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FORUM REVIEW ARTICLE

DNA Polymerase Eta and Chemotherapeutic Agents

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Abstract

The discovery of human DNA polymerase eta (pol η) has a major impact on the fields of DNA replication/repair fields. Since the discovery of human pol η, a number of new DNA polymerases with the ability to bypass various DNA lesions have been discovered. Among these polymerases, pol η is the most extensively studied lesion bypass polymerase with a defined major biological function, that is, to replicate across the cyclobutane pyrimidine dimers introduced by UV irradiation. Cyclobutane pyrimidine dimer is a major DNA lesion that causes distortion of DNA structure and block the replicative DNA polymerases during DNA replication process. Genetic defects in the pol η gene, *Rad30*, results in a disease called xeroderma pigmentosum variant. This review focuses on the overall properties of pol η and the mechanism that involved in regulating its activity in cells. In addition, the role of pol η in the action of DNA-targeting anticancer compounds is also discussed. *Antioxid. Redox Signal.* 14, 2521–2529.

Introduction

DNA replication plays a vital role in cell proliferation. To ensure that the completion of the entire genome is duplicated faithfully within the S-phase during the cell cycle, DNA polymerases that are responsible for replicating the genome usually have high fidelity and efficiency characteristics. The two key human DNA polymerases that are responsible for genome replication are polymerase δ and ε. Both are B-family polymerases that have high efficiency and processivity [reviewed in (15)]. These polymerases incorporate several hundred nucleotides per second, and their error rates are estimated to be around one per million incorporations (26, 65).

There are about 25,000 DNA lesions generated per cell per day, which could result from either endogenous processes or exogenous agents, such as UV radiation. To maintain the high fidelity, replicative polymerases are highly selective for their substrates and have a low tolerance to abnormal DNA structures caused by damaged DNA [reviewed in (15)]. As a result, replicative DNA polymerases stall at DNA lesion site and therefore pause the replication process. Therefore, to avoid damaged DNA blocks replicative DNA polymerases during replication process, most forms of DNA damages are repaired by different repair mechanisms within the G_0/G_1 phases before DNA replication starts in the S phase. Nevertheless, damage introduced after replication has started or damage that has escaped the repair processes generate the possibility for the replicative DNA polymerases to encounter DNA lesions. For example, UV radiation introduces DNA intrastrand crosslinked cyclobutane pyrimidine dimers (CPDs), a four-member ring structure resulting from saturation of the pyrimidine 5,6 double-bond. CPD cause significant DNA distortion that blocks replicative polymerases and therefore stall the progression of DNA replication forks (55). In addition to CPD, UV radiation also elevates the oxidative stress in cells which leads to introduction of other types of DNA damages, including 8-oxoguanine, thymine glycol, and urea. Among these damages, thymine glycol and urea also block replicative polymerases. The prolonged stalling of replication fork will collapse, which form DNA breaks and ultimately lead to mutations or cell death.

Several DNA repair mechanisms are responsible for removing damaged DNA to reduce the chance for replicative DNA polymerases to encounter DNA lesions. The DNA nucleotide excision repair (NER) is the key mechanism that is responsible for recognizing and repairing bulky DNA adducts such as CPD [reviewed in (76)]. Genetic defects in NER have been shown to be associated with a disease called xeroderma pigmentosum (XP) (14). XP is a rare autosomal recessive disease characterized by sun sensitivity, photophobia, early onset of freckling, and subsequent neoplastic changes on sun-exposed skin. For XP patients, the incidence of primary cutaneous neoplasms, including melanoma, is $\sim$2000-fold higher than in normal individuals (10). In addition, neurological symptoms such as isolated hyporeflexia and progressive mental retardation have been reported (11). The XP patients typically have mutations in one of the seven complementation genes (XP-A to XP-G), which are the seven key enzymes that participate in carrying out the NER repair

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processes [reviewed in (76)]. In 1970, Jung E.G. reported a new form of XP and the cells derived from these patients have normal NER ability but suffer from uncharacterized deficiency in DNA synthesis after UV-irradiation (35, 46, 63). These patients develop typical XP phenotype but with milder symptoms and later onset. Since these patients have a variant form from the classical XP, they are categorized as XP variant (XP-V). About 20% of the total XP patients are XP-V. Since the discovery of XP-V, it has been speculated that a DNA polymerase may responsible for the XP-V symptoms. In 1999, Masutani *et al.* purified a DNA polymerase from human HeLa cells that can restore the activity to replicate across DNA containing CPD lesions for the cell extracts from to XPV cells (50). This polymerase was identified to be a human homolog of the yeast RAD30 and *E. coli* UmuC proteins (18, 29) and was named DNA polymerase eta (pol η). Human pol η comprises 713 amino acids that is encoded by the human *RAD30* gene (50), located on chromosome 6p21.1–6p12 (72). The pol η gene consists of 11 exons, whereas the first exon is not translated (72). Since the discovery of pol η, a growing number of DNA polymerases have been discovered, such as polymerases ι, λ, κ, and ζ [reviewed in (16)]. Based on the phylogenetic relationships, polymerases η, ι, κ, and Rev 1 are categorized into a new Y-family of polymerases (56).

