DNA Damage Control by Novel DNA Polymerases: Translesion Replication and Mutagenesis*

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DNA is constantly subjected to injuries inflicted by external agents such as UV light or cigarette smoke, by intracellular by-products of metabolism such as reactive oxygen species, or by spontaneous decay. DNA lesions interfere with replication and with transcription and if left in DNA can cause mutation, malfunction, and cell death. These deleterious effects are usually prevented by DNA repair mechanisms, which remove the damaged nucleotide and restore the original DNA sequence (for review, see Ref. 1). However, the repair mechanisms are not fully efficient, and some lesions persist in the DNA. The attempt to replicate such unrepaired lesions usually leads to an interruption of replication and to the formation of a ssDNA region carrying the damaged nucleotide, a gap-lesion structure.

Filling in of gap-lesion structures can be done by one of two known mechanisms: recombinational repair and translesion replication. Recombinational repair consists of patching the gap with a DNA segment that was cut out from the undamaged strand in the fully replicated sister chromatid (2, 3). This converts the damaged region into the dsDNA form, enabling a second attempt of error-free repair. Alternatively, the gap can be filled in by DNA synthesis, a process that is inherently mutagenic because of the mismoding nature of most damaged nucleotides. This pathway was, therefore, termed translesion replication (TLR)2, translesion synthesis, error-prone repair, mutagenic repair, bypass synthesis, or lesion bypass (4–6). A third mechanism that may exist was termed copy choice replication, but only little is known about it (7–9). In the last 2 years a major breakthrough has occurred with the discovery that TLR is carried out by specialized DNA polymerases that belong to a novel superfamily. These DNA polymerases, which were found in a number of organisms ranging from Escherichia coli to humans, exhibit a high frequency of errors during in vitro DNA synthesis. Some of them clearly function in TLR, whereas the functions of others are unknown yet (for recent reviews, see Refs. 10–14). This review will present an overview of the new DNA polymerases, focus on E. coli DNA polymerase V and human DNA polymerase η, and conclude with a discussion of some general issues in TLR.

An Overview of Translesion Replication Systems

In E. coli TLR is regulated by the SOS response. The main component of this reaction is one of the novel DNA polymerases, a product of the umuC gene termed pol V (15, 16).3 The umuC gene is a typical SOS gene, which is repressed by LexA and induced by RecA (for a review on the SOS system see Ref. 1). The lesion bypass activity of pol V requires three additional proteins: UmuD9, a shorter form of UmuD formed by RecA-mediated proteolysis (17), RecA, and SSB (15, 16). In addition, it is stimulated by the processivity subunits of pol III, namely the β subunit sliding clamp and the γ complex clamp loader (15). Based on genetic evidence pol V is the main lesion bypass polymerase in E. coli. Inactivating TLR by a umuC mutation leads to a modest reduction in resistance to DNA-damaging agents such as UV light, suggesting that TLR has a small contribution to survival or DNA repair. On the other hand, the umuC mutation strongly decreases mutagenesis by DNA-damaging agents, implying that most of the mutations are caused by pol V-dependent TLR (1, 17).

E. coli contains another member of the new DNA polymerase family, pol IV, the product of the dinB gene. Pol IV is a low fidelity DNA polymerase (18), which is responsible for a special branch of mutagenesis observed in unirradiated phage λ when it infects an irradiated E. coli host (19). Acting in this pathway or when over-produced in E. coli cells, pol IV leads to the preferential production of frameshift mutations (20–22). It was suggested that pol IV can perform lesion bypass in vivo, at least in specific cases (23), and that it is involved in spontaneous mutagenesis (24); however, its full biological role is not clear.

Remarkably, homologs of umuC are carried on natural conjugative plasmids present in bacteria (25). These plasmids often carry multiple antibiotic resistance genes and are responsible, in part, for the growing problem of resistance toward antibiotics among bacterial pathogens (26). One of these homologs, mucB, is present in plasmid R46 and in its derivative pKM101, which is used to increase the sensitivity of the Streptomyces coelicolor test for mutagenesis (27). MucB was shown to be pol RI, a DNA polymerase specialized for lesion bypass (28). Like pol V, the bypass activity of pol RI requires also the plasmid-encoded MucA protein (homolog of UmuD9) and the host RecA and SSB proteins. An intriguing possibility is that these mutation-producing (mutase) polymerases have a role in the phenomenon of antibiotics resistance among bacterial pathogens (28).

