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Facilitation of Base Excision Repair by Chromatin Remodeling

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Abstract

Base Excision Repair (BER) is a conserved, intracellular DNA repair system that recognizes and removes chemically modified bases to insure genomic integrity and prevent mutagenesis. Aberrant BER has been tightly linked with a broad spectrum of human pathologies, such as several types of cancer, neurological degeneration, developmental abnormalities, immune dysfunction and aging. In the cell, BER must recognize and remove DNA lesions from the tightly condensed, protein-coated chromatin. Because chromatin is necessarily refractory to DNA metabolic processes, like transcription and replication, the compaction of the genomic material is also inhibitory to the repair systems necessary for its upkeep. Multiple ATP-dependent chromatin remodelling (ACR) complexes play essential roles in modulating the protein-DNA interactions within chromatin, regulating transcription and promoting activities of some DNA repair systems, including double-strand break repair and nucleotide excision repair. However, it remains unclear how BER operates in the context of chromatin, and if the chromatin remodelling processes that govern transcription and replication also actively regulate the efficiency of BER. In this review we highlight the emerging role of ACR in regulation of BER.

Keywords

Chromatin remodeling; DNA damage; nucleosomes; glycosylase; AP endonuclease; Polymerase β; ligase; SNF2; BRG1; PARP-1; SWI/SNF; RSC; ISWI; INO80

1. Introduction

The folding of chromosomes into chromatin, entailing distinct levels of compaction among a variety of DNA-associated proteins, is essential for assuring the organization and condensation of the genetic material in the small volume of the nucleus. The first order of chromatin compaction is that of the nucleosome, its core consisting of ~147 bp DNA wrapped ~1.7 times around an octamer of DNA-contacting histone proteins (2 each of the

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four histones, H2A, H2B, H3, and H4), separated by short stretches of linker DNA (~20 – 90 bp in length) and associated linker histones (H1 or H5) [1]. The inherently inaccessible nature of the DNA within chromatin is the mechanism by which this structure regulates DNA dependent activities such as transcription and replication. Whether it is in response to environmental stimuli, or the differentiation of cells in a multicellular organism, it is the chromatin, and its epigenetic function of allowing selective access of transcription factors to specific DNA sequences, that promotes expression of the proteins necessary for cellular function. Access to target DNA sequences in chromatin is granted through the coordinated action of ATP-dependent chromatin remodeling (ACR) complexes, large protein assemblies that utilize the energy of ATP hydrolysis by a central ATPase subunit to slide, eject, and restructure nucleosomes [2]. Often recruited to chromosomal targets by posttranslational modifications to histones, these ACR complexes have some overlapping functions but also play distinct roles in gene expression, as well as regulating other DNA metabolic activities in the cell. Notably, in the tightly controlled genomic environment, in which the prevention of both specific and non-specific protein-DNA interactions are essential for its function, chromatin acts as an impediment for the DNA repair systems necessary for maintenance of the genomic material itself [3,4].

The DNA repair systems in the cell play a key role in prevention of mutations and chromosomal rearrangements, and ensure genomic stability, through the recognition and removal of the respective DNA lesions for which each is responsible. Among these is Base Excision Repair (BER) that is responsible for remediation of the numerous and wide ranging chemical modifications to bases. These potentially mutagenic lesions include, but are not limited to, many species of oxidation, methylation, deamination or complete loss of the base (from hydrolysis of the N-glycosidic bond), which occur at rates estimated as high as 100,000 lesions/cell/day [5,6]. As the majority of DNA in the eukaryotic cell is associated with nucleosomes, many chemical modifications normally repaired by BER are physically occluded by chromatin-associated proteins and thus could remain unrecognized or unrepaired indefinitely. Hence, it is logical to postulate that factors that provide accessibility to the DNA for transcription and replication, including the activity of ACR complexes, contribute to the efficiency of BER. Indeed, there is already strong evidence for a directed active role of these remodeling factors in facilitating other DNA repair systems, including double-strand break repair (DSBR) and nucleotide excision repair (NER) [7] (see elsewhere in this issue).

