACT

The one-electron oxidation product of guanine, 8-oxo-7,8-dihydroguanine (8-oxoG), is an abundant lesion in genomic, mitochondrial, and telomeric DNA and RNA. It is considered to be a marker of oxidative stress that preferentially accumulates at the 5′ end of guanine strings in the DNA helix, in guanine quadruplexes, and in RNA molecules. 8-OxoG has a lower oxidation potential compared to guanine; thus it is susceptible to oxidation/reduction and, along with its redox products, is traditionally considered to be a major mutagenic DNA base lesion. It does not change the architecture of the DNA double helix and it is specifically recognized and excised by 8-oxoguanine DNA glycosylase (OGG1) during the DNA base excision repair pathway. OGG1 null animals accumulate excess levels of 8-oxoG in their genome, yet they do not have shorter life span nor do they exhibit severe pathological symptoms including tumor formation. In fact they are increasingly resistant to inflammation. Here we address the rarely considered significance of 8-oxoG, such as its optimal levels in DNA and RNA under a given condition, essentiality for normal cellular physiology, evolutionary role, and ability to soften the effects of oxidative stress in DNA, and the harmful consequences of its repair, as well as its importance in transcriptional initiation and chromatin relaxation.

Introduction

Molecules of living organisms are continuously modified by reactive oxygen species (ROS), reactive nitrogen species (RNS), and nonradical species arising from environmental exposures and oxidative cellular metabolism. Oxidatively damaged proteins, lipids, and RNA are usually subjected to degradation, whereas DNA base and strand lesions should be repaired to reestablish genomic integrity [1]. When left unrepaired, they may be mutagenic and carcinogenic or compromise normal cell physiology and cell viability [2–6]. DNA base excision repair (BER) is the major pathway for repair of oxidized lesions [5–8]. During BER of DNA, 8-oxo-7,8-dihydroguanine (8-oxoG) is predominantly recognized and excised by the specific 8-oxoguanine DNA glycosylase 1 (OGG1). OGG1 generates a single strand gap with 3′ α,β-unsaturated aldehyde and 5′-phosphate. These DNA ends require further processing by apurinic/apyrimidinic endonuclease 1 (APE1), before gap filling by polymerases and ligation [6,9–11].

The objectives of this review are to address the rarely discussed aspects and significance of guanine oxidation, such as the physiological, nonmutagenic role of 8-oxoG in biological systems. Guanine-rich DNA regions and susceptibility of guanine to reactive oxygen and nonradical species might reflect a natural strategy of organisms to adapt and evolve and utilize or abuse 8-oxoG.

Oxidatively induced DNA damage

Oxidative stress

Oxidative stress is an imbalance between the production of reactive species and the ability of cells to eliminate them or repair the resulting damage. Oxidative stress caused by ROS and nonradical species originates primarily from dysfunctional mitochondria and is generated by activated oxidases (e.g., cytochrome P450 enzymes, NADPH oxidases, lipoperoxidases) located in peroxisomes and cellular membranes. During normal physiological processes 0.1–2% of molecular oxygen (O_2) is converted to superoxide anion ($O_2^{\bullet-}$) [12,13]. Significant amounts of oxidative stress are caused directly by ozone, ionizing and ultraviolet-light irradiation, and environmental pollutants or indirectly by their ability to activate oxidases and induce mitochondrial dysfunction. The molecular mechanism of ROS formation, their chemistry, and their health- and age-related significance are extensively documented and reviewed [14–17].

Oxidative stress and longevity

Commonly, reactive species are considered unfavorable for living organisms because of their reactive/damaging nature and their ability to

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alter physiological cell activation signaling [18]. In fact, many hypotheses have linked ROS and RNS to the induction and exacerbation of various diseases and the aging process [19–23]. One such aging hypothesis suggests that O_2 conversion to reactive species causes oxidative stress, leading to macromolecular damage and accumulation of oxidative genomic and mitochondrial DNA lesions that result in decreased longevity [20,21,24,25]. In aged tissues, increased ROS generation adversely affects mitochondrial function, which leads to a vicious cycle of continuous mitochondrial dysfunction and chronic oxidative stress that is considered to be one of the causative factors in aging processes [26–32].

On the other hand, studies are in conflict with the well-accepted, oxidative stress theory of aging processes, because it has been shown that increased cellular oxidative metabolism could lead to beneficial effects that would extend the life span [33–39]. These interpretations are supported by the facts that exercise increases oxidative stress level and physical activity is positively correlated with longevity [40,41]. In fact, antioxidant supplementation may even decrease the life span [42]. These observations support the notion that cellular ROS levels can be described by the hormesis curve [43].

Studies on *Caenorhabditis elegans* have revealed that enhanced levels of oxidative stress can result in an increased life span, which was prevented by antioxidant supplementation [44]. It has been suggested that *C. elegans* compensates for decreased levels of glycolytic ATP by an enhanced production of mitochondrial ATP. The metabolic shift from glycolytic to mitochondrial metabolism is initiated by the AMP-activated protein kinase α subunit in the nematode [44]. In line with these findings, manganese superoxide dismutase null nematodes live longer than do wild-type worms [45].

