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Simian Virus 40 as a Probe for Studying Inducible Repair Functions in Mammalian Cells

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We describe the use of Simian Virus 40 (SV40) as a molecular probe for studying the cellular functions induced in cultured monkey kidney cells in response to DNA damaging agents.

(a) Ultraviolet (UV) irradiation of SV40-infected cells inhibits viral DNA replication. Replication forks are blocked by the first pyrimidine dimer encountered. In some cases, a single-strand break seems to occur at the level of the dimer inhibiting the fork of replication. This break, which can be visualized by electron microscopy studies, might be the first step in an excision repair pathway.

(b) Treatment of monkey kidney cells with acetoxy-acetyl-aminofluorene or UV light before infection with UV-irradiated SV40 induces a mutagenic replication mode, as shown by an increase of the mutation frequency of thermosensitive SV40 mutants.

(c) A possible recombination assay using various SV40 mutants infecting the same cell is proposed and discussed.

Key words: SV40, DNA repair, SOS functions, mutagenesis, carcinogenesis, recombination

Most of the DNA damaging agents which block the progression of replication forks induce in bacteria a series of pleiotropic effects which are called "SOS functions." The expression of these functions is responsible for the lysogenic induction of λ phage in lysogenic bacteria, the reactivation and the mutagenesis of UV-irradiated phage (Weigle's reactivation), and the filamentous growth of bacteria [1-3]. These functions are under the coordinate control of *recA* and *lexA* genes and the molecular mechanism of their expression is well understood. Treatment of Escherichia coli with DNA damaging agents drastically increases the synthesis of the RecA protein. This protein in the presence of single-stranded DNA, due to DNA damage or DNA repair of damages, is partly activated into a protease. This protease activity cleaves the *lexA* gene product, which is the repressor of several SOS function genes *(recA, lexA, uvrA, uvrB, umuC, sfiA,* . . . genes). The cleavage of LexA protein results in the expression of SOS genes. The RecA

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protease activity is also specific for the cleavage of the λ repressor whose consequence is lysogenic induction [4] (see [5, 6] for review). The expression of *umuC* gene seems to be responsible for reactivation and mutagenesis of UV-irradiated λ phage.

The discovery and the analysis of SOS functions in bacteria provide a good model for the study of the expression of genetic information. Is this model generalizable to eukaryotic systems?

It is of interest to recall here that the elaboration of the SOS repair hypothesis by Radman [1] was essentially based upon experiments on repair and mutagenesis in E coli bacteriophages. Consequently, the obvious way to study these functions in eukaryotic cells was to analyze the DNA repair and mutagenesis of mammalian viruses. These experiments have been, in fact, carried out using either Herpes simplex virus, adenovirus, Simian Virus 40, or parvovirus [7]. It has been reported that DNA damaging treatment of mammalian host cells before infection increases the survival of these viruses which have been previously UV-irradiated. Furthermore, this enhanced survival is usually accompanied by an increase of the mutation frequency of the repaired virus, and both seem to be inducible [7]. These results have been interpreted in the same way as Weigle reactivation in bacteria [8].

The obvious question is whether the host genome is a substrate for the expression of these induced functions. D'Ambrosio and Setlow have shown in Chinese hamster and in human cells that postreplication repair was more efficient after a split dose of UV irradiation than after a single dose [9]. If this repair process, which requires a de novo protein synthesis, is identical to the one which increases virus survival, it may also be mutagenic. However, in a few studies examining the effects of split doses of UV irradiation on the host mutation expression, the presence of an inducible error-prone pathway has not been detected [10]. Enhanced survival and, in some cases, lower mutation frequencies were observed in these experiments. The reason for these conflicting results is not known.

The purpose of this paper is to determine whether induction of new cellular functions in response to DNA-damaging agents is observed in mammalian cells. This study is difficult to undertake with mammalian cells because numerous pathways are sought at the same time and because there are no well-defined mutants available. In theory, the use of viruses has several advantages in studying inducible repair functions, especially because (a) viral DNA can be damaged under reproducible conditions in vitro before infection; and (b) various treatments of the host cell can be performed without any interferences with the input viral DNA.