In this review, we will discuss the evidence for the role of the ACR complexes in promoting BER. We summarize the available data that support the conclusion that BER is enabled by the processes of ACR, though it currently remains unclear if these chromatin remodeling activities are employed to directly support this excision repair system.

2. Base Excision Repair

BER constitutes the highly conserved stepwise process of a series of enzymes that each act upon the product of the previous step for the removal of base lesions and intermediates created at each stage of repair (see elsewhere in this issue and Fig. 1). Repair is initiated by recognition of a chemically modified base by one of a number of different DNA

glycosylases, each with a range of specificity for distinct lesions, such that together they recognize a wide breadth base modifications. Upon binding to the lesion, the glycosylase cleaves the N-glycosidic bond, separating the damaged base from its deoxyribose sugar moiety, creating an apurinic/apyrimidinic (AP) site [8,9]. AP sites can also form by the spontaneous hydrolysis of the N-glycosidic bond, and these abasic lesions, like the modified bases, are potentially mutagenic when replicated [10,11]. In metazoans, AP sites are bound by the primary AP endonuclease APE1, which cleaves the DNA backbone on the 5′ side of the abasic deoxyribose phosphate, creating a single-strand break (or nick) in the DNA [12]. The synthesis step of BER employs either repair polymerase Pol β which binds to the cleaved abasic sites and uses the intact, undamaged strand as a template for DNA synthesis, adding a single nucleotide (called short patch repair), or one of the processive polymerases, Pol δ or Pol ε adding up to 13 nucleotides (called long patch repair), to the 3′ hydroxyl group of the nucleotide 5′ of the nick [11]. The remaining deoxyribose phosphate is removed by the dRPase activity of Pol β in short patch repair, whereas the 5′ stretch of nucleotides displaced during long patch repair is cleaved by the flap endonuclease FEN-1 [13]. The final step of BER is ligation of the nicked strand, generally performed by DNA ligase IIIα in a complex with its partner protein, XRCC1 [14]. In addition to the enzymes responsible for distinct steps of BER, the protein PARP-1 (Poly (ADP-ribose) polymerase-1) assists the repair process by binding to the single-strand break intermediate and, by synthesizing poly(ADP-ribose) polymers affixed to itself and other repair factors (PARylation), enhances recruitment of Pol β and XRCC1-DNA ligase IIIα [15–18].

Each step of BER requires direct, unobstructed access to DNA for its associated activity. Moreover, since each step of BER generates a DNA lesion with greater mutagenic and toxic severity than that of the original base lesion (e.g. AP sites and single strand breaks), it is essential that the entire process of BER be coordinated and balanced once repair is initiated [19]. Indeed, some BER proteins act in a concerted effort beyond simply recognizing the product of the previous step, with their presence at the site of repair promoting the activity of other steps in the process [20–23]. Thus, completion of BER in the chromatin substrate requires more then just accommodation of each individual BER enzyme, but also the time and space in which the complete process can be completed.

2.1 BER in the context of chromatin *in vitro*

There is strong evidence for reduced activity of BER in chromatin based on several *in vitro* studies that measured individual activities of purified recombinant BER proteins on reconstituted nucleosome core particles (NCPs) (see elsewhere in this issue). Using NCPs with different DNA lesions as templates for repair studies it has been found that, generally, each step of BER is negatively impacted by the presence of histones. Glycosylases that recognize uracil residues or oxidative lesions in nucleosomes interact efficiently with target bases when the DNA backbone is outwardly-oriented; that is, facing away from the histones. Conversely, access to inwardly-oriented lesions is greatly reduced, likely requiring transient dissociation of the DNA from the histones, either by unwrapping at the ends of the DNA, or rotational movement of the DNA on the nucleosome surface [24–31]. Recognition of abasic sites by APE1 is also impaired on the nucleosome surface in an orientation-specific manner [32,33]. However, in general APE1 is inhibited by the presence of histones, even at

