Published in final edited form as:

Free Radic Biol Med. 2010 August 15; 49(4): 587–596. doi:10.1016/j.freeradbiomed.2010.05.008.

8-oxo-7,8-dihydroguanine: Link to gene expression, aging and defense against oxidative stress

Zsolt Radak¹ and Istvan Boldogh²

¹Research Institute of Sport Science, Faculty of Physical Education and Sport Science, Semmelweis University, Budapest, Hungary

²Department of Microbiology and Immunology, Sealy Center for Molecular Medicine, University of Texas Medical Branch at Galveston, Galveston, Texas 77555, USA

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, 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 genotoxic/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, while they do not have shorter lifespan, nor exhibit severe pathological symptoms including tumor formation. In fact they are increasingly resistant to inflammation. Here we address rarely considered significance of 8-oxoG such as its optimal level in the DNA and RNA in a given condition, essentiality for normal cellular physiology, evolutionary role, ability to soften the effects of oxidative stress in DNA, harmful consequences of its repair, as well as its importance in transcriptional initiation and chromatin relaxation.

1. Introduction

Molecules of living organisms are continuously modified by reactive oxygen (ROS), reactive nitrogen (RNS) and non-radical species arising from environmental exposures and oxidative cellular metabolism. Oxidatively damaged proteins, lipids and RNA are usually subjected to degradation, while 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 a specific 8-oxoguanine DNA glycosylase 1 (OGG1). Thus a first step in BER is the removal of base lesions by specific DNA glycosylase, which produces either 3'-hydroxyl or 5'-

© 2010 Elsevier Inc. All rights reserved.

Correspondence: **Zsolt RADAK, Ph.D.**, Research Institute of Sport Science, Faculty of Physical Education and Sport Science, Semmelweis University, Alkotás u. 44, Budapest, Hungary, radak@mail.hupe.hu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

deoxyribose phosphate ends (e.g. uracil DNA glycosylase or 3' α , β -unsaturated aldehyde and 5'-phosphate, as in the case of OGG1s). These DNA ends require further processing by apurinic/apyrimidinic endonuclease 1 (APE1), polynucleotide kinase or tyrosyl-DNA phosphodiesterase 1 before gap filling by polymerases and ligation [6,9–11].

The objectives of the present review are to address rarely discussed aspects and significance of guanine oxidation, such as the physiological, non-mutagenic role of 8-oxoG in biological systems. Guanine-rich DNA regions and susceptibility of guanine to reactive oxygen and non-radical species might reflect a natural strategy of organisms to adapt and evolve and utilize or abuse 8-oxoG. A wide range of observations also raises the possibility that oxidation of guanine in DNA and RNA might be described by a J-shape dose-response curve, meaning an optimal, supra-optimal but not suboptimal level of 8-oxoG for cellular physiological processes.

2. Oxidatively induced DNA damage

2.1. Oxidative stress

Oxidative stress is an imbalance between the production of reactive species and the ability of the cells to eliminate them or repair the resulting damage. Oxidative stress caused by ROS and non-radical 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 with their ability to activate oxidases and induce mitochondrial dysfunction. The molecular mechanism of ROS formation their chemistry, health-and age-related significance are extensively documented and reviewed [14–17].

2.2 Oxidative stress and longevity

Commonly reactive species are considered unfavorable for living organisms due to their reactive/damaging nature and their ability to 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, 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 are 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, since 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 fact 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 (C) 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 alpha subunit in the nematode [44]. In line with these findings, the 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 SOD (transgenic and heterozygous knock out), thioredoxin 2, glutathione peroxidase, and mitochondrial targeted catalase, as well as mutant mice 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].

3. 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 (A) thymine (T) (A:T) pairs, since they are linked by three hydrogen bonds versus two in A:T [50]. Due 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, since G:C content in the DNA showed a significant relationship to temperature in organisms living at different marine temperatures.

Besides the possible evolutionary role of G:C pairs in relation to thermo regulation, 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 content 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 O₂ 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 combat and/or soften the effects of ROS, especially the effects of hydroxyl radical ([•]OH), which readily reacts with guanine. G:C content is also linked to thermoregulation, since, 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 as 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 level 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 non-monotonic response. The sensitivity of guanine to reactive oxygen and non-radical species might reflect a natural strategy of organisms to use or abuse 8-oxoG. The hormesis theory appears also to be valid for the rate of amino acid carbonylation, i.e., a small degree of carbonylation might govern physiological processes, like 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].

4. 8-oxo-7,8-dihydroguanine

4.1. 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 $\cdot\text{OH}$ and singlet oxygen ($^1\text{O}_2$) [58]. For example, guanine's interaction with $\cdot\text{OH}$ at C8 result 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 it located at 5'-end of a series of guanine [61,62]. This phenomenon has been attributed to the migrating radical cation to the guanine having the lowest redox potential, with termination by trapping and product formation [61,62]. Due to 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-formamidopyrimidine (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].

4.2. 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 has been observed and then it abruptly increased in most tissues [82]. An increase in 8-oxoG levels is thought to result from the supra-physiological levels of reactive species and/or decrease in OGG1 activity during normal aging processes [83–85]. A decrease in 8-oxoG repair could be due to combinations of events, such as an age-associated inability to import/target OGG1 into nuclear and mitochondrial compartments [86–88] and/or suboptimal post-translational modifications [89–91]. Oxidative stress associated with aging processes or physical exercise was found to alter the subcellular targeting of OGG1 in parallel with post-translational modifications and lowered 8-oxoG incision activity of the enzyme in aged, but not in young tissues [86–88]. Similar observations were made in an LPS-challenge inflammatory mouse model. Specifically, while 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 that was shown to regulate OGG1 activity [87,92,93].

These observations raise the possibility that decreased activity of OGG1 in DNA-containing compartments is either due to the inability of aged cells to distribute and/or optimally modify OGG1 for removal of 8-oxoG, or this phenomenon actually is a defense against the aging processes. Cell culture studies support the latter hypothesis as an ectopic expression of OGG1 in *ogg1*^{-/-} cell-induced arrest of cell proliferation, senescent-like morphology, and increased expression of senescent-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 release it from DNA.

In support, studies showed that repeated low-dose ionizing radiation (IR) exposure increased lifespan. IR via formation of $\cdot\text{OH}$ 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, due to 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 IR exposures, but not by other genotoxicants, -e.g., UV light or alkylating agents, the APE1 and p53 were activated selectively and increased cell survival [100]. Coleman and co-workers [101] have shown that a 5-Gy prime 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.

4.3. 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, the relatively lesser association with protecting proteins, even cellular distribution, and their 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 (m) RNA due to their chemical stability and lack of repair machinery in contrast to DNA [102,104–106]. In general, oxidative guanine-based RNA lesions are approximately 10 times higher than that of DNA [107–110]. Both guanine and 8-oxoG have low oxidation potential, it has been hypothesized that in the RNA they may serve as an acceptor of charges from reactive species before damage to genomic and mitochondrial DNA (mtDNA) occur [102]. Further, with regard to the amounts of RNAs being ~4-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 appear to have less pathological relevance than do genomic mutations. However, this scenario does not seem to be the case for bacterial cells since rRNA and tRNA constitute the majority of cellular RNA and are not degraded during exponential growth in bacteria, so damaged RNA decreased the viability of the cells [112]. In mammalian cells, due to 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 believing that RNA oxidation is etiologically associated with pathologies in humans, such as Alzheimer's Disease (AD), 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 cells are not equipped with more effective measures to protect from oxidation or degrade oxidatively damaged RNA [107]. It may be proposed that various RNAs containing guanine, indeed, could have specialized antioxidant functions. Specialized nucleases for degradation of RNA have been identified [64,82,116], and Y box-binding

protein (YB-1) is one of them. YB-1 discriminates between oxidized and undamaged RNA, thereby sequestering the 8-oxoG-RNA from the 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].

5. Repair of genomic 8-oxoG

5.1. Recognition and repair of 8-oxoG

8-OxoG and FapyG is recognized and excised from DNA by formamidopyrimidine-DNA glycosylase (Fpg, also called MutM) in *Escherichia coli*. The eukaryotic homolog is known as OGG1 [25,77–81,121,122]. Two alternatively spliced forms of human mutM homolog OGG1 (hOGG1 or hMMH) mRNAs have been identified and classified into two types, based on their last exons. Type 1 (or alpha with exon 7) and type 2 (or beta with exon 8) mRNAs are the major types found in human tissues [111,123–127]. These OGG1 mRNAs are ubiquitously expressed in cells, while their abundance is tissue specific [128]. OGG1 promoter resembles a typical housekeeping gene promoter. The two types of OGG1 ~ 39 kD and ~44 kD 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.,-differ by only two atoms [8,67,121,122,127,129]. There are a number of theories about how OGG1s recognize the damaged base 8-oxoG. Most frequently proposed include the possibility that OGG1 recognizes 8-oxoG, based on the free energy difference between 8-oxoG and guanine, then forces it out from DNA helix and engulfs it into the active site of the enzyme prior to excision [129,130].

