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A New Perspective on Oxidation of DNA Repair Proteins and Cancer

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Abstract

Reactive oxygen and nitrogen species (RONS) are formed as byproducts of many endogenous cellular processes, in response to infections, and upon exposure to various environmental factors. An increase in RONS can saturate the antioxidation system and leads to oxidative stress. Consequently, macromolecules are targeted for oxidative modifications, including DNA and protein. The oxidation of DNA, which leads to base modification and formation of abasic sites along with single and double strand breaks, has been extensively investigated. Protein oxidation is often neglected and is only recently being recognized as an important regulatory mechanism of various DNA repair proteins. This is a review of the current state of research on the regulation of DNA repair by protein oxidation with emphasis on the correlation between inflammation and cancer.

Keywords

Oxidative stress; DNA damage; oxidation of DNA repair proteins; double strand break repair; base excision repair

1. Introduction

Balanced reduction and oxidation reactions (redox), which are mediated by reactive oxygen and nitrogen species (RONS), are important to maintain cellular homeostasis as they play a key role in cell signaling [1-3]. About 10^9 RONS are produced per cell per hour as a result of oxidative phosphorylation, NADPH oxidation, histone demethylation, along with other reactions [4-7]. In addition, environmental factors, such as ultraviolet light (UV) and pesticides, along with other toxins, lead to RONS production [8, 9]. RONS act as secondary messengers in various physiological processes including vasodilation, thrombosis, neuronal activity, transcription activation, and also in response to pathogens (e.g. macrophages release

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nitric oxide for the defense against pathogens) [10-15]. It is essential to tightly regulate RONS levels in order to maintain cellular integrity and prevent macromolecular damage. This is achieved by a number of functionally redundant radical scavengers such as peroxiredoxins, glutathione and peroxidases [16-18]. Glutathione is the most abundant oxygen radical scavenger in the cell (0.1-10 mM), localized mainly in the cytosol (90%), with a small percentage in the nucleus [19, 20]. Additionally, superoxide dismutase converts superoxide into hydrogen peroxide, which is converted into water by catalase [21]. RONS scavengers are reversibly oxidized to maintain cells under reducing conditions, which prevents nonspecific protein modifications [22]. Elevated levels of RONS can saturate the antioxidant machinery, leading to oxidative stress [23, 24]. For example, as a result of the inflammatory response to pathogens, RONS are produced by NADPH oxidase and nitric oxide synthase, leading to oxidative stress [25-30]. Inflammation and oxidative stress are both hallmarks for cancer, which is a disease of genomic instability [31-34]. Thus, the relationship between genomic instability, inflammation, and oxidative stress in cancer merits a deeper appreciation [35]. Specifically, inflammation is correlated with cancer progression and has been shown to increase the incidence of cancer, contributing to 25% of cancer cases [34-36]. Moreover, in response to pathogens, macrophages and neutrophils release cytokines and RONS, leading to damage of both DNA and the repair proteins, which results in genomic instability (Figure 1) [37]. Additionally, the cytokine TNFα is a driver of inflammation and is produced at high levels in tumors, leading to oxidative stress and subsequently genomic instability [38-40]. Therefore, activation of the inflammatory response increases the risk of oxidation of DNA and proteins, which increases the risk for cancer (Figure 1) [25, 34, 35, 41].

DNA is an unstable molecule, making it susceptible to damage with about 20,000-70,000 lesions forming per cell per day under physiological conditions [42-44]. Oxidation is the most predominant type of DNA damage with more than 100 different oxidized lesions identified [44-46]. The most abundant type of oxidized lesion is 8-oxoguanine [47]. Cancer cells accumulate 8-oxoguanine at a frequency of 10^5 per cell per day [44, 48]. To prevent the accumulation of damaged DNA, various repair pathways are utilized in the cell to target specific lesion types [43, 49-53]. Thus, a deficiency in DNA repair leads to a mutator phenotype and to genomic instability [33, 54].

In addition to damaging DNA, oxidative stress can target proteins, specifically DNA repair proteins, which may further regulate levels of DNA damage [55-58]. Under oxidative stress, cysteine residues (Cys) are targeted for modification because of the oxidizable sulfhydryl group [57, 59]. Protein oxidation has been shown to act as a post-translational modification, which regulates protein structure and function, allowing cells to adapt to the environment by activating or inhibiting different cellular functions [60, 61]. Oxidation has also been proposed to diversify many protein functions by two orders of magnitude [62-64]. Alternatively, oxidative modification can cause nonspecific and irreversible damage to the protein's function [65]. Though protein oxidation is an important regulatory mechanism, it is often overlooked that proteins involved in the recognition and repair of DNA damage can also be modified. Oxidation of DNA repair proteins by RONS can act as a specific regulatory mechanism of protein structure and function (activation vs inhibition) [66, 67]. Oxidative modification can also act to select a DNA repair pathway [5, 68, 69].

Alternatively, oxidation can lead to nonspecific inactivation of DNA repair [70]. Thus, modulating DNA repair by oxidative modification can amplify or attenuate the effect of RONS on DNA damage. As a consequence of DNA repair inhibition, DNA lesions accumulate, leading to genomic instability and cancer [44]. Alternatively, activating repair proteins leads to efficient DNA repair, and potentially resistance to chemo- and radiotherapy (Figure 1) [71, 72].

This review focuses on the effect of oxidation on the activity of DNA repair proteins involved in the repair of double strand breaks (DSBs) and base damage (Table 1) and how oxidation may contribute to genomic instability and lead to cancer. It is important to understand the effect of oxidative stress on DNA repair in order to design therapeutic targets for cancer treatment and to understand the resistance of certain cancers to chemo- and radiotherapy.

