Genetic Control of Translesion Synthesis on Leading and Lagging DNA Strands in Plasmids Derived from Epstein-Barr Virus in Human Cells

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ABSTRACT DNA lesions in the template strand block synthesis by replicative DNA polymerases (Pols). Eukaryotic cells possess a number of specialized translesion synthesis (TLS) Pols with the ability to replicate through DNA lesions. The Epstein-Barr virus (EBV), a member of the herpesvirus family, infects human B cells and is maintained there as an extrachromosomal replicon, replicating once per cycle during S phase. Except for the requirement of the virus-encoded origin-binding protein EBNA1, replication of plasmids containing the EBV origin of replication (oriP) is controlled by the same cellular processes that govern chromosomal replication. Since replication of EBV plasmid closely mimics that of human chromosomal DNA, in this study we examined the genetic control of TLS in a duplex plasmid in which bidirectional replication initiates from an EBV oriP origin and a UV-induced cis-syn TT dimer is placed on the leading- or the lagging-strand DNA template. Here we show that TLS occurs equally frequently on both the DNA strands of EBV plasmid and that the requirements of TLS Pols are the same regardless of which DNA strand carries the lesion. We discuss the implications of these observations for TLS mechanisms that operate on the two DNA strands during chromosomal replication and conclude that the same genetic mechanisms govern TLS during the replication of the leading and the lagging DNA strands in human cells.

IMPORTANCE Since replication of EBV (Epstein-Barr virus) origin-based plasmids appropriates the cellular machinery for all the steps of replication, our observations that the same genetic mechanisms govern translesion synthesis (TLS) on the two DNA strands of EBV plasmids imply that the requirements of TLS Pols are not affected by any of the differences in the replicative Pols or in other proteins that may be used for the replication of the two DNA strands in human cells. These findings also have important implications for evaluating the significance of results of TLS studies with the SV40 origin-based plasmids that we have reported previously, in which we showed that TLS occurs similarly on the two DNA strands. Since the genetic control of TLS in SV40 plasmids resembles that in EBV plasmids, we conclude that TLS studies with the SV40 plasmids are as informative of TLS mechanisms that operate during cellular replication as those with the EBV plasmids.
malian cell-free systems with circular plasmids have shown that bidirectional replication ensues from an SV40 origin sequence in the presence of T antigen (17–20), which functions both as an origin-binding protein and as a DNA helicase for the unwinding of duplex DNA (16, 21–23). In the reconstituted system, T antigen, replication protein A (RPA), DNA polymerase α, and topoisomerase I are sufficient for primer synthesis (24). The loading of proliferating cell nuclear antigen (PCNA) by clamp loader replication factor C (RFC) affects the switch from synthesis by Polα to highly processive synthesis by Polδ (25–27). Although studies with the purified proteins in reconstituted systems have been informative regarding how the initiation, elongation, and Okazaki fragment maturation processes could occur in vitro, it still remains unclear whether the replication of SV40-based plasmids in human cells primarily utilizes the cellular replication machinery or whether the use of T antigen as a DNA helicase precludes the need for many of the proteins such as the MCM2-7 DNA helicase. Also, because Polδ is sufficient for replicating both the DNA strands in the reconstituted SV40 system, whereas Polε may also be required for chromosomal replication (28, 29), the replication of SV40 plasmids may differ from chromosomal replication in significant ways.

SV40 origin-based plasmid systems have been used extensively for DNA repair studies with mammalian cell-free extracts (30–33), and more recently, in our studies for analyzing the roles of translesion synthesis (TLS) DNA polymerases in human cells, we utilized a duplex plasmid system in which bidirectional replication initiates from an SV40 origin in the presence of T antigen (34–36). From these analyses, we inferred that TLS occurs very similarly on the leading and lagging DNA strands. However, since the SV40 system utilizes Polδ for the replication of both the leading and the lagging DNA strands, whereas genetic studies in Saccharomyces cerevisiae have suggested that Polδ replicates the lagging strand and Polε replicates the leading strand (37, 38), TLS on the two DNA strands could differ during mammalian chromosomal replication, if in mammalian cells Polε also replicates the leading strand and Polδ replicates the lagging strand. It is not known whether in human cells, Polδ replicates both the DNA strands or whether Polε and Polδ replicate the leading and lagging strands, respectively, as in yeast.