To examine the role of oxidative stress in aging, various studies use transgenic and knockout mammalian models with an altered expression of superoxide dismutase (transgenic and heterozygous knockout), thioredoxin 2, glutathione peroxidase, or mitochondrial-targeted catalase, as well as mutant mouse models that have been genetically manipulated to increase mitochondrial dysfunction and mutations. A majority of these studies are in agreement concerning the role of oxidative stress in age-related diseases affecting primarily the central nervous system and increasing cancer incidence; however, with regard to longevity per se, the data either do not hold up or are inconclusive [26–31,39,46–49].

Guanine in evolution

There is a significant difference in the number of guanine (G) and cytosine (C) pairs (G:C) in the DNA of various species, and evolutionary genomics suggests a positive link between evolution and G:C content. G:C pairs are more stable than adenine:thymine pairs (A:T), because they are linked by three hydrogen bonds versus two in A:T [50]. Owing partly to these bonds, higher concentrations of G:C pairs have been suggested to be advantageous against heat stress, which could explain why birds and mammals have higher concentrations of G:C than do cold-blooded animals. Although this concept has been challenged [51,52], it has not been ruled out, because G:C content in the DNA has shown a significant relationship to temperature in organisms living at different marine temperatures.

In addition to the possible evolutionary role of G:C pairs in relation to thermoregulation, it has been proposed that high G:C content and low A:T might be a selective way to decrease the ultraviolet light irradiation-related generation of thymine dimers [53]. Naya and co-workers [54] found that aerobic organisms have higher concentrations of G:C than do anaerobes. A recent study from the same group examined the G:C content over 64,000 microbial communities and found a link between G:C content and O_2 concentration of the seawater column [55]. This finding is in line with the observation that aerobic organisms have larger DNA than do anaerobes, and larger DNA is known to contain a proportionally higher concentration of G:C [56]. Aerobic metabolism is associated with the constant generation of ROS, so it may be proposed that the redox potential of guanine might have an evolutionary importance to combating and/or softening the effects of ROS, especially the effects of hydroxyl radical ($^{\bullet}OH$), which readily reacts with guanine. G:C content is also linked to thermoregulation, because, with heat production, the generation of ROS also increases. Higher G:C content in aerobic organisms could be due to an evolutionary setup, which raises the question as to why a nucleated base, with such a low redox potential and attractiveness to ROS, is so dense in DNA, RNA, and telomeres?

The oxidation of guanine in DNA and RNA is generally considered genotoxic damage. However, the biochemical and physiological consequences of this "damage" might be more complex. Available information suggests that the way organisms handle 8-oxoG levels fits very well into the hormesis theory, a dose–response phenomenon characterized by a low dose of stimulation and high dose of inhibition, resulting in either a J-shaped or an inverted U-shaped dose–response curve, a nonmonotonic response. The sensitivity of guanine to reactive oxygen and nonradical species might reflect a natural strategy of organisms to use or abuse 8-oxoG. The hormesis theory seems also to be valid for the rate of amino acid carbonylation, i.e., a small degree of carbonylation might govern physiological processes, such as controlling the compactness of chromatin, therefore being beneficial on one hand, but on the other, destructive in that massive amounts of carbonylation could risk cell viability by inactivating proteins [57].

8-Oxo-7,8-dihydroguanine

8-OxoG formation

Guanine has the lowest oxidation potential (−1.29 mV vs nickel hydrogen electrode (NHE), midpoint potential) among DNA bases, rendering it the most easily oxidizable nucleic acid base by $^{\bullet}OH$ and singlet oxygen ($^1O_2$) [58]. For example, guanine's interaction with $^{\bullet}OH$ at C8 results in the generation of a reducing neutral radical that reacts with O_2 and, via electron transfer, forms 8-oxoG [59,60]. It is preferentially oxidized when located at the 5′ end of a series of guanines [61,62]. This phenomenon has been attributed to the radical cation migrating to the guanine having the lowest redox potential, with termination by trapping and product formation [61,62]. Because of 8-oxoG's even lower redox potential (0.74 mV vs NHE) [58], it further oxidizes, e.g., to spiroiminodihydantoin and guanidinohydantoin [63,64]. Its reduction results in 2,6-diamino-4-hydroxy-5-formamido-pyrimidine (FapyG) [59,65]. Therefore 8-oxoG and its modified products are the most abundant DNA lesions upon oxidative exposure [64,66]. The base level of 8-oxoG is estimated to be 1–2 per 10^6 guanine residues in nuclear DNA and about 1–3 per 10^5 in mitochondrial DNA [67,68]. Estimates suggest that up to 100,000 8-oxoG lesions could be formed in DNA per cell daily [58,69,70].