Among the numerous mammalian viruses available for such experiments, we have chosen Simian Virus 40 for the following reasons: (a) SV40 DNA is easy to isolate and its DNA sequence is known; (b) SV40 has a small DNA genome (3.5×10^6 d) which exists as a minichromosome quite similar to a mammalian chromosome; (c) SV40 depends entirely upon host cell enzymes for its cycle except for the initiation of viral DNA replication which requires the viral-coded T antigen protein; and (d) numerous mutants of SV40 have been isolated, many of which are well characterized (see [11] for review).

For these reasons, we have used SV40 as a biological probe for studying inducible DNA repair pathways in monkey kidney cells. We have tried to answer the following three questions. (1) What is the effect of pyrimidine dimer lesions on

SV40 DNA replication? (2) Is there an error-prone replication process induced in DNA-damaged monkey cells? (3) Is a recombinogenic activity detectable in carcinogen-treated cells?

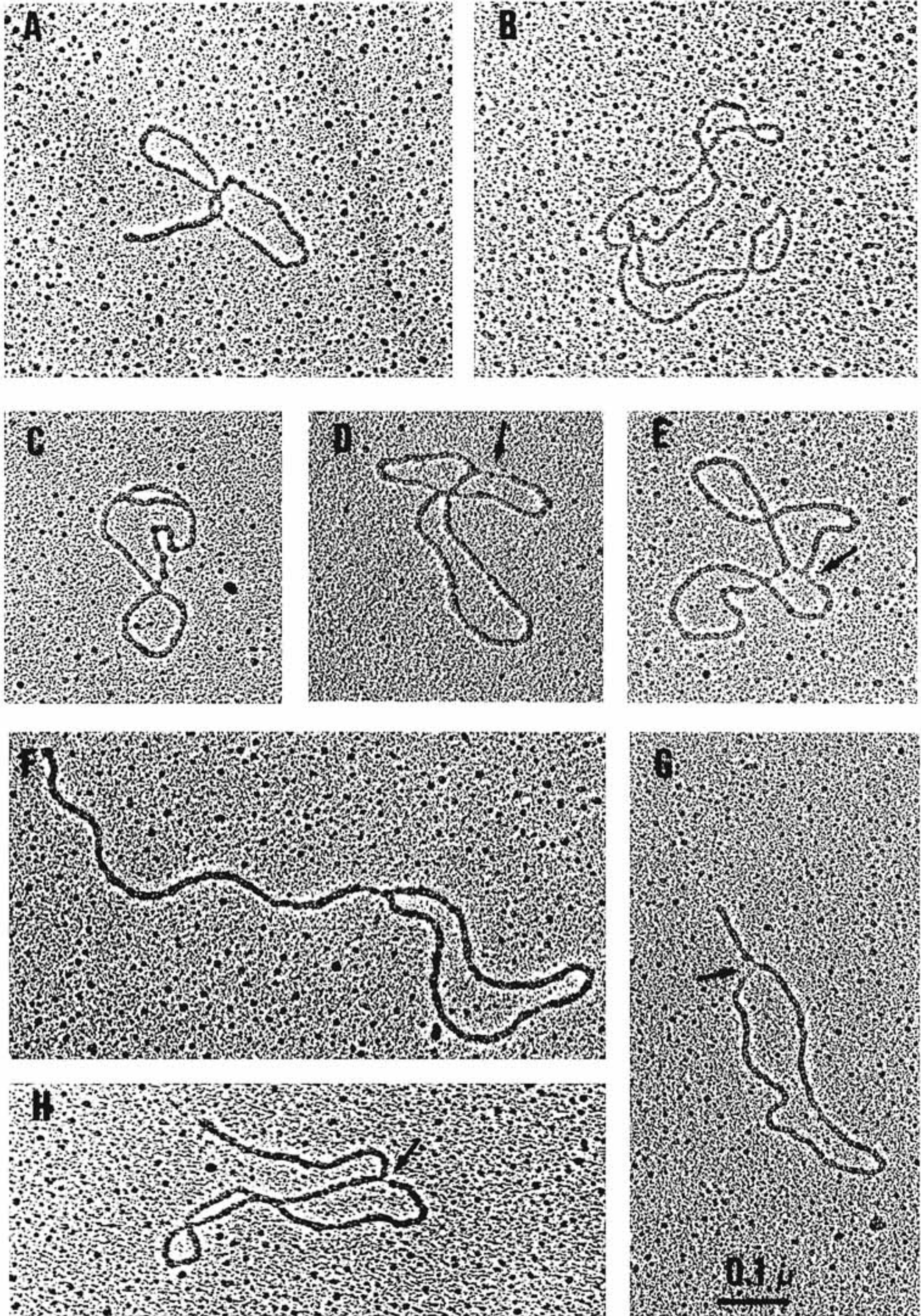
SV40 DNA Replication on UV-Irradiated Templates