2. Repair of double strand breaks

DSBs occur from exposure to ionizing radiation and also from collapsed replication forks that encounter damage [87]. The inability of cells to repair DSBs induces cell death [88-90]. Additionally, inaccurate repair leads to the formation of chromosomal translocations, deletions, and mutations, which can result in genomic instability [33, 91]. DSBs are mainly repaired by two pathways, homology directed repair (HDR) or nonhomologous end joining (NHEJ) [92]. HDR occurs during the G2 and S phases of the cell cycle and requires a sister chromatid for accurate repair [93]. On the other hand, NHEJ occurs during the G1 phase of the cell cycle and allows the rejoining of DNA ends, which can produce deletions and insertions [94]. Various members of these repair pathways are prone to oxidation (Figure 2, Table 1), which results in either regulating specific activities, inhibiting repair, or coordinating the selection of DNA repair pathway. For example, in the presence of hydrogen peroxide and DNA breaks, NHEJ is reduced and HDR is induced [68]. Therefore, it is important to understand the effect of oxidative stress on proteins involved in the repair of DSBs (Figure 2).

2.1. ATM

Ataxia-telangiectasia mutated protein kinase (ATM) is a member of the PI3K-like protein kinase family [95]. It is a 350 kDa protein with 3,056 amino acids (89 Cys). ATM is activated in the presence of damage by the Mre11-Rad50-Nbs1 (MRN) complex, which further activates the repair of DSBs [96]. In the presence of DSBs, ATM is converted into the active monomer from the inactive homodimer in an MRN-dependent manner [97]. The kinase domain of ATM is located in the C-terminus and functions as a serine/threonine kinase [98]. Autophosphorylation of ATM triggers the recruitment and activation of a myriad of DNA repair proteins including p53 and Chk2, which are important for regulating the cell cycle [95, 97, 99-102]. Loss of a functional ATM is correlated with genomic instability and with ataxia-telangiectasia (A-T) syndrome [103]. Patients with this syndrome also exhibit high levels of oxidative stress [104].

It has been recently shown that ATM is regulated by the oxidative modification of Cys, which sensitizes ATM to cellular redox state [66, 95]. Oxidation is proposed to act as a

regulatory mechanism along with phosphorylation and acetylation [66, 105]. In the presence of oxidative stress, ATM has been shown to increase its activity by phosphorylating downstream proteins [106]. Additionally, under oxidative stress, ATM can be activated, as indicated by autophosphorylation and by phosphorylation of p53 and Chk2, independent of MRN and in the absence of DNA damage (as indicated by lack of γH2AX staining) [66, 73]. The affinity of ATM to its substrates, p53 and ATP, is also increased in the presence of hydrogen peroxide independent of MRN, suggesting that the oxidized ATM undergoes conformational changes that allow it to bind tightly to its substrate [66, 73]. Furthermore, phosphorylation of p53 by ATM (independent of MRN) was inhibited in the presence of the antioxidant N-acetyl-cysteine (NAC), indicating that Cys modification may be responsible for the redox sensitivity of ATM [66, 73]. It has been shown that the active form of ATM is a dimer in the presence of hydrogen peroxide, as opposed to a monomer in the case of MRN activation [66, 73, 97]. Further analysis identified that the active dimer is linked by a disulfide bond using a Cys located near the kinase domain (Cys2991). A mutation at this Cys prevents the redox sensitivity of ATM but retains its ability to be activated by DNA damage and MRN [66, 74]. These results indicate that the oxidation state of this Cys allows for a separation of function between the two activation pathways of ATM (through MRN or by oxidative stress).

Furthermore, *in vitro* analysis of an ATM truncation mutation present in A-T patients, where the last 10 amino acids of ATM are deleted (R3047X), suggests that the R3047X variant is insensitive to oxidative stress, similar to the Cys mutant [66, 73]. This truncation mutation is located near the redox-sensitive Cys2991. Both the Cys and truncation mutants had similar responses to that of the wild-type in the presence of camptothecin (CPT), which is a non-oxidative stress DNA-damage-inducing agent [66, 73]. Thus, the Cys and truncation mutants can be activated by DNA damage but not by oxidative stress [66, 73]. These findings led to the conclusions that ATM acts to sense oxidative stress in cells and this may be important for a novel function of ATM, which is independent of DNA damage [66, 74, 75, 107]. The ability of ATM to respond to oxidative stress by forming disulfide bonds may activate an alternate cellular response pathway that is necessary to prevent DNA damage by oxidative stress. Therefore, this activity is specifically important under oxidative stress conditions, when DNA is targeted for damage.

2.2. XRCC3

X-ray repair cross complementing 3 (XRCC3) is a Rad51 paralog important for DNA repair by HDR [108, 109]. It contains 346 amino acids, eight of which are Cys, and has a molecular weight of 37 kDa. XRCC3 deficiency has been shown to impair RAD51 foci formation and inhibit HDR, which results in genomic instability [110, 111].

