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APE1: A skilled nucleic acid surgeon

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ABSTRACT

Before a deleterious DNA lesion can be replaced with its undamaged counterpart, the lesion must first be removed from the genome. This process of removing and replacing DNA lesions is accomplished by the careful coordination of several protein factors during DNA repair. One such factor is the multifunctional enzyme human apurinic/apyrimidinic endonuclease 1 (APE1), known best for its DNA backbone cleavage activity at AP sites during base excision repair (BER). APE1 preforms AP site incision with surgical precision and skill, by sculpting the DNA to place the cleavage site in an optimal position for nucleophilic attack within its compact protein active site. APE1, however, has demonstrated broad surgical expertise, and applies its DNA cleavage activity to a wide variety of DNA and RNA substrates. Here, we discuss what is known and unknown about APE1 cleavage mechanisms, focusing on structural and mechanistic considerations. Importantly, disruptions in the biological functions associated with APE1 are linked to numerous human maladies, including cancer and neurodegenerative diseases. The continued elucidation of APE1 mechanisms is required for rational drug design towards novel and strategic ways to target its associated repair pathways.

1. Introduction

Human apurinic/apyrimidinic endonuclease 1 (APE1) is the primary cellular apurinic/apyrimidinic (AP) endonuclease, playing a pivotal role in not only the removal and repair of numerous DNA lesions, but also as a redox activator of numerous transcription factors, including Egr1, NF- κ B, p53, and HIF1 α [1]. These two major functions of APE1, repair and redox, are independent in their actions, as shown by the observation that mutations abolishing the DNA repair function do not affect the redox function, and vice versa [2,3]. Expression of the gene encoding APE1 is essential, presumably due to its central role in the repair of DNA lesions [4]. That said, the biological significance of the APE1 redox activity in eukaryotic transcriptional regulation of gene expression has yet to be fully elucidated [5]. Since the primary focus of this perspective is its DNA repair activity, we direct the readers to references [6] and [1,7] for a more thorough discussion of the APE1 redox and alternative functions, respectively.

During DNA repair APE1 functions as a nuclease, cleaving at select phosphodiester bonds that compose the DNA backbone. For a comprehensive review of DNA repair nucleases, we point readers to an

insightful perspective from a previous issue in this series by Dr. Susan Tsutkawa from the Tainer lab [8]. APE1 is exceedingly multifunctional even among its nuclease activities, exhibiting endonuclease, 3' phosphodiesterase, 3' to 5' exonuclease, and RNA cleavage activities [1]. Due to a wealth of structural and biochemical data, it is well understood how APE1 endonucleolytically cleaves at AP sites during base excision repair (BER) [1,9,10]. Recent X-ray crystal structures have revealed the fundamentals of the 3' to 5' exonuclease mechanism, which can function to proofread 3' mismatches inserted by DNA polymerase β during BER and remove 3' DNA end damage at single strand breaks [11]. This newly uncovered mechanism used by APE1 for its exonuclease activity provides new insights into the strategies used by APE1 to cleave during some of its less-studied nuclease activities, such as those utilized during nucleotide incision repair (NIR) and RNA metabolism. In this perspective, we examine what is known about the numerous APE1 cleavage reactions as well as the mechanistic features and activities that remain enigmatic with this essential multifaceted enzyme.

Abbreviations: 1-nt, 1-nucleotide; 5OHU, 5-hydroxy-2'-deoxyuridine; 8-oxoG, 8-oxoGuanine; AP, apurinic/apyrimidinic; APE1, human apurinic/apyrimidinic endonuclease 1; APE2, apurinic/apyrimidinic endonuclease 2; BER, base excision repair; DHT, 5,6-dihydrothymidine; DHU, 5,6-dihydro-2'-deoxyuridine; dRP, deoxyribonucleotide-phosphate; IR, ionizing radiation; NIR, nucleotide incision repair; pBQ-C, benzetheno exocyclic adduct of cytosine; PG, phosphoglycolate; PNK, polynucleotide kinase; PUA, α,β -unsaturated aldehyde; ROS, reactive oxygen species; THF, tetrahydrofuran; Tdp1, tyrosyl-DNA phosphodiesterase 1; XRCC1, X-ray repair cross-complementing protein 1

