Chapter

Regulation of Oxidized Base Repair in Human Chromatin by Posttranslational Modification

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Abstract

Base excision repair (BER) is the major pathway for the repair of oxidized bases and apurinic/apyrimidinic (abasic; AP) sites produced by reaction with reactive oxygen/nitrogen species (ROS/RNS). These metabolites are generated spontaneously by endogenous cellular processes and also by environmental agents. Because most of these lesions are promutagenic, linked to diverse disease-associated somatic mutations, as well as heritable single nucleotide polymorphisms (SNPs) in the normal human population, their prompt repair is warranted. Impairment of repair leading to mutation, a hallmark of cancer, underscores the essentiality of BER for maintaining genome integrity in humans and other mammals. In mammals, repair of oxidized bases and other BER substrates is initiated by DNA glycosylases (DGs), which excise the damaged bases and cleave the DNA strands at the resulting AP sites, followed by sequential end processing, gap-filling DNA synthesis, and ligation. *In vitro* BER performed with naked DNA substrates has been extensively studied, which delineates its basic mechanistic steps and subpathways. However, recent interest is directed to unraveling BER in cell chromatin, including its regulation via posttranslational modifications (PTMs), which occurs possibly in concert with nucleosome remodeling. Emerging reports on various PTMs of BER enzymes indicate that the PTMs, while dispensable for the enzymatic activity, regulate overall repair by modulating interactions with other repair proteins and chromatin factors, assembly of BER complexes, as well as turnover of the proteins, and may ultimately dictate the cellular phenotype. Here, we discuss recent advances in the BER field by reviewing the PTMs and how they regulate BER in chromatin.

Keywords: oxidative stress, base oxidation, base excision repair, posttranslational modifications, acetylation, phosphorylation, SUMOylation, methylation, chromatin

1. Introduction

DNA, the genetic repository of all cellular functions, is packaged with histones into chromatin consisting of nucleosome units. One hundred forty-seven base pair (bp) segments in DNA wrap ~1.65 times in a left-handed superhelical turn around a histone octamer consisting of two histone H2A-H2B dimers and a H3-H4 tetramer, which form the nucleosome core; the adjacent nucleosomes are separated by some

50 bp unfolded, linker DNA bound to histone H1 or H5. Organization of DNA into chromatin enables the compaction required to accommodate large eukaryotic genomes inside the cell nucleus. This compaction renders DNA inaccessible to any DNA transaction machinery. Replication and transcription are tightly coordinated with specific interactions of their complexes with DNA [1, 2].

The integrity of DNA is under constant threat, naturally from endogenous sources, as well as by environmental factors in the form of a chemical addition, an alteration in the nitrogen base structure, thereby creating an abnormal nucleotide, or a break in one or both strands of DNA [3–8]. Cellular metabolic processes including mitochondrial respiration and hydrolytic reactions generate reactive molecules, such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and alkylating agents. Some chemical bonds in DNA are susceptible to spontaneous hydrolysis. About 70,000 lesions are generated per cell, per day in humans. Single-strand breaks (SSBs), as well as a plethora of oxidized bases, are formed during oxidative genome damage. In addition, deamination, depurination, depyrimidination, double-strand breaks (DSBs), propano-, etheno-, and malondialdehyde-derived DNA adducts, base propenals, and alkylated bases are also formed endogenously. Environmental factors such as UV rays, ionizing radiation (IR), heat, and chemicals from tobacco smoke and industrial sources pose additional risks to DNA.

2. Oxidative genome damage and oxidized bases

For aerobic organisms, oxygen acts like a double-edged sword; while it is absolutely essential for life, it is also a threat to the life, recognized as the "Oxygen Paradox" [9–11]. ROS, which include the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and the hydroxyl radical ($^{\bullet}OH$), along with RNS, for example, peroxynitrite ($ONOO^-$) react with all biological molecules including DNA. The hydroxyl radical having the highest reduction potential is mainly generated from Fenton reaction between reduced redox active metal ions (Fe^{2+}, Cu^+) and H_2O_2 [12], as well as by the IR-induced radiolysis of water [13]. A wide variety of cellular antioxidant defense mechanisms including both redox-buffering enzymatic and nonenzymatic systems have evolved, for example, superoxide dismutases, catalases, glutathione peroxidases, peroxiredoxins, and glutaredoxins; these counteract the detrimental effect of oxidative stress to the biological molecules, and an imbalance in their homeostasis leads to increased damage to the biomolecules [14].

A plethora of oxidized base lesions are generated mostly from guanine (G) in DNA, which has the lowest redox potential among the natural bases. Other lesions including 2-deoxyribose modifications, SSBs, DSBs, and protein-DNA cross-links are also ROS reaction products in DNA [10, 14–17]. Nearly 100 such lesions have been identified; however, because of the lack of sensitivity of the techniques used to identify the lesions and inherent instability of some of them, the total number formed in the genome under a pro-oxidant environment is likely to be much higher [18].

The most commonly formed oxidized base lesion is 7,8-dihydro-8-oxoguanine (8-oxoguanine, 8-oxoG), which was discovered by Kasai and Nishimura in 1983 and coined as 8-hydroxyguanine [19–21]. All the nucleobases are also ionized by IR and by high intensity 266-ns laser photolysis. The DNA bases undergo one-electron oxidation (one electron ionization potential of G<A<C~T). 8-oxoG is generated at a much higher level (>5-fold) than the combined level of other one-electron base oxidation products. Singlet oxygen ($^1O_2$), the major ROS in UVA-mediated oxidation of DNA, specifically targets G and 2-deoxyribose moiety [22–24]. Other major oxidized base lesions are 5-hydroxy-6-hydrothymine, thymine glycol (TG), cytosine glycol (CG), 5-hydroxycytosine (5-OHC), uracil glycol (UG), 5-hydroxyuracil