Upon exposure of cells to UVA, which produces singlet oxygen in the presence of photosensitizers (6-thioguanine, 6TG), DNA synthesis is inhibited, although HDR is stimulated [8, 76, 112]. This indicates that HDR does not contribute to the effect of UVA on DNA synthesis [76]. This phenomenon prompted a study on the sensitivity of XRCC3 to oxidative stress caused by UVA. When cells were exposed to UVA, a change in the electrophoretic mobility of XRCC3 was observed, suggesting a potential conformational

change as a result of oxidation [76]. Additionally, a reduction in the ability to detect XRCC3 with a C-terminal-specific antibody confirmed that the C-terminus undergoes a conformational change that occludes the antibody detection region [76]. The C-terminus of XRCC3 contains Cys328, which can be a target site for oxidation. The oxidative sensitivity was reversible in the presence of a reducing agent, confirming the contribution of Cys oxidation [76]. Additionally, this effect was abolished when all Cys residues were mutated to Ser.

The specificity of XRCC3 oxidation to singlet oxygen was confirmed because in the presence of singlet oxygen scavengers (NaN_3, L-Histidine) oxidation of XRCC3 was prevented [76]. Molecular modeling studies suggest that two Cys residues (Cys86 and Cys328) can form an intermolecular disulfide bond in the presence of oxidants [76]. Cells expressing XRCC3 with either the Cys86Ser or Cys328Ser mutation have similar sensitivity to CPT as the wild-type, however, when all Cys residues were mutated into Ser, the cells were more sensitive to CPT treatment. This provides evidence that Cys residues, other than Cys86 and Cys328, are important for HDR [76]. Furthermore, Cys221 modification, which is located near a phosphorylation site (Ser225), may affect XRCC3 phosphorylation by ATM and ATR upon the induction of DNA damage [113]. This indicates that Cys residues in XRCC3 are not only important for the redox sensitivity effect, but also for the response to DNA damage [76]. Therefore, the oxidation state of XRCC3 may serve to differentiate two functions of XRCC3 in response to oxidative stress or DNA damage.

2.3. Ku

Ku is a heterodimer protein composed of two subunits with molecular weights 70 and 80 kDa (Ku70 and Ku80). This complex is important in the repair of DSBs as part of the NHEJ pathway [114]. It has been shown that Ku forms a ring at the DNA ends and functions to rejoin DNA ends [67, 114]. This complex binds DNA with high affinity and translocates along the DNA, though the mechanism of dissociation is unknown [115]. Previous work suggests that Ku is prone to oxidation by UVA, which inhibits NHEJ [116]. Specifically, it has been shown that Ku binding to DNA is inhibited in the presence of oxidative stress and that this inhibition is reversible in the presence of a reducing agent [67]. Upon oxidation, Ku undergoes a conformational change that leads to higher rates of dissociation from DNA, which reduces its binding affinity [117]. Furthermore, limited tryptic digestion suggests that Ku80 undergoes conformational changes dependent on the redox state of the protein. Ku is more prone to limited tryptic digestion under reduced conditions as compared to the oxidized form [67]. As part of the complex, Ku80 is a 732 amino acid protein with ten Cys residues. Cys493 and Cys638 of Ku80 were identified as being susceptible to oxidative modification [67, 118]. Both of these residues are located in the C-terminus, which is important for the recruitment of the downstream binding partner, DNA-PKcs [114]. Furthermore, it has been shown that binding of Ku to DNA-PKcs is sensitive to the redox state of Ku [118]. This suggests that a reduced state of Ku is required for DNA binding and for recruiting downstream proteins. The inhibitory effect of oxidative stress on Ku suggests that oxidation may regulate the selection of the DNA repair pathway at an early stage in the repair process, which may help the cell decide on the specific repair pathway.

2.4. DNA-PKcs

DNA dependent protein kinase catalytic subunit (DNA-PKcs) is important for the repair of DSBs by NHEJ [119]. It is important for the early stage detection of DNA damage and for DNA repair [119]. This protein has 4128 amino acids (87 Cys) and has a molecular weight of 469 kDa. DNA PKcs has been shown to be sensitive to oxidative stress and to be targeted for nitrosylation [120, 121]. However, the effect of nitrosylation on activity has not been identified. Nitrosylation has also been shown to have an indirect effect on DNA-PKcs. In the presence of nitric oxide (NO), the expression levels of DNA-PKcs increase 5-fold due to higher binding of the transcription factor, SP1, to the promoter region of DNA PKcs [122]. This also results in a 4-fold increase in activity, which may provide a protective role against DNA damage [122]. NO is produced as a result of an inflammatory response by nitric oxide synthase [123]. Therefore, nitrosylation of DNA repair proteins may define the relationship between inflammation and cancer. It may also help guide future studies into the resistance of certain cancers to chemo- and radiotherapy.

Additional studies suggest that sustained production of RONS sensitizes cells to genotoxic drugs by reducing the kinase activity of DNA-PKcs [77]. As a result, DNA repair is inhibited and toxic DSBs accumulate in the cell [77]. Therefore, the reactivity and specificity of DNA-PKcs towards RONS may determine the effect on its activity.

3. Base Excision Repair

Base excision repair (BER), along with direct removal of damage by specialized enzymes, is responsible for the repair of a large percentage of base lesions [124]. This includes the repair of oxidative and methylated lesions, along with abasic sites and single strand breaks, in order to maintain genomic stability [124]. The inability to repair DNA damage results in propagation of errors, DNA breaks, and in genomic instability [33]. Various members of the BER pathway have been shown to be modified and inhibited under oxidative stress. This inactivation may fully account for the accumulation of DNA damage in the presence of oxidative stress and under inflammatory conditions. Therefore, inhibition of BER by oxidative stress helps with defining the relationship between oxidative stress and cancer (Figure 3). Furthermore, the inactivation of BER may act as a stress signal to trigger the activation of alternative pathways in order to conserve energy and invest it into essential functions that promote cell survival. Though this area needs to be investigated. The current state of literature regarding the oxidative modification of BER proteins is presented (Table 1).