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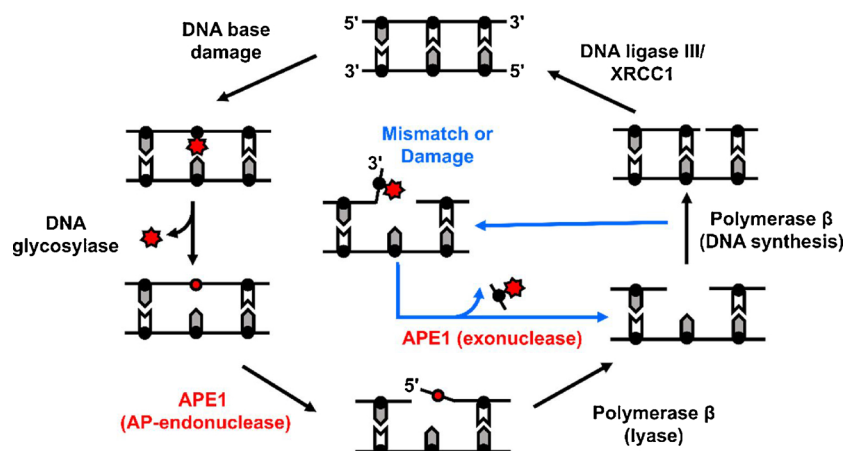


Fig. 1. Schematic of the BER pathway (black) showing the role of APE1 AP-endonuclease activity and APE1 exonuclease activity (blue) in proofreading 3' mismatches and removing 3' end damage. DNA damage and mismatches are highlighted in red.

2. APE1 overview

Reactive oxygen species generated by both endogenous and exogenous sources continuously bombard our DNA, resulting in oxidation and fragmentation of the DNA nucleobases. Both oxidative DNA damage itself and its repair mediate the progression of many prevalent human diseases. The major pathway tasked with removing and replacing oxidative DNA damage, and hence maintaining genomic integrity, is BER (Fig. 1). The BER pathway requires the coordinated activity of at least five enzymes including: (1) a DNA glycosylase capable of excising the modified base; (2) an AP-endonuclease, such as APE1, to generate a nick at the lesion site; (3) DNA polymerase β , which performs both lyase and DNA synthesis activities to remove the 5' dRP (deoxyribose-phosphate) and fill the resulting gap; and, finally (4) DNA ligase III and (5) XRCC1 (X-ray repair cross-complementing protein 1) scaffolding to seal the nick and complete the repair, (Fig. 1). For a more detailed discussion of BER, its protein components, and its relationship to human disease, we direct the readers to the following references [12,13].

During BER, damage specific DNA glycosylase-catalyzed reactions often result in an apurinic/apyrimidinic (AP) site, which is a baseless sugar moiety. AP sites are among the most abundant oxidative DNA damage types and can also occur as the result of spontaneous hydrolysis of the N-glycosyl bond [14,15]. AP sites exert cytotoxic effects by blocking DNA replication, repair, and transcription, and their lack of coding potential can result in mutagenesis through base substitutions, insertions, or deletions if bypassed by a DNA polymerase [15,16]. APE1 cleaves the DNA phosphodiester backbone on the 5' side of an AP site, generating a nick in the DNA with 3' hydroxyl and 5' dRP termini. The pre-steady state kinetic description of strand incision at AP sites by APE1 is that rapid catalysis is followed by slow product release [17,18]. This rapid catalysis is vital for genomic stability given the prevalence of AP sites in the genome, while the slow catalysis step has been proposed to conceal cytotoxic BER intermediates during DNA-damage processing and facilitate substrate channeling between BER enzymes.

X-ray diffraction and site-directed mutagenesis experiments have shown that APE1 is composed of a rigid globular C-terminal nuclease domain and a flexible N-terminal domain [9,10]. The N-terminal domain is responsible for the redox activity of APE1 and is thought to additionally mediate alternative APE1 functions and/or its protein-protein interactions, whereas the C-terminal domain is responsible for DNA binding and backbone cleavage activity. The nuclease domain of APE1 belongs to the phosphoesterase superfamily of enzymes that contain a common four-layered α/β sandwich structural core and bear variable loop regions and active site characteristics to provide substrate specificity. This domain binds directly to the DNA and slides along the

strand in search of an AP site primarily through interacting with the DNA phosphate backbone [19–21]. The original crystal structures of APE1 bound to DNA revealed a “flipped out” AP site positioned within a compact active site, stabilized by four loops and an α -helix, leaving an orphan base in the opposite strand [10]. Specifically, APE1 is proposed to stabilize the flipped out abasic site via a double-loop mechanism involving interactions with both the minor and the major grooves at the AP site. The other two loop domains also interact with the DNA on the 5' and 3' side of the AP residue respectively to facilitate the formation of a stable APE1:DNA complex. The role of these additional loop domain interactions, Mg^{2+} ions, and active-site residues in defining substrate specificity have been further characterized using site-specific APE1 variants [22–24].

