Review

Translesion DNA Synthesis and Hsp90

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Translesion DNA synthesis (TLS) is an essential mechanism for DNA damage tolerance during genome duplication by bypassing DNA lesions with use of specialized low-fidelity polymerases. Thus, TLS is inherently mutagenic, which is presumed to be involved in cancer initiation and progression. Increasing attention has focused on post-translational regulatory mechanisms of TLS polymerases, including covalent modification (e.g., phosphorylation) and proteasomal degradation. In this review article, we focus on our findings on Hsp90-mediated regulation of TLS polymerases and discuss potential pharmacological effects of Hsp90 inhibitors in cancer therapy.

Key words: translesion DNA synthesis, Y-family polymerase, Hsp90

Introduction

Precise and efficient duplication of the genome is essential for faithful inheritance of genetic information and maintenance of cellular architecture in multi-cellular organisms. Failure in this process causes various pathological disorders associated with mutations, genomic rearrangements and cell death, including cancers and degenerative diseases. Normal replication is hampered by various types of DNA damage on the template generated by environmental genotoxic agents (e.g., UV light and chemicals) and endogenous metabolic products (e.g., reactive oxygen species). Although most of these DNA lesions are removed by highly-coordinated multiple DNA repair pathways, some unrepaired lesions block the progression of replication forks catalyzed by high-fidelity DNA polymerases (Pols), which may lead to downstream re-initiation of DNA synthesis leaving single-stranded DNA gaps. Translesion DNA synthesis (TLS) is an essential mechanism for bypassing such replication blocks and post-replicative gaps by employing specialized TLS Pols, including Pol η , Pol κ , Pol ι and REV1, members of the Y-family Pols (Y-Pols), and Pol ζ , a member of the B-family (Fig. 1) (1–5). These TLS Pols display low stringency for the active site and a lack of proofreading, thus they potentially contribute to mutagenesis as well as to DNA damage tolerance.

Fig. 1. Structures of TLS polymerases.

Regulatory Mechanisms of TLS Pols

Accumulating evidence has revealed that functions of TLS Pols are tightly regulated at different levels. One critical step is localization of TLS polymerases “at the right place at the right time”. For this purpose, covalent modification of PCNA, an accessory factor of DNA polymerases, has an essential role. When replication stalls at sites of DNA damage, PCNA is monoubiquitinated at K164 by the Rad6/Rad18 complex and/or CRL4^{Cdt2} ubiquitin ligase (6–8). Y-Pols associate with PCNA via PCNA-interacting domains such as PIPs, but they bind to a monoubiquitinated form of PCNA (Ub-PCNA) with much higher affinity via their ubiquitin-binding domains such as UBZs and UBMs (Figs. 1 and 2), thereby replacing high-fidelity replicative Pols (Fig. 3) (9–13). In addition, REV1-mediated protein-protein interactions have critical roles in the regulation of TLS. Although REV1 has a deoxycytidyl transferase activity, this catalytic activity is dispensable for REV1-mediated TLS (14). Several studies indicate the functional importance of the N-terminal BRCT domain, which is partly explained by its binding to PCNA

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Fig. 2. Interactions between proteins involved in TLS (modified from Ref. 2).

Fig. 3. Hypothetical model of Hsp90-mediated regulation of Pol η targeting for TLS (modified from Ref. 44). Two major regulatory pathways are illustrated. Stalling of a replicative DNA polymerase at a site of DNA damage induces Rad6/Rad18-mediated generation of Ub-PCNA, whereas USP1 deubiquitinates Ub-PCNA. Pol η is in a cycle between an active form and an inactive form, and transient association with Hsp90 facilitates Pol η folding into the active form. PIP (P), UBZ (U) and catalytic (C) domains of Pol η are schematically shown. In the inactive form, PIP and UBZ are masked by intramolecular (or intermolecular) mechanisms. When 17-AAG inhibits the ATP-dependent chaperone cycle of Hsp90, a pool of the active form decreases; and an increased pool of the inactive form is targeted to proteasomal degradation. Hsp90 regulates REV1 by similar mechanisms.