Biochemical and Biophysical Properties of Pol η

In contrast to the replicative polymerases that have a high degree of accuracy and are often blocked by structurally distorted DNA lesions, the Y-family polymerases have the ability to perform translesion synthesis across various types of DNA lesions (43). The Y-family polymerases have a much higher error rate of 10^{-2}–10^{-3} (51, 52) compared to the mutation rate of 10^{-6} of replicative polymerases (26, 65). The observed low fidelity is partly due to the lack of intrinsic 3′–5′ exonuclease proofreading activity in the Y-family polymerases (50). The low fidelity characteristic makes them unsuitable for replication of undamaged DNA.

Biochemical studies have shown that purified pol η has better binding affinity to bind to DNA template containing CPD than to the undamaged DNA and similar efficiency in replicating either CPD containing DNA template or undamaged DNA (75). Pol η replicates across CPD up to two nucleotides beyond CPD sites before it disassociates from DNA (44, 53). Interestingly, pol η preferentially inserted two complementary adenines opposite the TT dimer but shows a relatively high error rate in replicating undamaged DNA (51).

In addition to the lack of associated exonuclease, pol η has a very different structure as compared to the replicative polymerases. The structural biology has also contributed significant knowledge to understanding the fidelity and mechanisms of action of lesion bypass polymerases. The polymerase activity of human pol η resides within the first 512 amino acids of the N-terminal region, which contains five motifs conserved among all the Y-family polymerases and the C-terminal region of pol η has been discovered to be important for protein interactions (Fig. 1). The structural analysis of Dpo4, a Y-family polymerase from *Sulfolobus solfataricus* and the catalytic core of pol η from *S. cerivisiae*, revealed a very distinct architecture from other replicative DNA polymerases (47, 48, 73). Both Dpo4 and yeast pol η resembled a right hand with "thumb," "finger," and "palm" domains, similar to the structures of the prokaryotic Pol I family, bacteriophage RB69, and phage T7 polymerase. However, an additional novel polymerase-associated domain (PAD), or so called "little finger" domain (47, 48, 73), was discovered in the Y-family polymerases. This PAD creates a more relaxed polymerase active center, which allows pol η to accommodate the damaged DNA template and the incoming nucleotides (47, 48, 73). It has also been shown that pol η uses Hoogsteen base pairing, which has less discrimination against the incoming substrates (47). However, a recent report on the cocrystal structures of human truncated pol η (amino acid 1–432) with either the undamaged DNA or the CPD containing DNA at different incorporation stages (12) provided detailed mechanisms at molecular level for the specificity and efficiency of pol η in replicating across CPD DNA lesion. Structural data suggest that the PAD domain rotates away from the finger and palm structures, which opens up the active site of pol η to accommodate the bulky lesions (12). The similar structure is not observed in other Y-family polymerases. The augmented active center allows pol η to house two consecutive incoming nucleotides opposite the crosslinked thymines in contrast to only one nucleotide observed in other polymerases. This unique feature enables formation of hydrogen bonds and van der Waals forces between the crosslinked CPD containing DNA template and the two incoming adenines, which strengthens the interactions between the CPD containing template and the two incoming adenines. These interactions facilitate the correct incorporations of the adenines opposite CPD. These additional interactions are not present for the undamaged DNA, which provided an explanation for the observed lower fidelity of pol η while replicating undamaged DNA. This unique structure and ability of pol η provides an explanation for the higher fidelity of pol η in bypassing the CPD as compared to other translesion synthesis polymerases. In addition, the recent structures also revealed that human pol η acts as a "molecular splint" to absorb the lesion-induced perturbations and maintain the rigidity of a B-form conformation of DNA in spite of the presence of CPD (12), which is also not observed in other Y-family DNA polymerases. Together, these special features enable pol η to efficiently and accurately replicates across CPDs in DNA.