8-OxoG in aging processes

It is a well-established hypothesis that accumulation of damage in nuclear and mitochondrial DNA over time causes a gradual decline in the cellular function and manifestation of aging [71–76]. Among oxidized DNA base lesions, the accumulation of 8-oxoG has attracted the most attention and has often been linked to various age-associated pathological conditions, including tissue and organ dysfunctions, carcinogenesis, neurodegenerative and cardiovascular diseases, and aging processes [25,77–81]; however, the mechanism is elusive. Accumulation of 8-oxoG in DNA is not continuous, e.g., by the end of middle age, no significant increase is observed, and then it abruptly increases in most tissues [82]. An increase in 8-oxoG levels is thought to result from the supraphysiological levels of reactive species and/or a decrease in OGG1 activity during normal aging processes [83–85]. A decrease in 8-oxoG repair could be due to a combination of events, such as an age-associated inability to import/target OGG1 into nuclear and mitochondrial compartments [86–88] and/or suboptimal

posttranslational modifications [89–91]. Oxidative stress associated with aging processes or physical exercise was found to alter the subcellular targeting of OGG1 in parallel with posttranslational modifications and lowered 8-oxoG incision activity of the enzyme in aged, but not in young, tissues [86–88]. Similar observations were made in a lipopolysaccharide (LPS)-challenge inflammatory mouse model. Specifically, whereas LPS induced a rapid increase in nuclear level and activity of OGG1 in young animals, in aged groups it was delayed by hours [87]. Interestingly, a similar phenomenon was observed for APE1, which was shown to regulate OGG1 activity [87,92,93].

These observations raise the possibility that decreased activity of OGG1 in DNA-containing compartments is due to the inability of aged cells to distribute and/or optimally modify OGG1 for removal of 8-oxoG or that this phenomenon actually is a defense against the aging process. Cell culture studies support the latter hypothesis as an ectopic expression of OGG1 in $Ogg1^{-/-}$ cells induced arrest of cell proliferation, senescent-like morphology, and increased expression of senescence-associated β-galactosidase activity [94]. Combining these data with the consideration that there is no change in the longevity of $Ogg1^{-/-}$ mice, it may be proposed that 8-oxoG in the DNA does not directly relate to senescence/aging processes, but, in fact, it is more advantageous to accumulate 8-oxoG than to release it from DNA.

In support, studies showed that repeated low-dose ionizing radiation (IR) exposure increased life span. IR via formation of $^{\bullet}OH$ and other reactive species (e.g., hydrated electrons, hydrogen atoms, generated from cellular water) increases 8-oxoG levels along with clustered DNA damage and DNA strand breaks [95–97]. Unexpectedly, because of adaptive cellular responses, IR increased life span in *Drosophila* and rodent models [96]. Mice exposed to low-dose IR (0.125 Gy neutrons, 0.5 Gy X-rays) had increased 8-oxoG levels (and other DNA lesions) and lived significantly longer than did unexposed controls [98]. The molecular mechanism of life-span extension remains largely unknown, but may be explained by a beneficial adaptive cellular response to ROS and DNA damage [99]. In support, in response to sublethal exposure to IR, but not other genotoxicants, e.g., UV light or alkylating agents, APE1 and p53 were activated selectively and increased cell survival [100]. Coleman and co-workers [101] have shown that a 5-Gy priming dose IR followed by repeated 2-Gy doses increased the expression of BER and cell-cycle regulatory, stress-response proteins and antioxidant genes in human cells. In consideration of the foregoing body of data, it may be hypothesized that regular, intermittent increases in oxidative stress and genomic 8-oxoG levels may be beneficial and lead to an extended health and life span.

8-OxoG on RNA

Compared to DNA, RNA is more prone to oxidative damage under similar conditions [102,103]. This phenomenon is related to RNA's single-stranded nature, relatively lesser association with protecting proteins, even cellular distribution, and close proximity to sites of ROS generation. Accordingly, 8-oxoG is the most abundant RNA lesion, as guanine has the lowest oxidation potential among RNA bases. Estimates show that 8-oxoG is present in 30–70% of the messenger RNA because of its chemical stability and lack of repair machinery in contrast to DNA [102,104–106]. In general, levels of oxidative guanine-based RNA lesions are approximately 10 times higher than those in DNA [107–110]. Both guanine and 8-oxoG have low oxidation potential; it has been hypothesized that in RNA they may serve as acceptors of charges from reactive species before damage to genomic and mitochondrial DNA occurs [102]. Further, with regard to the amount of RNA being approximately four times that of DNA, it is possible that the RNA pool plays an essential role in the cellular antioxidant mechanism [102,111].

Defects in RNA molecules and subsequent errors in proteins seem to have less pathological relevance than do genomic mutations. However, this scenario does not seem to be the case for bacterial cells because rRNA and tRNA constitute the majority of cellular RNA and are not degraded during exponential growth in bacteria, so damaged RNA decreases the viability of the cells [112]. In mammalian cells, the mispairing of 8-oxoG in triplet codons on mRNA and anticodons on tRNA during codon recognition may lead to decreased and/or synthesis of defective proteins. These form the basis for the belief that RNA oxidation is etiologically associated with pathologies in humans, such as Alzheimer disease, Down syndrome, dementia of Lewy bodies, subacute sclerosing panencephalitis, xeroderma pigmentosum inflammatory processes in atherosclerosis, and skeletal muscle atrophy [102,111,113–115].

Thus, oxidative base lesions in RNA have significant effects on cells and organisms and thus, the question is, why are cells not equipped with more effective measures to protect from oxidation or degrade oxidatively damaged RNA [107]. It may be proposed that RNAs containing guanine, indeed, could have antioxidant functions. Specialized nucleases for degradation of RNA have been identified [64,82,116], sequestering the 8-oxoG-RNA from translation and directing it to degradation [104,105]. However, extensive RNA degradation seems to be avoided as it may result in increased levels of 8-oxoG-containing nucleosides in cells, which could have cellular physiological consequences, i.e., senescence for cell fate [117–120].