outward-oriented lesions. The DNA synthesis step of BER by Pol β, which requires a large degree of distortion in the template strand of the DNA (~90°), is also impacted in nucleosomes. Repair of the gapped BER intermediate is either reduced [31,34] or completely eliminated [25,35], depending on the DNA sequences and the positioning of gaps along the DNA. Rotational orientation of the DNA gap also influences Pol β efficiency, but the effects differ depending on the translational position along the DNA [31]. The final ligation step by DNA ligase IIIα-XRCC1 is completely inhibited by the presence of histones, likely due to the requirement of the complex to encircle its substrate [30]. Thus, the presence of nucleosomes decreases efficiency of BER by directly occluding the repair proteins from their respective lesions, thus preventing the substrate dynamics necessary to accommodate the molecular interactions and conformations required for catalysis. Since BER efficiently occurs in cells, the results from these *in vitro* experiments imply that chromatin rearrangement happens at DNA damage sites *in vivo*.

2.2 BER in the context of chromatin *in vivo*

A number of studies in cells demonstrate an inverse correlation between the level of chromatin compaction and BER activity. Oxidative stress of HeLa cells triggers preferential assembly of BER complexes on open chromatin regions, including the OGG1 glycosylase that recognizes oxidized guanine, but are excluded from the more compact heterochromatin domains [36]. In addition, studies with stem cells demonstrate robust and highly efficient BER in pluripotent cells, in which chromatin is generally in a more open, less compact form. With cell differentiation, as chromatin assumes a less accessible conformation, there is progressive decrease in BER capacity [37,38]. Furthermore, it has been recently reported that only the initial step of BER (base removal) occurs in highly inaccessible sperm chromatin. The rest of the repair process is truncated and downstream BER components are not detectable on the DNA in the sperm cell [39]. These observations suggest that open chromatin allows more efficient recruitment, assembly and activity of BER proteins than highly compacted chromatin.

Notably, BER is actively involved in the process of DNA demethylation during mammalian genome reprograming, such as the resetting of epigenetic information during primordial germ cell development [40]. Such demethylation of DNA occurs in the context of chromatin decondensation, which is accompanied by increased activation of BER. This results from an up-regulation of BER factors at both levels: transcription and translation. Thus, the regulation of epigenetics during development highlights a regulatory link between chromatin compaction, chromatin remodeling and BER efficiency [40].

Intriguing evolutionary evidence also implicates reduced efficiency of BER in chromatin. By comparison of DNA sequences in proximity of transcriptional start sites in two strains of Japanese killifish (a.k.a. Medaca), a periodic pattern of increased genetic variation was discovered to correlate with the conserved nucleosome positions in those regions [41]. Single nucleotide polymorphisms (SNPs) peaked at a 200 bp periodicity, being highest at the nucleosome dyads, and lowest at the linker regions between nucleosome cores, underscoring the increased mutagenesis associated with nucleosome placement. A similar nucleosome-driven pattern of SNPs is seen at transcriptional start sites in humans vs.

chimpanzees [42]. Finally, among humans SNPs were found to closely correlate with nucleosome positions throughout the genome [43].

3. ATP-dependent chromatin remodeling

There are four distinct, structurally related families of ACR complexes: SWI/SNF (switching defective/sucrose nonfermenting), ISWI (imitation switch), CHD (chromodomain, helicase, DNA binding) and INO80 (inositol requiring 80), classified based on their homologous central ATPase subunits from the SWI2/SNF2 superfamily [2,44,45]. See Table 1 for a brief summary of the roles of ACR complexes in select cellular activities.