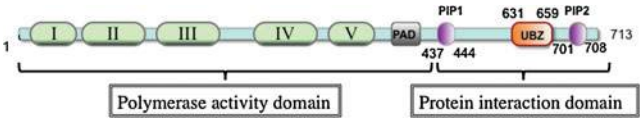

FIG. 1. Protein map of DNA polymerase η. The polymerase domain resides with the N-terminal of the protein containing five conservative polymerase motif and a polymerase associated domain. The C terminal is the protein interaction domain that contains two PCNA-interacting protein domains and an ubiquitin-binding zinc finger domain. PAD, polymerase associated domain; PCNA, proliferating cell nuclear antigen; PIP, PCNA-interacting protein; UBZ, ubiquitin-binding zinc. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

Regulation of Pol η Activity

Pol η is the key enzyme to replicate through CPD. Studies have also shown that pol η has the ability to replicate across other DNA lesions that block the replicative polymerases

[reviewed in (60)], such as cisplatin intrastrand crosslinked DNA. Therefore, the novel ability of pol h provides cells an alternative route to survive under hazardous environment. The UV irradiation-induced higher mutation rates in the XP-V cells and the increased incidence of cancer development for XP-V patients indicate the important biological role of pol η. In the absence of pol η, other low fidelity translesion polymerases, such as ι, κ, or ζ, can compensate the loss of pol η and contribute to the translesion synthesis, which usually results in a higher mutation rate. Although pol η replicates through CPDs with a high efficiency inserting correctly adenines (17), several reports have shown that pol η has a much higher error rate while replicating the undamaged DNA in comparison to the replicative polymerases. Pol η itself is a low fidelity enzyme and the overexpression of pol η from high copy number episomal vectors may be toxic to cells in culture (24). These results indicated that the activity of pol η in the cell has to be tightly regulated to balance between cell survival and mutagenesis. Figure 2 illustrates the current hypothesis of how pol η participates in translesion synthesis across a CPD lesion.

Enzyme activity is usually regulated at either transcriptional or post-translational levels. In the case of pol η, alternative splicing has been suggested as a mechanism that regulates pol η gene expression (24). The C-terminal domain of human pol η (amino acids 513–713) has been shown to be important for protein–protein interactions (Fig. 1). Therefore, the roles of protein–protein interactions or post-translational modifications through protein–protein interactions in regulating pol η activity have also been heavily explored. Confocal microscopy studies indicated that UV irradiation induces pol η to form nuclear foci and these foci colocalized with CPD sites (37). The intracellular relocation of pol η to stalled replication forks in responding to UV irradiation is critical for its cellular activity since pol η that fails to relocate to the stalled DNA replication forks induced by UV irradiation cannot complement the pol η function in XP-V cells (37). It has been suggested that protein–protein interactions or post-translational

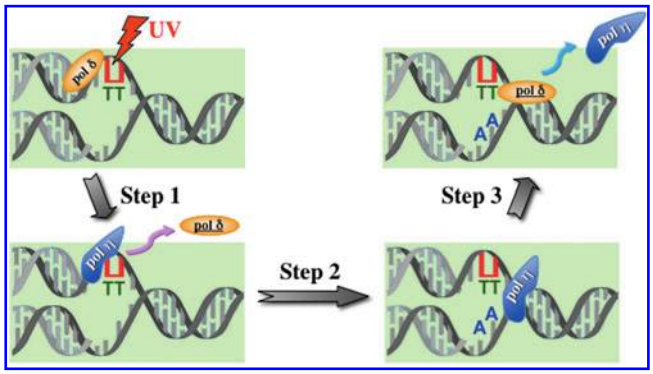

FIG. 2. Translesion synthesis model of pol η on a T-T dimer containing DNA. The replicative DNA pol δ encounters the T-T dimer and stall at the lesion site. Step1: Pol η is recruited to the stalled replication fork to replace pol δ. Step2: Pol η perform the translesion synthesis across the T-T dimer, usually, pol η inserts adenines. Step 3: Pol η is released from the replication fork after bypassing the lesion; pol δ rebound to the replication fork to continue the replication process. pol η, DNA polymerase eta. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

modifications are important for the intracellular relocation of pol η in responding to DNA damaging agents.

Postreplication repair (PRR), first identified in bacteria, is a mechanism that provides cells an alternative route for the replication machinery to bypass the blocking lesions without repairing the damages (67). PRR helps to avoid the prolonged replication forks stalling-induced collapse of replication forks, formation of DNA breaks, and ultimately cell death. Protein ubiquitination process plays a key role in PRR In eukaryotes, which is not observed in the prokaryotic system. One of the critical enzyme in the eukaryotic PRR, RAD6, is an E2 ubiquitin conjugase (40, 69) that plays an important role in PRR to tolerate damaged DNA [reviewed in (45)]. In response to UV radiation, Rad6 forms complexes with the E3 ubiquitin ligase Rad18 (6, 67) and the Rad6/Rad18 complexes induce monoubiquitination of proliferating cell nuclear antigen (PCNA) at lysine 164 site. PCNA is an important accessory protein that plays vital roles in DNA replication, recombination, and repair. PCNA forms a donut-shape ring on the DNA to tether the replicative polymerases to the primer–template junction and therefore enhance the processivity and efficiency of polymerases. In addition to replicative polymerases, PCNA has also been shown to interact with a lot of proteins involves in DNA replication, recombination, repair, and DNA damage responses.