Repair of genomic 8-oxoG

Recognition and repair of 8-oxoG

8-OxoG and FapyG are recognized and excised from DNA by formamidopyrimidine-DNA glycosylase (also called mutM) in *Escherichia coli*. The eukaryotic homolog is known as OGG1 [25,77–81,121,122]. Two alternatively spliced forms of the human mutM homolog OGG1 mRNAs have been identified and classified into two types, based on their last exon. Type 1 (or α with exon 7) and type 2 (or β with exon 8) mRNAs are the major types found in human tissues [111,123–127]. These OGG1 mRNAs are ubiquitously expressed in cells, but their abundance is tissue specific [128]. The OGG1 promoter resembles a typical housekeeping gene promoter. The two types of OGG1, ~39 and ~44 kDa, recognize and cleave 8-oxoG with nearly similar efficiencies [111,123–127].

8-OxoG is efficiently recognized by OGG1 when paired with cytosine in DNA helices despite its nearly identical structural similarity to guanine, i.e., they differ by only two atoms [8,67,121,122,127,129]. There are a number of theories about how OGG1 recognizes the damaged base 8-oxoG. The most frequently proposed include the possibility that OGG1 recognizes 8-oxoG based on the free energy difference between 8-oxoG and guanine and then forces it out from the DNA helix and engulfs it into the active site of the enzyme before excision [129,130].

Unrepaired 8-oxoG forms the mutagenic 8-oxoG:A pair during DNA replication. MutY (hMYH is a human homolog) an adenine-specific-DNA glycosylase removes A from the 8-oxoG:A pair. It is established that the binding of mutY to damaged DNA lesions facilitates the oxidation of 4Fe–4S ($[4Fe–4S]^{2+} \rightarrow [4Fe–4S]^{3+}$) and that such changes influence both recognition and catalysis of base removal [131–134]. A subsequent reduction of 4Fe–4S on the enzyme mediates its dissociation from DNA. Importantly, a modified base such as 8-oxoG would be expected to short-circuit this charge-transfer process, which, therefore, helps the enzymes locate the lesion [131–134]. Reactive species such as nitric oxide efficiently modify 4Fe–4S to form a dinitrosyl iron complex with the concomitant inactivation of enzymatic activity. Thus, it is proposed that the iron–sulfur cluster may also act as a sensor of intracellular redox and thereby an increase in redox state downregulates recognition and excision of base lesions [135]. The evolutionary significance of the lack of the iron–sulfur cluster in OGG1 is not known, although its activity is affected (primarily downregulated) under oxidative stress conditions [90,136–138].

Regulation of OGG1 activity

Oxidative stress increases the level of 8-oxoG in DNA and, thus, an enhancement in OGG1 activity would be expected. However, this is

not the case because the reduced state of the redox-sensitive residues is important for OGG1's glycosylase activity. Observations showed that oxidative stress decreases the activity of OGG1, which returns once the cellular redox status is normalized [89,90]. An interaction between APE1 and OGG1 has been previously reported for regulation of OGG1 activity [92,93]. APE1 is also known as a powerful redox factor and, accordingly, in this scenario APE1 may serve to modulate OGG1's redox state for processing damaged sites in DNA [139].

Phosphorylation of OGG1 is mediated via protein kinase C, cyclin-dependent kinase 4 (Cdk4), and c-Abl tyrosine kinase [140]. Cdk4-mediated phosphorylation of OGG1 at serine/threonine increases its 8-oxoG incision activity and also affects OGG1's AP lyase activity, whereas tyrosine phosphorylation by c-Abl has no effect on its glycosylase activity. Furthermore, DNase-sensitive, chromatin-associated OGG1 is phosphorylated on a serine residue, whereas the nuclear matrix-associated OGG1 seems to be unphosphorylated [141]. These results support the notion that phosphorylation may influence functions of OGG1 other than its repair activity [140,142].

A considerable percentage of OGG1 is present in an acetylated form. OGG1 is acetylated by p300/CBP, histone acetyltransferase at Lys338/Lys341 [143,144]. Importantly, acetylation on these sites has been shown to significantly increase OGG1 activity [87,143]. Acetylation also alters the activity of BER proteins, including APE1, Flap endonuclease 1, and DNA polymerase β [91,143,145,146]. Recently a great deal of research interest has been focused on sirtuins, which are NAD-dependent protein deacetylators [147,148]. Under oxidative stress conditions, such as those induced by exercise, SIRT1 (mammalian ortholog of the yeast silencing information regulator (SIR2)) and SIRT6 are activated [86,149]. Results from animal model studies show a possible reverse relationship between the activities of OGG1 and SIRT1, and this may suggest that the "turn on" is executed by p300/CBP acetyltransferase and the "switch off" by the deacetylase SIRT1 [86].

Interventions such as caloric restriction and regular exercise have been shown to increase the activity of SIRT1, thereby decreasing the levels of OGG1 acetylation and, hence, OGG1 activity in both nuclear and mitochondrial matrices [150–154]. Together these observations along with the redox sensitivity of kinases, phosphatases, acetylases, and deacetylases, make it possible to strongly suggest that a reverse correlation exists between OGG1 activity and oxidative stress. Thus, what could be the advantage for a cell/organism to transiently or permanently accumulate a mutagenic DNA lesion, 8-oxoG, except that it has an important physiological role or negative consequences?