The SWI/SNF subfamily is the most extensively studied and best characterized in both yeast and mammalian systems. The mammalian SWI/SNF analog BAF (BRG1 associated factors) has diverse functions in early embryonic development, stem cell proliferation and differentiation, and in development of the heart, muscle, and immune and neuronal systems [7,46]. The core ATPase subunit of the BAF complex, BRG1, has been reported to be frequently inactivated in many cancer cell lines and primary tumors such as lung, pancreatic, breast, prostate, and colon cancers [47]. In addition, BRG1 is known to bind or regulate the expression of proteins involved in cancer development, such as MYC [48], P53 [49], BRCA1, beta-catenin, LKB1, FANCA and RB [50]. Furthermore, it has been recently found that loss of SWI/SNF leads to genome instability in human lung cancer [51].

ISWI complexes control nucleosome spacing, regulate gene transcription, stimulate replication in heterochromatin, and generate and maintain higher order chromatin organization [52]. ISWI complexes are also implicated in regulation of DNA repair activities, including homologous recombination, non-homologous end joining and NER [52].

The CHD family of ATP-dependent chromatin remodeling complexes are involved in nucleosome spacing, chromatin assembly, and nucleosome sliding. In addition, these complexes have been implicated in embryonic development and tumor suppressor functions [53–55]. The CHD complexes are emerging players in the maintenance of genomic stability through: the regulation of the double strand break response (including repair, checkpoint arrest, apoptosis and/or senescence), the response to oxidative stress, and p53-mediated tumor suppression.

The INO80 complexes regulate nucleosome sliding and eviction. They have cellular functions as diverse as regulators of transcription, DNA replication, double-strand break repair, NER and DNA damage checkpoint responses [56–60].

3.1 Impact of ACR activity on BER efficiency

Selected *in vitro* studies provided strong evidence for enhanced BER of nucleosome DNA in the presence ACR complexes. Purified ISW1 and ISW2 chromatin remodelers significantly facilitate the polβ synthesis step in uracil-containing oligonucleosomes [61]. Likewise, purified SWI/SNF complex greatly stimulated glycosylase, AP endonuclease and Polβ activities in mononucleosomes containing the oxidative lesion 8-oxoG [35]. In addition,

removal of 8-oxoG from dinucleosomes, either in the linker DNA or in one of the two nucleosome cores, was enhanced in the presence of purified RSC (Remodels Structure of Chromatin) complex, a member of SWI/SNF subfamily [62]. Notably in this study, access to the lesion in linker DNA by OGG1 was also provided by the histone chaperone NAP-1, which can remove histone H1 from nucleosomal DNA. However, NAP-1 alone was not sufficient to allow lesion access within a nucleosome core without the remodeling activity of the RSC complex [62]. Thus, it is possible that purified ACR complexes are capable of remodeling nucleosomes in the presence of recombinant BER proteins, which in turn have increased activity on their otherwise difficult to access substrates.

There are also *in vivo* studies that implicate ACR activities in BER, although evidences are limited and mostly indirect. Yeast mutant cells deficient in subunits of the SWI/SNF (rsc2, rsc1, sth1, sfh1, snf2, snf5) and INO80 (ino80) remodeling complexes showed increased sensitivity to the DNA alkylating agent methyl methanesulfonate (MMS) [63–65], suggesting the potential role of ACR in facilitating removal of methylated DNA bases. Our recent studies in yeast provide solid evidence implicating the RSC in regulation of BER. We found that conditional depletion of STH1, the essential ATPase subunit of RSC, results in a substantial, gene-specific and genome-wide inhibition of BER. Indeed, depletion of STH1 leads to a genome-wide reduction in chromatin accessibility to micrococcal nuclease digestion. Albeit correlatively, these data highlight the important role of RSC in regulation of both BER and chromatin structure in yeast [66]. MMS-sensitive yeast cells deficient in INO80 remodeling activity do not show a genome-wide reduction in BER, implying that INO80 is not involved in promoting BER in chromatin. However, this does not exclude the possibility that INO80 may have a specialized role in promoting BER in specific chromatin regions, such as silent heterochromatin [65]. In fact, INO80 has been shown to promote NER at the silent HML locus in yeast, but was not necessary for global genomic NER [67].

