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Review

Regulation of Translesion DNA Synthesis in Mammalian Cells

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The genomes of all living cells are under endogenous and exogenous attacks every day, causing diverse genomic lesions. Most of the lesions can be timely repaired by multiple DNA repair pathways. However, some may persist during S-phase, block DNA replication, and challenge genome integrity. Eukaryotic cells have evolved DNA damage tolerance (DDT) to mitigate the lethal effects of arrested DNA replication without prior removal of the offending DNA damage. As one important mode of DDT, translesion DNA synthesis (TLS) utilizes multiple low-fidelity DNA polymerases to incorporate nucleotides opposite DNA lesions to maintain genome integrity. Three different mechanisms have been proposed to regulate the polymerase switching between high-fidelity DNA polymerases in the replicative machinery and one or more specialized enzymes. Additionally, it is known that proliferating cell nuclear antigen (PCNA) mono-ubiquitination is essential for optimal TLS. Given its error-prone property, TLS is closely associated with spontaneous and drug-induced mutations in cells, which can potentially lead to tumorigenesis and chemotherapy resistance. Therefore, TLS process must be tightly modulated to avoid unwanted mutagenesis. In this review, we will focus on polymerase switching and PCNA mono-ubiquitination, the two key events in TLS pathway in mammalian cells, and summarize current understandings of regulation of TLS process at the levels of protein–protein interactions, post-translational modifications as well as transcription and noncoding RNAs. Environ. Mol. Mutagen. 61:680–692, 2020.

Key words: DNA damage tolerance; translesion DNA synthesis; TLS polymerase; chemotherapy

INTRODUCTION

DNA in cells continually suffers from lesions arising through endogenous as well as exogenous processes. Endogenous sources of DNA damage include spontaneous deamination, reactive oxygen species (ROS), apurinic or apyrimidic sites, DNA methylation, and active enzymatic DNA processes. Examples of exogenous sources of DNA damage include ultraviolet (UV), ionizing radiation, tobacco smoke carcinogens, alcohol, and DNA damaging chemotherapeutics. As failure to maintain DNA integrity may lead to cell death, premature aging, and cancer, all organisms have evolved DNA damage response network to sense and repair DNA damage and pass their genomes on to the next generation intactly (Jackson and Bartek, 2009; Ciccia and Elledge, 2010). It has been estimated that between 10^{17} and 10^{19} DNA damaging events occur in a human body every day (Lindahl and Barnes, 2000). Even though the majority of DNA damage is removed through DNA repair mechanisms, many lesions nevertheless persist during S-phase when the DNA at the replication fork is unwound and the repair template is lacking. To avoid DNA breaks and replication fork collapse, cells replicate bypass the damage and restart DNA replication through DNA damage tolerance (DDT) pathways. DDT pathways can be achieved mainly by error-prone translesion synthesis (TLS) and error-free template switching (TS) (Zhao and Washington, 2017). TLS recruits low-fidelity DNA polymerases to directly replicate across the

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damaged template, whereas TS uses the nascent sister chromatid as a template for bypass. Both pathways must be tightly controlled to prevent the accumulation of mutations that can occur from the dysregulation of DDT proteins (Lehmann et al., 2007).

Many DNA lesions cannot be used as a template by the highly stringent replicative DNA polymerases, which are optimized to replicate the entire genome with high accuracy and efficiency. Replication forks stall when they encounter damaged DNA, leading to the generation of long stretches of single-stranded DNA (ssDNA) coated by replication protein A (RPA) (Burns et al., 1996). These RPA-coated ssDNA regions trigger the activation of Ataxia telangiectasia mutated and Rad3-related (ATR) checkpoint (Lupardus et al., 2002; Zou and Elledge, 2003; Byun et al., 2005) and TLS initiated by proliferating cell nuclear antigen (PCNA) mono-ubiquitination or TS initiated by PCNA poly-ubiquitination (Hoege et al., 2002; Kannouche et al., 2004; Watanabe et al., 2004; Motegi et al., 2006; Motegi et al., 2008; Unk et al., 2008; Lee et al., 2014). Lesion bypass by TLS is performed by specialized DNA polymerases, which can use damaged DNA as templates and insert nucleotides opposite the lesions or replication impediments. These specialized TLS polymerases generally lack 3′–5′ exonucleolytic proofreading activity, avoiding an additional kinetic barrier to TLS. They also have larger active sites that are flexible enough to accommodate bulky DNA adducts, thereby enabling replication to proceed directly past the lesions (Sale, 2013).

Mammalian TLS polymerases include REV1, Polη, Polι, Polκ, Polζ, Polλ, Polμ, Polβ, Polθ, Polυ, and PrimPol. Based on protein sequence, TLS polymerases are divided into A- (comprising Polθ and Polυ), B- (comprising Polζ), X- (comprising Polλ, Polμ and Polβ), Y- (comprising REV1, Polη, Polι and Polκ), and PrimPol (primase and polymerase) families (Ito and Braithwaite, 1991; Filée et al., 2002; Rudd et al., 2014) (Fig. 1). The term TLS polymerases generally refer to the Y-family polymerases and B-family Polζ, which clearly have specialized roles involved primarily in lesion bypass. There is a specific Little-Finger domain, also known as PAD, essential for DNA binding except for palm, thumb, and finger domains in Y-family polymerases (Ling et al., 2001; Yang and Woodgate, 2007). All the Y-family polymerases have a conserved N-terminal domain containing the catalytic active site (~350–450 amino acids), and a variable-length C-terminal region important for their localization and utilization at stalled replication forks (Yang and Gao, 2018). Y-family TLS polymerases can be specifically recruited to sites of DNA lesions through direct interaction with mono-ubiquitinated PCNA via their ubiquitin-binding zinc finger (UBZ, ~20 amino acids in Polη and Polκ) or helical ubiquitin-binding motifs (~30 amino acids in Polι and REV1) (Bienko et al., 2005). Additional interactions with PCNA occur through the canonical PCNA-interacting peptide (PIP) box found in Polη, Polι, and Polκ, whereas REV1 interacts with PCNA through its N-terminal BRCA1 C-terminus (BRCT) domain (Guo et al., 2006a; Pustovalova et al., 2013). Mutations within the PIP box or ubiquitin-binding domain impair damage-induced association of TLS polymerases with mono-ubiquitinated PCNA and their accumulation at replication forks (Bienko et al., 2005; Guo et al., 2006a).