Negative consequences of 8-oxoG repair

OGG1 is essential for maintaining genomic integrity, although there are cases in which removal of 8-oxoG is not advantageous; in fact it is associated with disease phenotypes. For example, removal of the oxidized guanine base lesion 8-oxoG from CAG triplets by OGG1 has etiologically been related to Huntington disease (HD) [155]. Expansion of guanine-containing triplet repeat sequences (CAG and/or CTG) in the genome has been associated with not only HD, but also myotonic dystrophy and spinocerebral ataxias [155,156]. Transgenic mice containing exon 1 of the human *HD* gene (include the CAG repeat) generate the toxic HD protein in brain because of an increase in number and length of CAG as animals age [157]. The CAG expansion is specifically dependent on OGG1, because it did not occur in animals lacking OGG1 activity. Thus, when HD transgenic mice were crossed with $Ogg1^{-/-}$ ones the expansion of CAG within the human *HD* transgene was significantly decreased along with the generation of toxic proteins and symptoms resembling those of HD. Studies showed that OGG1-mediated CAG expansion occurs through a strand displacement/slippage mechanism [155]. These results suggest that other DNA glycosylases, nucleotide excision, or mismatch repair machinery in the absence of OGG1 are not involved in CAG extension [155]. In conclusion, as a result of aging, the guanine oxidation–excision–expansion cycle escalates, thereby providing a unique cellular milieu in which the presence of 8-oxoG on the genome is less harmful than the excision and repair by OGG1. It was also demonstrated that the CAG/CTG trinucleotide repeat in a hairpin conformation is more sensitive to guanine oxidation than if located in the helix. It was hypothesized that CAG extension by OGG1 is rendered 700-fold slower for excision of 8-oxoG at the hairpin region than in it is in the duplex [158].

The effects of deletion of OGG1

$Ogg1^{-/-}$ mice were developed to study the role of 8-oxoG in mutagenesis [159]. In $Ogg1^{-/-}$ mice, supraphysiological levels of 8-oxoG did not play a critical role in embryonic development; the mice had a normal life span and only modestly increased mutagenesis as well as tumor formation [160–162]. The 8-oxoG level in the nuclear DNA of hepatocytes was 7-fold higher in $Ogg1^{-/-}$ mice than in the wild type at 14 months of age. Unexpectedly, the 7-fold increase in the 8-oxoG level resulted in a 2.3-fold increase in mutation frequency without tumor development. Despite the presence of high levels (>20-fold increase vs wild-type) of 8-oxoG in the mitochondrial DNA, mitochondria were functionally normal, and there were no detectable changes in maximal respiration rates nor in mitochondrial ROS generation [163,164]. Under chronic oxidative stress, the 8-oxoG level may increase by 250-fold in $Ogg1^{-/-}$ mice without severe consequences [165], e.g., the liver regenerated to the same extent as did that in untreated $Ogg1^{-/-}$ or $Ogg1^{+/+}$ mice [166]. More surprisingly, at 52 weeks, $Ogg1^{-/-}$ mice had no incidence of precancerous lesions or tumors in the kidneys, lungs, liver, spleen, thymus, stomach, or intestine [166]. It seems that high, steady-state levels of 8-oxoG can be tolerated without major consequences; in fact, it could be advantageous, as $Ogg1^{-/-}$ mice were shown to be resistant to inflammation [167].

An inverse correlation between OGG1 activity and inflammation

It is well accepted that inflammation via oxidative stress induces DNA damage; however, the role of 8-oxoG repair in inflammation has only recently been proposed. Unexpectedly a defect in 8-oxoG repair mediated a protective role against inflammation and mutagenicity [168,169]. For example, *Helicobacter pylori* infection has been reported to be mutagenic (as measured by the incidence of GC → TA transversions) owing to oxidatively induced DNA damage, most likely at guanine, involving an inflammatory host response [169]. Infection of $Ogg1^{-/-}$ mice with *H. pylori* resulted in two unforeseen observations: (1) gastric inflammation due to the infection was less severe in the absence of OGG1 and (2) frequency of GC → TA transversions was significantly less compared to that in wild-type mice. These results may be interpreted as lower infection-associated oxidative stress and thereby less DNA damage at the gastric epithelial cells, or OGG1 as a multifunctional protein could have a proinflammatory effect. Although these possibilities have yet to be sorted out, this is an example of the beneficial effects of resident 8-oxoG in DNA.

The impact of OGG1 deficiency in endotoxic shock, diabetes, and contact hypersensitivity models of inflammation was investigated [167]. Compared to the wild-type mice, the $Ogg1^{-/-}$ mice showed significantly less inflammatory response in LPS-induced shock, type 1 diabetes (induced by multiple low-dose streptozotocin), and contact hypersensitivity (triggered by oxazolon), as shown by proinflammatory chemokine/cytokine (e.g., MIP-1α, TNF-α, IL-4, IL-10, IL-12) production, inflammatory cell accumulation, and tissue/organ dysfunction. Authors have concluded that OGG1 may also function as an inflammatory/immune system modulator.