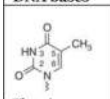
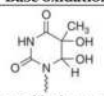
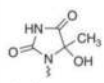
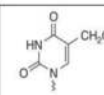
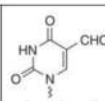
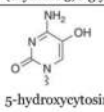
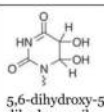
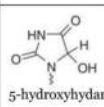
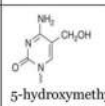
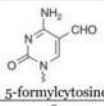
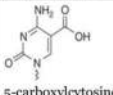
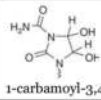
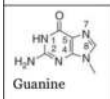
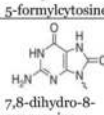
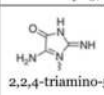
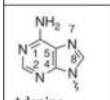
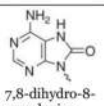
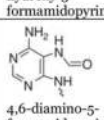
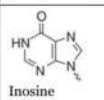
DNA bases	Base oxidation products			
 Thymine	 5,6-dihydroxy-5,6-dihydrothymine (thymine 5,6-glycol)	 5-hydroxy-5-methylhydantoin	 5-hydroxymethyluracil	 5-formyluracil
 R=H Cytosine R=CH3 5-methyl cytosine	 5-hydroxycytosine	 5,6-dihydroxy-5,6-dihydrouracil	 5-hydroxyhydantoin	 5-hydroxymethylcytosine
	 5-formylcytosine	 5-carboxylcytosine	 1-carbamoyl-3,4-dihydroxy-2-oxoimidazolidine	
 Guanine	 7,8-dihydro-8-oxoguanine	 2,6-diamino-4-hydroxy-5-formamidopyrimidine	 2,2,4-triamino-5(2*H*)-oxazolone	
 Adenine	 7,8-dihydro-8-oxoadenine	 4,6-diamino-5-formamidopyrimidine	 Inosine	

Table 1.
Common oxidized bases detected in DNA.

(5-OHU), 8-hydroxyadenine, and 2-hydroxyadenine [14, 17]. Hypochlorous acid (HOCl), generated by myeloperoxidase in neutrophils during inflammation, chlorinates both DNA and RNA bases [25, 26], and the main products are 5-chlorocytosine, 8-chloroadenine, and 8-chloroguanine. A summary of commonly formed oxidized bases detected in cellular DNA is shown in **Table 1** [16]. Apart from ROS-induced generation of oxidized bases, 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) are formed enzymatically during transcriptional reprogramming involving oxidative demethylation of 5-methyl C (5mC), mostly localized in promoter CpG islands, induced by TET dioxygenases [27, 28]. However, enzymatically generated 5-methyl C oxidation products are produced >2-fold higher than that from direct oxidative damage to DNA [29, 30]. Additionally, tandem base lesions are produced by radicals generated from $^{\bullet}OH$ or one-electron oxidation reactions. Examples include the addition of either 5-(uracilyl)methyl radicals or 6-hydroxy-5,6-dihydrocytosin-5-yl radicals to 5′-adjacent guanine moieties in the DNA of cells exposed to H_2O_2 [31, 32] and formation of a guanine-thymine cross-link upon initial formation of guanine radical cation [33, 34]. One-electron oxidation also leads to DNA-protein cross-links. UVA irradiation of 6-thioguanine-containing DNA forms DNA-protein cross-links in human cells [33, 35].

3. Fate of oxidized bases and accumulation of mutations

ROS-induced oxidized base lesions and AP sites if left unrepaired are replicated by replicative or DNA translesion synthesis (TLS) polymerases [36]. Their misreplication generates mutations, a hallmark of cancer genomes, which account for two-thirds of single base pair substitutions [37–40]. Furthermore, single nucleotide polymorphisms (SNPs), observed in normal human genomes, also likely result from such spontaneous single base pair substitutions. U and 5-OHU, the spontaneous and ROS-induced oxidative deamination product of C, respectively, preferably pair with A during replication, resulting in GC → AT transition mutation; 8-oxoG,

the predominant oxidized base lesion mispairs with A, leading to GC → TA transversion mutation [41, 42]. In response to continuous assault by both endogenous and environmental factors, cellular defense mechanisms including diverse DNA repair pathways have evolved in all organisms to correct these base modifications and maintain genomic integrity.

4. Base excision repair of oxidized bases

Base excision repair (BER) is responsible for repairing most oxidized base lesions, AP sites, and DNA SSBs. The basic mechanism of BER first elucidated in *Escherichia coli* is broadly conserved across all organisms, as highlighted in several reviews [43–46]. BER requiring only four or five enzymes in the basic reaction steps is initiated with excision of the damaged base by a monofunctional DNA glycosylase (DG), for example, uracil-DNA glycosylase (UDG) or 3-methyladenine-DNA glycosylase, generating an abasic apurinic/apyrimidinic (AP) site due to hydrolysis of the N-glycosidic bond of the damaged base. The AP endonuclease (APE1 in mammalian cells) cleaves the resulting AP site in the second step and generates 3′ OH and 5′ deoxyribose phosphate (dRP) termini. The DNA polymerase in the third step fills in the single nucleotide gap. In mammalian cells, DNA polymerase β (Pol β) also has intrinsic dRP lyase activity, which cleaves the dRP residue and generates 5′ phosphate; the resulting nick after incorporation of the correct base is sealed by DNA ligase III (Lig III) complexed with XRCC1 in the final step.

The BER initiating DGs for oxidized bases, on the other hand, are bifunctional with intrinsic AP lyase activity. The bifunctional oxidized base-specific DGs further process the AP site via β or βδ lyase reaction. The Nth family of DGs, OGG1, and NTH1, via β eliminations generates 3′ phospho α,β-unsaturated aldehyde (3′ PUA; formally named 3′ phospho 4-hydroxylpentenal) and 5′ phosphate at the strand break. NTH1 prefers oxidized pyrimidines as substrates, and 8-oxoG and ring opened guanine, that is, formamidopyrimidine (Fapy-G), are preferred substrates for OGG1. The Fpg/Nei family DGs NEIL1, NEIL2, NEIL3, discovered by us and others [47–51] catalyze βδ elimination and remove the deoxyribose residue to produce a 3′ phosphate and 5′ phosphate at the strand break. NEILs prefer modified pyrimidine substrates, NEIL1 having preference for ring-opened purines, for example, Fapy-A and Fapy-G. The activity and substrate specificity of NEILs depend on the DNA structure, and NEILs have significant 5-OHU excision activity with single-stranded or bubble, forked DNA. In contrast, OGG1 and NTH1 prefer double-stranded DNA substrates. Usually, the base excision and lyase reactions act in a concerted sequence. However, due to weak lyase activity of OGG1, intact AP sites are the major product after OGG1-catalyzed cleavage of 8-oxoG [52, 53]. All these bifunctional DGs have broad and overlapping substrate range and possess backup activity for many base lesions. This accounts for the fact that only few DGs have been discovered so far for much larger number of oxidized bases and for the nonessentiality of individual DGs.