The yeast Saccharomyces cerevisiae contains two TLR systems: the pol ζ (REV) system and the pol η (RAD30) system. The REV system contains three genes: REV1, REV3, and REV7 (29). REV3 encodes the DNA polymerase subunit, which together with REV7 forms pol ζ (30). Interestingly, pol ζ is similar to the "classical" pol δ rather than to UmuC. In vitro, pol ζ was shown to bypass a thymine-thymine cyclobutyl pyrimidine dimer (CPD), although with moderate efficiency (30). In addition, pol ζ was shown to extend mismatches with high efficiency, including nucleotides inserted opposite a lesion (31). REV1 is similar to the E. coli umuC; however, it has dCMP transferase activity rather than DNA polymerase activity (32). Inactivation of the REV system causes mild or no UV sensitivity, but it greatly reduces UV mutagenesis, indicating that pol ζ is important in TLR in S. cerevisiae (29). In addition, S. cerevisiae contains an additional homolog of umuC, termed RAD30. This gene encodes pol η, a DNA polymerase that is specialized for replicating certain lesions. Most remarkably, pol η replicates a thymine-thymine CPD with the same efficiency and the same accuracy as it replicates a non-damaged thymine-thymine sequence (33). Pol η provides the paradigm for the new phenomenon of non-mutagenic, relatively error-free bypass of DNA lesions. No homolog of dinB was found in S. cerevisiae.

Human cells contain TLR systems similar to the S. cerevisiae pol ζ and pol η ones and two additional novel DNA polymerases similar to pol η. Humans contain homologs of the yeast REV3 (34) and REV7 (35) genes and are therefore likely to have pol ζ, although this was not yet proven biochemically. Humans contain also a homolog of REV1, which was reported to have dCMP transferase activity (36), similar to the yeast enzyme. In vivo experiments with human cultured cells have shown that decreasing the expression of REV3 (34) or of REV1 (37) with antisense RNA led to a reduction in

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‡ The abbreviations used are: ssDNA, single-stranded DNA; dsDNA, double-stranded DNA; TLR, translesion replication; pol, polymerase; CPD, cyclobutyl pyrimidine dimer; ATP-γ-S, adenosine 5′-3′-O-(thiophosphoryl)...
3 We prefer the term translesion replication over translesion synthesis because the former clearly implies a DNA reaction.
4 We term the umuC gene product pol V, whereas Goodman and colleagues (15) term the complex of UmuD9C pol V. Until the role of UmuD9 is clearly defined, we prefer to call UmuD9 pol V.

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UV mutagenesis, suggesting a major role for the REV system in TLR. Interestingly, the attempts to knock-out REV3 in mice led to embryonic lethality, and no cell line could be established from these embryos (38–40). This indicates a vital role for pol ε and possibly for TLR in mammals.

Similar to S. cerevisiae, humans contain a TLR system based on pol θ. pol η is encoded by the XP-V gene (41, 42), which is mutated in the variant form of the genetic disease xeroderma pigmentosum (XP; the other forms of the disease are caused by mutations in error-free nucleotide excision repair). This disease is characterized by sun sensitivity and cancer predisposition, and cell lines established from XP-V patients exhibit hypermutability by and sensitivity to UV radiation (1, 43). Thus, although pol η-dependent TLR is not essential in humans, it does act as a major anti-mutagenic and therefore anti-cancer mechanism.

This provides the most convincing example that TLR may be functionally non-mutagenic under certain biologically important circumstances.

Humans contain two additional homologs of umuC: hRAD30B, encoding DNA polymerase ε (44, 45), and hDINB1, encoding pol κ (termed also pol δ) (46–48, 52). The biological functions of these polymerases are unknown yet. pol ε is distinguished by its remarkable violation of the base pairing rules common to all known DNA polymerases; it prefers to insert dGMP opposite a template T (31, 44, 45). Surprisingly it was found that pol ε has an associated deoxyribose-phosphate lyase activity, similar to that of pol β (53). This raises the possibility that pol ε is a polymerase tailored to correct a potential mutagenic T in a template, e.g. in a T:G mismatch, where the thymine residue was formed by deamination of 5-methylcytosine (53). pol κ has the ability to bypass some lesions in vitro (47, 48), and like the other DNA polymerases of its family, it is highly mutagenic on undamaged DNA (46, 52, 54). However, its biological function is still unknown.