3.1. AAG

Alkyl-adenine DNA glycosylase (AAG) is a monofunctional glycosylase important for the recognition and removal of methylated DNA bases as part of the BER pathway [125]. It is composed of 298 amino acids, seven of which are Cys, and has a molecular weight of 33 kDa. Treatment of cells with methyl methanesulfonate (MMS) results in the production of methylated DNA lesions, which are recognized and removed by AAG [126]. MMS treatment results in the accumulation of BER DNA intermediates but to a greater extent in the presence of GSNO [80]. Levels of BER intermediates formed immediately after MMS

treatment were similar in the presence and absence of GSNO. However, when cells were allowed to recover from MMS treatment, cells treated with GSNO had higher levels of BER intermediates as compared to no GSNO treatment. Additionally, in the absence of AAG, GSNO treatment did not increase levels of alkylated bases. This indicates that GSNO treatment induces cells to be susceptible to damage from MMS in an AAG dependent manner [80].

Furthermore, studies have shown that GSNO can transfer an NO group onto AAG, which enhances the activity of AAG [80]. Therefore, GSNO leads to the activation of BER by AAG and results in increased production of abasic sites. In the presence of GSNO, AAG has been shown to be nitrosylated at the active site Cys167 leading to increased activity [127]. Though a mutation at this site completely inhibits AAG activity, modification of Cys167 is proposed to decrease substrate specificity of AAG [80]. High levels of GSNO also inhibit the downstream protein APE1 (see below), which leads to the accumulation of abasic sites [80]. Abasic sites are toxic to the cells. An adenine can be misincorporated opposite the abasic site, which leads to increased mutations [128]. Alternatively, abasic sites are prone to hydrolysis, leading to single strand breaks and ultimately DSBs [129]. Therefore, accumulation of abasic sites, resulting from increased activity of AAG in the presence of GSNO, can be detrimental to the cells.

3.2. OGG1

8-oxoguanine glycosylase is a bifunctional glycosylase important for the recognition and removal of oxidized DNA bases, creating abasic sites [130]. Additionally, OGG1 has a slow lyase activity, which cleaves the DNA backbone, creating single strand breaks [130]. Studies performed with OGG1 null mice suggest that OGG1 is solely responsible for removal of 8-oxoguanine lesions [124]. It is a 39 kDa protein with 345 amino acids, eight of which are Cys. OGG1 has been proposed to be sensitive to oxidative stress by various oxidants. When the cellular redox state is altered from exposure to cadmium, OGG1 activity is inhibited [70]. Cadmium is an environmental toxin that exerts an effect on glutathione, leading to its depletion and accumulation of RONS [131]. It has been shown that cadmium treatment results in OGG1 inhibition *in vitro* independent of chelating agents but dependent on antioxidants (such as NAC) [70]. Cadmium treatment also results in a shift in the electrophoretic mobility of OGG1, which is reversible in the presence of reducing agents, indicating that cadmium changes the oxidation state of OGG1 [70]. Therefore, it is suggested that the oxidation state of Cys residues in OGG1 is modified in the presence of cadmium, which alters the activity of OGG1 [70]. Additionally, OGG1 has been shown to be regulated by nitrosylation [81]. Cells exhibit sensitivity to NO in a manner dependent on OGG1, which suggests that nitrosylation inhibits OGG1 [81]. These studies were initiated because NO release causes an accumulation of oxidized DNA bases even though it does not itself oxidize DNA directly [132]. Lastly, singlet oxygen, which is produced from UVA exposure, has also been shown to modify and inhibit OGG1, resulting in the accumulation of oxidative DNA damage [8, 116].

The sensitivity of OGG1 to oxidation state has also been observed in the presence of a common OGG1 cancer-associated variant, Ser326Cys, which is associated with various

cancers (lung [133]. gastric [134] along with others). This variant has been shown to be redox sensitive as a result of the introduced Cys residue [135-137]. Ser326Cys exhibits minimal catalytic alterations (2-fold reduction in glycosylase rates), however, under oxidative stress, it is inactivated [138]. Specifically, the glycosylase activity of Ser326Cys OGG1 is abolished upon exposing cells to oxidative stress inducing agents (TNFα or hydrogen peroxide) [138]. Though these agents can generate DNA damage directly, they also inhibit the enzyme responsible for the repair, which amplifies the effect of oxidative stress on DNA. Ser326Cys has been shown to form disulfide bonds in the presence of oxidative stress, which results in the dimerization of OGG1 [138, 139]. The dimer is proposed to bind DNA in a nonproductive manner, preventing activity [138]. The inhibition of Ser326Cys is reversed in the presence of NAC, which suggests that the Cys in Ser326Cys is responsible for the inhibition by oxidants [138]. Along with sensitivity to TNFα, cells expressing this variant are sensitive to NO [81]. The variant loses the ability to bind DNA tightly and to coordinate with additional BER steps [81]. As a result, DNA damage accumulates, which results in genomic instability [81]. The effect of this variant on genomic instability is more pronounced with inflammation. TNFα is a cytokine produced as part of an inflammatory response and causes high oxidative stress [140]. Additionally, NO is also released as part of an inflammatory response [123]. Therefore, the studies discussed above, which suggest that OGG1 is inhibited in the presence of TNFα and NO, highlight the relationship between inflammation and cancer risk.