It is established that the binding of MutM to damaged DNA lesions (8-oxoG, FapyG) facilitates the oxidation of 4Fe-4S ($[4\text{Fe}-4\text{S}]^{2+} \rightarrow [4\text{Fe}-4\text{S}]^{3+}$), and that such changes impact 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, and, therefore, helps localizing the lesion by the enzymes [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]. Evolutionary significance of the lack of the iron-sulfur cluster in OGG1 is not known, while its activity is affected (primarily down regulated) in oxidative stress conditions [90,136–138].

5.2 Regulation of OGG1's activity

Oxidative stress increases levels of 8-oxoG in DNA, and, thus, an enhancement in OGG1's activity would be expected. However, this is not the case because the reduced state of the redox-sensitive residues is important for OGG1's glycosylases 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 and c-Abl tyrosin kinase [140]. Cdk4-mediated phosphorylation of OGG1 at serine/threonine increases its 8-oxoG incision activity and also affects OGG1's AP lyase activity, while

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 appears to be un-phosphorylated [141]. These results support that phosphorylation may influence additional 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's activity [87,143]. Acetylation also alters the activity of BER proteins including APE1, flap endonuclease 1 and DNA polymerase beta [91,143,145,146]. Recently a great deal of research interest was 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 SIR2: Silencing Information Regulator) and SIRT6 are activated [86,149]. Results from animal model studies show a possible reverse relationship between the activity of OGG1 and SIRT1, and these 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 mt matrix [150–154]. Together these observations along redox sensitivity of kinases, phosphatases, acetylases and deacetylases, it is possible to strongly suggest that a reverse correlation exists between OGG1's 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?

5.3. Negative consequences of 8-oxoG repair

OGG1 is essential for maintaining genomic integrity, while there are cases when 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's 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 in 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 due to an increase in number and length of CAG as animals age [157]. The CAG expansion is specifically dependent on OGG1, since it did not occur in animals lacking OGG1 activity. Thus, when HD transgenic mice crossed with *ogg1*^{-/-} ones expansion of CAG within the human *HD* transgene was significantly decreased along with 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 is 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 where 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 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].

5.4. The effects of OGG1's deletion

OGG1 null (*ogg1*^{-/-}) mice were developed to study the role of 8-oxoG in mutagenesis [159]. In OGG1 null mice, supra-physiological levels of 8-oxoG did not play a critical role in embryonic development mice maintained a normal lifespan and had only modestly increased mutagenesis as well as tumor formation [160–162]. The 8-oxoG level in the nuclear DNA of hepatocytes was seven-fold higher in *ogg1*^{-/-} mice than in the wild type at 14 months of age. Surprisingly, the seven-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 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 those in non-treated *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 appears 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].

5.5. An inverse correlation between OGG1's 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) due 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 were significantly less compared to those in wild-type mice. These results may be interpreted as lower infection-associated oxidative stress and thereby there is less DNA damage at the gastric epithelial cells, or OGG1 as a multifunctional protein could have a pro-inflammatory effect. While these possibilities have yet to be sorted out, this is an example of the beneficial effects of resident 8-oxoG in DNA.

Impact of OGG1 deficiency in endotoxic shock, diabetes, and contact hypersensitivity models of inflammation was investigated [167]. Surprisingly, compared to the wild-type mice, the *ogg1*^{-/-} mice showed significantly less inflammatory response in LPS-induced shock, type I diabetes (induced by multiple low-dose streptozotocin), and contact hypersensitivity (triggered by oxazolone), as shown by pro-inflammatory chemokine/cytokine (e.g., MIP-1 α , TNF- α , IL-4, IL-10, IL12) 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 in inflammatory conditions OGG1's 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, down regulation of OGG1's 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, results in 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 II patients contain an increased level/activity of OGG1 in mitochondria [170].

6. Guanine as a defense against ROS

6.1. Guanine quadruplexes protect telomere 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 (e.g., histone could be another example). The oxidation of methionine residues, which can be over 50% of surface residues, is without any significant effect, while 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 results 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 with 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 non-transcribing region of the genome might overtake the reactivity of free radicals, providing local protection for histones in order to be able to 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 genetic material [175]. There are 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 (G-quadruplex) [176]. Guanine is the most readily oxidizable base on the DNA helix, and it has been found that 50% more guanines were oxidized in quadruplexes than guanine 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 appears that the G-quadruplexes indeed can serve as a protective shield against oxidants in order 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 G-quadruplexes in order to preserve histone residues from oxidative modification (Figure 1).

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

Protect 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 (rRNA) contains a larger amount of guanine, thus serving as a potential sink for ROS 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 does 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 three-to-five days in post-mitotic 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 the 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 appears 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 levels of 8-oxoG containing RNA [110,188]. It is possible that besides 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 a RNA chaperone to target 8-oxoG containing RNA for degradation [189]. Interventions like long-term caloric restriction or physical exercise were also shown to decrease RNA levels 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 direct 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 in order to minimize the consequences of oxidative stress (Figure 1).

7. Role of 8-oxoG and OGG1 in transcription

7.1. Role of 8-oxoG in accommodation of transcription initiation complex

For RNA transcription to occur, cells need a mechanism by which they relax chromatin. One of the examples for chromatin relaxation is nicking of DNA by OGG1 at the 8-oxoG lesion in the promoter region. Estrogen exposure of cells increases 8-oxoG levels in DNA and recruits OGG1 and topoisomerase II β (Topo II β) to estrogen-responsive DNA elements (ERE) in the promoter region of 17 β -estradiol (E2)-responsive genes [191–193]. E2-receptor complex binding to chromatin is triggered by demethylation of dimethyl-Lys4 in histone H3 (H3K4me2), and this demethylation by lysin-specific demethylase generates H₂O₂. H₂O₂ 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 II β accumulated preferentially to ERE sites. It has been proposed that removal of the 8-oxoG by OGG1 produces nicks that function as entry points for Topo II β . The DNA strand gap allows Topo II β -mediated relaxation of the DNA strands and allows chromatin bending to accommodate the transcription initiation complex. Estrogen receptor alpha 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 II β to the promoter. These observations are pioneering to show that 8-oxoG generation might be regarded differently, than genuine, mutagenic DNA base damage.

7.2. 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 yeast SWI/SNF (SWItch/Sucrose NonFermentable) the chromatin remodeling protein complex controls these regulations [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 co-workers

[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 effect 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 SWI/SNF complex significantly facilitated the removal of 8-oxoG by BER (but not NER processes) in conventional but not in H2A.Bbd nucleosomes [196], thereby remodeling facilitated BER on a conventional template, which might be important for the efficient repair of lesions. Co-localization of OGG1 with mitotic chromosomes resembles those of several other nuclear proteins: the SWI/SNF-like protein ATRX (alpha thalassemia/mental retardation syndrome X-linked), the heterochromatin-binding protein 1 and DNA topoisomerase II alpha [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 nucleosomal fragmentation and formation of apoptotic nuclear bodies. Topoisomerase I (Top 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, Top 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 Top I cleavage complex (Top Icc, an 80-kDa C-terminal fragment of Top I, generated by caspase-3) is trapped at the proximity of oxidative 8-oxoG DNA lesion generated by TRAIL-induced ROS. Importantly, this phenomenon may be general, as the ROS-dependent formation of 8-oxoG appears to represent a common mechanism for the trapping of Top Icc during apoptosis induced by arsenic trioxide and chemotherapeutic agents, including staurosporine and etoposide [200–202].

7.3. 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 inhibited 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 non-transcribed 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 protein [207]. Together these data show that physiological levels of 8-oxoG seems not to endanger transcription. In fact, when 8-oxoG is in the promoter, it mediates DNA helix relaxation and allows gene transcription (rev in 7.1).