Because the EBV plasmid system uses the cellular machinery for all aspects of DNA replication in human cells, whereas such information has been lacking for the in vivo replication of SV40 origin-based plasmids, we have designed a duplex plasmid system in which bidirectional replication initiates from the EBV origin and the genetic control of TLS on both the leading and lagging DNA strands can be determined separately. Here, we present our analyses of TLS opposite a site-specific UV-induced cis-syn TT dimer present on the template for synthesis of the leading or the lagging DNA strand, and show that in the EBV plasmid also, similar genetic mechanisms control TLS on the two DNA strands. We discuss the implications of these observations for TLS during chromosomal replication in human cells.

RESULTS

Construction of heteroduplex target vectors containing an EBV origin of replication and a site-specific cis-syn TT dimer. To construct the EBV plasmid for TLS studies, the 2-kb EBV replication origin sequence was PCR amplified from pCEP4 (Invitrogen) and used to replace the SV40 origin in the SV40-based plasmids that we have used for TLS studies. As shown in Fig. 1, the final EBV vector (pBSA/pSBA) contains an EBV origin and a heteroduplex adduct site, one strand of which carries a site-specific cis-syn TT dimer and the other of which contains an AgeI+ site. Since EBV replication requires the EBNA1 protein, we expressed EBNA1 in human cells. Because the DNA lesion located on either the leading strand DNA template or the lagging strand template is in frame with the LacZ’ sequence, and the lesion containing DNA strand contains the kan+ gene, replication through the DNA lesion by TLS will produce blue colonies among Kan+ colonies, whereas white colonies among Kan+ colonies would result from template switching. That is because the other strand has the AgeI+ site opposite the TT dimer, which puts the LacZ’ gene out of frame, and since template switching utilizes sequence information from the strand with the AgeI+ site for copying past the lesion site, this lesion bypass mechanism produces white colonies.

Replication efficiency of EBV plasmid in human cells. We first carried out control experiments to verify that the replication of the EBV plasmids we constructed was strictly dependent upon the presence of the EBV origin sequence and the EBNA1 protein. For this purpose, we used SV40-transformed 293T cells, EBV-transformed 293E cells, and NER-defective xeroderma pigmentosum group A (XPA) human fibroblasts stably expressing the EBNA1 protein and examined the replication efficiency of undamaged plasmids bearing the SV40 or the EBV origin sequence relative to the replication of the pCDNA3.1 zeocin resistance (Zeoc+) plasmid, which has the SV40 origin. As shown in Table 1, in SV40-transformed 293T cells, neither of the pBSA or pSBA EBV plasmid was able to replicate, whereas the SV40 origin-bearing plasmids PBS and PSB and the pCDNA3.1 Zeo+ plasmid replicated. In contrast, in EBV-transformed 293 E cells, only the plasmids pBSA or pSBA carrying the EBV origin replicated, and in SV40-transformed XPA cells in which the EBNA1 protein is also expressed, all the plasmids replicated. As indicated from the relative numbers of ampicillin-resistant colonies, which represent the replication of EBV origin- or SV40 origin-bearing plasmid, and zeocin-resistant colonies, the EBV plasmids replicated ~80% as efficiently as the SV40 origin-based pCDNA3.1 Zeo+ plasmid. We conclude from these observations that the EBV origin-containing plasmids we have constructed replicate efficiently in human cells and that their replication requires the EBV origin and the EBNA1 protein.