The physical interactions between pol η and replication proteins PCNA have been demonstrated *in vitro* (25). Biochemical studies have shown that PCNA alone does not enhance the processivity of pol η (30). However, PCNA in combination with the replication proteins RFA and RFC stimulate the synthetic activity of pol η about 12-fold (30). Cellular studies have shown that the pol η foci colocalizes with PCNA foci in the nuclei after UV irradiation (24). Since PCNA acts as an anchor protein that interacts with multiple replication proteins and replicative polymerases, the colocalization of pol η and PCNA implies that PCNA plays an important role in recruiting pol η to stalled DNA replication forks after UV irradiation (26). Kannouche *et al.* further reported that pol η exclusively interacts with the monoubiquitinated at Lysine 164 amino acid residue of PCNA in response to UV irradiation but not the unmodified PCNA and suggested that monoubiquitination of PCNA is required for recruiting pol η to stalled DNA replication forks (27). Further *in vitro* studies have shown that only those PCNA that have already assembled on DNA are being ubiquitinated, and such ubiquitination enhances its interactions with pol η, but the ubiquitinated PCNA showed no interactions with either pol δ or pol ζ (79). In addition, the ubiquitination on Lys 164 of PCNA prohibits pol δ to replace pol η from the replication machinery bound on DNA (79). Bienko *et al.* identified two ubiquitin binding domains in Y-family polymerases that are important for intracellular relocation to the stalled DNA replication fork and their interactions with monoubiquitinated PCNA (10). Further, pol η was shown that itself can be monoubiquitinated *in vivo* (10) and was proposed that the monoubiquitination prevents the accidental binding of pol η to replication machinery in the absence of damaged DNA (11).

While the hypothesis on the role of PCNA monoubiquitination in recruiting pol η is developing, different results have been reported about the interactions between PCNA and pol η. Genetic studies reported by Acharya *et al.*

indicated that mutations in the C_2H_2 motif of the yeast pol η ubiquitin-binding zinc (UBZ) domain (Fig. 1) confers no impact on pol η function as well as its interactions with either ubiquitinated or unubiquitinated PCNA (1). In addition, mutations within the UBZ domain of human pol η did not affect the interactions of pol η with PCNA since the pol η UBZ mutant proteins have the same synthetic activity as the wild-type protein (2). *In vitro* study showed that both the PCNA-interacting protein (PIP) domain and the UBZ domains within pol η are critical for pol η to bind to the stalled DNA replication fork (2). A recent report has shown that the UBZ deletion mutant pol η has the same function as the wild type; however, particular mutations, such as D652A and F655A, significantly decreased the translesion synthesis activity of human pol η (Fig. 3). The authors therefore concluded that the UBZ domain is not required for PCNA interactions. Nevertheless, the UBZ domain may play other important roles in modulating the activity of pol η, which is currently not understood and needs further investigation.