8. Conclusion

One the oxidation product of guanine 8-oxoG is the most abundant DNA base lesion. As a base, 8-oxoG is excised from DNA double helix primarily by OGG1 during the BER pathway. A major fraction of 8-oxoG, however, is not removed from DNA, and it seems that its level at a given condition fits well into the cellular hormesis phenomenon, which is characterized by suboptimal, optimal (or physiological) and supra-optimal levels. Taking

into consideration that extreme 8-oxoG levels did not effect the *ogg1*^{-/-} mice's fertility, development and age, and, in fact, they are resistant to inflammation raises the question as to what are the benign and toxic levels of 8-oxoG. Supra-optimal 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 in inflammatory oxidative stress conditions. In fact, its excision from DNA by OGG1 could lead to, e.g., HD, myotonic dystrophy or its missrepair to malignancies. Although it is controversial, 8-oxoG in the DNA helix does not obstruct RNA transcription, has an important role in transcriptional initiation, 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 the normal physiological processes and life of organisms.

Acknowledgments

This work was supported by Hungarian grants: ETT 38388, TT JAP13/02, and OTKA K75702 grants to Z. Radk, and NIH/NIA AG 021830; NIAID AI062885 and NIEHS ES018948 to I. Boldogh.

References

1. Friedberg EC. DNA damage and repair. *Nature*. 2003; 421:436–440. [PubMed: 12540918]
2. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009; 461:1071–1078. [PubMed: 19847258]
3. Mena S, Ortega A, Estrela JM. Oxidative stress in environmental-induced carcinogenesis. *Mutat Res*. 2009; 674:36–44. [PubMed: 18977455]
4. Meek DW. Tumour suppression by p53: a role for the DNA damage response? *Nat Rev Cancer*. 2009; 9:714–723. [PubMed: 19730431]
5. Mitra S, Boldogh I, Izumi T, Hazra TK. Complexities of the DNA base excision repair pathway for repair of oxidative DNA damage. *Environ Mol Mutagen*. 2001; 38:180–190. [PubMed: 11746753]
6. Mitra S, Hazra TK, Roy R, Ikeda S, Biswas T, Lock J, Boldogh I, Izumi T. Complexities of DNA base excision repair in mammalian cells. *Mol Cells*. 1997; 7:305–312. [PubMed: 9264015]
7. Hazra TK, Hill JW, Izumi T, Mitra S. Multiple DNA glycosylases for repair of 8-oxoguanine and their potential in vivo functions. *Prog Nucleic Acid Res Mol Biol*. 2001; 68:193–205. [PubMed: 11554297]
8. Nishimura S. Mammalian OGG1/Mmh gene plays a major role in repair of the 8-hydroxyguanine lesion in DNA. *Prog Nucleic Acid Res Mol Biol*. 2001; 68:107–123. [PubMed: 11554290]
9. David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. *Nature*. 2007; 447:941–950. [PubMed: 17581577]
10. Fortini P, Dogliotti E. Base damage and single-strand break repair: mechanisms and functional significance of short- and long-patch repair subpathways. *DNA Repair (Amst)*. 2007; 6:398–409. [PubMed: 17129767]
11. D'Errico M, Parlanti E, Dogliotti E. Mechanism of oxidative DNA damage repair and relevance to human pathology. *Mutat Res*. 2008; 659:4–14. [PubMed: 18083609]
12. Boveris A, Chance B. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochem J*. 1973; 134:707–716. [PubMed: 4749271]
13. Brand MD. The efficiency and plasticity of mitochondrial energy transduction. *Biochem Soc Trans*. 2005; 33:897–904. [PubMed: 16246006]
14. Calabrese V, Cornelius C, Mancuso C, Lentile R, Stella AM, Butterfield DA. Redox homeostasis and cellular stress response in aging and neurodegeneration. *Methods Mol Biol*. 2010; 610:285–308. [PubMed: 20013185]
15. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med*. 2010; 48:749–762. [PubMed: 20045723]

16. Hernandez-Garcia D, Wood CD, Castro-Obregon S, Covarrubias L. Reactive oxygen species: A radical role in development? *Free Radic Biol Med*. 2010
17. Powers SK, Duarte J, Kavazis AN, Talbert, E. E. Reactive oxygen species are signalling molecules for skeletal muscle adaptation. *Exp Physiol*. 2010; 95:1–9. [PubMed: 19880534]
18. Sohal RS, Mockett RJ, Orr WC. Mechanisms of aging: an appraisal of the oxidative stress hypothesis. *Free Radic Biol Med*. 2002; 33:575–586. [PubMed: 12208343]
19. Cortopassi GA, Wong A. Mitochondria in organismal aging and degeneration. *Biochim Biophys Acta*. 1999; 1410:183–193. [PubMed: 10076026]
20. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol*. 1956; 11:298–300. [PubMed: 13332224]
21. Harman D. The biologic clock: the mitochondria? *J Am Geriatr Soc*. 1972; 20:145–147. [PubMed: 5016631]
22. Miquel J, Economos AC, Fleming J, Johnson JE Jr. Mitochondrial role in cell aging. *Exp Gerontol*. 1980; 15:575–591. [PubMed: 7009178]
23. Van Remmen H, Richardson A. Oxidative damage to mitochondria and aging. *Exp Gerontol*. 2001; 36:957–968. [PubMed: 11404044]
24. Beckman KB, Ames BN. Mitochondrial aging: open questions. *Ann N Y Acad Sci*. 1998; 854:118–127. [PubMed: 9928425]
25. Beckman KB, Ames BN. Detection and quantification of oxidative adducts of mitochondrial DNA. *Methods Enzymol*. 1996; 264:442–453. [PubMed: 8965717]
26. Golden TR, Melov S. Mitochondrial DNA mutations, oxidative stress, and aging. *Mech Ageing Dev*. 2001; 122:1577–1589. [PubMed: 11511398]
27. Osiewacz HD. Mitochondrial functions and aging. *Gene*. 2002; 286:65–71. [PubMed: 11943461]
28. Perez-Campo R, Lopez-Torres M, Cadenas S, Rojas C, Barja G. The rate of free radical production as a determinant of the rate of aging: evidence from the comparative approach. *J Comp Physiol B*. 1998; 168:149–158. [PubMed: 9591361]
29. Sastre J, Pallardo FV, Vina J. Mitochondrial oxidative stress plays a key role in aging and apoptosis. *IUBMB Life*. 2000; 49:427–435. [PubMed: 10902575]
30. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A*. 1994; 91:10771–10778. [PubMed: 7971961]
31. Sohal RS, Sohal BH. Hydrogen peroxide release by mitochondria increases during aging. *Mech Ageing Dev*. 1991; 57:187–202. [PubMed: 1904965]
32. Sohal RS, Sohal BH, Orr WC. Mitochondrial superoxide and hydrogen peroxide generation, protein oxidative damage, and longevity in different species of flies. *Free Radic Biol Med*. 1995; 19:499–504. [PubMed: 7590400]
33. Houthoofd K, Braeckman BP, Lenaerts I, Brys K, De Vreese A, Van Eygen S, Vanfleteren JR. No reduction of metabolic rate in food restricted *Caenorhabditis elegans*. *Exp Gerontol*. 2002; 37:1359–1369. [PubMed: 12559405]
34. Johnson TE, Henderson S, Murakami S, de Castro E, de Castro SH, Cypser J, Rikke B, Tedesco P, Link C. Longevity genes in the nematode *Caenorhabditis elegans* also mediate increased resistance to stress and prevent disease. *J Inherit Metab Dis*. 2002; 25:197–206. [PubMed: 12137228]
35. Kharade SV, Mittal N, Das SP, Sinha P, Roy N. Mrg19 depletion increases *S. cerevisiae* lifespan by augmenting ROS defence. *FEBS Lett*. 2005; 579:6809–6813. [PubMed: 16336970]
36. Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev*. 2005; 126:987–1002. [PubMed: 15893363]
37. Vanfleteren JR. Oxidative stress and ageing in *Caenorhabditis elegans*. *Biochem J*. 1993; 292(Pt 2):605–608. [PubMed: 8389142]
38. Zarse K, Schulz TJ, Birringer M, Ristow M. Impaired respiration is positively correlated with decreased life span in *Caenorhabditis elegans* models of Friedreich Ataxia. *FASEB J*. 2007; 21:1271–1275. [PubMed: 17215485]
39. Ristow M, Zarse K. How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). *Exp Gerontol*. 2010