It is notable that under inflammatory conditions OGG1 activity is decreased in parallel with a significant increase in 8-oxoG level [48,49,90,136–138]. This phenomenon is associated with redox-mediated downregulation of OGG1 activity and may be because accumulation of 8-oxoG in the genome is more advantageous than its

release. A reason could be that OGG1, by excising 8-oxoG, causes the generation of single-strand gaps in the DNA, which could be recognized by DNA-damage-dependent kinases to trigger inflammation. This hypothesis may also be valid for Ogg1$^{-/-}$ mice and, thus, in the absence of 8-oxoG repair significantly fewer DNA nicks are generated, thus there is a less inflammatory response. In support, e.g., it has been shown that the human pancreatic islet cells of diabetes 2 patients contain an increased level/activity of OGG1 in mitochondria [170].

Guanine as a defense against ROS

Guanine quadruplexes protect telomeres from oxidation

In addition to the possible importance of 8-oxoG, it cannot be excluded that guanine at telomere residues plays a role in the DNA similar to that of methionine residues in proteins, serving as a buffer to protect vital positions in the "core" protein molecule from damage caused by ROS (histone could be another example). The oxidation of methionine residues, which can be over 50% of surface residues, is without any significant effect, whereas one of the inner core residues could result in a loss of activity of the enzyme [171,172]. As shown earlier, histone carbonylation is decreased with aging, which is in contrast to findings with other proteins. It is accepted that increased levels of ROS associated with aging result in damage to macromolecules, which is in contrast to the decreased levels of histone carbonylation [57,173,174]. This observation may be explained by the increased turnover rate of histones in aged cells; however, this is in contrast to the general phenomenon that aging slows down turnover rates [57]. Taking an analogy of methionine residues protecting the core portion of protein, we propose the possibility that guanine located at the nontranscribing region of the genome might overtake the reactivity of free radicals, providing local protection for histones so they may maintain the chromatin structure.

The telomere sequence is a repeating series of TTAGGG, between 3 and 20 kb long in humans, and facilitates the protection of chromosome ends [175]. There are an additional 100–300 kb of telomere-associated regions between the telomere and the rest of the chromosome. In these regions, the guanine-rich, single-stranded DNAs can form a guanine quadruplex [176]. It has been found that 50% more guanines were oxidized in quadruplexes than in duplexes [177,178]. UVB radiation more readily oxidizes guanine in the telomere than in the helix, and the one-electron oxidation of guanine can be explained by the less efficient energy transfer from excited G to C and T in the telomere [178]. It seems that the G quadruplexes indeed can serve as a protective shield against oxidants to keep the integrity of the telomeric DNA [179,180]. As above, the DNA helix can conduct electrical charges by nucleobase cations and anions [181,182]. In addition to guanine's low oxidation potential, the associated cations at the G quadruplexes might be very useful to attract oxidants. This could be especially important during age-associated increases in ROS production. It is interesting that rodents with much higher metabolic rates and ROS production than humans have telomeres that are about 10 times longer [183]. Based upon these observations, we hypothesize that the age-associated changes in the compactness of the chromatin structure, which includes the carbonylation status of histone proteins [57], could include the selective and targeted oxidation of G quadruplexes to preserve histone residues from oxidative modification (Fig. 1).

RNA as a potential buffer to reload the oxidative stress from DNA

RNA is single-stranded and lacks protecting histones and structural complexity, so it is more prone to guanine oxidation than is double-stranded DNA. Notably, among RNAs, ribosomal RNA contains a larger amount of guanine, thus serving as a potential sink for ROS, which thus could protect against the oxidative modification of guanine in DNA. In support, the same dose of UVA-light irradiation causes more extensive RNA damage than DNA oxidation [184]. Although the consequences of guanine oxidation in RNA are not fully understood, at this time it cannot be ruled out that guanine oxidation in RNA is less harmful than in DNA. The half-life of rRNA is about 3 to 5 days in postmitotic or slowly growing tissues [185], and accordingly, the oxidatively modified and possibly functionally altered molecules are replaced in a shorter period of time. In addition, it is important to note that polynucleotide phosphorylase (PNP), along with other enzymes, has the capability of binding especially to 8-oxoG-containing RNA. This would inhibit cell growth, probably by the withdrawal of most of the 8-oxoG-containing mRNA from transcription [186]. However, this may not always be the case, as oxidation of luciferase mRNA resulted in the formation of short polypeptides, which suggested that the oxidation of mRNA causes premature termination of the translation process and proteolytic degradation [187]. This seems to be an important mechanism to prevent propagation of damage, and it could partly explain the lack of linear relationship between mRNA content and protein levels under certain physiological conditions.

Little is known about how cells eliminate 8-oxoG from RNA. But it has been shown that after a bout of oxidative challenge, an effective mechanism decreases the levels of 8-oxoG-containing RNA [110,188]. It is possible that in addition to PNPase, RNase-mediated selective degradation is involved to minimize the effects of damaged RNA [103]. Moreover, human YB-1 protein has also been demonstrated to work as an RNA chaperone to target 8-oxoG-containing RNA for degradation [189]. Interventions such as long-term caloric restriction or physical exercise were also shown to decrease levels of RNA containing 8-oxoG in humans [190]. Although guanine oxidation of RNA is not without risk, one could argue that it is less dangerous than the oxidative modification of guanine in DNA. Thus, this could be an effective mechanism of the cells to relocate/transfer the oxidizing capacity of ROS from DNA to RNA to minimize the consequences of oxidative stress (Fig. 1).