The 3′ phosphate generated by the NEILs by βδ elimination is a poor substrate for mammalian APE1 and is processed by polynucleotide kinase phosphatase (PNKP) [54–57]. Thus, for oxidized bases, the DGs actually define the subsequent steps. APE1 is responsible for processing the β elimination product of OGG1 and NTH1, whereas PNKP is required for generating 3′-OH termini from 3′ phosphate, a βδ elimination product of NEILs. Furthermore, AP sites and 3′ PUA generated by other DNA glycosylases can also be processed through a NEIL-PNKP-dependent pathway [53, 57]. This alternative repair route provides the functional redundancy in mammalian BER for genome safeguarding against a plethora of endogenous and induced oxidative damages.

BER, in the simplistic model, generates a 1-nucleotide gap after excision of the damaged base and has been termed single nucleotide BER (SN-BER) or short-patch BER (SP-BER). In contrast, long-patch BER (LP-BER) involves repair synthesis of two to eight deoxynucleotides. The 5′ blocking group after oxidation of AP sites cannot be removed by Pol β via its dRP lyase activity. Instead it is removed by 5′-flap endonuclease 1 (FEN-1), which is normally required for removing the 5′ RNA primers from Okazaki fragments during DNA replication. Thus, the subsequent steps of LP-BER are identical to that of DNA replication, utilizing DNA replication machinery, involving DNA polymerases δ/ε (Pol δ/ε) and DNA ligase I (Lig I). These enzymes including FEN-1 are recruited by the sliding clamp PCNA, loaded by replication factor-C (RFC), as in replication [58]. Thus, the choice of LP-BER vs. SN-BER depends on the 5′-terminus at the base cleavage site. With unaltered aldehyde group in deoxyribose, Pol β could carry out SN-BER by excising the 5′-dRP. LP-BER becomes necessary for repairing the oxidized AP sites, which cannot be processed by the 5′ end cleaning lyase activity of Pol β. The nuclear replicative Pol δ/ε lack dRP lyase activity and thus repair synthesis by these enzymes have to follow the LP-BER subpathway. Because Pol β-depleted cells are resistant to oxidative stress, Pol δ/ε can substitute for DNA Pol β and carry out the preferred LP-BER. The BER subpathways are schematically shown in **Figure 1**, adapted from [44].

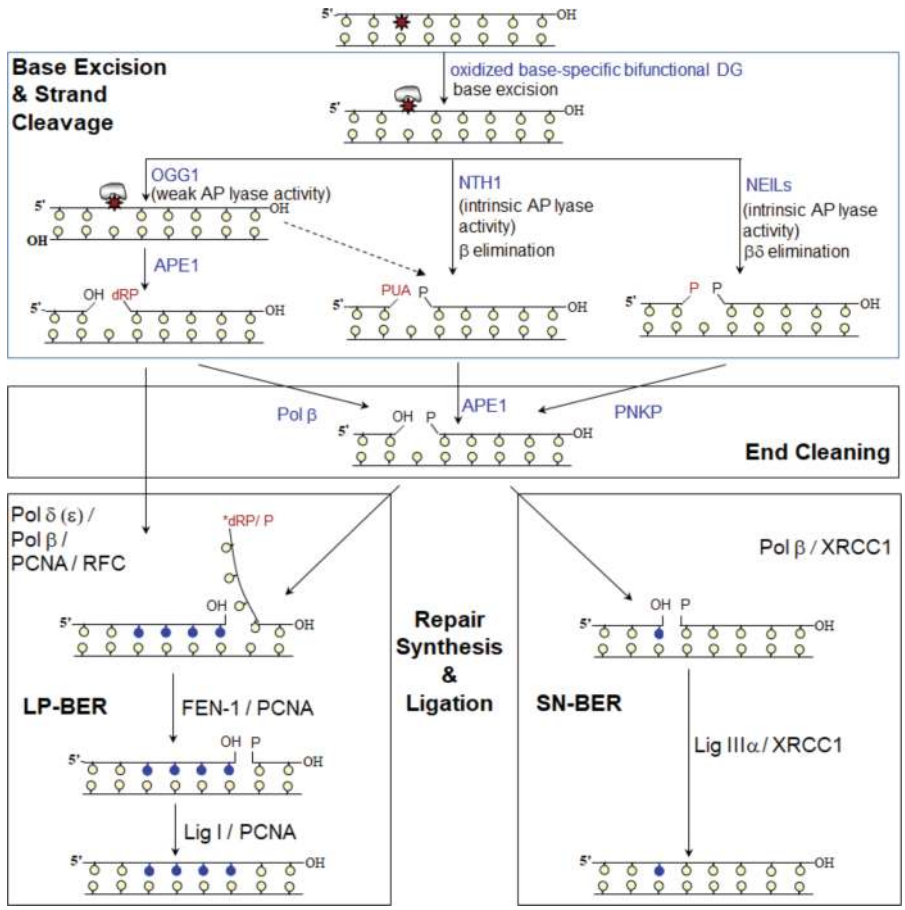


Figure 1.
A schematic representation of oxidized base-specific BER subpathways. The damaged base is represented as ✸. BER is initiated by the DGs: OGG1, NTH1, NEILs, and converge to common steps for end cleaning, followed by repair synthesis and ligation. See text for details.

5. Prereplicative BER of oxidized bases

The genomic integrity is particularly vulnerable during replication. Transient single-stranded (ss) DNA serving as a template during DNA replication after unwinding of the duplex genome is particularly vulnerable to ROS, which induces oxidized bases, sugar fragments, as well as strand breaks. Most oxidized bases do not stall replicative DNA polymerases, but they mispair during replication, thereby causing mutations. In contrast, bulky lesions, which stall replicative polymerases, block replisomes so as to allow repair. However, blocked replication may also lead to fork collapse, causing significant alteration in genomic stability. Furthermore, oxidized deoxynucleotides may be incorporated into the progeny strand during replication. If left unrepaired, these mutations could accumulate in progeny cells, a recipe for pathologies linked to genomic instability, including cancer, accelerated aging, and degenerative brain diseases [59, 60]. Repair of oxidative lesions, which are generated at much higher abundance than the bulky adducts in the replicating genome, is thus critical to maintain genomic fidelity. Mammalian cells have developed multiple ways to faithfully repair such base damages via prereplicative repair in the template strand and postreplicative repair in the progeny strand, immediately after replicative synthesis. Both the pathways involve an intricate collaboration of specific repair machinery with the replication proteins, likely via formation of dynamic "preformed" "repair-replication complexes" at the replication fork [61, 62].