It has been generally accepted that eukaryotic TLS requires two steps, namely insertion and extension (Johnson et al., 2000; Livneh and Shachar, 2010). In the first step, one Y-family TLS polymerase replaces the normal replicative DNA polymerase at the stalled replication fork to incorporate a nucleotide opposite the lesion site directly. In the second step, an extender polymerase (usually Polζ, composed of catalytic subunit REV3 and accessory subunit REV7) replaces the inserter polymerase and then extends the nucleotides downstream of the lesion (Prakash et al., 2005). Usually, the Y-family polymerases exhibit a remarkable diversity in their substrate specificity and efficiency during lesion bypass. For example, Polη is specifically efficient and accurate while incorporating nucleotides opposite the UV-induced cyclobutane pyrimidine dimers, and also platinum-induced intrastrand crosslinks formed at adjacent guanines by anticancer drugs (Masutani et al., 1999a; Masutani et al., 2000; Zhao et al., 2012). In line with that, Polη plays an important role in protecting mammals from UV-induced carcinogenesis that is manifested by xeroderma pigmentosum variant patients lacking functional Polη (Masutani et al., 1999b). However, on the other hand, Polη facilitates tumor progression through reducing the efficacy of platinum-based chemotherapy. Recently, human Polη has been identified to contribute to the accumulation of cytidine monophosphate (rCMP) in the genome, particularly opposite modified guanines (Mentegari et al., 2017). Polκ is specialized in its ability to bypass N2-adducted dG lesions relative to an undamaged dG with high accuracy and strikingly increased catalytic efficiency, such as N2-furfuryl-dG and N2-dG-BPDE residues (Zhang et al., 2000; Huang et al., 2003; Liu et al., 2014). Significantly, Polκ also functions as an extender polymerase in the extension step of lesion bypass (Haracska et al., 2002; Washington et al., 2002; Jha and Ling, 2018). REV1 is a DNA template-independent dCMP transferase that uses its own residue arginine 324 as template, while Polι uniquely utilizes Hoogsteen pairing of the incoming nucleotides with the template bases and often misincorporates dGMP opposite T bases (Yang and Gao, 2018). It is known that suppression of REV1 can significantly inhibit UV- and chemotherapy-induced mutagenesis and resistance to front-line chemotherapy (Gibbs et al., 2000; Xie et al., 2010; Yamanaka et al., 2017). Intriguingly, although REV1 is required for the mutagenic TLS in eukaryotes, its polymerase catalytic activity is not essential for mutagenesis (Yamanaka et al., 2017). REV1 is believed to primarily function as a scaffolding protein to mediate the introduction of mutations into the genomes of eukaryotes via its interactions with other TLS polymerases. Furthermore, the absolute number of nucleotides incorporated