More recent, higher-resolution APE1 product and substrate structures have provided not only additional mechanistic details, but also clarification of mechanistic ambiguity of the APE1 AP-endonuclease catalytic reaction [9,25–32]. Fig. 2A highlights the APE1 active site residues when in a pre-catalytic complex with DNA containing tetrahydrofuran (THF, a stable AP site analog). These structures further elucidated the APE1 AP-endonuclease mechanism. Prechemistry snapshots identified a single Me^{2+} coordinated by Asp70, Glu96, and a water molecule in contact with a non-bridging oxygen of the phosphate. Additionally, the nucleophilic water is in position for inline attack of the phosphorus atom and is coordinated by Asn212 and Asp210. The structures imply a pentacovalent intermediate stabilized by Me^{2+} and key active site contacts. It has been proposed that during catalysis the metal shifts to coordinate a phosphate non-bridging oxygen and the newly generated $O3'$ [33,34]. Fig. 2B shows the AP site within the compact APE1 active site. In addition to clarifying the mechanism of APE1 on AP sites, the product structure identified novel contacts that mediate product release during APE1 catalysis.

3. APE1 DNA 3' end processing activities

In contrast to the AP-endonuclease activity, the 3' DNA end processing activities of APE1 remain relatively poorly understood. The 3' to 5' exonuclease activity of APE1 removes 3' end groups, including damaged DNA bases, chain terminating drugs, blocked termini, and mismatched bases [35–38]. The AP-endonuclease and exonuclease activities have significantly different optimal salt and pH conditions and it remains unclear how these two activities are coordinated within the cell [38]. It has been shown that the APE1 exonuclease activity is slower than its exceedingly fast AP-endonuclease activity [17,18,39]. This has often led to the misimpression that the exonuclease activity is not biologically relevant. However, it is more appropriate to compare the rate of APE1 exonuclease activity to the rates of the end processing

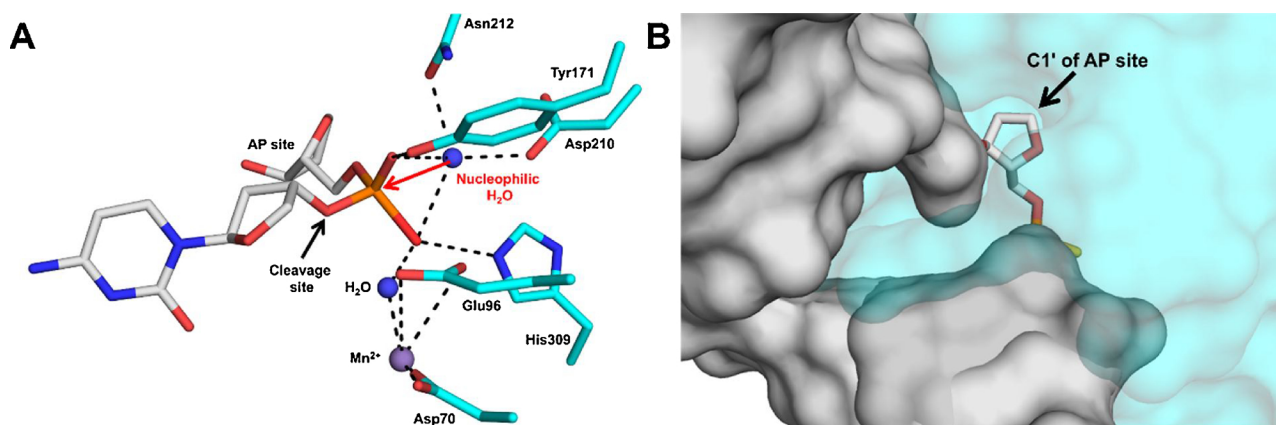


Fig. 2. APE1 AP-endonuclease reaction. (A) The APE1 active site showing the nucleophilic water and key active site residues. (B) Surface representation of the APE1:AP-DNA complex demonstrating the flipped out AP site and compact active site. Protein is shown in cyan and DNA residues in gray.

Table 1

Catalytic efficiencies for selected BER and end processing enzymes. Substrates for end processing enzymes are indicated in parentheses.