It has been reported that SV40 DNA replication, like other mammalian replication systems, is strongly inhibited by UV irradiation [12–14]. We have studied the molecular mechanism of this inhibition by analyzing the characteristics of viral replicative intermediate molecules (RI) made shortly after UV irradiation.

African green monkey kidney cells were infected with SV40 virus. At 24 hr postinfection, when the viral DNA synthesis rate is maximal, they were pulse-labeled with [^{3}H] thymidine. Viral replicative intermediates were purified by sucrose gradient centrifugation followed by benzoylated–naphtoylated DEAE (BND)-cellulose chromatography (for details see the legend to Fig. 1). DNA samples were then spread for electron microscopy analysis by the formamide procedure [15]. As seen in Figures 1A and B, SV40 RI isolated from unirradiated cells present a structure of two branches of equal length representing the replicated portion of the molecule and a supercoiled branch representing the parental unreplicated portion of the molecule; a break in the supercoiled parental DNA gives a θ-shaped structure representing a replication eye, with a single-stranded region (as indicated by the arrow in Fig. 1) at the replication fork (Figs. 1C, D, and E). These observations are in good agreement with the model for the SV40 DNA replication already published [see 11]: There is a unique replication origin from which two replication forks progress bidirectionally at the same speed. We carried out similar experiments after UV irradiation of host cells during SV40 replication; 24 hr after SV40 infection, cells were UV irradiated with a germicidal lamp at 125J/m^2. We measured that this UV dose induces about 5.5 pyrimidine dimers per SV40 DNA molecule (3.5×10^6 d) by using the T_4 endonuclease V assay, as described by P. C. Seawell et al [16].

Electron microscopy analysis of RI purified from irradiated cells (UV-RI) was carried out using the same method as for unirradiated cells. Almost all UV-RI (95%) synthesized during the first 40 min after irradiation show a surprising structure composed of a circle equal to the size of a SV40 genome (1.72 μg $\pm$ 6%) with a double-stranded DNA tail of variable length (Figs. 1F, G, and H). According to the size of the circle, the analysis of 77 UV-RI molecules shows an average length of the tail equal to 41% $\pm$ 2% of the genome.

We also measured the size of newly synthesized DNA made during the first 40 min after irradiation by alkaline sucrose gradient sedimentation. We found that the number average molecular weight ($\bar{M}n$) of ^{3}H-labeled DNA is equal to 0.7×10^6 daltons, which corresponds approximately to 40% of single-stranded SV40 genome. This value is identical to the size of the interdimer spacing, which corresponds to 37% of the single-stranded genome (since we put 5.5 dimers per molecule), thus confirming that the SV40 replication fork is blocked at the first pyrimidine dimer encountered. Consequently, the blockage of one strand by a pyrimidine dimer at the replication fork does not completely block the progression of the other strand and, therefore, should give single-stranded portions. Indeed, electron microscopy analysis shows single-stranded regions at the replication fork [Fig. 1].