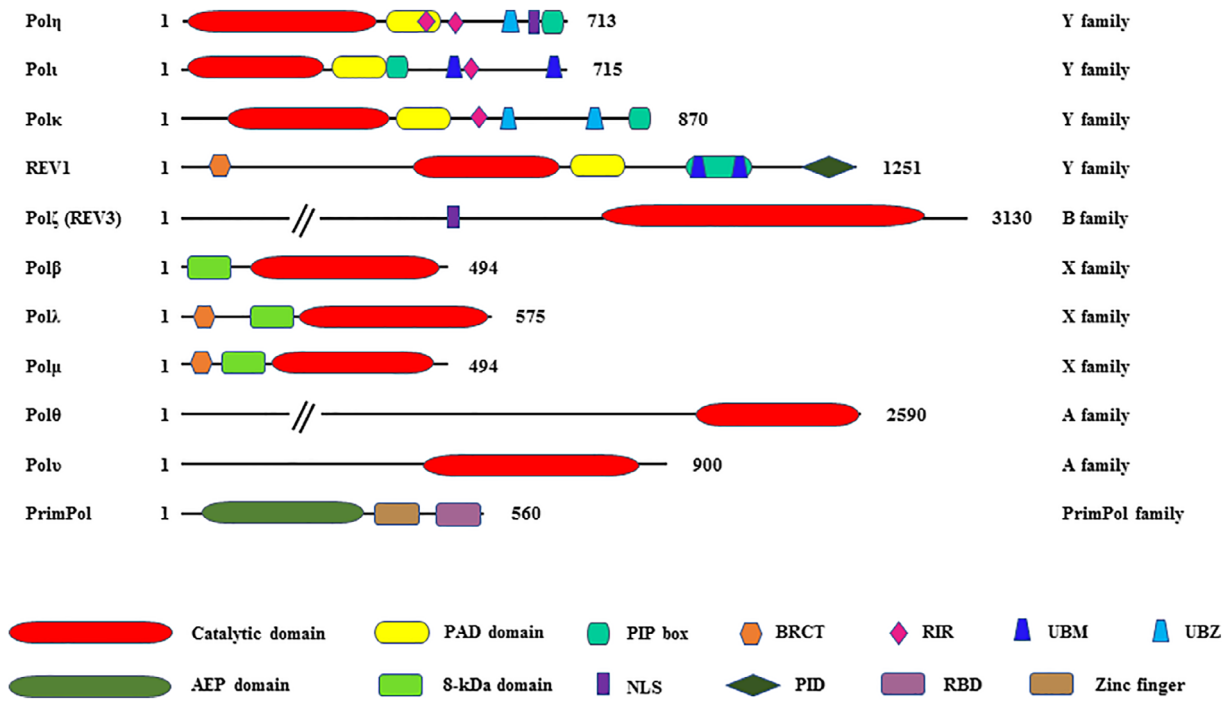

Fig. 1 Domain structure of mammalian translesion synthesis polymerases. AEP domain, archaeo-eukaryotic primase domain; BRCT, BRCA1 carboxyl terminus; NLS, nuclear localization signal; PAD, polymerase-associated domain (also known as the little finger); PID, polymerase interacting domain (of REV1); PIP, PCNA-interacting peptide; RBD, RPA binding domain (RBD); RIR, REV1-interacting region (of other Y-family polymerases); UBM and UBZ, ubiquitin-binding domains.

per DNA binding event varies among individual Y-family members, from very low, such as 2–3 nucleotides for Polι or REV1, to moderate, about 20–30 nucleotides in the case of Polκ in vitro (Vaisman and Woodgate, 2017).

So far, it has been documented that protein–protein interactions (PPIs), post-translational modifications (PTMs), transcription and noncoding RNAs modulate the key events during TLS in mammalian cells, including PCNA mono-ubiquitination (PCNA-mUb) and polymerase switching, thereby limiting mutagenic TLS from undamaged DNA and assuring optimal TLS at stalled DNA lesions to rescue replication. Moreover, TLS is implicated in both pathogenesis and chemoresistance of multiple cancer types, and represents an important target for cancer treatment. This review aims to summarize recent studies on the regulation of TLS in mammalian cells, which will benefit the development of potential TLS inhibitors for sensitizing tumors cells to chemotherapy.

KEY EVENTS IN TLS

Polymerase Switching

At present, there are three different mechanisms proposed for polymerase switching at stalled replication forks, namely PCNA "toolbelt," REV1 "bridge," and four-subunit Polζ complex (Fig. 2).

It is known that mono-ubiquitination of the sliding clamp PCNA is a central event in TLS (Kannouche et al., 2004). Upon fork stalling, all three monomers of PCNA can be monoubiquitinated and bind different TLS polymerases simultaneously, thereby functioning as a "toolbelt" by allowing rapid exchange of TLS polymerases to facilitate the selection of appropriate polymerases for lesion bypass (Kannouche et al., 2004; Kanao et al., 2015; Boehm et al., 2016; Leung et al., 2018; Slade, 2018). Additionally, E3 ligase $CRL4^{Cdt2}$-dependent proteasomal degradation of PIP (PCNA-interacting protein) degron proteins also plays an important role in the switch of PCNA partners and facilitates TLS polymerase recruitment after DNA damage treatment (Tsanov et al., 2014).

Next to PCNA, REV1 can recruit other TLS polymerases through its C-terminal domain (CTD) (Guo et al., 2003; Guo et al., 2009). In particular, REV1 CTD has been found to use different regions to associate with Y-family polymerases and the REV7 subunit of Polζ (Zhao and Washington, 2017). The N-terminal of the REV1 CTD is involved in an interaction with the short REV1 interacting region (RIR) motifs of Polη, Polι, and Polκ, as well as of p66 subunit of Polδ, while the C-terminal of REV1 CTD binds REV7