In addition to ubiquitination, other processes may also participate in regulating the cellular activity of pol η. It is well established that various types of DNA damages signal the activation of checkpoint proteins and many different classes of protein kinases, such as ataxia–telangiectasia mutated, ataxia–telangiectasia mutated Rad3-related (ATR), PI3-kinases, and DNA-PK (28) [reviewed in (78)]. The stalled replication fork activates the checkpoint response in the S phase and phosphorylation is commonly observed in regulating protein activity in cells in responding to DNA damages. ATR is known to play key roles in DNA damage-induced checkpoint in responding to DNA replication stresses, such as UV radiation (77). In addition, anticancer platinum-based compounds and nucleoside analogs, including cytarabine, cytosine-1-β-D-arabinofuranoside (AraC), and gemcitabine, also activated ATR (24, 38, 70). It is known that once replication forks are blocked by DNA lesions, replication protein A binds to the exposed single-stranded DNA within the stalled replication fork vicinity (49), together with ATR interacting protein, and the complexes recruit ATR to the stalled DNA replication forks (80). An enhanced ATR signaling in XP-V cells after UV irradiation has been observed (13). The ATR expression-downregulated cells show a decreased amount of UV-induced pol η foci at stalled DNA replication fork as compared to the parental cells (23), suggesting that ATR contributes to the pol η recruitment to stalled DNA replication forks in response to UV radiation. In addition, an increased phosphorylation level of pol η was observed after UV irradiation, and several mutations on the pol η putative phosphorylation sites diminished the intracellular relocation of pol η in response to UV irradiation (23). Together, these results imply that phosphorylation participates in modulating the pol η activity in cells and ATR is involved in the processes. The detailed mechanism of action of ATR participates in regulating pol η activity is not clear to date and need further investigation. One possible linkage is through the ATR-p53-p21 pathway. According to the plasmid-based mutation assay studies, the wild-type p53-expressing cells exhibit a lower mutation frequency than the p53 null cells after UV irradiation (5), suggesting that p53 may also participate in the translesion synthesis processes. Although the impact of p53 may not directly affect the pol η expression level, as reported by Avkin *et al.* (5) and other studies (74), p53 and p21 affect the monoubiquitination of the chromatin bound PCNA (5). p21, a cyclin-dependent kinase inhibitors, can interact with PCNA and such interaction prevents the formation of the PCNA trimer ring onto the primer–template junction. As a result, it significantly reduces the mounting of replicative DNA polymerase δ onto the primer–template junction and therefore reduces the PCNA driven DNA replication *in vitro* (79). p21 has also been shown to have an impact on both NER and TLS. Soria *et al.* reported that p21 impairs the PCNA-pol η interaction and blocks the recruitment of pol η to stalled replication foci after UV irradiation, suggesting that p21 is a negative regulator for TLS through its modulation of both the loading of pol η to PCNA and the PCNA ubiquitylation status (68). This observation is different from that $p21^{-/-}$ cell lines show increased TLS efficiency and associated mutagenesis (5). Bendjennat *et al.* showed that UV induces proteolytic degradation of p21 in a ubiquitin-dependent manner and the activation of ATR pathway is essential to mediate this process (9).

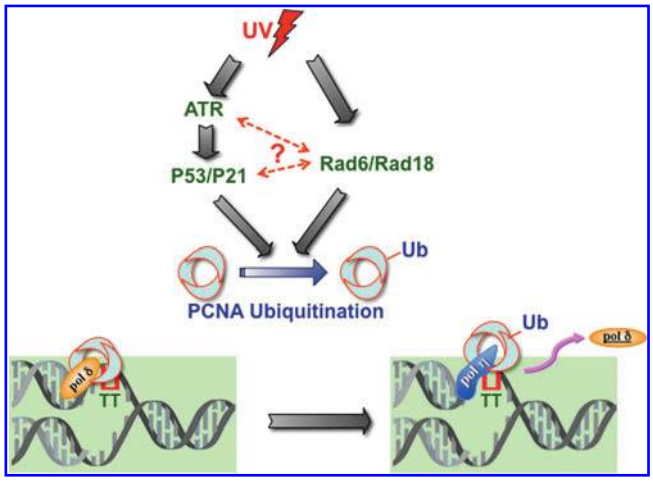

FIG. 3. A model for pol η recruitment to stalled DNA replication fork. UV irradiation activates ataxia–telangiectasia mutated Rad3-related and p53/p21, which promote the ubiquitin-dependent proteolysis of p21 that bound to PCNA on the replication fork. As p21 being degraded, Rad6/Rad18 complex introduces monoubiquitin on PCNA at Lys164. The monoubiquitinated PCNA has a higher affinity to pol η but a reduced affinity to pol δ, which promotes the switch of polymerases to perform the translesion synthesis. ATR, ataxia–telangiectasia mutated Rad3-related. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

Further, it is also critical to understand the release of pol η from the damage sites once it completes the bypass reaction to avoid the introduction of mutations by pol η, given that pol η exhibits low fidelity while replicating the undamaged DNA. The recent structural studies showed that pol η has lower affinity to bind to the undamaged DNA two nucleotides after the CPD sites (12). A recent report indicated that an E3 ubiquitin ligase protein Pirh2 can interact with pol η and such interactions promote pol η protein degradation by the 20 S proteasome in an ubiquitin-independent manner after UV irradiation (36), which could also contribute to modulate pol η activity after it completes the translesion reactions.

Overall, the current information indicates that multiple mechanisms are involved in regulating the activity of pol η in cells, including both protein phosphorylation and ubiquitination (Fig. 3). The UV-induced stalled replication activates ATR/ataxia–telangiectasia mutated, which activates p53/p21

and stimulates the p21 proteolysis. The degradation of p21 facilitates the ubiquitination of PCNA by Rad18. The mono-ubiquitinated PCNA has a preference to bind to pol η but a reduced affinity to replicative polymerases (79), which facilitates the release of replicative polymerases and recruitment of pol η to the stalled replication fork to perform the translesion synthesis. However, there are still questions remaining to be addressed. For example, if monoubiquitination of pol η is important to prevent it accidentally binds to the replication in the absence of DNA damages (11), it will be crucial to investigate the functions of the un-ubiquitinated pol η, which is still the majority form of pol η present in the cell even after UV irradiation (11).