Examination of posttranslational modifications to histones that target recruitment of ACR complexes after DNA damage could be indicative of chromatin remodelling during BER. For instance, acetylation of histone H3 at lysine 56 (H3K56Ac) is increased in chromatin following MMS treatment in both, yeast and mammalian cells [68,69]. H3K56Ac is concentrated at sites of double strand break repair and is responsible for SWI/SNF complex recruitment during transcription [70]. However, histone modifications and activation of ACR in response to DNA-damaging agents may be part of the cellular DNA damage and repair response [69]. Indeed, after DNA damage H3K56Ac is enriched near genes involved in response to DNA damage, which is more indicative of transcription-associated enhancement than a lesion-targeted reaction.

Collectively, a number of independent studies provided evidence for the ability of ACR complexes to enhance BER activity. However, the activities of these two cellular processes may simply be coincidental, with BER occurring in chromatin primarily where (and when) DNA is accessible, such as at sites undergoing remodeling. Thus, although it seems likely, it has yet to be determined if ACR has a specific function in condensed chromatin to facilitate assembly of BER proteins and coordinate the repair process. In most experiments, the caveat of assessing cells with defects in ACR is that reduction in such remodelling activities affects other cellular processes like transcription that, in turn, impact BER activity. Fore example,

loss of catalytic subunits, like the yeast RSC and STH1 correlates with significantly decreased expression of the BER AP endonuclease APN1 [66], and down-regulation of *APN1* has been seen in microarray studies on rsc2 mutant cells [71].

4. Different requirements for ACR in DNA repair

In both yeast and mammals, ACRs have been directly implicated in the coordination of the spatio-temporal steps of NER and double strand break repair. As direct regulation of these repair processes falls under the prevue of ACR complexes, it seems reasonable to assume that BER, which is responsible for repairing the majority of DNA lesions in the nucleus [5,6], would be granted a similar accommodation. However, there are some key differences between the two excision repair pathways, and the damage they are responsible for mitigating, which do not predict identical responses by, or requirements for, ACR.

The nature of the DNA lesions repaired by the NER complex, and the chromatin-disrupting activities of some of its own proteins could prime ACR. The bulky DNA adducts recognized by NER are helix-distorting lesions that enhance the dynamics of the DNA on the histone octamer in nucleosomes [72], effectively initiating the process of DNA accessibility and likely aiding NER protein binding without intervention of other factors. On the other hand, the base modifications recognized by BER generally cause minimal disruption to the DNA helix or perturbation of the nucleosome [31], such that any increase in exposure of the lesions to repair proteins would likely require intervention by nucleosome-disrupting activity. In addition, some NER proteins have SWI2/SNF2 domains and possess chromatin-remodelling activities. For example, the human CSB/ERCC6 complex [73], which remodels chromatin in an ATP-dependent manner [74], and the yeast Rad16, which translocates along DNA and changes chromatin structure by modulation of superhelical torsion [75]. In addition, Rad16 mediates acetylation of histone H3 via the histone acetyltransferases Gcn5, initiating the modification-associated recruitment of ARC complexes to the sites of DNA repair [76]. Though no BER enzymes have the SWI2/SNF2 domains, the XRCC1-DNA ligase IIIα complex has the ability to disrupt nucleosomes *in vitro*, playing a role in assisting the DNA synthesis and ligation steps of BER in the context histone proteins [30]. There are also evidences for direct interactions between NER and ACR subunits, which have not yet been found in BER. The NER lesion recognition proteins Rad4 and Rad23 interact with proteins of the SWI/SNF complex after UV exposure in yeast [77], and the BRG1 ATPase of the mammalian SWI/SNF complex interacts with NER-initiating proteins DDB2 [78] and XPC [79]. Yeast Ino80 of the INO80 ACR complex also interacts with the Rad4-Rad23 repair complex [67], though it remains unclear if INO80 plays a role in initiation of repair, or in restoration on nucleosomes after lesion removal.