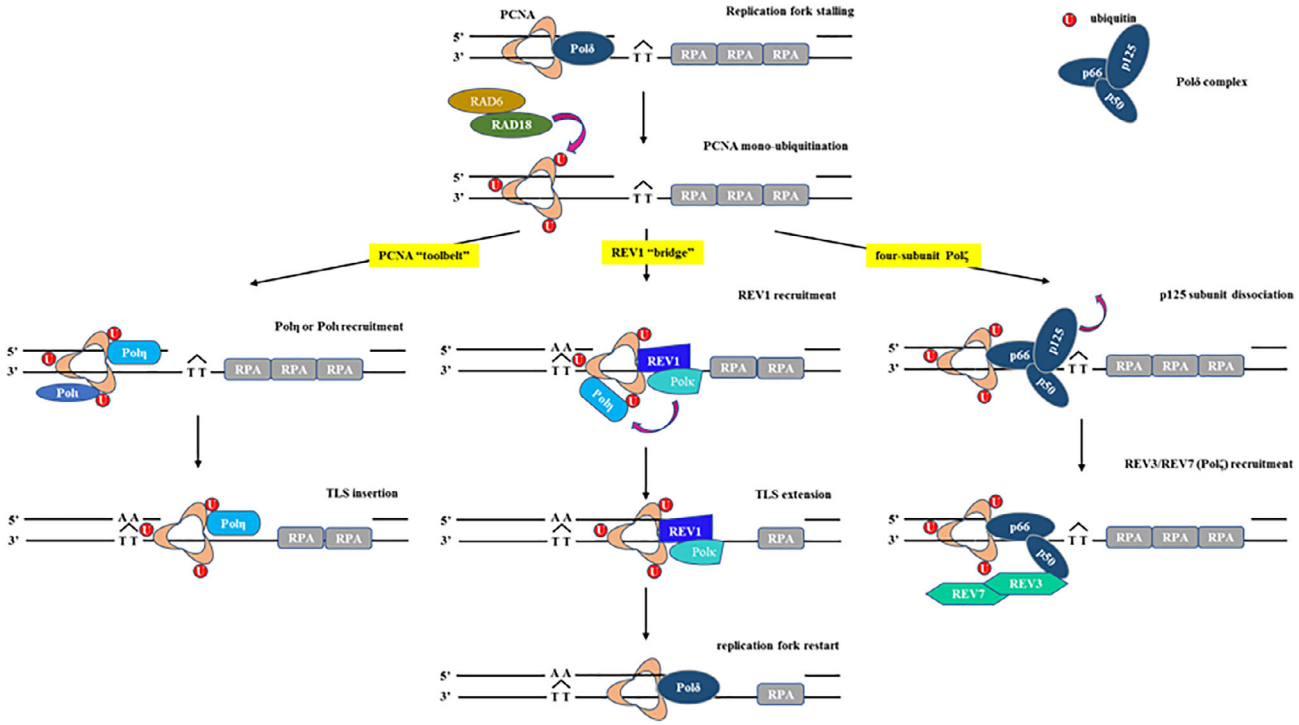

Fig. 2 Models for polymerase switching during translesion synthesis (TLS). In the PCNA "toolbelt" model, mono-ubiquitinated PCNA recruits the TLS polymerases, such as Polη or Polι via their UBD domain. If Polδ is replaced by Polη for the insertion step, complementary AA is incorporated opposite TT dimer. In the REV1 "bridge" model, REV1 binds PCNA through its BRCT/PAD domain following the insertion step across the lesion. REV1 functions as a "bridge" to recruit Polκ or Polζ (REV3/REV7) for the extension step. In the four-subunit Polζ model, p125, the catalytic subunit of Polδ, dissociates and is replaced by REV3/REV7 subunits of Polζ to bypass the lesion upon replication fork stalling.

(Kikuchi et al., 2012; Pozhidaeva et al., 2012; Xie et al., 2012; Wojtaszek et al., 2012a; Wojtaszek et al., 2012b; Pustovalova et al., 2016). Combined with the interaction between REV1 and PCNA mediated by the REV1 BRCT and PAD domains, REV1 functions as a molecular "bridge" between PCNA and TLS polymerases to facilitate the insertion and extension polymerase switching to complete TLS (Boehm et al., 2016; Zhao and Washington, 2017).

Interestingly, upon Polδ stalling at a DNA lesion, its catalytic subunit p125 dissociates to facilitate the REV3/REV7 complex to gain access to the stalled replication fork, forming a four-subunit Polζ complex (comprising REV3, REV7, and the p50 and p66 subunits of Polδ). The switching from Polδ to Polζ by sharing accessory subunits represents another mechanism for polymerase switching (Baranovskiy et al., 2012; Johnson et al., 2012; Makarova et al., 2012). It has been reported that REV7 undergoes a significant conformational change upon REV3 binding, which locks REV7 in a closed conformation and creates a REV7 binding site for the REV1-CTD domain (Hara et al., 2010). In addition to REV3–REV7 interactions, the four-subunit Polζ complex is stabilized by interactions between p50 and the REV3 C-terminal region, which contains an iron–sulfur 4Fe-4S cluster and a zinc-finger domain (Netz et al., 2011; Baranovskiy et al., 2012; Yang and Gao, 2018), and between p50 and p66 N-terminal domain (Baranovskiy et al., 2008). The four-subunit Polζ exhibits a more efficient and processive activity than the REV3/REV7 complex (Baranovskiy et al., 2012; Makarova et al., 2012; Lee et al., 2014; Makarova and Burgers, 2015). The PIP box and RIR motifs in the C-terminal of p66 subunit enhance Polζ interactions with PCNA and REV1, helping switch an inserter TLS polymerase with the extender Polζ upon REV1/Polζ-dependent TLS (Pustovalova et al., 2016).

PCNA Mono-Ubiquitination

PCNA, a homotrimeric DNA clamp, acts as a central hub regulating a myriad of processes during DNA replication, tolerance, and repair. PCNA-mUb catalyzed by the principal E3 ubiquitin ligase RAD6/RAD18 on lysine 164 (K164) is essential for optimal TLS activity in mammalian cells (Hendel et al., 2011). It is known that a common consequence of replication fork stalling is the uncoupling of replicative polymerase and helicase movements, leading to the generation of extensive stretches of ssDNA, which can be rapidly bound by RPA (Zou and Elledge, 2003; Nam and Cortez, 2011). Several studies

have revealed that RPA is involved in the regulation of PCNA-mUb by interacting directly with RAD18 on chromatin and in the nucleoplasm (Davies et al., 2008; Hedglin et al., 2019). Notably, under native conditions, "DNA-free" RPA directly interacts with RAD18 and inhibits mono-ubiquitination of free PCNA. During DNA replication stress, RPA binds ssDNA and undergoes a conformational change to increase its affinity with RAD18 for efficient PCNA-mUb (Hedglin et al., 2019). Interestingly, RAD18-mediated PCNA NEDDylation at K164 is also reported to antagonize PCNA-mUb after H_2O_2 or UV treatment (Guan et al., 2018). Moreover, RAD18 partner, MAGE-A4 (melanoma-associated antigen-A4), can protect it from ubiquitin-mediated proteolysis and increases the level of PCNA-mUb and TLS activation (Gao et al., 2016).