A
B
C
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E
F
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0.1 μ

The tight homology between the size of newly synthesized DNA made after UV irradiation (40%), the average length of the tail measured in the same samples by electron microscopy analysis (41%), and the average distance between two pyrimidine dimers measured with the T_4 endonuclease V (37%) lead us to suggest the following model: The viral replication fork blocked by a pyrimidine dimer leaves a single-stranded region in the opposite strand where an endonucleolytic cleavage may occur to generate the tail (Fig. 2). This model is confirmed by other experiments where we have shown, by electron microscopy analysis, that UV-RI purified from infected cells irradiated with different UV doses, present a tail whose average length is proportional to the interdimer distances [manuscript in preparation]. Now, the obvious question is whether this cleavage is the result of the endonuclease activity of a specific cellular enzyme or a nonspecific break on the single-stranded portion made during purification or spreading procedures. If an artifactual break had taken place because of the single-stranded region at the replication fork, similar observations would have been made with normal RI, which also contain single-stranded regions. In our experiment, similar tailed molecules have never been observed without UV irradiation of the infected cells. This observation suggests that an enzymatic cleavage at the replication fork is responsible for the generation of the tail in SV40 UV-RI. It is possible that this break is due to the activity of a cellular UV-specific endonuclease, as a first step in the excision-repair process. Similar studies on UV-RI purified from SV40-infected xeroderma pigmentosum fibroblasts could provide some insight into this mechanism.

A possible alternative explanation for the production of this break in UV-RI could be a nicking–closing enzyme associated with the replication fork. Such an enzyme has been found to be associated with the SV40 DNA [17]. Due to the steric distortion of the double helix by the dimer, it could be possible that this enzyme is not able to seal the nick which has been made on the parental strand during the progression of the replication fork.

It is known that a very small ratio of SV40 DNA molecules can escape from the bidirectional replication mode in order to replicate according to the unidirec-

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Fig. 1. Electron microscopy analysis of SV40 RI isolated from unirradiated cells (A–E) and UV-irradiated cells (F–H). Confluent monolayers of monkey kidney cells were infected with wild-type SV40 (VA-4554 strain). After 24 hr postinfection, infected cells were pulse-labeled with 50 μCi of [^{3}H] thymidine per petri dish (80 Ci/mmole from New England Nuclear) and incubated for 5 min at 37°C. At the same postinfection time duplicate cultured cells were UV-irradiated at 125 J/m^2 and ^{3}H pulse-labeled for 40 min. Viral DNA was extracted by the Hirt procedure, deproteinized by 10 hr incubation with proteinase K at 37°C (200 μg/ml), and concentrated by ethanol precipitation. RI and UV-RI were purified on 5–20% sucrose gradients containing 20 mM Tris–HCl, pH 7.8, 20 mM EDTA, 0.2 M NaCl. Centrifugation was performed in a Beckman SW 27.1 rotor at 21.000 rpm for 18 hr at 4°C. ^{14}C-labeled supercoiled form I DNA was added to the gradients as marker. RI were recovered in the 26 S peak; UV-RI sediment broadly at about 18 S. Fractions corresponding to the peaks were pooled and dialyzed against 10^{-2} M Tris–HCl, pH 7.8, 10^{-3} M EDTA (TE) buffer. SV40 RI and UV-RI were purified by chromatography through a benzoylated–naphtoylated DEAE-cellulose column. RI and UV-RI were eluted with a buffer containing 10 mM Tris–HCl, pH 7.8, 0.1mM EDTA, 1 M NaCl, and 2% caffeine. Fractions corresponding to the RI peak were pooled, dialyzed extensively against TE buffer, and spread for electron microscopy analysis. Arrows indicate single-stranded portions of DNA.