40. Lindsted KD, Tonstad S, Kuzma JW. Self-report of physical activity and patterns of mortality in Seventh-Day Adventist men. *J Clin Epidemiol*. 1991; 44:355–364. [PubMed: 2010779]
41. Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, Tyllavsky F, Bauer DC, Goodpaster BH, Harris TB. Daily activity energy expenditure and mortality among older adults. *JAMA*. 2006; 296:171–179. [PubMed: 16835422]
42. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. 2007; 297:842–857. [PubMed: 17327526]
43. Radak Z, Chung HY, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology*. 2005; 6:71–75. [PubMed: 15834665]
44. Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M. Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. *Cell Metab*. 2007; 6:280–293. [PubMed: 17908557]
45. Honda Y, Tanaka M, Honda S. Modulation of longevity and diapause by redox regulation mechanisms under the insulin-like signaling control in *Caenorhabditis elegans*. *Exp Gerontol*. 2008; 43:520–529. [PubMed: 18406553]
46. Jang YC, Remmen VH. The mitochondrial theory of aging: insight from transgenic and knockout mouse models. *Exp Gerontol*. 2009; 44:256–260. [PubMed: 19171187]
47. Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. Trends in oxidative aging theories. *Free Radic Biol Med*. 2007; 43:477–503. [PubMed: 17640558]
48. Mao G, Pan X, Zhu BB, Zhang Y, Yuan F, Huang J, Lovell MA, Lee MP, Markesbery WR, Li GM, Gu L. Identification and characterization of OGG1 mutations in patients with Alzheimer's disease. *Nucleic Acids Res*. 2007; 35:2759–2766. [PubMed: 17426120]
49. Shao C, Xiong S, Li GM, Gu L, Mao G, Markesbery WR, Lovell MA. Altered 8-oxoguanine glycosylase in mild cognitive impairment and late-stage Alzheimer's disease brain. *Free Radic Biol Med*. 2008; 45:813–819. [PubMed: 18598755]
50. Wada A, Suyama A. Local stability of DNA and RNA secondary structure and its relation to biological functions. *Prog Biophys Mol Biol*. 1986; 47:113–157. [PubMed: 2424044]
51. Galtier N, Lobry JR. Relationships between genomic G+C content, RNA secondary structures, and optimal growth temperature in prokaryotes. *J Mol Evol*. 1997; 44:632–636. [PubMed: 9169555]
52. Hurst LD, Merchant AR. High guanine-cytosine content is not an adaptation to high temperature: a comparative analysis amongst prokaryotes. *Proc Biol Sci*. 2001; 268:493–497. [PubMed: 11296861]
53. Singer CE, Ames BN. Sunlight ultraviolet and bacterial DNA base ratios. *Science*. 1970; 170:822–825. [PubMed: 5473414]
54. Naya H, Romero H, Zavala A, Alvarez B, Musto H. Aerobiosis increases the genomic guanine plus cytosine content (GC%) in prokaryotes. *J Mol Evol*. 2002; 55:260–264. [PubMed: 12187379]
55. Romero H, Pereira E, Naya H, Musto H. Oxygen and guanine-cytosine profiles in marine environments. *J Mol Evol*. 2009; 69:203–206. [PubMed: 19554248]
56. Sueoka N. On the genetic basis of variation and heterogeneity of DNA base composition. *Proc Natl Acad Sci U S A*. 1962; 48:582–592. [PubMed: 13918161]
57. Sharma R, Nakamura A, Takahashi R, Nakamoto H, Goto S. Carbonyl modification in rat liver histones: decrease with age and increase by dietary restriction. *Free Radic Biol Med*. 2006; 40:1179–1184. [PubMed: 16545685]
58. Steenken S, Jovanovic SV. How Easily Oxidizable Is DNA? One-Electron Reduction Potentials of Adenosine and Guanosine Radicals in Aqueous Solution. *Journal of the American Chemical Society*. 1997; 119:617–618.
59. Burrows CJ, Muller JG. Oxidative Nucleobase Modifications Leading to Strand Scission. *Chem Rev*. 1998; 98:1109–1152. [PubMed: 11848927]
60. Candeias LP, Steenken S. Reaction of HO* with guanine derivatives in aqueous solution: formation of two different redox-active OH-adduct radicals and their unimolecular transformation reactions. Properties of G(-H)*. *Chemistry*. 2000; 6:475–484. [PubMed: 10747414]
61. Hall DB, Holmlin RE, Barton JK. Oxidative DNA damage through long-range electron transfer. *Nature*. 1996; 382:731–735. [PubMed: 8751447]

62. Margolin Y, Cloutier JF, Shafirovich V, Geacintov NE, Dedon PC. Paradoxical hotspots for guanine oxidation by a chemical mediator of inflammation. *Nat Chem Biol.* 2006; 2:365–366. [PubMed: 16751762]
63. Luo W, Muller JG, Rachlin EM, Burrows CJ. Characterization of hydantoin products from one-electron oxidation of 8-oxo-7,8-dihydroguanosine in a nucleoside model. *Chem Res Toxicol.* 2001; 14:927–938. [PubMed: 11453741]
64. Niles JC, Wishnok JS, Tannenbaum SR. Mass spectrometric identification of 4-hydroxy-2,5-dioxoimidazolidine-4-carboxylic acid during oxidation of 8-oxoguanosine by peroxynitrite and KHSO₅/CoCl₂. *Chem Res Toxicol.* 2004; 17:1501–1509. [PubMed: 15540948]
65. Jaruga P, Kirkali G, Dizdaroglu M. Measurement of formamidopyrimidines in DNA. *Free Radic Biol Med.* 2008; 45:1601–1609. [PubMed: 18926902]
66. Niles JC, Wishnok JS, Tannenbaum SR. Spiroiminodihydantoin and guanidinohydantoin are the dominant products of 8-oxoguanosine oxidation at low fluxes of peroxynitrite: mechanistic studies with 18O. *Chem Res Toxicol.* 2004; 17:1510–1519. [PubMed: 15540949]
67. Nishimura S. Involvement of mammalian OGG1(MMH) in excision of the 8-hydroxyguanine residue in DNA. *Free Radic Biol Med.* 2002; 32:813–821. [PubMed: 11978483]
68. Nakamoto H, Kaneko T, Tahara S, Hayashi E, Naito H, Radak Z, Goto S. Regular exercise reduces 8-oxodG in the nuclear and mitochondrial DNA and modulates the DNA repair activity in the liver of old rats. *Exp Gerontol.* 2007; 42:287–295. [PubMed: 17204389]
69. Lindahl T. Instability and decay of the primary structure of DNA. *Nature.* 1993; 362:709–715. [PubMed: 8469282]
70. Roots R, Okada S. Estimation of life times and diffusion distances of radicals involved in x-ray-induced DNA strand breaks of killing of mammalian cells. *Radiat Res.* 1975; 64:306–320. [PubMed: 1197641]
71. Dolle ME, Snyder WK, Gossen JA, Lohman PH, Vijg J. Distinct spectra of somatic mutations accumulated with age in mouse heart and small intestine. *Proc Natl Acad Sci U S A.* 2000; 97:8403–8408. [PubMed: 10900004]
72. Izzotti A, Cartiglia C, Taningher M, De Flora S, Balansky R. Age-related increases of 8-hydroxy-2'-deoxyguanosine and DNA-protein crosslinks in mouse organs. *Mutat Res.* 1999; 446:215–223. [PubMed: 10635344]
73. Khrapko K, Collier HA, Andre PC, Li XC, Hanekamp JS, Thilly WG. Mitochondrial mutational spectra in human cells and tissues. *Proc Natl Acad Sci U S A.* 1997; 94:13798–13803. [PubMed: 9391107]
74. Lieber MR, Karanjawala ZE. Ageing, repetitive genomes and DNA damage. *Nat Rev Mol Cell Biol.* 2004; 5:69–75. [PubMed: 14708011]
75. Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, Yankner BA. Gene regulation and DNA damage in the ageing human brain. *Nature.* 2004; 429:883–891. [PubMed: 15190254]
76. Siomek A, Gackowski D, Rozalski R, Dziaman T, Szpila A, Guz J, Olinski R. Higher leukocyte 8-oxo-7,8-dihydro-2'-deoxyguanosine and lower plasma ascorbate in aging humans? *Antioxid Redox Signal.* 2007; 9:143–150. [PubMed: 17115893]
77. Dherin C, Radicella JP, Dizdaroglu M, Boiteux S. Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations. *Nucleic Acids Res.* 1999; 27:4001–4007. [PubMed: 10497264]
78. Audebert M, Radicella JP, Dizdaroglu M. Effect of single mutations in the OGG1 gene found in human tumors on the substrate specificity of the Ogg1 protein. *Nucleic Acids Res.* 2000; 28:2672–2678. [PubMed: 10908322]
79. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci U S A.* 1993; 90:7915–7922. [PubMed: 8367443]
80. Cortopassi GA. A neutral theory predicts multigenic aging and increased concentrations of deleterious mutations on the mitochondrial and Y chromosomes. *Free Radic Biol Med.* 2002; 33:605–610. [PubMed: 12208346]