Roles of 8-oxoG and OGG1 in transcription

Role of 8-oxoG in accommodation of the transcription initiation complex

For RNA transcription to occur, cells need a mechanism by which they can relax chromatin. One of the examples of chromatin relaxation is nicking of DNA by OGG1 at the 8-oxoG lesion in the promoter region. Exposure of cells to estrogen increases 8-oxoG levels in DNA and recruits OGG1 and topoisomerase IIβ (Topo IIβ) to estrogen-responsive DNA elements (ERE) in the promoter region of 17β-estradiol (E2)-responsive genes [191–193]. E2–receptor complex binding to chromatin is triggered by demethylation of dimethyl-Lys4 in histone H3, and this demethylation by lysine-specific demethylase generates H_2O_2. H_2O_2 results in the production of 8-oxoG in discrete foci, which are efficiently inhibited by *N*-acetyl-L-cysteine [191]. Systematic analysis of the promoter revealed that OGG1 and Topo IIβ accumulated preferentially at ERE sites. It has been proposed that removal of the 8-oxoG by OGG1 produces nicks that function as entry points for Topo IIβ. The DNA strand gap allows Topo IIβ-mediated relaxation of the DNA strands and allows chromatin bending to accommodate the transcription initiation complex. Estrogen receptor α plays a pivotal role in directing oxidative signals to the promoter region, which emphasizes the selective characteristics of this pathway, including the recruitment of OGG1 and Topo IIβ to the promoter. These are pioneering observations that show that 8-oxoG generation might be regarded differently compared to genuine, mutagenic DNA base damage.

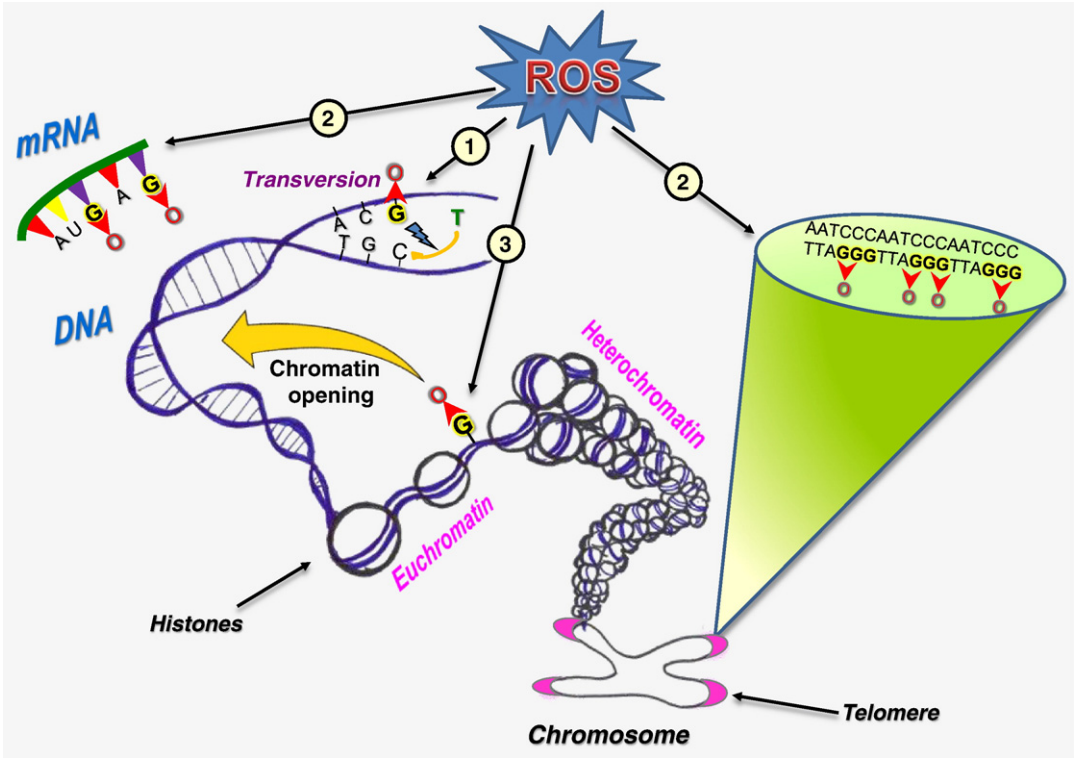

Fig. 1. The possible roles of oxidized guanine in cellular processes are shown. (Arrow 1) Massive oxidation of guanine in the helix could result in the replacement of cytosine by thymine and this could cause mutation. (Arrows 2) The abundance of ROS attracting guanine, because of the low redox potential, in the telomere and RNA could be a potential buffer for ROS, preventing significant oxidation of helix-located guanines. (Arrow 3) A moderate level of guanine oxidation could be important to open chromatin structure, which is an obligatory process for transcription.