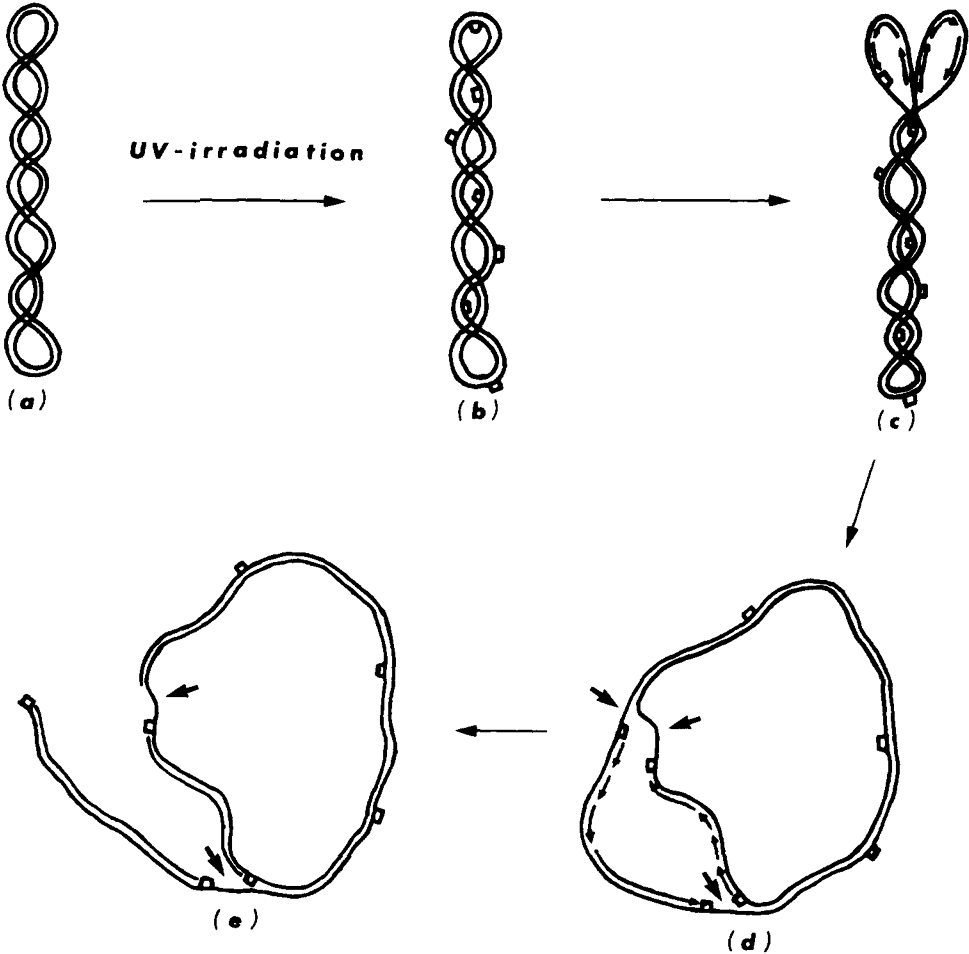

Fig. 2. Hypothetical model for SV40 DNA replication after UV irradiation. The arrows in (d) and (e) indicate the single-stranded regions close to the dimer which could be the possible sites of the cleavage. The presence of the dimer at the end of the tail in (e) is hypothetical, since it could not be detected by electron microscopy. This scheme is a more advanced model compared to the one published by Sarasin and Hanawalt [14].

tional rolling-circle model [11]. By electron microscopy analysis, these molecules also present a tail; we do not think that the molecules we observed are due to a rolling-circle mode of DNA replication for the following reasons. First, in the rolling-circle replication model, molecules with a tail length several times the size of the original circle are very frequently generated, and in our experiments no molecule with a tail greater than the SV40 genome is observed. Secondly, Sarasin and Hanawalt have shown, in UV-RI digested by Hind-III restriction endonuclease, the presence of a decreasing gradient of DNA replication from those fragments close to the replication origin to those located around the termination point, thus suggesting a bidirectional progression of the replication forks [14].