However, residual PCNA-mUb was detected in RAD18-deficient cells (Simpson et al., 2006), indicating the existence of an alternative E3 ligase for PCNA-mUb. Later, E3 ligases RNF8 (ring finger protein 8) and $CRL4^{Cdt2}$ (Cullin-4-RING ligase (CRL4)-Ddb1-Cdt2) were reported to catalyze PCNA-mUb. Upon exposure to UV radiation and the alkylating agent, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG), RNF8 can readily mono-ubiquitinate PCNA in the presence of UbcH5c, an E2 conjugating enzyme (Zhang et al., 2008). Under unperturbed conditions, $CRL4^{Cdt2}$ catalyzes PCNA-mUb and synergizes with RAD6/RAD18 to promote TLS (Terai et al., 2010). Nevertheless, compared with RAD18, the contribution of RNF8 and $CRL4^{Cdt2}$ in the PCNA-mUb is considered rather minor.

Given its essential role in TLS process, the level of PCNA-mUb must be strictly regulated to prevent mutagenesis by excessive TLS. Ubiquitin-specific peptidase 1 (USP1) in complex with USP1-associated factor 1 (UAF1) is the most investigated deubiquitinase of PCNA-mUb in the absence of DNA damage, that is directed by hELG1 (enhanced level of genomic instability 1), an alternative subunit of the RFC clamp loader complex (Lee et al., 2010). In response to UV irradiation, USP1 is degraded through autocleavage leading to the accumulation of PCNA-mUb and the activation of TLS (Huang et al., 2006; Niimi et al., 2008). ROS can also cause a rapid PCNA-mUb (Zlatanou et al., 2011). Interestingly, oxidative stress does not affect the steady-state level of USP1, but inactivates USP1 DUB activity through transient oxidization (Cotto-Rios et al., 2012; Lee et al., 2013). In addition to USP1, another deubiquitinase ubiquitin-specific peptidase 7 (USP7) was found to suppress PCNA-mUb, especially for the suppression of ROS-induced PCNA-mUb (Kashiwaba et al., 2015). Notably, USP7 is also reported to stabilize Polη and RAD18 from proteasomal degradation through deubiquitinating Mdm2-mediated Polη poly-ubiquitination (Jung et al., 2012) and RAD18 auto-ubiquitination (Zeman et al., 2014; Lecona et al., 2016), thereby leading to efficient PCNA-mUb (Kashiwaba et al., 2015; Qian et al., 2015; Zlatanou et al., 2015). Moreover, as a replisome-associated SUMO deubiquitinase (SDUB), USP7 helps to maintain a SUMO-rich, Ub-poor environment by limiting the ubiquitination of SUMOylated proteins and their segregation at replication forks, to sustain DNA replication (Lecona et al., 2016). Therefore, USP7 can regulate TLS through multiple aspects. Considering that ROS- and UV-induced PCNA-mUb ultimately disappear even in cells depleted of both USP1 and USP7, other mechanisms for scavenging ubiquitinated PCNA could still be available. Supportingly, it was reported that upon completion of TLS, monoubiquitinated PCNA could be modified by interferon-stimulated gene 15 (ISG15) at K164 and K168 catalyzed by EFP, an ISG15 E3 ligase, leading to the recruitment of USP10. Subsequently, ISGylated PCNA is deubiquitinated by USP10 followed by TLS polymerase release from replication fork for TLS termination (Park et al., 2014). Finally, PCNA is deISGylated for replicative polymerases switching back to resume DNA replication.

REGULATION OF TLS

Protein–Protein Interactions

Beyond above-mentioned E3 ligases and DUBs, PPIs also play important roles in regulating PCNA-mUb. Up to the present, several PCNA interacting partners have been reported to regulate PCNA-mUb and cellular TLS activity, which include p21, PAF15, and SPRTN (Moldovan et al., 2007; Mailand et al., 2013; Choe and Moldovan, 2017). As a regulator of TLS (Avkin et al., 2006; Soria et al., 2006), p21 interacts with PCNA via its PIP box, which has a much higher intrinsic affinity for PCNA than other known PCNA-interacting partners (Bruning and Shamoo, 2004). The interaction between PCNA and p21 can impair Polη association with PCNA and inhibit Polη focus formation (Soria et al., 2008). After UV radiation, p21 is degraded through a PCNA-coupled manner by E3 ligase $CRL4^{Cdt2}$, facilitating efficient PCNA-mUb and Polη recruitment (Soria and Gottifredi, 2010; Mansilla et al., 2013). The p21-PCNA dissociation can also be modulated by PIDD (p53-induced protein with a death domain) in response to UV irradiation, whose loss was reported to cause a defect in PCNA-mUb and Polη chromatin binding (Logette et al., 2011). PAF15 (PCNA-associated factor 15) is another TLS regulation factor, which can be double monoubiquitinated at lysine 15 and 24 during normal DNA replication (Povlsen et al., 2012), possibly by UHRF1 (ubiquitin-like PHD and RING finger domain-containing protein 1) (Karg et al., 2017). Upon replication fork stalling, the lysine 15/24-ubiquitinated PAF15 is displaced from PCNA to facilitate the association between Polη and possibly other TLS polymerases with PCNA-mUb (Povlsen et al., 2012). In addition, PAF15 can also promote the release of Polη after lesion bypass to reduce UV-induced mutagenesis. Recently, PAF15 was found to inhibit the activity of