Repair of most mutagenic base lesions except 8-oxoG, for example, 5-OHU, TG, 5-OHC, Fapy-A, 8-oxoA, and UG must be carried out prior to replication in order to prevent mutation fixation. How such lesions, which do not block replicative Pol δ, are flagged for prereplicative repair without causing DSBs was unclear. Our recent study showed that the mammalian DG NEIL1 binds to the oxidized lesion sites in ss DNA substrates *in vitro* to facilitate fork regression and participates in prereplicative repair of the damaged base in the reannealed duplex DNA [61, 62]. We compared the function of NEIL1 in stalling the replication fork at the damage sites for the prereplicative repair to the function of a "cow catcher" attached to the front of early steam locomotives that served to push aside animals or debris from the track ahead of the train's traversal, in a simplistic analogy to this exquisitely orchestrated process [63]. The key features of this "cow catcher" model are the ability of NEIL1 to recognize base lesions in ss DNA templates and its nonproductive binding to lesions in ss DNA, which, while preventing lethal DSB formation, causes the stalling of the replication fork. Subsequent fork reversal allows base lesion repair in the reannealed duplex. High expression and activation of NEIL1 in replicating cells, together with its stable physical and functional association with proteins in the DNA replication complex [48, 64–66], are consistent with this surveillance role of NEIL1. The human genome during each cell division may be at higher risk for oxidative damage whose repair would prevent accumulation of mutations in the daughter cells. Thus NEIL1's prereplicative BER function appears to be critical for preventing mutations and maintaining genome fidelity during cell division.

6. Posttranslational modifications of BER proteins

In vitro BER studies, carried out during the last couple of decades, are straightforward, mainly documenting functions of the repair proteins; however, in the complex cellular environment, the pathways are tightly regulated by interactions among the partner proteins in multiprotein complexes, which in turn also dictates the stability of the complexes. The stability and subcellular localization of these proteins are

regulated by site-specific posttranslational modifications (PTMs), primarily involving acetylation, methylation, phosphorylation, SUMOylation, ubiquitination, and PARylation. Thus PTMs are at the root of major regulatory processes, by bestowing novel biochemical properties to the modified proteins, including changes in enzymatic activity, subcellular localization, interaction partners, protein stability, and DNA binding. Although purified recombinant BER proteins without any PTMs are proficient in their enzymatic activities, *in cellulo* BER is significantly affected by these PTMs. In this section, we discuss all the major PTMs of BER proteins identified so far.

The hallmark of mammalian DGs and early BER proteins is the presence of nonconserved, intrinsically disordered appendages at the N or C terminus, which are absent in their bacterial orthologs. Some examples are the N-terminal extension in human NTH1 absent in the *E. coli* Nth, C-terminal extension in human NEIL1 which is lacking in *E. coli* Nei, N-terminal extension in human APE1 lacking in *E. coli* Xth [44, 65, 67, 68]. Although the unfolded sequence generally exists at the N or C terminus, this could also exist internally as in Human NEIL2, where it may serve as a linker of the two domains. Analogous to the situation of histones H3 and H4, where mostly all PTMs occur in the disordered N-terminal tail [69, 70], PTMs in many early BER proteins are clustered in their disordered domains. See **Table 2** for the major BER PTMs known so far.

6.1 Acetylation

Acetylation of histones was discovered back in 1963 after the Nobel prize-winning discovery of acetyl CoA [71–74], and acetylation of histones at the ε-amino group of Lys residues in their disordered N-terminal region was shown to suppress their abilities to inhibit transcription [75]. Following these pioneering discoveries that linked histone acetylation to chromatin decondensation and transcriptional activation [76–78], diverse acetylation modifiers were identified and characterized. These include various histone acetyltransferases (HATs) such as E1a-binding protein p300 (p300), CREB-binding protein (CBP), ortholog of yeast transcription regulator Gcn5, TAF(II)250 subunit of transcription factor IID, several members of the MYST family (MOZ, YBF2/SAS3, SAS2, and TIP60) and p300/CBP associated factor (PCAF). Histone deacetylases (HDACs) were subsequently discovered as "erasers," which include distinct members, HDACs1–11 and SIRTs in different transcriptional repressor complexes SIN3, NURD, etc., which regulate acetylation/deacetylation cycle in cells [79–81]. These discoveries set the stage for epigenetic regulation of gene expression. Simultaneously, the concept of "reader" proteins [80, 82] that specifically recognize acetylated Lys residues through their bromodomains was introduced in addition to the "writers" (HATs) and "erasers" (HDACs). Although the first discovered nonhistone protein acetylation dated back in 1997 for the tumor suppressor TP53 [83], the overwhelming numbers of nonhistone protein acetylation, particularly in large macromolecular complexes involved in chromatin remodeling, DNA repair, cell cycle, etc., were appreciated much later, after 2006, from mass spectrometric-based proteomic approaches, and provided the global scenario of "cellular acetylome" [81, 84–86].