Error-Prone Replication of SV40 in Carcinogen-Treated Cells

The treatment of mammalian cells with various physical or chemical agents that damage DNA prior to infection with UV-irradiated virus enhances virus survival. This phenomenon, which has been called induced virus reactivation or enhanced virus reactivation, was first demonstrated with UV-irradiated Herpes virus infecting lightly UV-irradiated monkey kidney cells [18]. This result has now been confirmed using a variety of UV-irradiated viruses, such as Simian adenovirus [19], SV40 [20], and parvoviruses [21], which replicate their DNA in the cell nucleus. UV-irradiated SV40 is a very good probe for analyzing this induced virus reactivation. Sarasin and Hanawalt [20] have shown that almost all test drugs which inhibit scheduled DNA synthesis (UV, acetoxy-acetyl-aminofluorene, metabolized aflatoxin B_1, MMS, EMS, hydroxyurea, cycloheximide) induced a new repair mode able to replicate UV-irradiated SV40 DNA better.

From these data we have hypothesized that virus reactivation may be due to a third mechanism for DNA-damage recovery as has been proposed for bacteria [3].

Since the "SOS repair pathway" has been shown to be highly mutagenic in bacteria, it is of interest to know whether induced virus reactivation is also a mutagenic event in mammalian cells. In order to answer this question, we used temperature-sensitive mutants of SV40, and we selected for reversion toward a wild-type growth at the non-permissive temperature (41°C). We used either an early mutant of SV40 (ts A58), which is defective in initiation of DNA replication because of a point substitution on the T antigen gene, or a late mutant of SV40 (tsB201), which is defective in virus production because of a mutation on the VP1-protein gene. Unirradiated or 1500 J/m² UV-irradiated ts SV40 are used to infect carcinogen-treated monkey kidney cells for one lytic cycle at 33°C (72 hr) and the progeny survival is measured at both 33 and 41°C. The mutation frequency is determined as the ratio of progeny survival at 41°C over progeny survival at 33°C. Treatment of monkey kidney cells with the chemical carcinogen acetoxy-acetyl-aminofluorene (AAAF) 24 hr before infection with UV-irradiated SV40 mutants strongly increases the mutation frequency in the surviving viruses (Fig. 3B). Unirradiated SV40 mutants did not exhibit a significantly increased mutation frequency in AAAF-treated monkey cells (Fig. 3A). However, because of the very low spontaneous mutation level (10^{-8}), we observed a large standard deviation in these results, and an increase by a small factor could not have easily been detected. This result confirms the increased mutation frequency we have seen with UV-irradiated monkey cells [22] and the one seen by Das Gupta and Summers using UV-irradiated Herpes simplex virus growing in UV-irradiated monkey cells [23]. Using the same experimental procedure, Cornelis et al [24] have confirmed the enhanced SV40 reactivation process which occurs after infection of UV-irradiated SV40 or after transfection with UV-irradiated SV40 DNA in UV-irradiated monkey kidney cells. These authors also showed a slightly increased back-mutation frequency of unirradiated tsBC SV40 mutants in UV-irradiated monkey cells. However, no significantly increased mutation frequency was seen for UV-irradiated virus grown in UV-irradiated cells. This conflicting result could be due to the high survival of their 1500 J/m² UV-irradiated SV40 (10%), to a high background of spontaneous