Two additional new DNA polymerases were discovered recently in humans, pol µ and pol λ. These polymerases belong to the X family, rather than the Umuc/DinB family. pol µ is similar to terminal deoxynucleotidyltransferase. It has a high error frequency in vitro, and based on its presence at elevated amounts in tissues of the immune system, it was suggested to be involved in the generation of somatic mutation in the immunoglobulin genes (55, 56). pol λ is a pol β-like DNA polymerase, which seems to be an accurate polymerase. It might be functioning in error-free repair in meiosis (56, 57).

The SOS Paradigm: Translesion Replication Is Performed by pol V, an Inducible Specialized DNA Polymerase

E. coli TLR was reconstituted with purified components first by the late H. Ehols and his co-workers (68), and more recently in the laboratories of Livneh (59) and Goodman (60). Soon thereafter it was found that the actual translesion replication step occurs in the absence of pol III holoenzyme and that UmuC is a DNA polymerase, termed pol V (15, 16). pol V by itself is an extremely weak DNA polymerase and is unable to bypass lesions. It has a low processivity (~6) and no exonucleolytic proofreading (15, 16). pol V is greatly activated and acquires the ability to bypass lesions upon addition of three additional proteins: UmuD, RecA, and SSB. Under these conditions pol V replicates effectively abasic sites (15, 16) and two major UV end products, a thymine-thymine CPD and a thymine-oxyribose (58) 6–4 adduct (61). Lesion bypass by pol V has a lesion-dependent specificity; mostly dAMP is inserted opposite an abasic site; two As are inserted opposite a thymine-thymine CPD and GA is inserted opposite a thymine-thymine 6–4 adduct (16, 61).

Replication of undamaged DNA by pol V is mutagenic (61, 62), producing point mutations at an average frequency of 1.3 × 10⁻⁷ nucleotide (62). All types of point mutations (transitions, transversions, and frameshifts) are increased by pol V, but it shows a preference for generating transversions at a frequency 74-fold higher than pol III holoenzyme (62). Based on these properties pol V has been suggested to be responsible for the phenomenon of untargeted mutagenesis, where mutations are formed under SOS conditions in undamaged regions of the chromosome (62). Mismatches formed by untargeted mutagenesis are subjected in vivo to mismatch repair (63). Interestingly, the mismatch repair system is less efficient in removing mismatches that lead to transversions (64). Therefore, pol V tends to produce mutations that can escape mismatch repair (62).

The TLR system based on pol V is, so far, the only multiprotein system reconstituted from purified components. Based on the current data, the following model can be drawn for TLR by pol V (Fig. 1). As the replication fork encounters an unrepaired lesion in the DNA, replication stops. At this stage the single-stranded region is bound by SSB, the single strand-binding protein. The major function of this protein is to dissolve secondary structures in DNA, such that the DNA can be easily replicated. SSB is a homotetramer, and the bound ssDNA is wrapped around the protein (65). Once replication stops, however, the binding of ssDNA around SSB exposes it to injuries. At this stage the RecA protein displaces SSB, forming a protective helical nucleoprotein filament around the DNA. This protein filament protects the DNA from degradation, as was shown in vivo and in vitro (3). In addition, the RecA-DNA filament promotes the cleavage of LexA, the global repressor of the SOS regulon. This in turn leads to induction of the SOS response, including transcriptional activation of genes involved in error-free excision repair and in the tolerance of DNA damage (e.g. recA, umuD, and umuC) (1). In addition to its protective and regulatory functions, RecA is also directed in the two major tolerance mechanisms; it is the major recombinaise in recombinational repair,

**FIG. 1. Model of SOS translesion replication by DNA polymerase V.**

The two DNA strands are shown as green lines, and the replication-blocking lesion is represented by the red rectangle. The three major steps in TLR are:

1. **Pre-initiation** and assembly of a RecA-DNA filament
2. Lesion bypass
3. Switch to pol III holoenzyme replication

The three major steps in TLR are **initiation** (2), in which the RecA protein nucleofilaments assemble; **lesion bypass** (3 and 4), which involves binding of pol V to the primer-template and loading of the β subunit DNA sliding clamp; and **lesion bypass** by pol V holoenzyme (5). SSB is suggested to help in displacing RecA from DNA both at the initiation and lesion bypass steps.
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and it is directly required for TLR. These multiple repair functions of RecA warrant the title “guardian of the bacterial genome.”

The first step in TLR is the pre-initiation stage, which involves the assembly of a RecA nucleoprotein filament (Fig. 1, step 2) (66). This filament, which assembles in the 5’→3’ direction, covers the ssDNA region and continues to the dsDNA region adjacent to the ssDNA region, including the primer terminus near the lesion (66). In the subsequent step of initiation (Fig. 1, step 3), pol V binds to the primer-template, guided by the RecA filament, which serves as a targeting platform (66, 67). Loading of pol V onto the primer-template is stabilized by at least three known protein-protein and DNA-protein interactions. UmuD’ interacts with the RecA nucleoprotein filament (67); UmuD’ interacts with UmuC (68, 69); and UmuC interacts with the primer-template. No direct interaction was demonstrated between UmuC and RecA. Initiation of TLR by pol V requires the local dissociation of RecA monomers from the DNA near the primer-template to allow proper binding of pol V to the DNA (Fig. 1, step 3). This suggestion is based on the strong inhibition of initiation of TLR caused by ATPγS, a poorly hydrolyzable ATP analog that strongly stabilizes RecA binding to DNA (66). This strong binding presumably inhibits displacement of RecA from the primer-template region by pol V. SSB is likely to help pol V in displacing RecA from DNA (70). It is noteworthy that SSB was shown to interact with pol RI (MucB) (71).

Once loaded on the DNA, the binding of pol V is further stabilized by the addition of the processivity subunits of pol III, the β subunit and the γ complex (Fig. 1, step 4). These proteins were shown to increase the processivity of pol V (61), although at this point it is not known whether they are involved in TLR in vivo. The pol V holoenzyme assembly commences DNA synthesis, and when encountering the lesion, it replicates through it (lesion bypass; Fig. 1, step 5). Experimental evidence was presented for SSB-driven dissociation of RecA during polymerization by pol V in the presence of ATPγS (70). In that system, based on a long synthetic oligonucleotide template, lesion bypass in the presence of ATP was extremely low; therefore, the validity of the conclusions for lesion bypass in the presence of the native cofactor ATP remains to be determined. In a TLR system based on a gapped plasmid, lesion bypass was found to be inhibited by ATPγS, consistent with the notion that progression of pol V causes disassembly of the RecA filament. The inhibitory effect of ATPγS on bypass by pol V was milder than the effect on initiation (66). These results suggest that once loaded on the primer-template at the initiation stage, the binding of pol V to DNA is strongly stabilized such that it can displace RecA from DNA, aided by SSB, even in the presence of ATPγS.

How does pol V TLR terminate? Once the lesion is bypassed, pol III holoenzyme should take over again (Fig. 1, step 6). The mechanism of polymerase switching is not clear. It was previously shown that RecA filament disassembles in a reaction requiring ATP hydrolysis (72). This led to the suggestion that bidirectional disassembly of RecA (70), from the 3’ end by the action of pol V and from the 5’ end spontaneously (or SSB-stimulated), leads to disassociation of pol V, such that pol III can take over.

Error-free Translesion Replication by DNA Polymerase γ: How Can Lesion Bypass Be Non-mutagenic?