6.2 Phosphorylation

Although enzymatic phosphorylation of proteins was discovered in 1954 [87], phosphorylated protein was known much earlier, based on identification of phosphate in vitellin [88], followed by detection of phosphoserine in this protein [89]. During the 1950s, ATP was discovered to be required for phosphorylation when the phosphate group was found to be covalently attached to specific serine/

Functional class	BER protein	PTM and identified site	BER activity	Protein stability	Reference
DNA glycosylases	Uracil DNA glycosylase (UNG)	Phosphorylation; T6, S23, T60, S64, T126	+	–	[127, 128, 213]
		SUMOylation		+	[214]
		Ubiquitination		–	[127, 215, 216]
	Single-strand-selective monofunctional uracil DNA glycosylase 1 (SMUG1)	Ubiquitination		–	[215, 216]
	Methyl CpG-binding domain protein 4, DNA glycosylase (MBD4)	Phosphorylation; S156,S262	+		[217]
	Thymine DNA glycosylase (TDG)	Acetylation; K94, K95, K98	–		[129, 130]
		Phosphorylation; S93, S96, S99	+		[129, 130]
		SUMOylation; K330 K341	– +		[131, 218–221]
		Ubiquitination		–	[222, 223]
	MutY DNA glycosylase homolog (MYH)	Phosphorylation; S524	+		[224, 225]
		Ubiquitination; C-terminal K between aa 475–535		–	[226]
	8-Oxo guanine DNA glycosylase 1 (OGG1)	Acetylation; K338, K341	+		[203]
		Phosphorylation; S326	+		[227, 228]
		Ubiquitination	–	–	[229]
	Nei-like DNA glycosylase 1 (NEIL1)	Acetylation; K296, K297, K298	+	+	[161]
		Phosphorylation; S61, S207, Y263, S269, S306			[230–232]
	Nei-like DNA glycosylase 2 NEIL2	Acetylation; K49, K153	–		[233]
	N-methylpurine DNA glycosylase (MPG)	Acetylation	+		[234]
		Phosphorylation; S172	+		[235]

Functional class	BER protein	PTM and identified site	BER activity	Protein stability	Reference
End processors	Apurinic/ apyrimidinic endonuclease 1 (APE1)	Acetylation; K6, K7, K27, K31, K32, K35	+	+	[135, 136, 236–238]
		Phosphorylation; T233	–		[239, 240]
		Ubiquitination; K6, K7, K24, K25, K27, K31, K32, K35		–	[137, 138, 241]
	Polynucleotide kinase phosphatase (PNKP)	Phosphorylation; S114, S126	+	+	[139–141]
		Ubiquitination; K414, K417, K484		–	[139]
	Flap endonuclease-1 (FEN-1)	Acetylation; K354, K355, K377, K380	–		[242]
		Phosphorylation; S187	–	–	[144, 145]
		Methylation; R192	+	+	[146]
		SUMOylation; K168		–	[143]
DNA polymerases	DNA polymerase β (Pol β)	Acetylation; K72	–		[147]
		Methylation; R137, R83, R152	+		[148, 149]
		Ubiquitination; K41, K61, K81		–	[150, 151]
	DNA polymerases δ (Pol δ)	Phosphorylation; S458 of p68 subunit	–		[243]
DNA ligases	DNA ligase IIIα (Lig IIIα)	Phosphorylation; S123			[244]
		Ubiquitination		–	[150, 245]
Accessory proteins	X-Ray repair cross-complementing 1 (XRCC1)	Phosphorylation; S518, T519, T523, C-terminal linker, T284, S371	+	+	[246–252]
		SUMOylation			[152, 253]
		Ubiquitination; BRCA1 C terminus (BRCT II) motif on the C-terminal end		–	[150, 245, 252]
	Poly(ADP-ribose) polymerase 1 (PARP-1)	Acetylation; K498, K505, K508, K521, K524			[254]
		Phosphorylation; S372, T373	+		[255]
		SUMOylation; K203, K482, and K486			[132, 133]
		Ubiquitination		–	[132, 245, 256]

Table 2.
PTMs of BER proteins.

threonine residues [90, 91]. Subsequently, various kinases that phosphorylate serine/threonine and later tyrosine residues were characterized for their ability to modulate protein functions [91–93]. As with acetylation, phosphorylation induces conformational changes in the protein that stimulates its enzymatic activity and modulates protein-protein interactions [92, 94, 95]. Although the initial studies in protein phosphorylation were focused on cellular communications and signal transduction pathways, eventually the critical role of protein kinases and the relevance of phosphorylation/dephosphorylation events in DNA damage response (DDR) are extensively acknowledged, and mass spectrometry-based global screening approaches enabled identification of diverse phosphorylation targets [96, 97].

6.3 Ubiquitination and SUMOylation

Proteins are also posttranslationally modified via isopeptide bond formation with small proteins, which leads to nonlinear polypeptides [98, 99]. Ubiquitin is the first-discovered and well-characterized member of this growing family of small peptide modifiers, which covalently modify diverse proteins involved in chromatin organization, gene expression, signal transduction, DDR, DNA repair, and protein degradation [100–102]. Ubiquitin signals are generated by an enzymatic cascade involving E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. Ubiquitination is a highly dynamic process with deubiquitinases (DUBs) involved in this signaling, and growing evidence indicates the involvement of ubiquitination/deubiquitination in BER, as shown in **Table 2**.

Small ubiquitin-related modifier (SUMO), containing 100 amino acid (aa) residues protein, is ubiquitin-like polypeptide, which is conjugated to substrates in a manner similar to ubiquitination [102, 103]. The SUMO paralogs are synthesized as precursor proteins that are cleaved by a family of SUMO isopeptidases [104]. Mature SUMO is subsequently activated by a heterodimeric E1-activating enzyme Aos1/Uba2 (SAE1/SAE2) forming a thioester bond between its catalytic cysteine and the C-terminal carboxyl group of mature SUMO. Then SUMO is transferred to the catalytic cysteine of the E2-conjugating enzyme Ubc9. In contrast to the ubiquitin system where dozens of E2 enzymes have been identified, Ubc9 is the only known SUMO E2 conjugating enzyme. Finally, an isopeptide bond is formed between SUMO and the substrate by E3 ligases. A consensus SUMO acceptor site has been identified consisting of the sequence ΨKXE, where Ψ is a large hydrophobic amino acid and K is the site of SUMO conjugation [105]. There are at least four SUMO paralogs in humans, SUMO1, SUMO2, SUMO3, and SUMO4, which have more than 1000 protein targets. SUMOylation is highly dynamic and can be reversed by the action of deSUMOylating enzymes (SENPs). SUMOylation regulates protein-protein interactions involving SUMO-interacting motifs (SIMs), and it targets a group of proteins in the same pathway to facilitate association of multiprotein complexes for transcription, nuclear transport, chromatin assembly and modification, chromosome segregation, DNA damage repair, replication, and cell signaling [106, 107].