(12,15,16). In addition, REV1 has a C-terminal region that binds Pol η , Pol κ and Pol ι as well as Pol ζ , a heterodimer of REV3 and REV7 (Figs. 1 and 2) (17–21), and recent findings indicate the functional significance of these interactions (21–23). Thus, it is proposed that REV1 acts as a scaffold protein to coordinate TLS polymerase switching (1–5).

Increasing attention has focused on conformational and stability control of TLS Pols by post-translational mechanisms, including covalent-modification, proteasomal degradation and chaperone-mediated folding. Earlier studies indicated that the chaperone/proteasome system has an important role in the regulation of Y-Pols in bacteria and lower eukaryotes. In *Escherichia coli*,

the GroE chaperone helps Y-Pols fold correctly to function (24,25); and, in *Saccharomyces cerevisiae*, the proteasome controls Pol η stability and modulates mutagenesis (26–28). In recent studies, Pol η and REV1, conserved throughout the eukaryotes, have been extensively studied. Various types of covalent modifications, including monoubiquitination, phosphorylation and sumoylation, are reported to regulate protein interactions and stability of Pol η in higher eukaryotes (29–32). Chen and colleagues reported that Pirh2 and Mdm2 ubiquitin ligases are involved in UV-induced proteasomal degradation of Pol η in human cells (33,34). As to the regulation of Rev1, most of our knowledge is based on studies in yeasts. In *Saccharomyces cerevisiae*, Mec1 protein kinase, the ortholog of human ATR, phosphorylates Rev1, promoting efficiency of mutagenic TLS in a Pol ζ -dependent manner (35–37). Yeast Rev1 protein levels increase to be ~50-fold higher during the G2/M phase compared to during the G1 and S phases, whereas its transcript levels vary only ~3-fold over the same phases, suggesting post-transcriptional control of Rev1 levels (38). Indeed, a recent study revealed that proteasomal degradation is involved in cell cycle-linked Rev1 regulation (39).

Hsp90: A Promising Target for Cancer Therapeutics

Hsp90 is an abundant, evolutionarily conserved molecular chaperone, which has a vital role in conformational regulation of a relatively selective group of ‘client’ proteins (40,41). This function of Hsp90 depends on its ability to bind and hydrolyze ATP. Hsp90 not only promotes proper folding of newly synthesized proteins into mature forms but also regulates stability, trafficking, and protein-protein interactions of mature clients. To fulfill these functions, Hsp90 usually cooperates with Hsp70 and cochaperones, such as p23 and CDC37. Many Hsp90 clients play key roles in cell survival/growth; representative clients include receptor and non-receptor protein kinases (e.g., ErbB2 and Akt), steroid receptors, transcriptional factors (e.g., p53), telomerase and chromatin remodeling proteins. In addition, Hsp90 promotes stability and activity of mutant or over-expressed oncoproteins (42). Thus, Hsp90 is an attractive target for cancer therapeutics. Indeed, specific inhibitors of Hsp90 are under development as promising anti-tumor agents. For instance, geldanamycin, a benzoquinone ansamycin antibiotic with potent anti-tumor activity, binds to the ATP-binding pocket of Hsp90 and inhibits its function. Because of its toxicity in animal models, several less toxic derivatives, including 17-allylamino-17-demethoxygeldanamycin (17-AAG), were developed and entered clinical trials a decade ago; a dozen of different classes of Hsp90 inhibitors are currently in clinical trials (42). Thus, un-

derstanding pharmacological effects of Hsp90 inhibitors would provide new insights into clinical effects of the drugs.

Hsp90 Regulates Pol η and REV1-mediated TLS

Some preclinical studies documented that Hsp90 inhibitors and genotoxic agents have synergistic effects in tumor cell killing, raising the possibility that Hsp90 regulates DNA damage response. Indeed, some proteins in the DNA damage response network, such as Chk1 and FANCA, were shown to be Hsp90 clients (43–45). We recently identified Hsp90 as an essential regulator of two major Y-Pols, Pol η and REV1 (46,47) (Fig. 3).