Enzyme	k_{cat}/K_M ($\text{s}^{-1} \mu\text{M}^{-1}$)	Reference
End Processing Enzymes		
APE1 (3'-PUA)	2.7	[54]
APE1 (3'-Mismatch)	1	[1,11]
APE2 (3'-Mismatch)	4×10^{-6}	[107]
PNK (3'-Phosphate)	30	[54]
Tdp1 (3'-Phosphotyrosine)	0.25	[108]
Aprataxin (5'-AMP)	3	[109]
Pol β (5'-dRP lyase)	0.15	[110]
BER Enzymes		
UNG	500	[110]
OGG1	0.03	[110]
APE1 (AP-DNA)	100	[110]
pol β (insertion)	1.5	[110]
Pol β (5'-dRP lyase)	0.15	[110]
Lig I	0.4	[110]

activities of other DNA repair enzymes. For example, the APE1 exonuclease activity is either faster or within a single order of magnitude of the catalytic rates for end processing by: apurinic/aprimidinic endonuclease 2 (APE2), tyrosyl-DNA phosphodiesterase 1 (Tdp1), aprataxin, polynucleotide kinase (PNK), and the lyase activity of DNA polymerase β to name a few (Table 1). In addition, the APE1 exonuclease activity occurs at a similar rate to the activities of other enzymes in the BER pathway (Table 1). Variety in the type of end blocking group and the assortment of possible DNA termini (i.e., nicks, gaps, overhangs, and double strand breaks) in need of processing during multiple different repair pathways, further combined with the existence of multiple end processing enzymes with varying substrate specificities has resulted in a murky picture of the exact biological role of each end processing enzyme, and underscores the importance of further characterizing these enzymes and their activities [37,40–53]. This substrate overlap implies a level of evolved redundancy among enzymes that may play a particular biological role during different cellular stages and in response to varying types of DNA damage. Despite this ambiguity and overlap, the biological relevance of the APE1 exonuclease activity has been identified in several instances, including: (1) APE1 removal of 3' α,β -unsaturated aldehyde (PUA) groups resulting from bi-functional glycosylases during BER [54]; (2) the cleansing of oxidatively damaged DNA dirty ends, such as 3' PG (phosphoglycolate) and 3' 8-oxoG (8-oxoGuanine) by APE1 both *in vitro* and in cellular extracts [55,56]; (3) APE1 proofreading of DNA ligation confounding misinsertions by DNA polymerase β during BER, [11,57–59]; and (4) the association between APE1 variants with reduced exonuclease activity and carcinogenesis [60–62]. Below, we will discuss intriguing biological models for some

of these APE1 scenarios and how one protein active site can accommodate an array of nucleic acid substrates.

3.1. Proofreading 3' mismatches during BER

The misincorporation of nucleotides by DNA polymerases during DNA replication and repair promotes mutagenesis and carcinogenesis. The primary BER DNA polymerase, polymerase β , only exerts moderate fidelity, with 1 nucleotide misincorporation per 4000 insertion events [63]. It is estimated that 20,000–80,000 base modifications take place daily per cell in our genome [64]; therefore, polymerase β , which lacks intrinsic proofreading activity, would be expected to introduce around ten mutations into our DNA per cell each day. However, BER has been shown to be robust and relatively error-free under normal conditions [13]. This has led to the hypothesis of an extrinsic proofreader of polymerase β during BER. Since the discovery of its exonuclease activity on DNA mismatches, APE1 has been proposed to serve as an extrinsic proofreader of polymerase β [22,33,65–67]. Supporting this notion, the fidelity of pol β has been suggested to be increased when the other BER components are present [66]. In addition, DNA polymerase β has been shown to form a complex with APE1 on DNA [68]. This model of APE1, utilizing 3' to 5' exonuclease activity, as an extrinsic proofreader results in a modified view of classical BER (Fig. 1, blue arrows). In this scenario, polymerase β misinsertions are proofread by the APE1 exonuclease activity, possibly within a larger BER complex during substrate channeling. How APE1 can accommodate a mismatched nucleotide base (as opposed to a baseless AP site) within its compact active site (Fig. 2B) is perplexing based on the APE1 AP-endonuclease structures alone. As a result, its precise biological relevance has been difficult to ascertain and the literature contains conflicting opinions on the mechanistic details of the APE1 exonuclease activity [11,35,39].