Genetic control of TLS opposite a cis-syn TT dimer carried on the leading- or lagging-strand DNA template of EBV plasmid. In our previous studies with a cis-syn TT dimer carried on the leading- or the lagging-strand DNA template of SV40 plasmids, we showed that on both strands, TLS occurs almost equally frequently and the same TLS Pols contribute to lesion bypass (36). For determining the genetic control of TLS on the two DNA strands of EBV plasmids, and to be certain of the similarities or differences between the SV40 and EBV plasmids, we carried out TLS studies in which we examined TLS in both plasmid systems concurrently. As is shown in Table 2, on both the DNA strands of the SV40 plasmid carried in XPA cells, TLS occurred with a frequency of ~35% in cells treated with control (NC) small interfering RNA (siRNA), and the frequency of TLS was reduced upon the depletion of Polη, Polκ, or Polξ but not depletion of Polλ. These independent sets of data resemble closely the more extensive TLS results we published previously (36).

The data for the effects of siRNA depletions of TLS Pols on
promoting replication through a *cis-syn* TT dimer carried on the leading- or the lagging-strand DNA template of EBV plasmids are shown in Table 3. In XPA cells treated with control siRNA, TLS on both the strands occurred with a frequency of ~30%. For both the DNA strands, Pol\(^\eta\)/H9257 depletion conferred an ~50% reduction in the frequency of TLS compared to that in control cells, and depletion of either Pol\(\kappa\) or Pol\(\zeta\) resulted in an ~30% reduction in TLS frequency. In contrast, Pol\(\eta\) depletion had no effect on TLS frequency for the lesion carried on either DNA strand. In our previous study with SV40 plasmids, we showed that Pol\(\eta\)/H9257, -H9260, and -H9256 function.

**FIG 1** Assay for determining the genetic control of TLS on the leading and lagging strands of an EBV origin-based plasmid. (A) The target 16-mer sequence containing a *cis-syn* TT dimer (T^T) is shown at the top. The sequence of the N-terminal part of the lacZ gene in the pBSA vector (leading strand), including the TT dimer, is shown. (B) Strategy for TLS. In the duplex plasmid, the DNA strand containing the TT dimer carries the wild-type kanamycin resistance gene (*kan\(^+\)) so that TLS opposite the UV lesion will result in a blue colony on LB/Kan plates containing IPTG and X-Gal. (C) Assay for TLS and for determining replication efficiency of damage-containing plasmids in siRNA-treated human cells. The purified DNA lesion-containing plasmid, undamaged pCDNA3.1-Zeocin plasmid, and siRNA are cotransfected into human cells that have been pretreated with siRNA for 48 h. After 30 h incubation, the rescued plasmid DNA is treated with DpnI to remove any unreplicated plasmid, and then transformed into XL-1 Blue *E. coli* cells. TLS frequency is determined from the frequency of blue colonies among kan\(^+\) colonies. The replication efficiency of undamaged EBV plasmid relative to that of the zeocin resistance plasmid was determined by the number of colonies that grew on LB/Amp plates, indicative of the EBV plasmid, and the number of colonies that grew on LB/Zeo plates, indicative of the zeocin plasmid.

**TABLE 1** Replication efficiency of undamaged (ND) duplex plasmids in which bidirectional replication initiates from an SV40 or EBV origin in SV40- or EBV-transformed human cell lines

| Cell type                  | Plasmid (origin) | Ampicillin | Zeocin |
|----------------------------|------------------|------------|--------|
| 293T (SV40 transformed)    | pBSA-ND (EBV)    | None       | 508    |
|                            | pSSA-ND (EBV)    | None       | 489    |
|                            | pBS-ND (SV40)    | 583        | 524    |
|                            | pSB-ND (SV40)    | 536        | 528    |
| 293E (EBV transformed)     | pBSA-ND (EBV)    | 486        | None   |
|                            | pSSA-ND (EBV)    | 502        | None   |
|                            | pBS-ND (SV40)    | None       | None   |
|                            | pSB-ND (SV40)    | None       | None   |
| XPA (SV40 transformed and expressing EBNA1 protein) | pBSA-ND (EBV) | 418        | 489    |
|                            | pSSA-ND (EBV)    | 397        | 524    |
|                            | pBS-ND (SV40)    | 496        | 428    |
|                            | pSB-ND (SV40)    | 463        | 508    |
TABLE 2 Effects of siRNA knockdowns of Pols on TLS opposite a cis-syn TT dimer located on the leading- or lagging-strand DNA template of SV40 plasmid carried in XPA human fibroblasts