In addition to repair by OGG1, oxidative DNA damage can also be repaired by MUTYH, a glycosylase with a complementary function to OGG1 [48]. MUTYH removes the adenine misincorporated opposite 8-oxoG by polymerases [48]. It is composed of 546 amino acids, twelve of which are Cys, with a molecular weight of 60 kDa. Mutations in MUTYH are associated with increased mutation frequency in the adenomatous polyposis coli gene (APC), which is a highly mutated gene in familial adenomatous polyposis [141, 142]. Therefore, individuals carrying mutations in MUTYH are at higher risk of developing colorectal cancer [143]. As a result, dysregulation of MUTYH activity is an important risk factor for developing cancer. MUTYH contains an iron sulfur cluster, which makes the enzyme susceptible to redox modification [144]. Consequently, MUTYH has been shown to be inhibited in the presence of oxidative stress by UVA [116]. This suggests that RONS produced from exposure to UVA can inhibit two of the enzymes responsible for detecting and removing oxidized DNA damage [116].

3.3. APE1

Apurinic/apyrimidinic endonuclease 1 (APE1) is composed of 318 amino acids (seven Cys) with a molecular weight of 35.5 kDa. The overexpression of APE1 is associated with resistance to chemotherapy [145]. APE1 is important in BER as an endonuclease that cleaves the DNA backbone 5’ of abasic sites to create DNA ends with 3’OH and 5’ deoxyribose phosphate [146, 147]. In addition to its function in BER, APE1 acts as a nuclear redox factor that regulates the redox state of various transcription factors, including AP-1, NFκB, HIF1α, and p53 [148]. The two APE1 functions are shown to be independent of each other [149]. The N-terminus of APE1 (35-127) is responsible for protein-protein binding and for the redox function of APE1, and the C-terminus is responsible for the endonuclease

activity [149, 150]. The redox domain contains three Cys residues. Though no disulfide bond is observed in the crystal structure, many have proposed that APE1 exhibits redox sensitivity by forming a disulfide bond [151]. Specifically, Cys65 has been shown to be important for the redox activity of APE1 [151]. A Cys65Ser mutation inhibits the redox function of APE1 by affecting folding and localization [82]. When Cys65 is oxidatively modified, APE1 is proposed to undergo conformational changes, which alters the subcellular localization of APE1 by exposing a nuclear export signal [82]. Additionally, nitrosylation at Cys93 and Cys310 allows APE1 to translocate from the nucleus to the cytoplasm, leading to accumulation of abasic sites [152]. APE1 is mainly localized in the nucleus, however, various cancers have high levels of cytoplasmic APE1, such as colon, breast and hepatocellular cancers [153]. Therefore, nitrosylation of APE1 and its effect on localization may act as a driving force for carcinogenesis. It has also been suggested that a known APE1 inhibitor, E3330, triggers the formation of a disulfide bond between Cys65 and Cys138, which is proposed to be the mechanism of action of this inhibitor [154].

The effect of oxidative modification on the endonuclease activity has also been documented [83]. In the presence of oxidative stress, APE1 has been shown to be modified by glutathionylation at Cys99 in a reversible manner in the presence of reducing agents. Glutathionylation of APE1 leads to reduced DNA binding capacity, which inhibits the endonuclease activity [83].

3.4. PARP1

Poly(ADP-ribose) polymerase 1 (PARP1) is a nuclear protein involved in the repair of DNA breaks through the BER pathway [155, 156]. It is a 113 kDa protein with 1,014 amino acids, fourteen of which are Cys. PARP1 binds DNA breaks and catalyzes autoribosylation using NAD^+ as a substrate, this in turn signals for additional repair proteins to be recruited to the break site [156, 157]. PARP1 contains 3 zinc finger domains, which are important for DNA-protein binding [158]. In these domains, a zinc is coordinated by either 4 Cys residues (C4), 3 Cys and 1 Histidine (C3H1) or C2H2 [159]. The presence of zinc is important structurally and also to protect Cys residues from oxidative modification [84]. In the presence of heavy metals, arsenic for example, zinc is released, which sensitizes the Cys residues to oxidation and results in inhibition of DNA binding [84, 85]. Specifically, arsenic has been shown to replace zinc in two zinc motifs C3H1 and C4, which inhibits PARP1 and allows the coordinating Cys residues to become more sensitive to cellular RONS [84].

In addition to being prone to inhibition by heavy metals, it has been suggested that nitrosylation acts as a regulatory mechanism of PARP1 activity [160]. Upon nitrosylation, the coordination of zinc is disrupted, which inhibits PARP1 activity and results in accumulation of DNA damage. NO is a released by macrophages in the presence of pathogens as a defense mechanism [123]. Thus, the correlation between inflammation and cancer can be deduced from inhibition of DNA repair factors.

3.5. XRCC1

XRCC1 is composed of 633 amino acids (six Cys) with a molecular weight of 69.5 kDa. It is a scaffolding protein involved in recruiting proteins as part of the BER pathway and is

shown to interact with PARP1, ligase III, APE1, and DNA polymerase beta (polβ) [161]. The N-terminal domain of XRCC1, which contains two redox sensitive Cys residues, has been shown to interact with polβ [162]. These Cys residues, Cys12 and Cys20, form a disulfide bond in the presence of an oxidant, leading to conformational changes at the N-terminus [86]. Oxidation of XRCC1 results in a 6.4 Å shift between Cys12 and Cys20, from 8.5 Å in the reduced to 2.1 Å in the oxidized form [86]. This shift changes the binding affinity of XRCC1 to polβ. When oxidized, XRCC1 binds 25-fold more tightly to polβ as compared to the reduced state [86]. This change in affinity occurs because XRCC1 oxidation makes the interaction interface with polβ more accessible. Cys12 is important for recruiting polβ; expressing the XRCC1 with Cys12Ala in cells leads to slower recruitment of polβ and faster rate of release [86]. Additionally, a proline carbamate adduct has been shown to form at position Pro2 from exposure to CO_2. This adduct results in stabilizing the oxidized state of XRCC1 [163]. Since XRCC1 is important for recruiting various members of the BER pathway, the effect of oxidation on conformational changes will have a direct effect on BER efficiency and DNA repair.