To better understand how APE1 accommodates mismatched nucleotides during the exonuclease activity, our group recently published X-ray crystal structures of APE1 in complex with a C/T mismatch [11]. This substrate represents a putative BER intermediate in which polymerase β has incorrectly inserted a C across from a templating T. Then, APE1 could enact its exonuclease activity to remove the 3' misinserted C. We chose a C/T mismatch because data collected in our lab, as well as previously published by others, indicates that mismatches containing C represent optimal substrates for the APE1 exonuclease activity [69–71]. The active site of APE1 is shown in Fig. 3A with a nicked DNA substrate containing a C/T mismatch at the 3' end and a phosphate at the 5' end. In contrast to the AP site analog THF, which flips into the active site during the AP-endonuclease reaction, the mismatched C rotates into the open intra-helical cavity while APE1 keeps the phosphate backbone, metal ion, and nucleophilic water in almost identical positions for cleavage (Fig. 3B). The base rotation is accommodated by

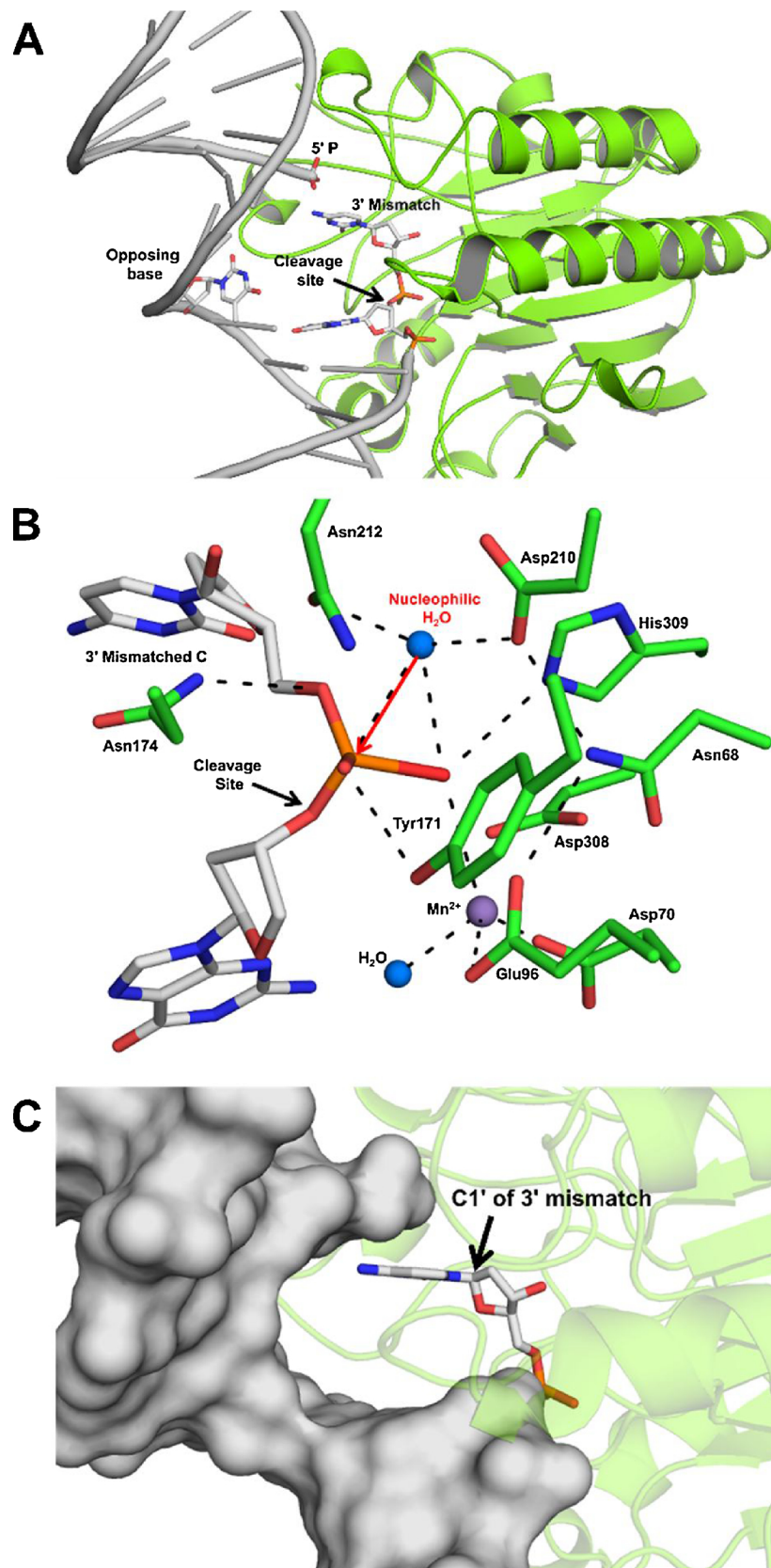


Fig. 3. The APE1 exonuclease reaction of a 3' mismatch. (A) Overview of exonuclease substrate complex. The site of cleavage is indicated by the arrow. The 3' mismatched cytosine, its flanking base, and the opposing base are shown in stick format (gray carbons). (B) Focused view of the APE1 exonuclease active site showing key catalytic residues, cleavage site, and nucleophilic water with key interactions indicated by dashed lines. (C) Surface representation of exonuclease DNA substrate showing the bend of the DNA to accommodate the 3' mismatched base. The protein is shown in green and the DNA in gray.

the extra intra-helical space in the exonuclease conformation, compared to the AP-endonuclease conformation (see positions of C1' in Fig. 2B and C). This results from several structural variations, including a 10° sharper bend in the DNA, displacement of the 5' phosphate at the nick, and instability of the mismatched base. Flexibility at the 3' end of a DNA nick facilitates the APE1 dependent sculpting of the DNA, thus providing a method to distinguish mismatches and other aberrant 3' ends from correctly matched DNA. Several residues are also positioned to interact with the 5' phosphate, providing an explanation for differences in incision efficiency based on the nature of the 5' terminal group [72,73]. Of note, comparison of the available APE1 structures indicate that the APE1 active site is quite rigid; variations in the DNA cleavage mechanisms between substrates likely result from altered DNA conformations instead of altered APE1 conformations. The observed differences in optimal reaction conditions between the exonuclease and AP-endonuclease activities may therefore likely reflect differences in either the DNA binding/sculpting event or intermediate catalytic steps, yet to be determined.

3.2. Removing 3' oxidative lesions