The involvement of PARP-1 in BER [15–18] connects repair with the potential regulation of chromatin condensation. PARP-1 can ADP-ribosylate histones H1 and H2B, adding a negative charge that is thought to disrupt histone-DNA interactions and loosen chromatin for increased DNA accessibility [80,81]. In addition, PARP-1 activity inhibits the histone demethylase KDM5B, thus promoting a more open, less compacted chromatin state [82]. However, the chromatin-modifying activities of PARP-1 are primarily associated with its role in regulating transcription [83].

5. Concluding remarks and future directions

The general view of DNA repair within the chromatin landscape is largely based on the Access-Repair-Restore model proposed for NER, which underscores the necessity of chromatin rearrangements to facilitate the accessibility of the DNA repair machinery to damaged DNA [84,85]. However, there remains a dearth in our understanding of how ACR, and the posttranslational modifications of histones that direct it, assists in the initiation and propagation of BER. While chromatin remodeling activity clearly enables BER, the enhanced repair activity may be based simply on a combination of promoting expression of BER genes and increased substrate binding opportunities in open chromatin, without any "intentional" assistance by ACR complexes at DNA lesions.

In vivo, enhancement of BER activity by ACR may be a result of BER function during other chromatin-disrupting activities in the cell, including replication and transcription, effectively riding the coat-tails of these processes that already involve removal of nucleosomes from the DNA. This would be akin to the transcription-coupled repair branch of NER, which always occurs on open DNA because it is initiated during transcription, when the RNA polymerase stalls at a bulky lesion in the transcribed strand and stimulates recruitment of NER factors [86,87]. While BER is not likely initiated in the same manner (as oxidative lesions, for example, do not generally stall RNA polymerases [88]), BER does seem to be enhanced on transcribed strands [89]. This apparent transcription coupling is likely due to the impact of BER intermediates (AP sites and nicked/gapped DNA) on RNA polymerase progression, and it is unclear if resolution of these lesions is completed by BER or by transcription coupled NER [24].

Any cellular process that regulates BER plays a role in genomic maintenance, mutagenesis, and eventually human longevity. Ultimately, understanding if and how ACR impacts BER activity is crucial for realizing the ramifications of using pharmaceuticals that modulate histone modifications and chromatin remodeling. While direct inhibition of BER may serve to sensitize tumor cells to chemotherapy, subtle manipulation of the repair pathway through ACR may allow for better tissue targeting, tighter modulation of repair capacity, and better overall efficacy of cancer treatment.

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Highlights

- There are 4 major ATP-dependent chromatin remodeling (ACR) families in eukaryotes
- ACR is responsible for regulation of transcription, replication, and some repair processes
- BER is responsible for the repair of most chemical modifications to DNA bases
- ACR activity facilitates BER through protein expression and opening of chromatin
- There lacks evidence of directed ACR activity to accommodate BER access to DNA