Pol η and Therapeutic Anticancer Agents

In addition to CPD, pol η can also perform synthesis across lesions introduced by other environmental or therapeutic DNA damaging agents. For examples, it efficiently bypasses *N*-acetyl-2-aminofluorene-modified guanine, 8-oxoG, O^6-methylguanine (O^6MeG), and cisplatin intrastrand cross-linked guanosines (Pt-GG) [reviewed in (60)]. O^6-methylguanine is a strong block to replicative DNA polymerases and a mispairing lesion to cause GC → AT transition mutations. Human pol η replicates through the lesion quite efficiently by inserting a C or a T opposite the lesion (31). The ability of pol η to replicate across these DNA lesions allows the cells to continue the DNA replication process in the presence of damaged DNA, which provides the cells an alternative pathway to survive under hazardous conditions.

Given that DNA duplication process is an essential step for cell proliferation and cancer cells have higher proliferation rates, inhibiting DNA replication process has been an important target for designing and developing anticancer agents. To date, there are many anticancer therapeutic compounds that are designed to inhibit DNA elongation by altering the DNA structure through cross linking, alkylation, or prevent elongation after their incorporations into DNA. Since pol η has the capability to tolerate abnormal DNA structures, therefore, the participates of pol η to help the replication machinery to overcome these anticancer agents induced abnormal DNA structure may reduce the activity of these therapeutic compounds. This has been another important field of pol η that has been extensively investigated.

The most extensively studied anticancer compounds that interact with pol η is cisplatin and its analogs (Fig. 4). Cisplatin and its derivatives oxaliplatin and carboplatin are the most widely clinically used compounds for cancer treatments. Carboplatin has similar spectrum of activity as cisplatin but reduced toxicity (57). Both cisplatin and carboplatin are effective against solid tumors such as small-cell lung, ovarian, head, and neck cancers. Oxaliplatin is often used for the treatment of primary advanced colorectal cancer and cisplatin-resistant ovarian cancers (57, 66). Although cisplatin and its analogs are widely used clinically, a major limitation for these compounds is the induced drug resistance. It is believed that the major mechanism of action of these compounds is through forming DNA adducts to block DNA replication, as cisplatin forms covalent complexes with DNA and the 1,2-intrastrand GG cross links (65%), and the 1,2-intrastrand AG cross links (25%) are the major adducts caused by cisplatin (20). In addition, other forms of minor lesions such as interstrand GG crosslinks and other monoadducts have also been reported (20, 25). These adducts formed by cisplatin or its analogs block DNA replication, stop DNA chain elongation, and ultimately cause cell death to achieve their anticancer activity (20).

Since cisplatin efficacy comes from formation of DNA adducts, DNA repair mechanisms have been investigated for their potential impact on the cisplatin-induced resistance. Among these DNA repair mechanisms, NER has been shown to be the main DNA repair pathway for the removal of cisplatin adducts.