The APE1 exonuclease activity is also involved in the cleaning of DNA “dirty ends”, including DNA damage generated by reactive oxygen species (ROS) during oxidative stress. Oxidative stress induced DNA damage is both a major driver of human disease and a product of environmental exposure, radiation, and chemotherapeutic cancer treatments. One common 3' damaged terminal end generated by ROS is phosphoglycolate (3' PG). This stable end product blocks replication and repair, and it must be removed prior to further DNA synthesis by a DNA polymerase. While multiple enzymes are capable of removing 3' PG ends, APE1 has been shown to be the major enzyme responsible for this activity [48,55,74,75]. In the context of BER, APE1 is capable of processing PG at the 3' end of a nick to produce a 1-nt (1-nucleotide) gapped DNA substrate with a 3' hydroxyl suitable for gap filling DNA synthesis by DNA polymerase β . Providing insight into how APE1 processes damaged DNA ends, we recently determined the crystal structure of APE1 bound to a double stranded, nicked DNA substrate containing a PG at the 3' end and a phosphate at the 5' end of the nick [11]. The structure revealed 3' PG in the APE1 active site with the cleavage site phosphate group and nucleophilic water in a similar position to that observed for a 3' mismatched base (described above). However, in the absence of an intact nucleobase at the 3' end, several waters are observed in the more spacious active site. The mechanistic role of these water molecules during catalysis and substrate specificity remains to be determined.

APE1 has additionally been shown to remove 3' 8-oxoG from nicked DNA substrates *in vitro* [59,76]. Cellular studies using whole cell extracts and immunoprecipitation experiments support a cellular role of APE1 in 3' 8-oxoG removal [76–78]. Not only can 3' 8-oxoG arise via strand breaks, but also via genomic insertion of 8-oxodGTP by a DNA polymerase [33,79–81]. This insertion is facilitated by 8-oxodGTP escaping general polymerase discrimination checkpoints by modulating the highly-charged DNA polymerase active site [33]. Work by our group and others has shown that 3' 8-oxoG is not only potentially mutagenic, but also destabilizes the primer termini, hindering DNA repair and causing abortive ligation [33,59,82]. Combining the APE1 proofreading model during BER (Fig. 1, blue arrows) with the observed 3' 8-oxoG exonuclease function raises the interesting possibility that APE1 removes 3' 8-oxoG during BER. Further biochemical, structural, and cellular studies are required to fully understand the mechanism and relevance of 8-oxoG removal by APE1. As previous studies have shown that APE1 exonuclease activity preferentially cleaves mismatches [11,57], it will be particularly interesting to see whether there is any preference and/or mechanistic differences between when 8-oxoG pairs with cytosine compared to its mutagenic base pairing partner, adenine [83,84].