81. Hart RW, Setlow RB. Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species. *Proc Natl Acad Sci U S A*. 1974; 71:2169–2173. [PubMed: 4526202]
82. Kaneko T, Tahara S, Matsuo M. Non-linear accumulation of 8-hydroxy-2'-deoxyguanosine, a marker of oxidized DNA damage, during aging. *Mutat Res*. 1996; 316:277–285. [PubMed: 8649461]
83. Cappelli E, Degan P, Frosina G. Comparative repair of the endogenous lesions 8-oxo-7, 8-dihydroguanine (8-oxoG), uracil and abasic site by mammalian cell extracts: 8-oxoG is poorly repaired by human cell extracts. *Carcinogenesis*. 2000; 21:1135–1141. [PubMed: 10837001]
84. Chen SK, Hsieh WA, Tsai MH, Chen CC, Hong AI, Wei YH, Chang WP. Age-associated decrease of oxidative repair enzymes, human 8-oxoguanine DNA glycosylases (hOgg1), in human aging. *J Radiat Res (Tokyo)*. 2003; 44:31–35. [PubMed: 12841596]
85. Yamaguchi R, Hirano T, Ootsuyama Y, Asami S, Tsurudome Y, Fukada S, Yamato H, Tsuda T, Tanaka I, Kasai H. Increased 8-hydroxyguanine in DNA and its repair activity in hamster and rat lung after intratracheal instillation of crocidolite asbestos. *Jpn J Cancer Res*. 1999; 90:505–509. [PubMed: 10391089]
86. Koltai E, Szabo Z, Atalay M, Boldogh I, Naito H, Goto S, Nyakas C, Radak Z. Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. *Mech Ageing Dev*. 2010; 131:21–28. [PubMed: 19913571]
87. Szczesny B, Bhakat KK, Mitra S, Boldogh I. Age-dependent modulation of DNA repair enzymes by covalent modification and subcellular distribution. *Mech Ageing Dev*. 2004; 125:755–765. [PubMed: 15541770]
88. Szczesny B, Hazra TK, Papaconstantinou J, Mitra S, Boldogh I. Age-dependent deficiency in import of mitochondrial DNA glycosylases required for repair of oxidatively damaged bases. *Proc Natl Acad Sci U S A*. 2003; 100:10670–10675. [PubMed: 12960370]
89. Bravard A, Vacher M, Gouget B, Coutant A, de Boisferon FH, Marsin S, Chevillard S, Radicella JP. Redox regulation of human OGG1 activity in response to cellular oxidative stress. *Mol Cell Biol*. 2006; 26:7430–7436. [PubMed: 16923968]
90. Jaiswal M, LaRusso NF, Nishioka N, Nakabeppu Y, Gores GJ. Human Ogg1, a protein involved in the repair of 8-oxoguanine, is inhibited by nitric oxide. *Cancer Res*. 2001; 61:6388–6393. [PubMed: 11522631]
91. Bhakat KK, Hazra TK, Mitra S. Acetylation of the human DNA glycosylase NEIL2 and inhibition of its activity. *Nucleic Acids Res*. 2004; 32:3033–3039. [PubMed: 15175427]
92. Chattopadhyay R, Wiederhold L, Szczesny B, Boldogh I, Hazra TK, Izumi T, Mitra S. Identification and characterization of mitochondrial abasic (AP)-endonuclease in mammalian cells. *Nucleic Acids Res*. 2006; 34:2067–2076. [PubMed: 16617147]
93. Hill JW, Hazra TK, Izumi T, Mitra S. Stimulation of human 8-oxoguanine-DNA glycosylase by AP-endonuclease: potential coordination of the initial steps in base excision repair. *Nucleic Acids Res*. 2001; 29:430–438. [PubMed: 11139613]
94. Bacsí A, Chodaczek G, Hazra TK, Konkel D, Boldogh I. Increased ROS generation in subsets of OGG1 knockout fibroblast cells. *Mech Ageing Dev*. 2007; 128:637–649. [PubMed: 18006041]
95. von Sonntag C. The chemistry of free-radical-mediated DNA damage. *Basic Life Sci*. 1991; 58:287–317. discussion 317–221. [PubMed: 1811474]
96. von Sonntag C. Radiation chemistry in the 1990s: pressing questions relating to the areas of radiation biology and environmental research. *Int J Radiat Biol*. 1994; 65:19–26. [PubMed: 7905905]
97. Kennedy LJ, Moore K Jr, Caulfield JL, Tannenbaum SR, Dedon PC. Quantitation of 8-oxoguanine and strand breaks produced by four oxidizing agents. *Chem Res Toxicol*. 1997; 10:386–392. [PubMed: 9114974]
98. Maisin JR, Gerber GB, Vankerkom J, Wambersie A. Survival and diseases in C57BL mice exposed to X rays or 3.1 MeV neutrons at an age of 7 or 21 days. *Radiat Res*. 1996; 146:453–460. [PubMed: 8927717]
99. Sasaki MS, Ejima Y, Tachibana A, Yamada T, Ishizaki K, Shimizu T, Nomura T. DNA damage response pathway in radioadaptive response. *Mutat Res*. 2002; 504:101–118. [PubMed: 12106651]

100. Ramana CV, Boldogh I, Izumi T, Mitra S. Activation of apurinic/aprimidinic endonuclease in human cells by reactive oxygen species and its correlation with their adaptive response to genotoxicity of free radicals. *Proc Natl Acad Sci U S A*. 1998; 95:5061–5066. [PubMed: 9560228]
101. Coleman MA, Yin E, Peterson LE, Nelson D, Sorensen K, Tucker JD, Wyrobek AJ. Low-dose irradiation alters the transcript profiles of human lymphoblastoid cells including genes associated with cytogenetic radioadaptive response. *Radiat Res*. 2005; 164:369–382. [PubMed: 16187739]
102. Kong Q, Lin CL. Oxidative damage to RNA: mechanisms, consequences, and diseases. *Cell Mol Life Sci*. 2010
103. Li Z, Wu J, Deleo CJ. RNA damage and surveillance under oxidative stress. *IUBMB Life*. 2006; 58:581–588. [PubMed: 17050375]
104. Hayakawa H, Kuwano M, Sekiguchi M. Specific binding of 8-oxoguanine-containing RNA to polynucleotide phosphorylase protein. *Biochemistry*. 2001; 40:9977–9982. [PubMed: 11502194]
105. Hayakawa H, Uchiumi T, Fukuda T, Ashizuka M, Kohno K, Kuwano M, Sekiguchi M. Binding capacity of human YB-1 protein for RNA containing 8-oxoguanine. *Biochemistry*. 2002; 41:12739–12744. [PubMed: 12379116]
106. Thorp HH. The importance of being r: greater oxidative stability of RNA compared with DNA. *Chem Biol*. 2000; 7:R33–R36. [PubMed: 10662699]
107. Hofer T, Badouard C, Bajak E, Ravanat JL, Mattsson A, Cotgreave IA. Hydrogen peroxide causes greater oxidation in cellular RNA than in DNA. *Biol Chem*. 2005; 386:333–337. [PubMed: 15899695]
108. Hofer T, Seo AY, Prudencio M, Leeuwenburgh C. A method to determine RNA and DNA oxidation simultaneously by HPLC-ECD: greater RNA than DNA oxidation in rat liver after doxorubicin administration. *Biol Chem*. 2006; 387:103–111. [PubMed: 16497170]
109. Fiala ES, Conaway CC, Mathis JE. Oxidative DNA and RNA damage in the livers of Sprague-Dawley rats treated with the hepatocarcinogen 2-nitropropane. *Cancer Res*. 1989; 49:5518–5522. [PubMed: 2477143]
110. Shen Z, Wu W, Hazen SL. Activated leukocytes oxidatively damage DNA, RNA, and the nucleotide pool through halide-dependent formation of hydroxyl radical. *Biochemistry*. 2000; 39:5474–5482. [PubMed: 10820020]
111. Martinet W, De Meyer GR, Herman AG, Kockx MM. RNA damage in human atherosclerosis: pathophysiological significance and implications for gene expression studies. *RNA Biol*. 2005; 2:4–7. [PubMed: 17132934]
112. Deutscher MP. Degradation of RNA in bacteria: comparison of mRNA and stable RNA. *Nucleic Acids Res*. 2006; 34:659–666. [PubMed: 16452296]
113. Shan X, Lin CL. Quantification of oxidized RNAs in Alzheimer's disease. *Neurobiol Aging*. 2006; 27:657–662. [PubMed: 15979765]
114. Wu J, Li Z. Human polynucleotide phosphorylase reduces oxidative RNA damage and protects HeLa cell against oxidative stress. *Biochem Biophys Res Commun*. 2008; 372:288–292. [PubMed: 18501193]
115. Hofer T, Marzetti E, Xu J, Seo AY, Gulec S, Knutson MD, Leeuwenburgh C, Dupont-Versteegden EE. Increased iron content and RNA oxidative damage in skeletal muscle with aging and disuse atrophy. *Exp Gerontol*. 2008; 43:563–570. [PubMed: 18395385]
116. Hailer MK, Slade PG, Martin BD, Rosenquist TA, Sugden KD. Recognition of the oxidized lesions spiroiminodihydantoin and guanidinohydantoin in DNA by the mammalian base excision repair glycosylases NEIL1 and NEIL2. *DNA Repair (Amst)*. 2005; 4:41–50. [PubMed: 15533836]
117. Hyun JW, Yoon SH, Yu Y, Han CS, Park JS, Kim HS, Lee SJ, Lee YS, You HJ, Chung MH. Oh8dG induces G1 arrest in a human acute leukemia cell line by upregulating P21 and blocking the RAS to ERK signaling pathway. *Int J Cancer*. 2006; 118:302–309. [PubMed: 16052517]
118. Kim HJ, Yoon SH, Ryu HO, Yoon BH, Choi S, Ye SK, Chung MH. 8-oxo-7,8-dihydroguanosine triphosphate(8-oxoGTP) down-regulates respiratory burst of neutrophils by antagonizing GTP toward Rac, a small GTP binding protein. *Free Radic Res*. 2007; 41:655–662. [PubMed: 17516238]