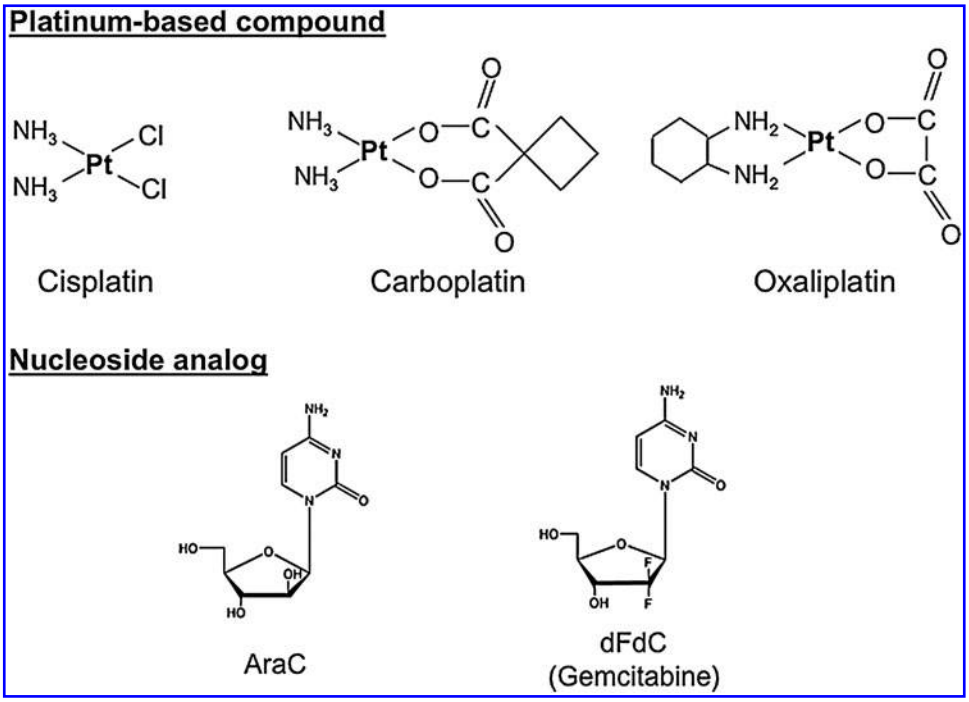

FIG. 4. Structure of anticancer therapeutic agents.

NER is also the key repair processes responsible for the removal of CPD and other bulky DNA adducts (61). As mentioned, the cisplatin mainly forms intrastrand crosslinked adducts, which distort normal DNA structure and block replicative polymerases. Therefore, in addition to the NER that removes cisplatin crosslinked DNA, the potential involvement of translesion DNA polymerases in bypassing the crosslinked DNA introduced by cisplatin-based compounds has also been investigated. Biochemical analysis on the interactions between cisplatin crosslinked DNA template and several translesion synthesis polymerases has shown that pol η has better efficiency in translesion synthesis past Pt-GG adducts as compared to other TLS polymerases, such as pol μ, β, and ζ (8, 20, 21, 32). For example, pol η bypasses the cisplatin adduct Pt-AGG with an overall three orders more efficient (k_{cat}/K_m) than pol β, including the insertion efficiency of 3′ and 5′ G of Pt-AGG and the extension for the T opposite the 5′A site of Pt-AGG (20). The cocrystal structure of a yeast pol η and cisplatin crosslinked GG containing DNA template have illustrated the mechanism for pol η to bypass the cisplatin crosslinked GG sites (4). It reveals that pol η correctly selects dCTPs by the complementarity of hydrogen bonding instead of the induced fit mechanism employed in high-fidelity polymerases (4). In addition to the structural and biochemical studies, a cellular study indicated that a 2–3-fold higher cisplatin-induced mutation frequency with the fibroblast cells derived from XP-V patients as compared to the isogenic XP-V cells complemented with pol η expression or the wild-type human fibroblasts (7). In addition, pol η-expressing cells are less sensitive to cisplatin treatment while comparing to the pol η expression downregulated or pol η-deficient cells in the cytotoxic studies (22). These results strongly suggested that pol η plays important roles in the error-free translesion synthesis across the cisplatin adducts. More important, a recent study indicated that the pol η expression level is correlated with the cytotoxicity of cisplatin non-small cell lung cancer. Further, this study also suggested that the expression level of pol η could be used as a predictive but not a prognostic marker in non-small cell lung cancer patient candidate to platinum-based chemotherapy (19).

In addition to cisplatin and platinum-based compounds, pol η has also been shown to affect the action of anticancer nucleoside analogs. Nucleoside analogs are another important class of DNA targeting anticancer agents that have long been used for cancer treatment (Fig. 4). Nucleoside analogs act predominantly by terminating DNA elongation process after their incorporation into cellular DNA (34, 58, 71), and their cytotoxicity is proportional to the amount of the analogs incorporated into DNA (34, 42, 58, 71). For example, AraC is used to treat leukemia (33) and gemcitabine, and β-D-2′,2′-difluorodeoxycytidine (dFdC) is used to treat various types of cancer, including non-small cell lung cancer (17), breast (59), and pancreatic cancers (39). Similar to cisplatin, the acquired drug resistance is also a limitation for nucleoside analogs. Several mechanisms have been reported, including enzymes involved in modulating the nucleotide pool (28), or DNA exonuclease that can remove these analogs from the 3′ termini of DNA and therefore diminish their activities (27). Structural and mechanistic studies showed that the arabinose sugar moiety of AraC and the di-fluoro group on the 2′ position of the sugar moiety of dFdC alter the DNA structure, which significantly reduced the extension efficiency for replicative DNA polymerases (41, 54). In comparison, pol η efficiently extends from either AraC or gemcitabine at the 3′ termini of DNA (22). In addition, pol η also replicates across both AraC and dFdC sites in the template DNA, which was shown to block DNA polymerases (62). Both the extension reaction of nucleoside analog from the 3′ termini and the bypassing reaction of these analogs in the template DNA could reduce the cytotoxic activities of both compounds, which may contribute to the observed drug resistance. Chen *et al.* have shown that pol η reduces the cellular sensitivity to both AraC and gemcitabine (22). Further, pol η expression cells demonstrated more than a 10-fold difference in cell sensitivity against the gemcitabine and cisplatin combination treatment as compared to the pol η deficient cells (22). The gemcitabine and cisplatin combination treatments are being tested against several types of tumors clinically. The information can have significant clinical value, suggesting that the expression level of pol η can affect the activities of these compounds. In combination with pol η expression analysis study (19), these cellular results also suggest that pol η should be considered as a predictive marker when designing chemotherapeutic treatments. The possible roles of pol η on the action of these therapeutic compounds are illustrated in Figure 5. More detailed structural and biochemical studies to investigate the interactions between anticancer nucleoside analogs and pol η is needed. Further investigation to examine the impact of pol η and other translesion synthesis polymerases on other clinically used nucleoside analogs, such as fludarabine, is necessary.