4. Direct Reversal Pathway, MGMT

O^6 methylguanine methyl transferase (MGMT) is important for the repair of O^6 methyl guanine [125]. It contains 207 amino acids, five of which are Cys, and has a molecular weight of 21 kDa. O^6 methylguanine is a mutagenic and toxic DNA lesion because DNA polymerases can misincorporate thymine opposite O^6 methylguanine, resulting in GC to AT mutations [164]. MGMT functions by transferring a methyl group from a methylated DNA base into an active site Cys (Cys145) [165]. MGMT is a suicide protein; it is targeted for degradation upon transferring the methyl group onto the active site Cys [165, 166]. This Cys is located near charged amino acids, which makes the sulfhydryl group reactive and prone to modification. Specifically, Cys145 has been shown to be targeted for nitrosylation by nitrosoglutathione (GSNO) [78, 79, 167]. The nitrosylation of MGMT inactivates the enzyme and leads to its degradation as it becomes ubiquitinated and targeted by proteasomes [168]. Nitrosylated MGMT has a reduced half-life, from 24 h to 1.3 h, though this sensitivity is abolished upon mutating Cys145 into Ala [78]. Furthermore, MGMT degradation results in the accumulation of DNA damage. The inability of cells to repair O^6 methylguanine as a result of MGMT nitrosylation has been proposed to lead to hepatocarcinogenesis [168]. In support of this, it is reported that in many hepatocellular tumors levels of NO synthase (which produces NO) are high, while levels of GSNOR (GSNO reductase, which degrades NO) are low [169].

5. Conclusions

Redox-dependent Cys modifications enhance the diversity of protein structure and function by two orders of magnitude [62]. Though most proteins are found in a reduced state, there are various examples of proteins that exist in the oxidized form in the cell [170, 171]. These proteins have reactive Cys residues that sense small changes in the redox potential. The sulfhydryl group in Cys is an ionizable group that is sensitive to changes in nearby environment (pH and redox potential) [172]. The protonation state of Cys is dependent on the location and secondary structure. At the N-terminal end of α helices, the p*K*a of the

sulfhydryl decreases due to the positive dipole moment; this renders the group more reactive, providing a basis for selectivity. The reactivity of Cys is also increased when positioned near a basic amino acid in the three dimensional space. Moreover, the redox potential of the cell has been documented to change depending on the cellular function including proliferation and apoptosis [173].Therefore, the potential for protein oxidation not only depends on oxidative stress induced in a disease state, it also depends on normal cellular functions.

In the context of DNA repair, protein modifications are important under conditions of oxidative stress, when there is an imbalance between oxidants and reductants and when DNA is more prone for damage. It is important to ensure that the activation of signaling proteins, such as ATM, occurs only under conditions when DNA is damaged, otherwise, if it is constitutively active, it will result in premature cell cycle arrest. The activation of ATM under oxidative stress may occur as a stress response and can act as a sensor to transmit a stress signal into a DNA repair response. Alternatively, when ATM is mutated at sites that prevent it from responding to oxidative stress, the cell will not be able to respond to oxidative stress and that may be associated with various diseases such as the A-T syndrome. This indicates that the oxidation state of ATM is important for homeostatic cellular functions.

The levels of ROS are correlated with aging and various neurodegenerative diseases and cancer. Though, the correlation between oxidative stress and these diseases is still not fully understood. Oxidative stress and the consequential oxidative modification of DNA repair proteins may result in their activation or inhibition, which will directly affect DNA repair and the accumulation of DNA damage. Consequently, these protein modifications may correlate with the incidence of various diseases, including cancer. Therefore, it is important to understand the full extent to which DNA repair proteins respond to oxidative stress. Modulating the response of proteins to oxidative stress by using small molecule inhibitors may provide a better handle for various oxidative stress-induced diseases such as neurodegenerative and autoimmune diseases and cancer. Therefore, it is important to identify residues within the DNA repair proteins that are sensitive to oxidative modification. In addition to directly oxidizing DNA repair proteins, other redox sensitive proteins which regulate the expression/localization/folding of DNA repair proteins may also indirectly affect DNA repair [174]. Thus, these regulatory proteins may act as novel therapeutic targets for cancer and other diseases.

In addition to the proteins discussed in this review, more proteins that are directly and indirectly involved in DNA repair have been shown to be targeted for oxidation: T4 ligase [175], p53 [176], HMGB1 [177], XPA [178], PCNA [179], RPA [116, 180-182]. Therefore, additional studies are necessary to perform in order to understand the comprehensive effect of oxidative stress on DNA damage and repair and to fully understand the relationship between inflammation and cancer. Additionally, various DNA repair proteins have cancer-associated variants where a Cys residue is introduced. These variants may alter the sensitivity of DNA repair to oxidation. Therefore, more studies are necessary in order to understand the effect of a Cys on the sensitivity of the protein to oxidative stress.