6.4 PARylation

Poly ADP-ribosylation (PARylation), a crucial PTM that appears rapidly at DNA damage sites, is catalyzed by poly(ADP-ribose) polymerases (PARPs). The human PARP family contains 17 members among which only PARP1, 2, and 3 are involved in DDR [108–111]. PARPs covalently attach the ADP-ribose unit via an ester bond to the carboxyl group of glutamate or aspartate and sometimes also attach to cysteine or lysine of the target proteins [112–114]. PARPs successively

transfer ADP-ribose units from NAD^+ to produce PAR chains containing up to 200 ADP-ribose units; however, in many cases, only single mono ADP-ribose moiety is transferred to the target proteins. Strand breaks in DNA activate PARP1, the founding and predominant member of the PARP family; the primary substrate of PARP1 is itself. Many proteins in the DDR pathways as well as the damage processing enzymes interact with PARP1 and/or are PARylated [112, 115]. In cells, PARylation/dePARylation is tightly and dynamically regulated; the PAR polymers are degraded by PAR glycohydrolase (PARG), possessing both exoglycosidic and endoglycosidic activities, and release free ADP-ribose moieties [116–118]. ADP-ribosyl-acceptor hydrolase (ARH) also exhibits PAR-degrading activity, although it has only exoglycosidase activity [119, 120]. Retention of PAR chains in cells triggers apoptotic cell death [121]. Although PARP1 interacts with the SSBR sensor XRCC1, as well as with other BER/SSBR proteins, and enables early recruitment of XRCC1 to the DNA lesions [122–126], there is no convincing evidence for PARylation of BER/SSBR proteins.

6.5 Cross-talks between different PTMs, their regulation, and effect on BER

Proteins employ diverse PTMs sequentially or concurrently to expand their repertoire of functions, thereby impacting global cellular signaling. The best example is the disordered N-terminal tail of histone H3, which has multiple sites for acetylation, methylation, phosphorylation, ubiquitination, and SUMOylation [69, 70]. These PTMS could act synergistically or via reciprocal exclusion to modulate chromatin organization, thus affecting the transcriptome. The same Lys residues (K9, K27) in H3 are targets for both acetylation (marker of active chromatin) and methylation; however, monomethylation of these residues are markers of active chromatin, while di- and trimethylation are associated with repression. Recent evidence on BER enzymes, summarized below, suggests that specific modification at one site can dramatically influence another modification at a different site, which may critically impact BER activity.

Cyclin-dependent kinase (CDK)-mediated phosphorylation of UNG2 (nuclear UDG) in S phase signals its ubiquitination-dependent degradation, and CDK-inhibitor roscovitine prevents such degradation [127, 128]. This suggests that phosphorylation-induced conformational change in UNG2 is a prerequisite for ubiquitination.

In the case of TDG, acetylation inhibits its repair activity by two distinct mechanisms. TDG acetylation at K94, K95, and K98 by p300/CBP suppresses BER by preventing APE1 recruitment to the damage site [129]. Protein kinase C (PKC)-mediated phosphorylation at S93, S96, and S99, close to the acetylation sites, may promote repair by sterically blocking repair-inhibitory acetylation of adjacent lysine residues [130]. On the other hand, SUMOylation at K341 inhibits TDG's interaction with CBP, preventing its acetylation and thereby promoting BER [131].

PARP1, SUMOylated at K203 and K486, is a target for ubiquitination and degradation, which is believed to be the mechanism for its turnover [132]. In contrast, PARP1's SUMOylation at K482 does not degrade the protein, rather stimulates PARylation of chromatin-associated proteins [133]. On the other hand, acetylation of PARP1, which stimulates its transactivation function, is inhibited by K486 SUMOylation. Thus, K486 SUMOylation restrains PARP1's transactivation function [134].

While acetylation of APE1 enhances its stability in chromatin and enzymatic activity [135, 136], CDK5-mediated phosphorylation enhances its ubiquitination and degradation [137, 138]. Thus, it is possible that phosphorylation and acetylation are mutually exclusive, acetylation stabilizing the protein, and phosphorylation guiding to its degradation.

In the case of PNKP, ATM-dependent phosphorylation was shown to prevent ubiquitination and hence its degradation. Thus, in response to oxidative stress, ATM phosphorylates and stabilizes PNKP in order to activate a coordinated DDR pathway [139–141]. Furthermore, PNKP interacts with the deubiquitination enzyme ataxin-3 (ATXN3), which enhances its stability and phosphatase activity [142].

Phosphorylation of FEN-1 by CDK1 at S187 was shown to promote SUMOylation at K168, which enhanced its polyubiquitination-dependent degradation [143]. Phosphorylation inhibits FEN-1's flap endonuclease activity [144, 145], which cross-talks with methylation, a lesser studied PTM of BER proteins. Methylation by arginine methyltransferase 5 at R192 prevents this phosphorylation and thus is proposed to be essential for the repair activities of FEN-1 [146]. Thus, in response to oxidative stress in cycling cells, methylation of FEN-1 could be a critical requirement for LP-BER.

Acetylation of Pol β at K72 inhibits its dRP lyase activity [147], and this could account for acetylation-induced inhibition of enzymatic activity and switch from SN-BER to LP-BER. Methylation of Pol β at R137 has no effect on dRP lyase or DNA polymerase activities but inhibits its interaction with PCNA [148] and could thus be predicted to inhibit LP-BER. In contrast, R83 and R152 methylation enhanced Pol β's DNA binding and increased processivity [149]. Cellular Pol β level appears to be maintained by two ubiquitin E3 ligases, Mule and CHIP. DNA Pol β is monoubiquitinated by Mule, which in turn is recognized and polyubiquitinated by CHIP in undamaged cells. In response to oxidative stress, it is deubiquitinated, thus ensuring its stability and oxidized base damage repair [150, 151].

A recent study shows how PARylation stimulates SUMOylation [152]. In response to DNA strand breaks induced by alkylating agent methylmethanesulfonate (MMS), PARP1 is activated and synthesizes PAR chains; this promotes recruitment of SUMO E3 TOPORS to XRCC1, which facilitates XRCC1 SUMOylation. XRCC1 SUMOylation recruits Pol β at the damaged sites and thus ensures completion of BER.