The activity of purified human pol γ was examined on several types of DNA lesions. It was found that there is a variability in the bypass capability of pol γ. A thymine-thymine 6–4 adduct is essentially a complete block to pol γ. AAF-modified guanine and 8-oxoguanine are bypassed well, whereas an abasic site and a cisplatin-guanine adduct are bypassed to a lesser but still significant extent (73–76). Analysis of the specificity of bypass revealed that pol γ inserts AA opposite a thymine-thymine CPD and primarily C opposite AAF-modified or cisplatin-modified guanines, which are the correctly inserted nucleotides (73, 74). When replicating through an abasic site pol γ inserts either an A or a G, whereas 8-oxoguanine inserts the insertion of primarily C but also A (73, 76, 77). The practical implication of these results is that replication by pol γ will lead to a relatively accurate bypass. It was reported that pol γ also inserts incorrect nucleotides opposite the lesions, but those are extended with a much lower efficiency (73).

Thus, the relatively accurate replication is achieved by (a) preferential insertion of the correct nucleotide and (b) preferential extension of the correct nucleotide. As described above, the biological significance of the non-mutagenic bypass of thymine-thymine CPD is evident from the fact that cells lacking pol γ are hypermutable by UV light, and XP-V patients show a high predisposition to sunlight-induced skin cancer (1, 49). Also the non-mutagenic bypass of 8-oxoguanine seems to be significant in vivo, at least in yeast. It is based on the observation (76) that GC → TA mutations (presumably caused by 8-oxoguanine) were increased in a synergetic manner when the gene coding for pol γ was knocked-out in a yeast strain lacking 8-oxoguanine glycosylase (which removes 8-oxoguanine from DNA). The action of pol γ in this case may be part of the repair of 8-oxoguanine-adenine mismatches by the mismatch repair system (78).

Determination of the accuracy of replication by pol γ on undamaged DNA revealed that it is highly error-prone. In one study misinsertion was estimated to be one in 100–1000 nucleotides polymerized (79) and one in 18–380 nucleotides in another (80). Most interestingly, the replication of an undamaged thymine-thymine sequence and a thymine-thymine CPD occurred with the same efficiency and the same error frequency of 1% (79). This error frequency is highly mutagenic when compared with the error frequency of a replicative polymerase opposite an undamaged template T (e.g. 10−6). However, when there is a lesion in DNA and coding information is compromised, the chances of misincorporation may be close to 100%. Compared with this, an error frequency of 1% is 1–2 orders of magnitude more accurate, making pol γ functionally accurate in bypassing the thymine-thymine CPD.

How can pol γ replicate lesions as diverse as a thymine-thymine CPD, cisplatin-guanine adducts, and AAF-guanine adducts with such accuracy? The common denominator of these lesions is that the regions involved in base pairing are not directly affected by the chemical modification. It is possible that pol γ can identify these non-modified regions and extract base pair information. Having possibly a flexible active site might allow, or even stabilize, an interaction with the native double helix. This would predict that non-mutagenic bypass by pol γ will be generally limited to base modifications that do not involve the base pairing atoms.

The Function of TLR in Microorganisms: DNA Repair or Promoting Genetic Variability?

In E. coli and in S. cerevisiae, inactivation of translesion replication causes a strong reduction in mutagenesis by agents such as UV radiation but only a slight decrease in the resistance (1). This is consistent with the observation (76) that GC → TA mutations are significantly increased by UV light, and XP-V patients show a high predisposition to sunlight-induced skin cancer (1, 49). Also the non-mutagenic bypass of 8-oxoguanine increases the error frequency of 1% (79). This error frequency is highly mutagenic when compared with the error frequency of a replicative polymerase opposite an undamaged template T (e.g. 10−6). However, when there is a lesion in DNA and coding information is compromised, the chances of misincorporation may be close to 100%. Compared with this, an error frequency of 1% is 1–2 orders of magnitude more accurate, making pol γ functionally accurate in bypassing the thymine-thymine CPD.

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exist in mammals. These findings argue that lesion bypass is a major pathway of tolerating DNA lesions, more important than recombination. How then are the mutagenic consequences of the bypass dealt with? One unexpected answer came from the finding that at least some lesions, which are frequently formed in DNA, can be bypassed with a relatively high accuracy, e.g. thymine-thymine CPD by pol γ. Another argument would be that the vast majority of the mammalian genome is composed of non-coding DNA, and therefore point mutations would not necessarily have adverse effects on the cell. This non-coding DNA contains many repetitive sequences, which may exist in mammals. These findings argue that lesion bypass is a major pathway of tolerating DNA lesions, more important than recombination.

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