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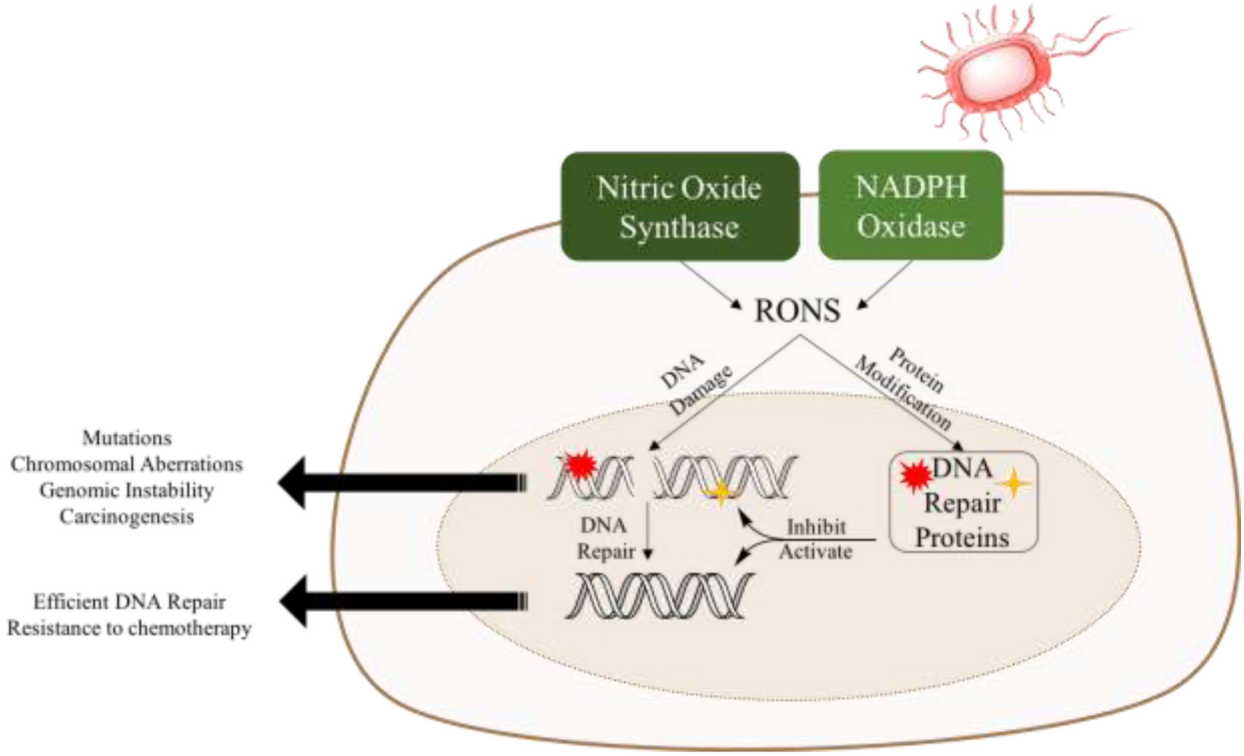

Figure 1:

Exposure to pathogens triggers the production of RONS by nitric oxide synthase and NADPH oxidase. Consequently, DNA and proteins are oxidized. Depending on the effect of oxidative modification on protein function, DNA repair can be inhibited, which results in the accumulation of damage and leading to carcinogenesis. Alternatively, protein modification may activate DNA repair, which may result in resistance to chemotherapy.