119. Lee SH, Taek Han S, Choi SW, Sung SY, You HJ, Ye SK, Chung MH. Inhibition of Rac and Rac-linked functions by 8-oxo-2'-deoxyguanosine in murine macrophages. *Free Radic Res.* 2009; 43:78–84. [PubMed: 19358003]
120. Rai P, Onder TT, Young JJ, McFaline JL, Pang B, Dedon PC, Weinberg RA. Continuous elimination of oxidized nucleotides is necessary to prevent rapid onset of cellular senescence. *Proc Natl Acad Sci U S A.* 2009; 106:169–174. [PubMed: 19118192]
121. Asagoshi K, Yamada T, Terato H, Ohyama Y, Monden Y, Arai T, Nishimura S, Aburatani H, Lindahl T, Ide H. Distinct repair activities of human 7,8-dihydro-8-oxoguanine DNA glycosylase and formamidopyrimidine DNA glycosylase for formamidopyrimidine and 7,8-dihydro-8-oxoguanine. *J Biol Chem.* 2000; 275:4956–4964. [PubMed: 10671534]
122. Tchou J, Kasai H, Shibutani S, Chung MH, Laval J, Grollman AP, Nishimura S. 8-oxoguanine (8-hydroxyguanine) DNA glycosylase and its substrate specificity. *Proc Natl Acad Sci U S A.* 1991; 88:4690–4694. [PubMed: 2052552]
123. Boiteux S, Dherin C, Reille F, Apiou F, Dutrillaux B, Radicella JP. Excision repair of 8-hydroxyguanine in mammalian cells: the mouse Ogg1 protein as a model. *Free Radic Res.* 1998; 29:487–497. [PubMed: 10098454]
124. Boiteux S, Radicella JP. The human OGG1 gene: structure, functions, and its implication in the process of carcinogenesis. *Arch Biochem Biophys.* 2000; 377:1–8. [PubMed: 10775435]
125. Hazra TK, Das A, Das S, Choudhury S, Kow YW, Roy R. Oxidative DNA damage repair in mammalian cells: a new perspective. *DNA Repair (Amst).* 2007; 6:470–480. [PubMed: 17116430]
126. Nishioka K, Ohtsubo T, Oda H, Fujiwara T, Kang D, Sugimachi K, Nakabeppu Y. Expression and differential intracellular localization of two major forms of human 8-oxoguanine DNA glycosylase encoded by alternatively spliced OGG1 mRNAs. *Mol Biol Cell.* 1999; 10:1637–1652. [PubMed: 10233168]
127. Zharkov DO, Rosenquist TA, Gerchman SE, Grollman AP. Substrate specificity and reaction mechanism of murine 8-oxoguanine-DNA glycosylase. *J Biol Chem.* 2000; 275:28607–28617. [PubMed: 10884383]
128. Hazra TK, Izumi T, Boldogh I, Imhoff B, Kow YW, Jaruga P, Dizdaroglu M, Mitra S. Identification and characterization of a human DNA glycosylase for repair of modified bases in oxidatively damaged DNA. *Proc Natl Acad Sci U S A.* 2002; 99:3523–3528. [PubMed: 11904416]
129. Bruner SD, Norman DP, Verdine GL. Structural basis for recognition and repair of the endogenous mutagen 8-oxoguanine in DNA. *Nature.* 2000; 403:859–866. [PubMed: 10706276]
130. Qi Y, Spong MC, Nam K, Banerjee A, Jiralerspong S, Karplus M, Verdine GL. Encounter and extrusion of an intrahelical lesion by a DNA repair enzyme. *Nature.* 2009; 462:762–766. [PubMed: 20010681]
131. Boal AK, Yavin E, Lukianova OA, O'Shea VL, David SS, Barton JK. DNA-bound redox activity of DNA repair glycosylases containing [4Fe-4S] clusters. *Biochemistry.* 2005; 44:8397–8407. [PubMed: 15938629]
132. Boon EM, Livingston AL, Chmiel NH, David SS, Barton JK. DNA-mediated charge transport for DNA repair. *Proc Natl Acad Sci U S A.* 2003; 100:12543–12547. [PubMed: 14559969]
133. Lukianova OA, David SS. A role for iron-sulfur clusters in DNA repair. *Curr Opin Chem Biol.* 2005; 9:145–151. [PubMed: 15811798]
134. Yavin E, Stemp ED, O'Shea VL, David SS, Barton JK. Electron trap for DNA-bound repair enzymes: a strategy for DNA-mediated signaling. *Proc Natl Acad Sci U S A.* 2006; 103:3610–3614. [PubMed: 16505354]
135. Ren B, Duan X, Ding H. Redox control of the DNA damage-inducible protein DinG helicase activity via its iron-sulfur cluster. *J Biol Chem.* 2009; 284:4829–4835. [PubMed: 19074432]
136. Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res.* 2000; 60:184–190. [PubMed: 10646872]