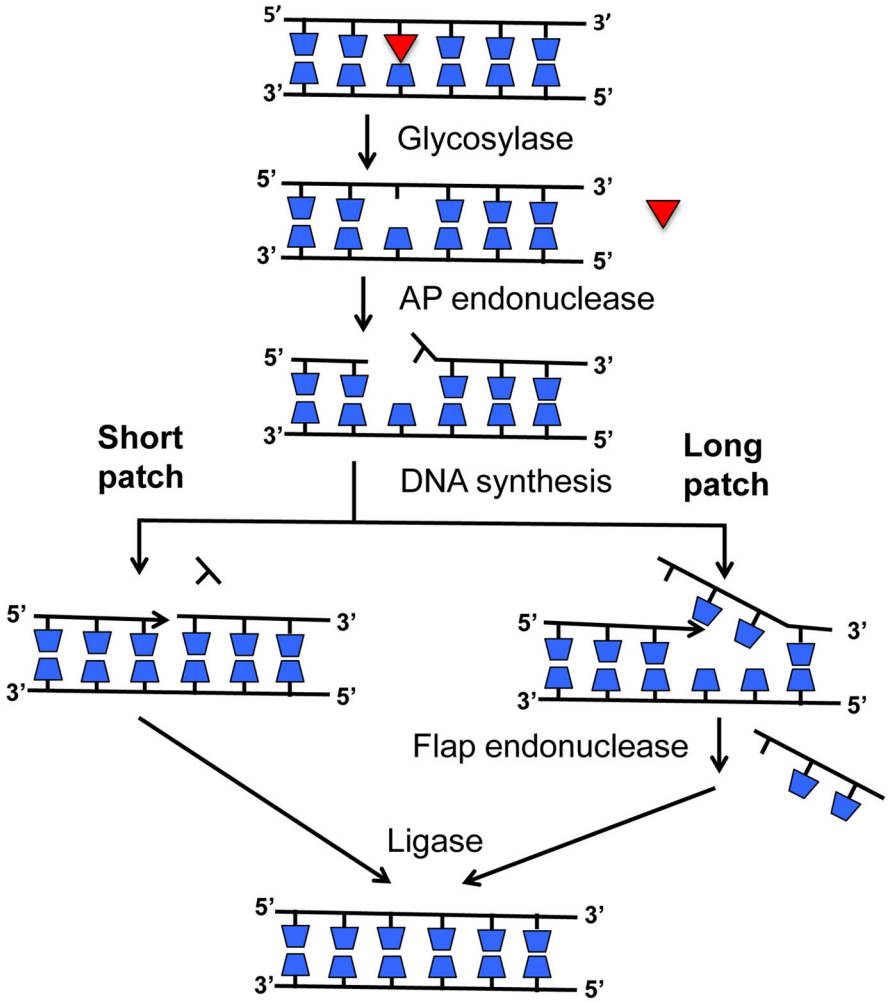

Fig. 1. Basic schematic of Base Excision Repair

A chemically modified base (red triangle) is recognized by a glycosylase, which cleaves the N-glycosidic bond leaving an abasic (AP) site. An AP endonuclease cleaves the DNA backbone on the 5′ side of the AP site, creating a single-strand break. BER is resolved in a "short patch" or "long patch" of DNA synthesis. In short patch repair the deoxyribose phosphate is removed and a single nucleotide is inserted and the site of the break. In long patch repair, up to 13 nucleotides are inserted, and the displaced strand entailing the abasic deoxyribose phosphate is cleaved by a "flap" endonuclease. Repair is completed by the action of a ligase.

Table 1

ACR Family	Chromatin Remodelling Activity	Role in DNA Replication	Role in DNA Transcription	Role in NER	Role in BER
SWI/SNF	Nucleosome sliding, displacement [90]	Required for efficient replication fork progression and replication elongation [91,92]	Master regulator of gene expression [93–96]	Enhances NER [77,79,97,98]	Stimulates BER *in vitro* [62] Promotes BER in yeast cells [99]
ISWI	Nucleosome sliding, spacing and assembly [100,101] Promotes formation and maintenance of higher order chromatin [102]	Stimulates replication in heterochromatin [103]	Regulates gene transcription, both activation and repression [104]	Facilitates NER in nucleosomes *in vitro* [105] Implicated in UV DNA damage response [106] Resolves lesion-stalled transcription [107]	Stimulates BER *in vitro* [61]
CHD	Nucleosome spacing, sliding, and chromatin assembly [108] Maintains open chromatin [109]	–	Promotes transcription elongation [110]	Implicated in repair of UV-induced damage [111]	–
INO80	Nucleosome spacing [112], eviction [113] Regulates H2A.Z localization [114] Mainatanence of silent chromatin [115]	Required for efficient DNA synthesis and S-phase progression [59,116] Promotes recovery of stalled replication forks [117,118]	Regulates gene transcription through activation and repression [119,120]	Promotes NER [60,67]	–