Concluding Remarks

DNA polymerase η is an important enzyme. It provides an alternative route for the cell to tolerate damaged DNA. The

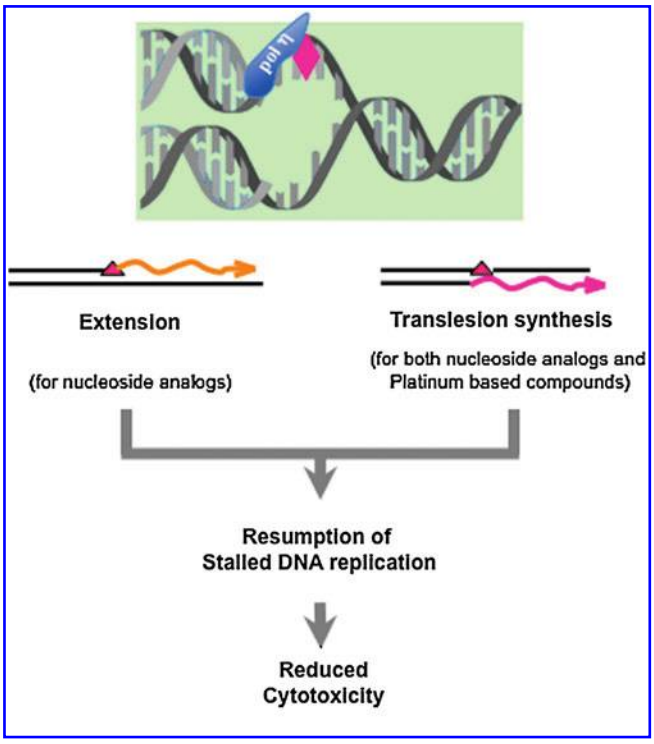

FIG. 5. Potential mechanism of action of pol η in the cellular resistance against anticancer therapeutic agents. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

main function of pol η is for replicating across the CPD lesion, which commonly observed in the skin and genetic defects of pol η gene result in XP-V disease. There are still questions remaining about this novel polymerase. For example, in addition to skin, pol η is expressed in different tissues (72). The functions of pol η in these tissues are currently unknown, since the opportunity for pol η to encounter CPD is very low in these tissues. The roles of pol η in somatic hypermutation have been investigated and are still evolving (64). In a different aspect, pol η may have significant roles in cancer chemotherapy, particularly for those agents exert their activity mainly by blocking DNA replication fork. The platinum-based compounds and nucleoside analogs activate the ATR and subsequently lead to phosphorylation of checkpoint protein chk1 and cause S-phase arrest, and enhance the recruitment of pol η to the stalled replication fork to overcome the lesions. Therefore, the combination of using these compounds with cell cycle checkpoint inhibitors like UCN-01 may promote the cytotoxicity of these compounds to achieve better therapeutic effects. Based on the current knowledge, pol η expression level can also be considered as a marker to predict the effectiveness of the DNA targeting anticancer compounds; however, further investigation is required.

Acknowledgment

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Abbreviations Used

AraC = cytarabine, cytosine-1-β-D-arabinofuranoside
ATR = ataxia–telangiectasia mutated Rad3-related
CPD = cyclobutane pyrimidine dimer
dFdC = gemcitabine, β-D-2′, 2′-difluorodeoxycytidine
NER = nucleotide excision repair
PAD = polymerase associated domain
PCNA = proliferating cell nuclear antigen
pol η = DNA polymerase eta
UBZ = ubiquitin-binding zinc
XP = xeroderma pigmentosum
XP-V = xeroderma pigmentosum variant

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