4. Other APE1 nuclease activities

4.1. Nucleotide incision repair (NIR)

Unexpectedly, APE1 is reported to recognize and incise at particular base damages within duplex DNA (i.e., 5,6-dihydro-2'-deoxyuridine (DHU), 5,6-dihydrothymidine (DHT), 5-hydroxy-2'-deoxyuridine (5OHU), and α -2'-deoxynucleotides), generating single-strand break ends with a 3' hydroxyl and a 5' dangling modified nucleotide [85,86]. The majority of these lesions are generated under ionizing radiation (IR) or exposure to certain DNA damaging therapeutics. This backbone cleavage activity is distinct from both the AP-endonuclease and exonuclease cleavage reactions, because the cleavage occurs in the absence of either an AP site or a nick in the DNA, and is proposed to initiate a damage response pathway termed nucleotide incision repair (NIR). In this case, NIR serves as a back-up for the glycosylase-initiated BER pathway discussed above. Reaction conditions, such as salt concentrations and pH, seem to affect the NIR function of APE1, with the optimal conditions for NIR activity very similar to those for the 3' to 5' exonuclease activity [85]. Moreover, NIR is active at a 100-fold lower $MgCl_2$ concentration than the APE1 AP-endonuclease activity. Interestingly, the N-terminal redox domain of APE1 (proposed to modulate protein-protein interactions, but not AP-endonuclease activity) contrarily stimulates its NIR activity [85]. Mutation of certain active site residues has been shown to influence (though with variable effects) both the APE1 NIR and BER activities, demonstrating that the APE1 active site involved in NIR and BER pathways is the same, but differing conformational requirements are responsible for their corresponding cleavage mechanisms [87]. As the reaction conditions are similar to those for the 3' to 5' exonuclease activity, and both substrates require similar active site real estate, perhaps NIR activity occurs via a similar mechanism reported for the removal of a mismatched base [11]. That said, it remains unclear how the absence of a DNA nick in the pre-catalytic complex would affect the DNA binding and cleavage conformations required to promote the conformational change within the DNA.

The NIR activity described above is consistent with earlier work which found that APE1 can incise at benzene-derived base adducts, similarly creating 3' hydroxyl and a 5' dangling modified nucleotide ends. Importantly, structural insight via molecular modeling of a duplex containing a benzetheno exocyclic adduct of cytosine (pBQ-C), and subsequent molecular dynamics simulations with APE1, implied that the pBQ-C adduct can be accommodated in the APE1 active site extrahelically in a similar fashion to an AP site by specific structural rearrangements of both the DNA and protein [86]. Our exonuclease structures indicate that the APE1 active site is quite rigid, with only modest changes to the structure of APE1 to accommodate binding of AP-DNA and 3' mismatched bases [11]. As a result, we propose that DNA conformational changes such as a modified intra-helical conformation of the adduct and increased DNA bending, akin to those in the exonuclease structures where the APE1 active site must accommodate mismatches and damage, may contribute more than previously expected.

4.2. RNA processing

APE1 is capable of endonucleolytically cleaving abasic RNA, suggesting it participates in some aspect of RNA quality control, presumably as a “cleansing” factor [88]. Importantly, RNA is single stranded and consequently its bases are not protected by hydrogen bonding, making it more susceptible to base oxidation than DNA. In addition, recent findings have shown APE1 to be involved in the removal of trapped RNA molecules in DNA–RNA duplex structures [89] and 3' phosphate groups from RNA decay products (facilitating their further degradation). Moreover APE1 cleavage within the coding region of *c-myc* RNA (specifically at UA and CA sites) was shown to result in down regulated expression of *c-myc*, directly linking the