7. Does chromatin organization affect BER? Understanding BER at the chromatin context

BER, as studied *in vitro* with naked DNA substrates, involves sequential enzymatic steps in which each enzyme utilizes the product of the previous step as the substrate. This observation inspired the prevailing dogma that the sequential steps in BER involves the hand-off process where the product of one step is handed over to the enzyme in the next step [153, 154]. Later steps generate intermediate product lesions that are more toxic than the original lesions. The BER intermediates such as AP sites and SSBs, which are highly mutagenic, interfere with replication and transcription, and hence the entire BER steps must be coordinated once the repair is initiated [155–158]. Cumulating evidence suggests that the BER proteins act in concert beyond simply recognizing and acting upon the product of the previous step, by being present at the site of the original lesion [43, 52, 61, 62, 64, 65, 125, 159, 160]. This is the basis for the emerging paradigm of "preformed BER complexes," named, "BERosomes" in mammalian cells. Being an integral part of complexes, it may be easier for the BER intermediates to be handed over to the next enzyme, which likely undergoes allosteric changes after binding to its substrate. Recent studies in our and collaborators' labs suggest that these "BERosomes" are constitutively chromatin-bound to ensure prompt repair in the event of any threat [62, 135, 161]. Simultaneously, recent interests in the BER field have evolved toward deciphering the role of different chromatin factors and the underlying chromatin remodeling in oxidized base repair.

Several *in vitro* studies showed reduced BER activity with reconstituted core nucleosome particles, where every step during repair of diverse lesions was found to be inhibited by histones [162–170]. Overall BER efficiency is strongly inhibited by the presence of nucleosomes, which interfere with the interaction between the repair proteins and their substrate lesions, thereby compromising physical interaction and catalysis. Because oxidized bases perturb the DNA structure only mildly [170], whether chromatin remodeling occurs during BER was questionable. But, as BER efficiently occurs in cells, the results from these *in vitro* experiments imply that chromatin rearrangement occurs at oxidized DNA damage sites *in cells*, as was shown in the case of repair of DSBs, UV ray-mediated damages, and mismatched base pairs [171–173].

An inverse correlation exists in cells between BER and chromatin compaction. ROS induces assembly of BER complexes preferentially on open chromatin regions [174], as we have also observed that the BER complexes are constitutively present on actively transcribing sequences [175]. Interestingly, BER is involved during active CpG demethylation in promoters, mediated by TET dioxygenase(s) during transcriptional activation [176–180]. The TET proteins oxidize 5mC to 5hmC, 5fC, and 5caC; 5fC and 5caC are the TDG substrates. Thus, this coordination between CpG DNA demethylation, an epigenetic process essential for chromatin decondensation during transcriptional activation, and base damage repair supports our notion that "open-chromatin prefers BER activity across the genomic landscape" and highlights a regulatory link between epigenetics, chromatin remodeling, and BER.

Various ATP-dependent chromatin remodeling (ACR) complexes, which play significant roles in protein/DNA and protein/protein interactions in chromatin and regulate transcription, DNA repair processes such as DSB repair (DSBR), nucleotide excision repair (NER), and cross-link repair, also affect BER. ACR complexes utilize the energy of ATP hydrolysis to restructure nucleosomes on chromatin [181–183], thereby affecting gene expression profile and DNA repair. Four structurally related, but functionally distinct, ACR complex families were identified: SWI/SNF (switching defective/sucrose nonfermenting; most extensively studied), ISWI (imitation switch), CHD (chromodomain, helicase, DNA binding), and INO80 (inositol requiring 80). *In vitro* BER studies with reconstituted nucleosomes showed enhanced repair activity in the presence of purified SWI/SNF or ISW1/ISW2 complexes [184–186]. There are some indirect evidences of ACR during BER in yeast and mammalian cells. Depletion of STH1 (ATPase subunit of RSC, a member of SWI/SNF family) causes genome-wide BER inhibition and thus emphasizes a link between chromatin organization and BER [187]. In a recent study, depletion of ALC1/CHD1L, another member of SWI/SNF, compromises chromatin relaxation, associated with BER inhibition and increased sensitivity to MMS and H_2O_2 in chicken cells [188]. On the contrary, INO80 deficiency in MMS-sensitive yeast cells has no effect on genome-wide BER [189]. K56 acetylation in histone H3 is increased in chromatin of both yeast and mammalian cells following MMS treatment, which generates alkylated base substrates for BER, [190, 191]. H3K56Ac was also found to be enriched at DSBR sites and responsible for SWI/SNF complex recruitment during transcription [192]. Thus, it would be interesting to examine if any specific PTM(s) would target ACR after oxidized base damage and illuminate the phenomenon of ACR during BER. In any event, additional studies are required to test if ACR plays a role in enabling BER in condensed chromatin. It would be also of interest to explore if the BER proteins possess inherent chromatin remodeling activities, similar to the NER proteins, which have SWI/SNF domains [193–195]. Though no known BER proteins have SWI/SNF domains, the XRCC1-Lig IIIα complex could disrupt nucleosomes *in vitro* and enable BER completion [166].

Poly-ADP-ribosylation of histones by PARP1 after genome damage adds negative charge on histones and disrupts histone-DNA interactions, thereby promoting chromatin decondensation and enhancing interaction between the proteins involved in DNA transactions and DNA [111, 196–198]. This could increase DNA accessibility to the BER proteins. Although PARP1's role in regulating transcription is well established, this would link chromatin remodeling to BER.

Nucleosomes pose obstruction to all DNA transactions and are likely disassembled to allow DNA replication, repair, and transcription, followed by their reassembly, which utilizes both parental histones and newly synthesized histones. Such replication-coupled nucleosome assembly in the S phase or replication-independent, transcription-coupled assembly throughout the cell cycle involves histone chaperones functioning at multiple steps of nucleosome formation [172, 199, 200]. Replication-coupled nucleosome assembly is aided by the chromatin assembly factor (CAF-1) and Rtt106 with the help of antisilencing function 1A (ASF1A) protein. Histone cell cycle regulator (HIRA) protein, along with Daxx, mediates replication-independent nucleosome assembly. While exploring chromatin-bound BER complexes, we serendipitously discovered CHAF1A (the largest subunit of CAF-1, along with other subunits CHAF1B and RBBP4), ASF1A, and various H3/H4 variants in the immunoprecipitation complex of NEIL1 or acetylated NEIL1 (201; unpublished). This underscores the importance of the diverse chromatin components in preformed "BERosomes," which could regulate oxidize base repair in chromatin. We showed that ROS-induced oxidized base lesions caused transient dissociation of CHAF1A, ASF1A, and histones from the BER complexes and were restored back after repair completion. The repair activities of NEIL1 and OGG1, as well as complete cellular BER, were found to be inhibited by CAF-1, as well as the CHAF1A monomer [201]. So, we propose a hypothesis of temporal regulation of BER by the histone chaperones, whose dissociation from BER complexes is essential to initiate BER [201]. This has been illustrated in **Figure 2**.