137. Jaiswal M, LaRusso NF, Shapiro RA, Billiar TR, Gores GJ. Nitric oxide-mediated inhibition of DNA repair potentiates oxidative DNA damage in cholangiocytes. *Gastroenterology*. 2001; 120:190–199. [PubMed: 11208728]
138. Shimoda R, Nagashima M, Sakamoto M, Yamaguchi N, Hirohashi S, Yokota J, Kasai H. Increased formation of oxidative DNA damage, 8-hydroxydeoxyguanosine, in human livers with chronic hepatitis. *Cancer Res*. 1994; 54:3171–3172. [PubMed: 8205535]
139. Saitoh T, Shinmura K, Yamaguchi S, Tani M, Seki S, Murakami H, Nojima Y, Yokota J. Enhancement of OGG1 protein AP lyase activity by increase of APEX protein. *Mutat Res*. 2001; 486:31–40. [PubMed: 11356334]
140. Hu J, Imam SZ, Hashiguchi K, de Souza-Pinto NC, Bohr VA. Phosphorylation of human oxoguanine DNA glycosylase (alpha-OGG1) modulates its function. *Nucleic Acids Res*. 2005; 33:3271–3282. [PubMed: 15942030]
141. Dantzer F, Luna L, Bjoras M, Seeberg E. Human OGG1 undergoes serine phosphorylation and associates with the nuclear matrix and mitotic chromatin in vivo. *Nucleic Acids Res*. 2002; 30:2349–2357. [PubMed: 12034821]
142. Dantzer F, Luna L, Bjoras M, Seeberg E. Human OGG1 undergoes serine phosphorylation and associates with the nuclear matrix and mitotic chromatin in vivo. *Nucleic Acids Res*. 2002; 30:2349–2357. [PubMed: 12034821]
143. Bhakat KK, Mokkapatil SK, Boldogh I, Hazra TK, Mitra S. Acetylation of human 8-oxoguanine-DNA glycosylase by p300 and its role in 8-oxoguanine repair in vivo. *Mol Cell Biol*. 2006; 26:1654–1665. [PubMed: 16478987]
144. Yang XJ, Ogryzko VV, Nishikawa J, Howard BH, Nakatani Y. A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. *Nature*. 1996; 382:319–324. [PubMed: 8684459]
145. Hasan S, El-Andaloussi N, Hardeland U, Hassa PO, Burki C, Imhof R, Schar P, Hottiger MO. Acetylation regulates the DNA end-trimming activity of DNA polymerase beta. *Mol Cell*. 2002; 10:1213–1222. [PubMed: 12453427]
146. Bhakat KK, Izumi T, Yang SH, Hazra TK, Mitra S. Role of acetylated human AP-endonuclease (APE1/Ref-1) in regulation of the parathyroid hormone gene. *EMBO J*. 2003; 22:6299–6309. [PubMed: 14633989]
147. Imai S, Armstrong CM, Kaerberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature*. 2000; 403:795–800. [PubMed: 10693811]
148. Lombard DB, Schwer B, Alt FW, Mostoslavsky R. SIRT6 in DNA repair, metabolism and ageing. *J Intern Med*. 2008; 263:128–141. [PubMed: 18226091]
149. Hipkiss AR. Energy metabolism, altered proteins, sirtuins and ageing: converging mechanisms? *Biogerontology*. 2008; 9:49–55. [PubMed: 17929190]
150. Radak Z, Chung HY, Goto S. Systemic adaptation to oxidative challenge induced by regular exercise. *Free Radic Biol Med*. 2008; 44:153–159. [PubMed: 18191751]
151. Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev*. 2008; 7:34–42. [PubMed: 17869589]
152. Radak Z, Kumagai S, Nakamoto H, Goto S. 8-Oxoguanosine and uracil repair of nuclear and mitochondrial DNA in red and white skeletal muscle of exercise-trained old rats. *J Appl Physiol*. 2007; 102:1696–1701. [PubMed: 17204574]
153. Radak Z, Naito H, Kaneko T, Tahara S, Nakamoto H, Takahashi R, Cardozo-Pelaez F, Goto S. Exercise training decreases DNA damage and increases DNA repair and resistance against oxidative stress of proteins in aged rat skeletal muscle. *Pflugers Arch*. 2002; 445:273–278. [PubMed: 12457248]
154. Stuart JA, Karahalil B, Hogue BA, Souza-Pinto NC, Bohr VA. Mitochondrial and nuclear DNA base excision repair are affected differently by caloric restriction. *FASEB J*. 2004; 18:595–597. [PubMed: 14734635]
155. Kovtun IV, Liu Y, Bjoras M, Klungland A, Wilson SH, McMurray CT. OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells. *Nature*. 2007; 447:447–452. [PubMed: 17450122]

156. Cummings CJ, Zoghbi HY. Trinucleotide repeats: mechanisms and pathophysiology. *Annu Rev Genomics Hum Genet.* 2000; 1:281–328. [PubMed: 11701632]
157. Mangiarini L, Sathasivam K, Mahal A, Mott R, Seller M, Bates GP. Instability of highly expanded CAG repeats in mice transgenic for the Huntington's disease mutation. *Nat Genet.* 1997; 15:197–200. [PubMed: 9020849]
158. Jarem DA, Wilson NR, Delaney S. Structure-dependent DNA damage and repair in a trinucleotide repeat sequence. *Biochemistry.* 2009; 48:6655–6663. [PubMed: 19527055]
159. Minowa O, Arai T, Hirano M, Monden Y, Nakai S, Fukuda M, Itoh M, Takano H, Hippou Y, Aburatani H, Masumura K, Nohmi T, Nishimura S, Noda T. Mmh/Ogg1 gene inactivation results in accumulation of 8-hydroxyguanine in mice. *Proc Natl Acad Sci U S A.* 2000; 97:4156–4161. [PubMed: 10725358]
160. Klungland A, Rosewell I, Hollenbach S, Larsen E, Daly G, Epe B, Seeberg E, Lindahl T, Barnes DE. Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage. *Proc Natl Acad Sci U S A.* 1999; 96:13300–13305. [PubMed: 10557315]
161. Larsen E, Reite K, Nesse G, Gran C, Seeberg E, Klungland A. Repair and mutagenesis at oxidized DNA lesions in the developing brain of wild-type and Ogg1^{-/-} mice. *Oncogene.* 2006; 25:2425–2432. [PubMed: 16369492]
162. Sakumi K, Tominaga Y, Furuichi M, Xu P, Tsuzuki T, Sekiguchi M, Nakabeppu Y. Ogg1 knockout-associated lung tumorigenesis and its suppression by Mth1 gene disruption. *Cancer Res.* 2003; 63:902–905. [PubMed: 12615700]
163. de Souza-Pinto NC, Eide L, Hogue BA, Thybo T, Stevnsner T, Seeberg E, Klungland A, Bohr VA. Repair of 8-oxodeoxyguanosine lesions in mitochondrial dna depends on the oxoguanine dna glycosylase (OGG1) gene and 8-oxoguanine accumulates in the mitochondrial dna of OGG1-defective mice. *Cancer Res.* 2001; 61:5378–5381. [PubMed: 11454679]
164. Stuart JA, Bourque BM, de Souza-Pinto NC, Bohr VA. No evidence of mitochondrial respiratory dysfunction in OGG1-null mice deficient in removal of 8-oxodeoxyguanine from mitochondrial DNA. *Free Radic Biol Med.* 2005; 38:737–745. [PubMed: 15721984]
165. Arai T, Kelly VP, Minowa O, Noda T, Nishimura S. High accumulation of oxidative DNA damage, 8-hydroxyguanine, in Mmh/Ogg1 deficient mice by chronic oxidative stress. *Carcinogenesis.* 2002; 23:2005–2010. [PubMed: 12507922]
166. Arai T, Kelly VP, Minowa O, Noda T, Nishimura S. The study using wild-type and Ogg1 knockout mice exposed to potassium bromate shows no tumor induction despite an extensive accumulation of 8-hydroxyguanine in kidney DNA. *Toxicology.* 2006; 221:179–186. [PubMed: 16494984]
167. Mabley JG, Pacher P, Deb A, Wallace R, Elder RH, Szabo C. Potential role for 8-oxoguanine DNA glycosylase in regulating inflammation. *FASEB J.* 2005; 19:290–292. [PubMed: 15677345]
168. Touati E, Michel V, Thiberge JM, Ave P, Huerre M, Bourgade F, Klungland A, Labigne A. Deficiency in OGG1 protects against inflammation and mutagenic effects associated with H. pylori infection in mouse. *Helicobacter.* 2006; 11:494–505. [PubMed: 16961812]
169. Touati E, Michel V, Thiberge JM, Wuscher N, Huerre M, Labigne A. Chronic Helicobacter pylori infections induce gastric mutations in mice. *Gastroenterology.* 2003; 124:1408–1419. [PubMed: 12730880]
170. Tyrberg B, Anachkov KA, Dib SA, Wang-Rodriguez J, Yoon KH, Levine F. Islet expression of the DNA repair enzyme 8-oxoguanosine DNA glycosylase (Ogg1) in human type 2 diabetes. *BMC Endocr Disord.* 2002; 2:2. [PubMed: 12003641]
171. Levine RL, Berlett BS, Moskowitz J, Mosoni L, Stadtman ER. Methionine residues may protect proteins from critical oxidative damage. *Mech Ageing Dev.* 1999; 107:323–332. [PubMed: 10360685]
172. Moskovitz J, Oien DB. Protein carbonyl and the methionine sulfoxide reductase system. *Antioxid Redox Signal.* 2010; 12:405–415. [PubMed: 19686038]
173. Mersfelder EL, Parthun MR. The tale beyond the tail: histone core domain modifications and the regulation of chromatin structure. *Nucleic Acids Res.* 2006; 34:2653–2662. [PubMed: 16714444]