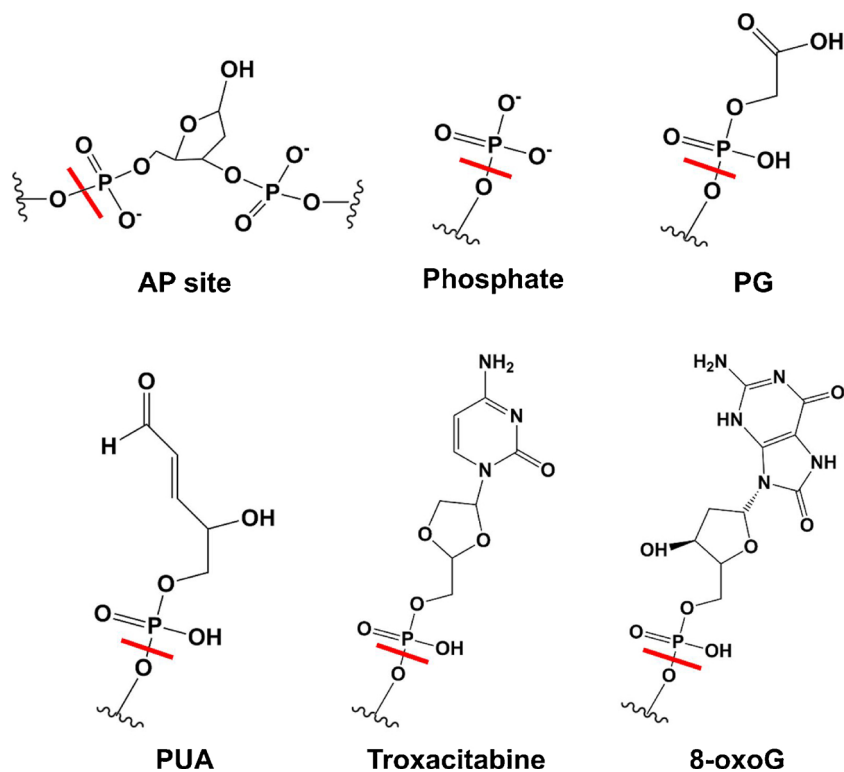


Fig. 4. Structures of several APE1 substrates demonstrating their diversity. Red lines indicate the site of APE1 cleavage.

endoribonuclease activity of APE1 with mRNA turnover. In this study, HeLa cells depleted of APE1 express two- to five-fold more *c-myc* RNA in comparison to control cells [88]. Other recent studies have demonstrated that APE1 cleavage of RNA is not unique to *c-myc*, as micro-RNAs, CD44, and components of the SARS-corona virus are also cleaved by APE1 [90,91]. Puzzlingly, APE1 cleavage of RNA does not require Me^{2+} [90]. However, cleavage does absolutely require the 2' hydroxyl [92]. These two striking features of the RNA cleavage reaction are unique to RNA, and have yet to be explained at the molecular level. We point readers to an elegant review recently published by the Tell lab to learn more about the biological role of APE1 in RNA processing [91].

5. Conclusions

In this perspective, we concentrated on the diverse nuclease functions and mechanisms of the nucleic acid surgeon APE1, applying particular emphasis on structural and mechanistic considerations. The base flipping mechanism used by APE1 to cleave the DNA at AP sites is well characterized, and recent structures of several biologically relevant exonuclease complexes have also shed new light on additional APE1 DNA repair mechanisms. While these structures have aided in our understanding of how a single active site can accommodate such a wide variety of substrates (Fig. 4), the precise mechanisms used by APE1 to cleave many of its other substrates remain mysterious. Along these lines, APE1 is the primary exonuclease that removes the stereochemically unnatural L-configuration anticancer nucleoside analogue, β -L-dioxolane-cytidine (brand name Troxacitabine), and other L-configuration nucleoside analogues from the 3' ends of DNA [93]. Additionally, APE1 can remove the anti-HIV nucleoside analogues 3'-azido-3'-deoxythymidine and 2',3'-didehydro-2', 3'-dideoxythymidine from 3' DNA termini [57]. As a result, APE1 might have an impact on the therapeutic index of certain anticancer and antiviral compounds that target DNA replication and repair pathways. Indeed, studies employing various methods have revealed that APE1 deficient cells exhibit hypersensitivity to a number of DNA damaging agents [94–102] and additionally promote cellular senescence [103].

In addition to its role in surgically removing DNA damage, APE1 is also a redox factor and involved in both RNA metabolism and antibody class switch recombination [91,104]. Disruptions in the multifarious biological functions associated with APE1 can be linked with various human pathologies such as cancer and neurodegenerative diseases [12,13]. Since APE1 has roles in both disease suppression and therapeutic agent resistance, it is apparent that if APE1 DNA repair activities can be strategically regulated that the protein would be a potentially druggable target in both preventative and therapeutic treatments. An entire array of knowledge on this multifunctional protein is necessary to completely understand the origination of these diseases and to develop methods of selectively perturbing the associated processes of repair, transcription, and cell proliferation for beneficial human health impacts as has been done in other nuclease systems [105,106]. The continued elucidation of APE1 mechanisms will hopefully provide additional ways to target the enzyme and the associated DNA/RNA repair pathways.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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