Polη-PCNA holoenzyme to bypass across a site-specific cisplatin lesion in vitro (De March et al., 2018). Another well studied TLS regulator is SPRTN (also known as DVC1 and C1orf124), which is a multi-domain protein containing a SprT-like domain, an SHP and PIP box as well as a UBZ domain (Centore et al., 2012; Davis et al., 2012; Ghosal et al., 2012; Juhasz et al., 2012; Machida et al., 2012; Mosbech et al., 2012; Kim et al., 2013). It has been reported that SPRTN is recruited to UV damage sites through its interaction with PCNA-mUb, mediated by its PIP box and UBZ domain (Centore et al., 2012). Beyond as a PCNA-mUb reader, SPRTN also interacts with RAD18 and facilitating RAD18 chromatin binding and PCNA-mUb (Centore et al., 2012). Interestingly, SPRTN also binds the ubiquitin-dependent molecular segregase p97 (also known as valosin-containing protein, VCP) complex via its SHP domain, and recruits p97 complex to sites of damage (Davis et al., 2012; Ghosal et al., 2012; Mosbech et al., 2012), facilitating removal of Polη from chromatin upon completion of TLS (Davis et al., 2012; Mosbech et al., 2012). Intriguingly, SPRTN also directly binds to p66, the accessory subunit of the replicative polymerase Polδ, via SprT domain. Depletion of SPRTN increases the interaction of p66 with REV1 and Polζ, and concomitantly elevates UV-induced mutagenesis (Kim et al., 2013). Thus, SPRTN can regulate TLS at multiple steps. Several other PCNA partners are also involved in the regulation of PCNA-mUb. It has been reported that WRN (Werner Syndrome RecQ Like Helicase) can suppress RAD18-dependent PCNA-mUb. Consequently, Werner syndrome cells show constitutive PCNA-mUb and interaction between PCNA and Rad18 in the absence of DNA damage (Kobayashi et al., 2010). E3 ubiquitin ligase Parkin is also found to play an important role in efficient ssDNA generation after UV irradiation. Depletion of Parkin impairs RPA foci formation and PCNA-mUb and Polη recruitment (Zhu et al., 2017). Another PCNA partner, mono-ADP-ribosyltransferase PARP10, which has a higher affinity with monoubiquitinated PCNA, promotes PCNA-mUb through a positive feedback loop, analogous to SPRTN/C1orf124 (Nicolae et al., 2014). Loss of PARP10 can inhibit TLS and cell proliferation and increase cell sensitivity to replication stress (Schleicher et al., 2018). Additionally, PCNA-interacting proteins CHK1, Claspin, and Timeless also facilitate RAD18 recruitment and PCNA-mUb after DNA damage treatment in an ATR-independent manner (Yang et al., 2008).

As mentioned above, the ubiquitin ligase RAD18 is the principle E3 to monoubiquitinate PCNA. So far, several factors have been reported to regulate RAD18 recruitment to stalled replication forks, including mutated in Nijmegen breakage syndrome (NBS1), Zinc finger and BTB domain-containing 1 (ZBTB1), Breast cancer type 1 susceptibility protein (BRCA1), and squamous cell carcinoma antigen recognized by T Cells 3 (SART3). NBS1 directly recruits RAD18 through a RAD6-like domain near the C terminus after UV irradiation and mediates the recruitment of RAD18 to sites of DNA damage. The RAD18-interacting domains of NBS1 and RAD6 allow the two proteins to interact with RAD18 homodimers simultaneously and are crucial for Polη-dependent UV tolerance. Disruption of NBS1 abolished RAD18-dependent PCNA-mUb and Polη focus formation, leading to elevated UV sensitivity and mutation (Yanagihara et al., 2011). ZBTB1 associates with Krüppel associated box (KRAB)-associated protein 1 (KAP1) and is required for localizing phosphor-KAP-1 to chromatin and enhancing RAD18 accessibility (Kim et al., 2014). BRCA1 can interact with RAD18, RPA, REV1, and Polη. BRCA1 deficiency impairs the UV-induced foci formation of these DDT factors and TLS activation (Tian et al., 2013). We recently found that SART3 can not only regulate UV-induced ssDNA generation and RPA focus formation but also promote RAD18/Polη association through its homodimerization (Huang et al., 2018). Depletion of SART3 significantly impairs UV-induced RAD18 focus formation and PCNA-mUb. Besides, Werner helicase-interacting protein 1 (WRNIP1) is reported to accumulate at UV-irradiated sites in a UBZ domain-dependent manner (Crosetto et al., 2008), displacing RAD18 from the DNA and stimulating polymerase switch from Polδ to Polη during TLS (Yoshimura et al., 2017).

Interestingly, although SIVA apoptosis-inducing factor 1 (SIVA1) and Polη are found to targeting RAD18 to PCNA and facilitating efficient PCNA-mUb in response to UV radiation (Durando et al., 2013; Han et al., 2014), Polη but not SIVA1 promotes damage-induced RAD18 redistribution. In addition, Polη-induced PCNA-mUb is dissociable from its catalytic activity. Moreover, as the chromatin recruitment of RAD18 is restricted by its dimerization with mono-ubiquitinated RAD18 (Zeman et al., 2014), we found that REV1 can promote PCNA-mUb through its competitive interaction with ubiquitinated RAD18, which facilitates the release of nonubiquitinated RAD18 from ubiquitinated RAD18 trapping and thereby RAD18 chromatin accumulation (Wang et al., 2016).