| siRNA  | Leading strand | Lagging strand |
|--------|----------------|----------------|
|        | No. of kan⁺ colonies | No. of blue colonies among kan⁺ colonies | TLS (%) | No. of kan⁺ colonies | No. of blue colonies among kan⁺ colonies | TLS (%) |
| NC     | 421             | 150            | 35.6   | 326             | 105            | 32.2   |
| Polη   | 340             | 57             | 16.8   | 368             | 52             | 14.1   |
| Polε   | 486             | 169            | 34.8   | 456             | 136            | 29.8   |
| Rev3   | 429             | 102            | 23.8   | 322             | 69             | 21.4   |
| Rev7   | 360             | 77             | 21.4   | 416             | 86             | 20.7   |

TABLE 3 Effects of siRNA knockdowns of Pols on TLS opposite a cis-syn TT dimer located on the leading- or lagging-strand DNA template of EBV plasmid carried in XPA human fibroblasts

| siRNA  | Leading strand | Lagging strand |
|--------|----------------|----------------|
|        | No. of kan⁺ colonies | No. of blue colonies among kan⁺ colonies | TLS (%) | No. of kan⁺ colonies | No. of blue colonies among kan⁺ colonies | TLS (%) |
| NC     | 678             | 194            | 28.6   | 621             | 175            | 28.2   |
| Polη   | 484             | 69             | 14.3   | 523             | 69             | 13.2   |
| Polε   | 580             | 175            | 30.2   | 589             | 174            | 29.5   |
| Rev3   | 525             | 102            | 19.4   | 535             | 104            | 19.4   |
| Rev7   | 496             | 98             | 19.8   | 498             | 96             | 19.3   |
| Polη + Polε | 620             | 90             | 14.5   | 426             | 60             | 14.1   |
| Polη + Polε | 423             | 39             | 9.2    | 465             | 38             | 8.2    |
| Polη + Rev3 | 396             | 35             | 8.8    | 536             | 46             | 8.6    |
| Polη + Rev7 | 367             | 34             | 9.3    | 478             | 40             | 8.4    |
| Polε + Rev3 | 469             | 76             | 16.2   | 356             | 60             | 16.9   |
| Polε + Rev7 | 566             | 89             | 15.7   | 412             | 63             | 15.3   |
TABLE 4 Effects of TLS Pols on mutation frequencies and nucleotides inserted opposite a cis-syn TT dimer carried on the leading-strand template of EBV plasmid in XPA human fibroblasts

| siRNA(s) | No. of kan<sup>+</sup> blue colonies sequenced<sup>a</sup> | No. with nucleotide inserted<sup>b</sup> | A | G | C | T | Mutation frequency (%) |
|----------|----------------------------------------------------------|--------------------------------------|---|---|---|---|-------------------------|
| NC       | 288 (4)                                                   | 284                                  | 1 (5′ T) | 0 | 1 (5′ T) | 1.4 |
| Polη      | 190 (5)                                                   | 185                                  | 1 (5′ T) | 0 | 1 (3′ T) | 2.6 |
| Polκ      | 240 (1)                                                   | 239                                  | 1 (3′ T) | 0 | 0         | 0.4 |
| Rev3      | 196 (0)                                                   | 196                                  | 0         | 0 | 0         | 0   |
| Rev7      | 278 (1)                                                   | 277                                  | 1 (3′ T) | 0 | 0         | 0.4 |
| Polη + Polκ | 178 (1)                                               | 177                                  | 0         | 0 | 1 (3′ T) | 0.6 |
| Polκ + Rev3 | 232 (2)                                               | 230                                  | 1 (3′ T) | 0 | 1 (3′ T) | 0.9 |
| Polκ + Rev3 | 288 (0)                                               | 288                                  | 0         | 0 | 0         | 0   |

<sup>a</sup> Numbers of mutant colonies are in parentheses.<br>
<sup>b</sup> The site where mutation occurred (the 3′ T or the 5′ T of the TT dimer) is shown in parentheses.