174. Wyrick JJ, Parra MA. The role of histone H2A and H2B post-translational modifications in transcription: a genomic perspective. *Biochim Biophys Acta*. 2009; 1789:37–44. [PubMed: 18675384]
175. Hande MP. DNA repair factors and telomere-chromosome integrity in mammalian cells. *Cytogenet Genome Res*. 2004; 104:116–122. [PubMed: 15162024]
176. Lipps HJ, Rhodes D. G-quadruplex structures: in vivo evidence and function. *Trends Cell Biol*. 2009; 19:414–422. [PubMed: 19589679]
177. Delaney S, Barton JK. Charge transport in DNA duplex/quadruplex conjugates. *Biochemistry*. 2003; 42:14159–14165. [PubMed: 14640683]
178. Kawai K, Fujitsuka M, Majima T. Selective guanine oxidation by UVB-irradiation in telomeric DNA. *Chem Commun (Camb)*. 2005:1476–1477. [PubMed: 15756341]
179. Heller A. Spiers Memorial Lecture. On the hypothesis of cathodic protection of genes. *Faraday Discuss*. 2000:1–13. [PubMed: 11197472]
180. Huang YC, Cheng AK, Yu HZ, Sen D. Charge conduction properties of a parallel-stranded DNA G-quadruplex: implications for chromosomal oxidative damage. *Biochemistry*. 2009; 48:6794–6804. [PubMed: 19530739]
181. Garcia-Teran JP, Castillo O, Luque A, Garcia-Couceiro U, Beobide G, Roman P. Supramolecular architectures assembled by the interaction of purine nucleobases with metal-oxalato frameworks. Non-covalent stabilization of the 7H-adenine tautomer in the solid-state. *Dalton Trans*. 2006:902–911. [PubMed: 16462950]
182. Garcia-Teran JP, Castillo O, Luque A, Garcia-Couceiro U, Beobide G, Roman P. Molecular recognition of adeninium cations on anionic metal-oxalato frameworks: an experimental and theoretical analysis. *Inorg Chem*. 2007; 46:3593–3602. [PubMed: 17375914]
183. Weinstein BS, Ciszek D. The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. *Exp Gerontol*. 2002; 37:615–627. [PubMed: 11909679]
184. Wamer WG, Wei RR. In vitro photooxidation of nucleic acids by ultraviolet A radiation. *Photochem Photobiol*. 1997; 65:560–563. [PubMed: 9077142]
185. Loeb JN, Howell RR, Tomkins GM. Turnover of ribosomal RNA in rat liver. *Science*. 1965; 149:1093–1095. [PubMed: 5826520]
186. Hayakawa H, Sekiguchi M. Human polynucleotide phosphorylase protein in response to oxidative stress. *Biochemistry*. 2006; 45:6749–6755. [PubMed: 16716086]
187. Tanaka M, Chock PB, Stadtman ER. Oxidized messenger RNA induces translation errors. *Proc Natl Acad Sci U S A*. 2007; 104:66–71. [PubMed: 17190801]
188. Aas PA, Otterlei M, Falnes PO, Vagbo CB, Skorpen F, Akbari M, Sundheim O, Bjoras M, Slupphaug G, Seeberg E, Krokan HE. Human and bacterial oxidative demethylases repair alkylation damage in both RNA and DNA. *Nature*. 2003; 421:859–863. [PubMed: 12594517]
189. Skabkin MA, Evdokimova V, Thomas AA, Ovchinnikov LP. The major messenger ribonucleoprotein particle protein p50 (YB-1) promotes nucleic acid strand annealing. *J Biol Chem*. 2001; 276:44841–44847. [PubMed: 11585833]
190. Hofer T, Fontana L, Anton SD, Weiss EP, Villareal D, Malayappan V, Leeuwenburgh C. Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. *Rejuvenation Res*. 2008; 11:793–799. [PubMed: 18729811]
191. Perillo B, Ombra MN, Bertoni A, Cuzzo C, Sacchetti S, Sasso A, Chiariotti L, Malorni A, Abbondanza C, Avvedimento EV. DNA oxidation as triggered by H3K9me2 demethylation drives estrogen-induced gene expression. *Science*. 2008; 319:202–206. [PubMed: 18187655]
192. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. *Cell*. 1995; 83:835–839. [PubMed: 8521507]
193. Shang Y, Hu X, DiRenzo J, Lazar MA, Brown M. Cofactor dynamics and sufficiency in estrogen receptor-regulated transcription. *Cell*. 2000; 103:843–852. [PubMed: 11136970]
194. Winston F, Carlson M. Yeast SNF/SWI transcriptional activators and the SPT/SIN chromatin connection. *Trends Genet*. 1992; 8:387–391. [PubMed: 1332230]

195. Chadwick BP, Willard HF. A novel chromatin protein, distantly related to histone H2A, is largely excluded from the inactive X chromosome. *J Cell Biol.* 2001; 152:375–384. [PubMed: 11266453]
196. Menoni H, Gasparutto D, Hamiche A, Cadet J, Dimitrov S, Bouvet P, Angelov D. ATP-dependent chromatin remodeling is required for base excision repair in conventional but not in variant H2A.Bbd nucleosomes. *Mol Cell Biol.* 2007; 27:5949–5956. [PubMed: 17591702]
197. Krebs JE, Fry CJ, Samuels ML, Peterson CL. Global role for chromatin remodeling enzymes in mitotic gene expression. *Cell.* 2000; 102:587–598. [PubMed: 11007477]
198. Morham SG, Kluckman KD, Voulomanos N, Smithies O. Targeted disruption of the mouse topoisomerase I gene by camptothecin selection. *Mol Cell Biol.* 1996; 16:6804–6809. [PubMed: 8943335]
199. Sordet O, Goldman A, Redon C, Solier S, Rao VA, Pommier Y. Topoisomerase I requirement for death receptor-induced apoptotic nuclear fission. *J Biol Chem.* 2008; 283:23200–23208. [PubMed: 18556653]
200. Li TK, Liu LF. Tumor cell death induced by topoisomerase-targeting drugs. *Annu Rev Pharmacol Toxicol.* 2001; 41:53–77. [PubMed: 11264450]
201. Sordet O, Goldman A, Pommier Y. Topoisomerase II and tubulin inhibitors both induce the formation of apoptotic topoisomerase I cleavage complexes. *Mol Cancer Ther.* 2006; 5:3139–3144. [PubMed: 17172417]
202. Sordet O, Khan QA, Plo I, Pourquier P, Urasaki Y, Yoshida A, Antony S, Kohlhaagen G, Solary E, Saparbaev M, Laval J, Pommier Y. Apoptotic topoisomerase I-DNA complexes induced by staurosporine-mediated oxygen radicals. *J Biol Chem.* 2004; 279:50499–50504. [PubMed: 15448130]
203. Doetsch PW. Translesion synthesis by RNA polymerases: occurrence and biological implications for transcriptional mutagenesis. *Mutat Res.* 2002; 510:131–140. [PubMed: 12459449]
204. Chang J, Taylor J. In vivo RNA-directed transcription, with template switching, by a mammalian RNA polymerase. *EMBO J.* 2002; 21:157–164. [PubMed: 11782435]
205. Marietta C, Brooks PJ. Transcriptional bypass of bulky DNA lesions causes new mutant RNA transcripts in human cells. *EMBO Rep.* 2007; 8:388–393. [PubMed: 17363972]
206. Tornaletti S, Maeda LS, Kolodner RD, Hanawalt PC. Effect of 8-oxoguanine on transcription elongation by T7 RNA polymerase and mammalian RNA polymerase II. *DNA Repair (Amst).* 2004; 3:483–494. [PubMed: 15084310]
207. Khobta A, Kitsera N, Speckmann B, Epe B. 8-Oxoguanine DNA glycosylase (Ogg1) causes a transcriptional inactivation of damaged DNA in the absence of functional Cockayne syndrome B (Csb) protein. *DNA Repair (Amst).* 2009; 8:309–317. [PubMed: 19061977]
208. Kuraoka I, Suzuki K, Ito S, Hayashida M, Kwei JS, Ikegami T, Handa H, Nakabeppu Y, Tanaka K. RNA polymerase II bypasses 8-oxoguanine in the presence of transcription elongation factor TFIIS. *DNA Repair (Amst).* 2007; 6:841–851. [PubMed: 17374514]
209. Charlet-Berguerand N, Feuerhahn S, Kong SE, Ziserman H, Conaway JW, Conaway R, Egly JM. RNA polymerase II bypass of oxidative DNA damage is regulated by transcription elongation factors. *EMBO J.* 2006; 25:5481–5491. [PubMed: 17110932]

Figure 1. A hypothetical role of oxidized guanines in cellular processes

Oxidation of guanine in the DNA helix could result in the replacement of cytosine by thymine, and this could cause a mutation (arrow 1). Due to its low redox potential guanine attracts reactive species; in the telomere quadruplexes and RNA it could thus be a potential buffer in preventing further oxidative damage to DNA helix-located guanines (arrow 2). Moderate levels of guanine oxidation could be important to an open chromatin structure, which is an obligatory process for transcription (arrow 3).