In addition to those mentioned PCNA and RAD18 partners, several other factors are also reported to regulate PCNA-mUb and TLS activation, which include MSH2, heat shock protein 90 (HSP90), and polymerase Polδ interacting protein 38 (PDIP38). Mismatch repair (MMR) protein MSH2 is discovered to physically interact with Polκ and REV1. We found that MSH2 can regulate post-UV focus formation of specialized DNA polymerases in both PCNA-mUb-dependent and -independent fashions (Lv et al., 2013). HSP90 is an ATP-dependent molecular chaperone, which can bind REV1 and Polη and promote their stability (Sekimoto et al., 2010; Pozo et al., 2011). Inhibition of HSP90 can disrupt the association between monoubiquitinated PCNA with REV1 and Polη, suppressing the UV-induced REV1 and Polη focus formation. PDIP38 can also directly interact with Polη and

REV1 (Tissier et al., 2010), and acts as a key regulator in preventing Polη from participation in normal DNA replication in unstressed cells. After UV exposure, PDIP38 is shuttled to spliceosomes for alternative splicing, and Polη is phosphorylated by ATR and PKC. The phosphorylated Polη then loses its ability to interact with PDIP38 and increases its association with monoubiquitinated PCNA (Peddu et al., 2018). Depletion of PDIP38 causes a shift from TLS to TS in DDT in chicken DT40 and human TK6 cells without affecting cellular sensitivity to UV or H_2O_2 (Tsuda et al., 2019). In addition, several factors in Fanconi anemia pathway were also reported to facilitate TLS, which include FAAP20 and FAN1 (Kim et al., 2012; Budzowska et al., 2015; Porro et al., 2017).

Post-Translational Modifications

PTMs of proteins, including ubiquitination, phosphorylation, SUMOylation, O-GlcNAcylation, and NEDDylation, play a pivotal role in controlling the different outcomes of damage bypass by modulating the residence time of individual factors in the fork vicinity and determining the probability of each TLS polymerase being used in replication past lesions. It is known that all the Y-family polymerase members involved in TLS have been identified to be ubiquitinated, regulating their access to chromatin and the interaction with PCNA (Sale et al., 2012). For example, a small amount of Polη is monoubiquitinated in the absence of damage in vivo. The mono-ubiquitination of Polη can occur on K682, K686, K694, and K709 located near its C-terminus, possibly catalyzed by E3 ligase PirH2 (Bienko et al., 2010; Jung et al., 2011). The attached ubiquitin on Polη has been identified to bind the UBZ of Polη, causing a conformational change in its C-terminus, blocking the PIP box located between the UBZ and K682, and then excluding Polη from the chromatin and replication foci (Bienko et al., 2010; Jung et al., 2011). After UV treatment, Polη is de-ubiquitinated, facilitating its association with PCNA-mUb for TLS (Bienko et al., 2010). So far, the DUB(s) responsible for removing the mono-ubiquitination modification from Polη remains unclear. Of interest, the expression level of Polη is also decreased following UV irradiation, which is likely mediated by E3 ligase MDM2 that polyubiquitinates Polη and marks it for proteasomal degradation (Jung et al., 2012). It was also reported that USP7 can deubiquitinate both Polη and MDM2, thereby tightly regulating the steady-state levels of Polη (Qian et al., 2015). Additionally, we recently showed that after completion of TLS by Polη, it can also be polyubiquitinated at K462 mediated by the E3 ligase $CRL4^{Cdt2}$, to promote p97-dependent removal of Polη from replication forks and to facilitate the switching between Polη with extension or replicative polymerases. Intriguingly, this polyubiquitination at K462 is promoted by the O-GlcNAcylation on adjacent T457 of Polη (Ma et al., 2017). Meanwhile, five other ubiquitinated lysine residues (K131, K163, K311, K453, and K494) in the Polη have also been identified, whose functions remain to be elucidated. There are over 27 potential ubiquitination sites within different functional domains of Polι identified by mass spectrometry analysis. Unlike Polη, which undergoes de-ubiquitinated after UV treatment, the level of Polι mono-ubiquitination remains unchanged after exposure to a wide array of DNA-damaging agents such as UV and MMC (McIntyre et al., 2015b). It is speculated that mono-ubiquitination of Polι enhances its interaction with Polη, facilitating its localization to stalled replication fork (McIntyre et al., 2013). Furthermore, Polι can be transiently polyubiquitinated via K11- and K48-linked ubiquitin chains after the inhibition of the lysine acetyltransferase p300 and subsequently targeted for degradation (McIntyre et al., 2015a). Although REV1 and Polκ can also be ubiquitinated, their modification sites and related functions remain largely unknown (Guo et al., 2006b; Guo et al., 2008; McIntyre and Woodgate, 2015).

Similar to ubiquitination, protein phosphorylation also plays important roles in TLS regulation. In addition to mono-ubiquitination at K164, PCNA phosphorylation on tyrosine 211 (Y211), catalyzed by epidermal growth factor receptor (EGFR), is required for stabilizing PCNA on chromatin (Wang et al., 2006). Abolishing Y211 phosphorylation can cause PCNA polyubiquitylation by Cullin 4-based ubiquitin ligase CRL4 and proteasomal degradation of PCNA (Lo et al., 2012). Additionally, the phosphorylation of PCNA at Y211 inhibits MMR via altering the interaction between PCNA and MMR proteins, resulting in error-prone DNA replication to promote tumor development and progression (Ortega et al., 2015). It is known that, in addition to promoting PCNA-mUb, RAD18 also associates with Polκ and Polη, helping chaperone these TLS polymerases to a stalled replication fork. Notably, RAD18 could be phosphorylated on S409 and S-box after UV radiation, mediated by c-Jun N-terminal kinase (JNK) and Dbf4/Drf1-dependent Cdc7 kinase (DDK), respectively (Day et al., 2010; Barkley et al., 2012). Given that these phosphorylated sites reside in the Polη-binding region of RAD18 (residues 401–445), the phosphorylation of RAD18 can increase its affinity for Polη and promotes Polη recruitment to stalled replication forks for TLS. Polη has been demonstrated to be phosphorylated by ATR on serine 601 (S601) (Göhler et al., 2011) and protein kinase C (PKC) on serine 587 (S587) and threonine 617 (T617) (Chen et al., 2008), which are necessary for efficient lesion bypass after exposure to UV radiation or chemotherapeutic drug treatment. In addition, Polη can also be phosphorylated by cyclin-dependent kinase 2 (CDK2) on serine 687 (S687) located in the NLS region upon UV stimulation (Dai et al., 2016), which is reported to diminish its interaction with PCNA and facilitate its departure from the replication fork after TLS. Additionally, Polη can be