TABLE 5 Effects of TLS Pols on mutation frequencies and nucleotides inserted opposite a cis-syn TT dimer carried on the lagging-strand template of EBV plasmid in XPA human fibroblasts

| siRNA(s) | No. of kan<sup>+</sup> blue colonies sequenced<sup>a</sup> | No. with nucleotide inserted<sup>b</sup> | A | G | C | T | Mutation frequency (%) |
|----------|----------------------------------------------------------|--------------------------------------|---|---|---|---|-------------------------|
| NC       | 190 (2)                                                   | 188                                  | 1 (5′ T) | 0 | 1 (3′ T) | 1.1 |
| Polη      | 142 (4)                                                   | 138                                  | 1 (5′ T) | 0 | 1 (3′ T) | 2.8 |
| Polκ      | 192 (1)                                                   | 191                                  | 1 (3′ T) | 0 | 0         | 0.5 |
| Rev3      | 186 (0)                                                   | 186                                  | 0         | 0 | 0         | 0   |
| Rev7      | 190 (1)                                                   | 189                                  | 0         | 0 | 1 (3′ T) | 0.5 |
| Polη + Polκ | 178 (1)                                               | 177                                  | 1 (3′ T) | 0 | 0         | 0.6 |
| Polη + Rev3 | 196 (2)                                               | 194                                  | 1 (3′ T) | 0 | 1 (3′ T) | 1.0 |
| Polκ + Rev3 | 194 (0)                                               | 194                                  | 0         | 0 | 0         | 0   |

<sup>a</sup> Numbers of mutant colonies are in parentheses.<br>
<sup>b</sup> The site where mutation occurred (the 3′ T or the 5′ T of the TT dimer) is shown in parentheses.
whereas in the other strand, the AgeI site puts the lesion-containing strand in frame with the lacZ sequence at the AflIII and SapI sites in pBS/pSB TLS vectors (Fig. 1C). The heteroduplex target sequence containing a cis-syn TT dimer in one strand and an Agel site opposite the TT dimer on the other strand is shown in Fig. 1A. The heteroduplex target sequence is placed into the lacZ sequence such that the lesion-containing strand is in frame with the lacZ sequence, whereas in the other strand, the Agel site puts the lacZ’ sequence out of frame (Fig. 1A). The wild-type kanamycin resistance gene (kan*) was placed on the same strand with the UV lesion, which is in frame with lacZ’ and MfeI site (Fig. 1B). The rest of the procedure for the construction of the final lesion-containing EBV vector (Fig. 1C) is identical to that described previously (36).

**In vivo translesion synthesis assays in human cells.** Since EBV replication requires Epstein-Barr nuclear antigen 1 (EBNA1), the host cell has to be EBV transformed or expressed the EBNA1 protein in trans. To test replication efficiency, we used HEK293T cells (American Type Culture Collection [ATCC]), EBV-transformed HEK 293 cells (ATCC), and XPA-deficient human fibroblasts (XP1D12E) stably expressing EBNA1. The siRNA knockdown efficiencies of TLS Pols have been shown previously (35, 36). For in vivo TLS assays, XPA cells were plated in six-well plates at 70% confluence (approximately 3 × 105 cells per well) and transfected with 100 pmol siRNAs. For the simultaneous siRNA knockdown of two TLS Pols, the siRNA knockdown of TLS Pol was followed by the siRNA knockdown of another TLS Pol. The clonogenicity assay was performed by the cloning efficiency assay (11).

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