8-OxoG in chromatin relaxation and apoptosis

It also can be proposed that oxidation of guanine might be a tool to open the DNA helix, which is packed into chromatin. This packing could prevent the access of DNA-binding factors. On SWI/SNF (switch/sucrose nonfermentable) yeast the chromatin remodeling protein complex controls this regulation [194]. A similar ATP-dependent system is also present in human cells and implicated in hormone receptor activation. A histone variant of H2A.Bbd (macro. H2A and Barr-body deficient) was identified by Chadwick and Willard [195] and proved to be localized in transcriptionally active regions of nuclei and is believed to be resistant to remodeling by SWI/SNF. DNA damage repair that includes 8-oxoG could be affected by chromatin remodeling and/or could affect chromatin remodeling. Indeed, 8-oxoG on the dyad axis was reduced in both conventional and variant H2A.Bbd nucleosomes compared to naked DNA [196]. It has been shown that the SWI/SNF complex significantly facilitated the removal of 8-oxoG by BER (but not nucleotide excision repair processes) in conventional but not in H2A.Bbd nucleosomes [196], and thereby the remodeling facilitated BER on a conventional template, which might be important for the efficient repair of lesions. Colocalization of OGG1 with mitotic chromosomes resembles that of several other nuclear proteins: the SWI/SNF-like protein ATRX (α-thalassemia/mental retardation syndrome X-linked), the heterochromatin-binding protein 1, and DNA topoisomerase IIα [142]. The question arises as to whether oxidative damage to guanine in DNA, which is able to initiate SWI/SNF mobilization, is coincidentally or physiologically associated with increased transcriptional availability to promote gene expression, especially during mitosis [197].

Another example: 8-oxoG plays a role in nucleosomal fragmentation and formation of apoptotic nuclear bodies. Topoisomerase I (Topo I) is ubiquitously expressed and essential in eukaryotic cells, and among its diverse functions are several that contribute to the recognition and elimination of apoptotic cells [198,199]. Specifically, Topo I plays a critical role in tumor necrosis factor-related, apoptosis-inducing ligand (TRAIL)-induced apoptosis during the formation and release of apoptotic nuclear bodies [199]. Sordet and colleagues [199] demonstrated that an apoptotic Topo I cleavage complex (Topo Icc; an 80-kDa C-terminal fragment of Topo I generated by caspase-3) is trapped at the proximity of oxidative 8-oxoG DNA lesions generated by TRAIL-induced ROS. Importantly, this phenomenon may be general, as the ROS-dependent formation of 8-oxoG seems to represent a common mechanism for the trapping of Topo Icc during apoptosis induced by arsenic trioxide and chemotherapeutic agents, including staurosporine and etoposide [200–202].

Transcriptional bypass of 8-oxoG

Both prokaryotic and eukaryotic RNA polymerases have been shown to bypass 8-oxoG (and uracil) lesions in DNA during a process called transcriptional mutagenesis, a term describing the formation of mutant RNA transcripts and introduced by Doetsch [203] and frequently observed [204–207]. Thus, according to these findings, 8-oxoG only transiently inhibits T7 RNA polymerase-mediated transcription. The read-through frequency was approximately 95% in the transcribing strand. A complete lesion bypass was observed when 8-oxoG was placed in the nontranscribed strand [206]. A study on a similar subject found that transcription elongation factor IIS (TFIIS) enabled RNA polymerase II to bypass 8-oxoG, but not the other types of damage (2-hydroxyadenine, 8-oxoadenine, or thymine glycol) on the transcribed strand [208]. The elongation factors elongin, Cockayne syndrome B protein (CSB), and TFIIS enhance the bypass of an 8-oxoG lesion and, thus, these factors may contribute to transcriptional mutagenesis [209]. Only higher levels of 8-oxoG in the transcribing strand mediate a decrease in gene expression, and this effect was enhanced in the lack of CSB [207]. Together these data show that physiological levels of 8-oxoG seem not to endanger transcription. In fact, when 8-oxoG is in the promoter, it mediates DNA helix relaxation

and allows gene transcription (see Role of 8-oxoG in accommodation of the transcription initiation complex).

Conclusion

The oxidation product of guanine, 8-oxoG, is the most abundant DNA base lesion. As a base, 8-oxoG is excised from the DNA double helix primarily by OGG1 during the BER process. A major fraction of 8-oxoG, however, is not removed from DNA, and it seems that its level under a given condition fits well into the cellular hormesis phenomenon, which is characterized by suboptimal, optimal (or physiological), and supraoptimal levels. Taking into consideration that extreme 8-oxoG levels did not affect the fertility, development, or age of $Ogg1^{-/-}$ mice and, in fact, they are resistant to inflammation, raises the question as to what are the benign and toxic levels of 8-oxoG. Supraoptimal levels of 8-oxoG in DNA and RNA have been correlated with age-related diseases; however, with regard to longevity, an etiological relationship is yet to be established. To date, it seems that a transient accumulation of 8-oxoG in DNA may be more advantageous for the organism than its repair, especially under inflammatory oxidative stress conditions. In fact, its excision from DNA by OGG1 could lead to, e.g., HD or myotonic dystrophy or its misrepair to malignancies. Although it is controversial, 8-oxoG in the DNA helix does not obstruct RNA transcription, has an important role in transcriptional initiation and chromatin relaxation, and, along with guanine, it could serve as a buffer against oxidative stress. Together these data suggest that a tissue- and cell-type-dependent, optimal level of genomic 8-oxoG is essential in normal physiological processes and the life of organisms.

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