SUMOylated at K163 by SUMO ligase PIAS1 through RAD18 bridging, which is required for Polη recruitment to replication forks during unperturbed S phase or under low replication stress to prevent under-replicated DNA (Despras et al., 2016). Since K163 could also be ubiquitinated (Ma et al., 2017), how these two different PTM modes interplay to regulate Polη function(s) remains to be determined.

Transcription and Noncoding RNAs

Beyond regulation by PPIs and PTMs, TLS pathway is also modulated transcriptionally, which is intricately associated with the maintenance of genome integrity (Barnes and Eckert, 2017). For example, the expression of Polκ and Polη can be upregulated at the transcriptional level by DNA damage in a p53-dependent manner (Velasco-Miguel et al., 2003; Liu and Chen, 2006; Guo et al., 2009; Tomicic et al., 2014; Lerner et al., 2017). Moreover, the half-life of *POLH* mRNA is decreased upon knockdown of poly(rC)-binding protein 1 (PCBP1), which directly binds to an atypical AU-rich element in the proximal *POLH* 3′-UTR (Ren et al., 2014).

Recently, several noncoding RNAs (ncRNAs), especially micro-RNAs (miRNAs) and long noncoding RNAs (lncRNAs), are also reported to regulate TLS core factors at the post-transcriptional level. RAD18 is found to be downregulated by the tumor suppressor miR-145, which can bind *RAD18* 3′-UTR directly (Liu et al., 2015). The negative effect of miR-145 on RAD18 expression can be reversed by lncRNA-ROR (regulator of reprogramming) through competing endogenous RNA regulation, thereby promoting DNA repair (Chen et al., 2018). Additionally, arylamine 4-aminobiphenyl (4-ABP)-induced miR-630 is also reported to downregulate *RAD18* mRNA in HepG2 cells (Huan et al., 2014). Apart from RAD18, several TLS polymerases are also reported to be downregulated by miRNAs. For example, Polη can be negatively regulated by miR-93 (Srivastava et al., 2015). The inverse correlation between miR-93 and *POLH* expression in multiple ovarian cancer stem cells implicates that a miR-93-Polη axis affecting the survival of these cells upon cisplatin treatment. Recently, several *POLH* transcripts with various lengths of 3′UTR through alternative polyadenylation (APA) are reported in lung and bladder cancer. Interestingly, the long *POLH* transcript with 6245-nt 3′UTR can be selectively inhibited by miR-619, whereas the short *POLH* transcript with 427-nt 3′UTR can escape miR-619-mediated repression and is responsible for high expression of Polη in cisplatin-resistant cells (Zhang et al., 2019). *REV1* 3′UTR can be targeted by miR-96 (Wang et al., 2012), which results in REV1 downregulation and is critical for miR-96-mediated cisplatin sensitivity. MiR-340, a microRNA down-regulated in colon cancer, was found to bind the 3′-UTR of *REV3* and downregulate REV3, which inhibits colon cancer cells proliferation and promote their apoptosis (Arivazhagan et al., 2017). Although most published studies on ncRNAs implicated in the TLS have focused on the role of miRNAs, the advent of high-throughput sequencing holds a promise for discovery of more new and unanticipated functional lncRNAs in the future.

CONCLUSIONS

Since its discovery over decades ago, our understanding of TLS has improved dramatically. As a major mode of DDT, TLS plays an important role in genome maintenance through preventing replication fork stalling. Defective TLS is closely associated with various diseases, including stem cell defects, aging, cancer, and neurological disorders (Pilzecker et al., 2019). In this review article, we have discussed how TLS is regulated in mammalian cells in detail, with the TLS polymerases limited to the Y-family polymerases and Polζ. In summary, three different but not mutually exclusive mechanisms have been proposed for polymerase switching at stalled replication fork, namely PCNA "toolbelt," REV1 "bridge," and four-subunit Polζ complex. In addition, as an essential event for optimal TLS activity in mammalian cells, PCNA-mUb is under stringent control at multiple levels, which include PPIs, PTMs, transcription, and noncoding RNAs.

Given its important role in spontaneous and acquired drug resistance for chemotherapy, development of inhibitors targeting TLS polymerases activity or TLS regulators holds promise for improvement of therapeutic efficacy (Yamanaka et al., 2017). Recent years, several potential TLS small molecule inhibitors, which can sensitize tumor cells to chemotherapeutics, have been identified, including JH-RE06, MLAF50, and ML323. While JH-RE06 and MLAF50 can block the interactions between REV1-CTD/REV7 (Wojtaszek et al., 2019) and REV1/PCNA-mUb, respectively (Vanarotti et al., 2018), ML323 inhibits the deubiquitination of PCNA through targeting the USP1/UAF1 DUB complex (Chen et al., 2011; Liang et al., 2014). Therefore, deeper understanding of TLS regulation in mammalian cells will not only unveil how polymerase switching happens after replication stress but also be beneficial for the development of high-specificity TLS inhibitors to improve chemotherapy efficacy.

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AUTHOR CONTRIBUTIONS

X.M., T.T. and C.G. discussed and wrote the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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