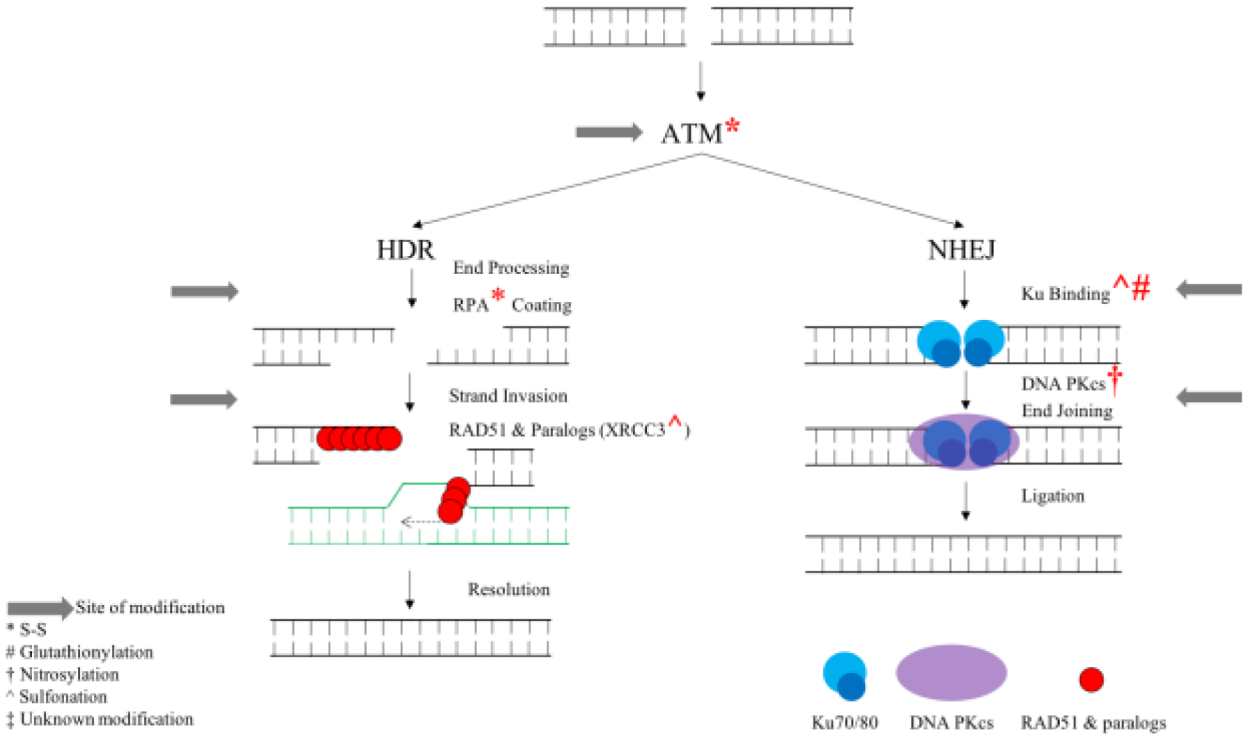

Figure 2:
The effect of RONS on the repair of double strand breaks by HDR and NHEJ.

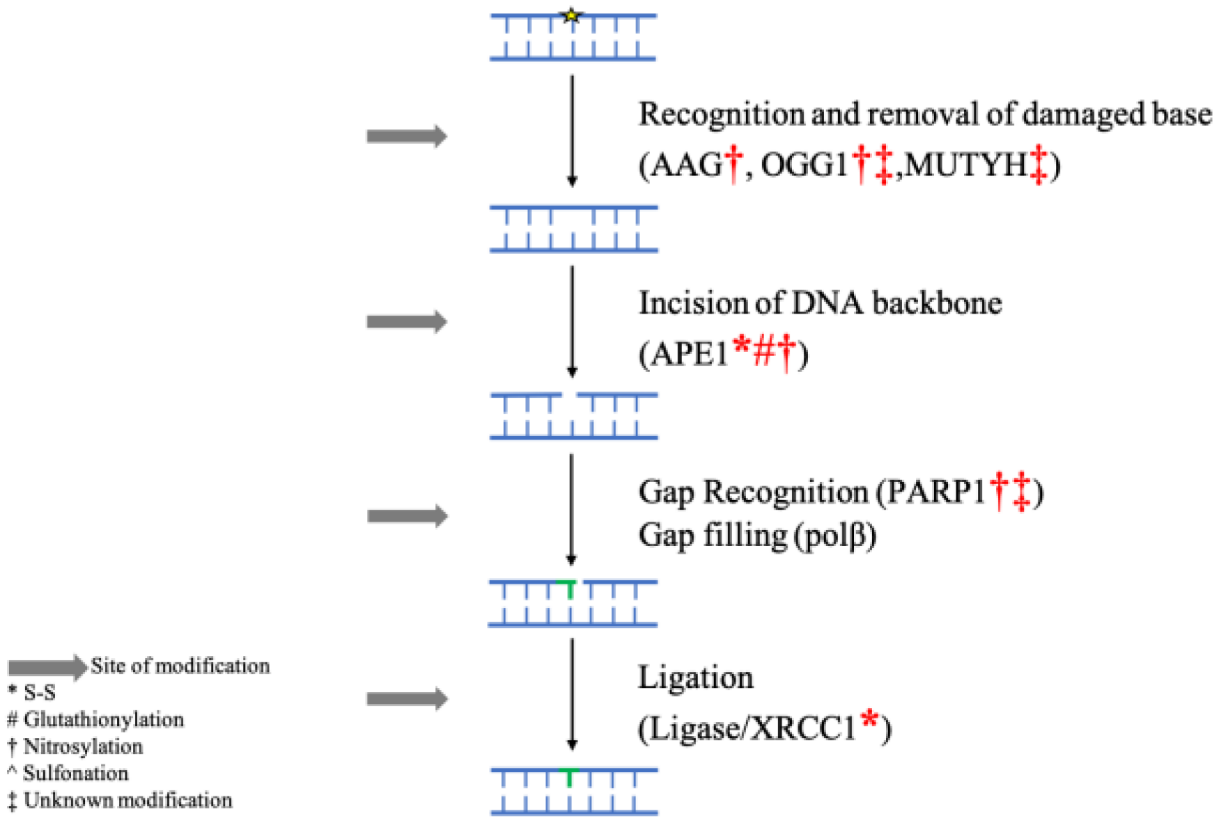

Figure 3:
The effect of RONS on the capacity of BER to repair small base lesions and single strand breaks.

Table 1.

DNA repair proteins targeted for oxidation regulation.

Name of protein	Pathway	Potential target site	Effect on activity	Reference
ATM	DSB repair	C-terminal Kinase domain	Activate alternate function	[66, 73-75]
XRCC3	DSB repair, HDR	C86, C328	Inhibit DNA synthesis	[76]
Ku	DSB repair, NHEJ	C-terminus	Reduced DNA binding, inhibit repair	[67]
DNA-PKcs	DSB repair, NHEJ	Unknown	Activation or Inhibition, depending on exposure	[77]
MGMT	Direct reversal, MGMT	Cys145	Inhibition of activity and protein degradation	[78, 79]
AAG	BER	Cys167	Decrease specificity, increase activity	[80]
OGG1	BER	Cys, unknown	Inhibition of activity	[70, 81]
APE1	BER	Cys65, Cys99	Alter localization; reduced DNA binding	[82, 83]
PARP1	BER	Zinc finger domain	Reduced DNA binding	[84, 85]
XRCC1	BER	Cys12, Cys20	Increased affinity to polβ	[86]