Recently, we discovered acetylation of NEIL1 at the disordered C-terminal K296-K298 by p300, which enhances its activity, and found that acetylated NEIL1 (AcNEIL1) could be detected only in the chromatin fraction and not in the soluble nuclear fraction [161]. Although the nonacetylable NEIL1 3KRmutant (Lys296–298 substituted with Arg) translocates to the nucleus and binds to chromatin, presumably due to retention of positive charges as in the WT enzyme, it forms less stable BER complexes with the histones, histone chaperones, and downstream BER proteins. Thus, as proposed earlier [65], the positive charge cluster in the disordered C-terminal region is required for NEIL1's nonspecific DNA binding, after which acetylation occurs on the chromatin. Hydrophobic interaction of NEIL1 after acetylation-mediated charge neutralization probably stabilizes NEIL1's complexes with nucleosome components and downstream BER proteins. Consequently, cells with acetylable NEIL1 exhibit enhanced BER efficiency and are less sensitive to oxidative stress. It is thus likely that unmodified NEIL1 binds to chromatin nonspecifically, and acetylation specifically at the promoter regions of actively transcribing genes by enhanced p300 activity actually stabilizes NEIL1's (and possibly other DG's) BERosomes on these preferred chromatin regions (**Figure 3**), which warrants further investigation.

In a separate study, while investigating how APE1 repairs AP sites in cells, our collaborator's lab found that acetylated APE1 (AcAPE1), like AcNEIL1, is exclusively and stably chromatin-bound throughout the cell cycle [135]. APE1 undergoes acetylation after binding to AP sites in chromatin, which enhances its enzymatic activity. In the absence of APE1 acetylation, cells accumulated AP sites and exhibited higher sensitivity to DNA damaging agents. We predict that other BER proteins OGG1 and MPG, whose repair activity is enhanced by acetylation, are similarly stabilized in chromatin-bound state.

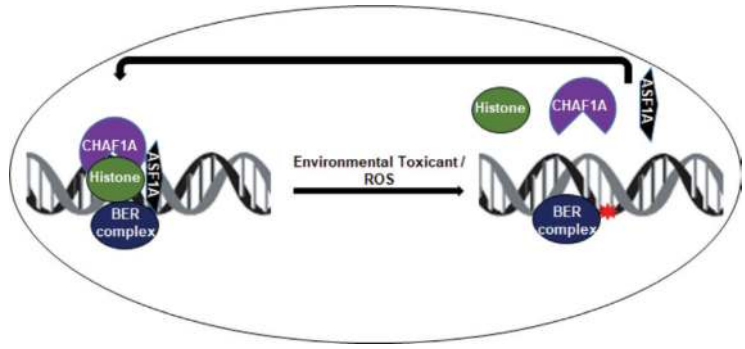


Figure 2.
A schematic showing chromatin-bound BER complexes with histones and histone chaperones. ROS-induced damage causes transient dissociation of histones and histone chaperones to initiate BER, which are restored back after repair completion.

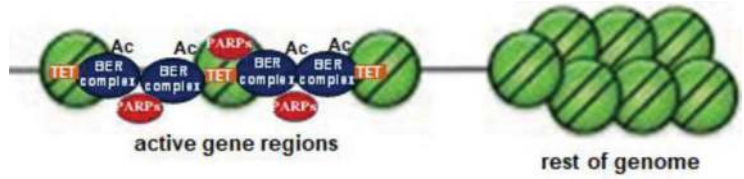


Figure 3.
An illustrative view of "open" chromatin regions, containing bound "BERosomes" with histones, histone chaperones, PARPs, TETs, etc., for preferential repair of these transcriptionally active regions.

8. Future perspectives

The genome-wide impact of various PTMs in the cross-talks among BER proteins, which dictates the overall repair efficiency, thus preserving genomic integrity against genotoxic insults from both endogenous and external oxidative stress, has not been investigated. In this NextGen era, holistic, whole-genome scanning approaches, although a daunting challenge, make it likely to map individual PTMs of BER proteins, the kinetics of their formation and removal, and their correlation with both intrinsic and ROS-induced BER efficiency across the genomic landscape. Because histone PTMs have been well established in chromatin remodeling, it is also important to explore how specific histone PTMs interfere with the BER PTMs.

The Access-Repair-Restore model [182, 202] provides an accepted view of DNA repair in chromatin, where chromatin remodeling is essential for the DNA repair machineries to get access to the damaged DNA. For BER, it is still not clear how chromatin remodeling and the associated histone PTMs initiate BER. The BER complexes constitutively bind to "open" chromatin regions, and chromatin remodeling could assist specific enzyme-substrate binding and enzyme catalysis needed to initiate and propagate BER. Moreover, although chromatin remodeling has been found to enable BER, the enhanced repair activity may be simply due to ROS-induced stimulation of BER genes' expression or their specific PTM (acetylation), as has been shown by us [203–205], along with enhanced substrate binding in "open" chromatin. This may underestimate the contribution of ACR complexes at oxidized base lesion sites to enhance BER. Alternatively, in cells, chromatin remodeling-stimulated BER could be linked to replication and transcription, similar to transcription-coupled NER, which always occurs on "open" chromatin [206]. Indeed, repair of oxidized bases preferentially occurs in the transcribed strand [175], which could be assisted by Cockayne syndrome protein B (CSB), a NER factor, in transcription-coupled but NER-independent fashion [207]. Because BER/SSBR proteins such as PARP1 and APE1 are emerging as potential

therapeutic targets [208–212], understanding if and how chromatin remodeling impacts BER activity is crucial to manipulating BER for effective modulation of repair activity in cancer cells. This would provide better efficacy and specificity in cancer therapy.

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Conflict of interest statement

The authors declare that there are no conflicts of interest associated with this study.

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