Our recent work provided several lines of evidence establishing that Pol η and REV1 are clients of Hsp90 (46,47). First, Hsp90 specifically interacted with these Pols *in vivo* and *in vitro*. Another line of evidence is that 17-AAG suppresses UV-induced accumulation of Pol η and REV1 at replication foci. In most cell types, 17-AAG reduced protein levels of these polymerases by accelerating proteasomal degradation. Moreover, RNAi-mediated depletion of Hsp90 reduced Pol η protein levels and UV-induced focus formation. Thus, Pol η and REV1 have the typical features of Hsp90 clients.

Importantly, the mild reduction of Pol η and REV1 in HEK293T cells allowed us to find that Hsp90 regulates the binding of these Y-Pols to Ub-PCNA. 17-AAG significantly suppressed the interaction between Pol η or REV1 and Ub-PCNA in chromatin immunoprecipitation. Furthermore, Pol η and REV1 extracted from 17-AAG-treated cells exhibited low binding to PCNA and/or Ub *in vitro*. Based on these results, we proposed a model in which the Hsp90 chaperone cycle is required for the folding of Pol η into an active form to enable efficient Ub-PCNA binding.

Finally, we showed that Hsp90 promotes Pol η - and REV1-mediated TLS by evaluating mutation rates in the *supF* reporter gene (46,47). However, these two Y-Pols have opposite effects on UV-induced mutagenesis: Pol η is engaged in error-free TLS across UV-induced thymine dimers, suppressing UV-induced mutagenesis; whereas REV1 is engaged in error-prone TLS, promoting UV-induced mutagenesis. Thus, the question arises what is the overall regulatory role of Hsp90 for TLS, although our knowledge is too premature to answer this question. In a current model, TLS consists of two major processes, insertion and extension: first, a TLS polymerase incorporates nucleotides opposite DNA lesions and then a second TLS polymerase extends a few additional nucleotides before restart of replicative DNA synthesis (1–5). Consistent with this model, recent studies indicate that UV-induced cyclobutane pyrimidine dimers are bypassed by Pol η by itself, whereas a combination of Pol ι or Pol κ -mediated error-prone insertion and a Pol ζ -mediated extension has a major role in mutagenic TLS

across the DNA lesion in Pol η -deficient cells (48–50). REV1 may function in the latter mutagenic TLS pathway through its interaction with Pol ι and Pol κ as well as Pol ζ , possibly facilitating a switch of Pols, although this regulatory function of REV1 in TLS is poorly defined. In this context, Hsp90 inhibition can have apparently paradoxical effects on UV-induced mutagenesis in Pol η -expressing and Pol η -deficient cells: Hsp90 suppresses and promotes UV-induced mutagenesis in the presence and absence of Pol η , respectively (46,47). Thus, the impact of Hsp90 inhibition probably depends on what TLS pathways and DNA lesions predominate.

TLS: A Novel Target of Hsp90 Inhibitors?

Carcinogenic activities of genotoxic agents, such as UV and benzo[a]pyrene, are mainly mediated by introduction of point mutations through error-prone TLS. Indeed, recent genomic analyses of cell lines derived from a melanoma and a lung cancer indicated that the majority of mutations were derived from mutagenic TLS across DNA lesions induced by UV and carcinogenic chemicals contained in tobacco smoke, respectively (51,52). Furthermore, several studies indicate that Pol η and REV1 contribute to cancer initiation and progression. For instance, it was proposed that Pol η is involved in mutagenic TLS across oxidative DNA damage generated by azathiopurine and UVA light, leading to occurrence of skin cancer in long-term survivors of organ transplantation (53). Furthermore, reduced expression of REV1 suppresses benzo[a]pyrene-induced development of lung cancer in mice (54), and cyclophosphamide-induced mutagenesis resulting in decreased acquisition of drug resistance in B-cell lymphoma transplanted in mice (55). Thus, Hsp90-targeting drugs may prevent TLS-mediated mutagenesis *in vivo*, thereby suppressing tumor initiation and/or progression.

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