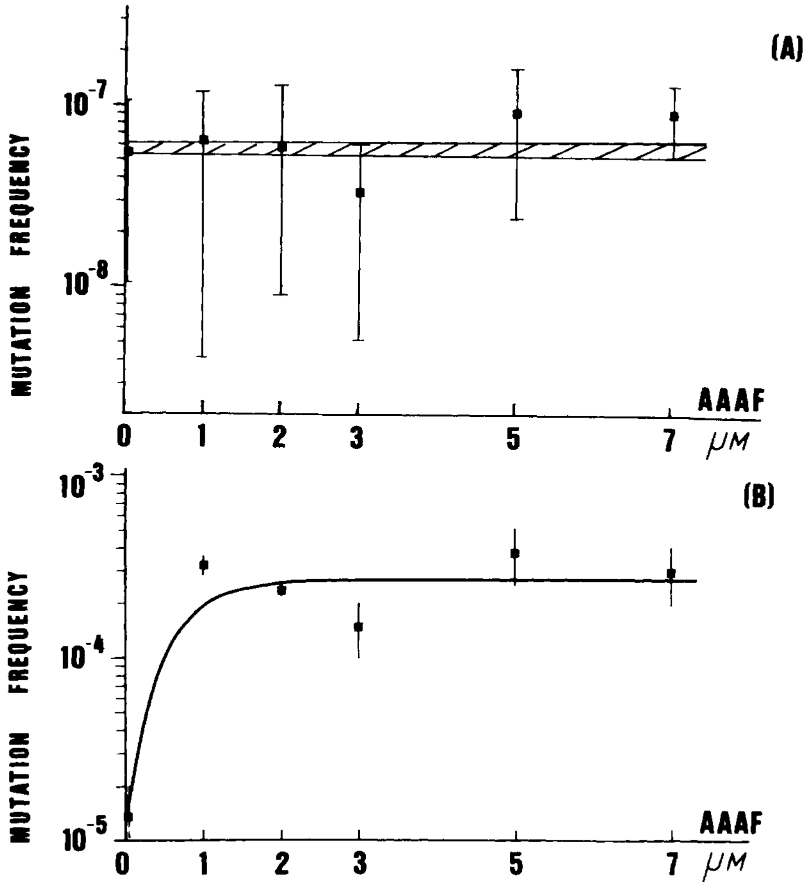

Fig. 3. Mutation frequencies toward wild-type phenotype of tsB201 SV40 mutant in AAAF-treated monkey kidney cells. Control or 1500 J/m² UV-irradiated tsB201 SV40 mutants were used to infect control or AAAF-treated CV1-P monkey cells during one lytic cycle at 33°C (72 hr). Mutation frequency is determined as the ratio of progeny survival at 41°C over progeny survival at 33°C. The error bars correspond to the standard error of the mean. Experimental details have already been described [22]. (A) Infection with unirradiated SV40 at a multiplicity of infection = 1. (B) Infection with 1500 J/m² UV-irradiated SV40 at a multiplicity of infection = 2×10^{-3}.

back-mutation (2.5×10^{14}), or to the very low factor of reactivation they obtained in their published mutation experiments.

We have analyzed the DNA sequence of one SV40 revertant (R-14-10) obtained during UV-induced reactivation and have shown that it involves a single base-pair substitution, an AT to TA transversion. This transversion occurs opposite a possible thymine dimer site, and it is located nine base pairs away from the original tsA mutation [25]. Consequently, this reversion must be due to suppression as already hypothesized [26]. A similar AT to TA transversion has been described as UV-mutation sites in E coli [27] and in yeast [28].

In conclusion, evidence for the induction of an error-prone mode of DNA replication has been presented using SV40-infected cells under conditions in which

cellular DNA synthesis has been inhibited. As we have seen in the previous section, SV40 DNA replication is normally blocked by a pyrimidine dimer. We might postulate that in carcinogen-treated cells, a new enzymatic activity is induced which will facilitate replication despite the dimer. As expected, the replication of DNA-containing lesions should be mutagenic and should increase virus survival. Nothing is known about this induced enzymatic activity which could be a new DNA polymerase or a new protein involved in the replication complex, or some inhibitor of proofreading activity. These inducible functions are particularly amenable to study using SV40 as a probe since without the use of exogenous DNA, the analysis of these inducible functions and how they might work on cellular DNA is much too complex and difficult to interpret [10].

Recombination After Carcinogenic Treatment in Mammalian Cells

Recombinational activity has not yet been clearly shown in somatic mammalian cells. If such an activity could be modified by treatment of cells with physical or chemical carcinogens, this would be of prime interest in demonstrating a DNA repair mechanism comparable to that shown in bacteria. This recombination pathway could result in altered gene expression as a consequence of chromosomal rearrangements. However, it is not easy to show the recombinogenic activity induced by any mutagenic or carcinogenic treatments in mammalian cells. Cytological indicators are often used to measure recombination such as sister chromatid exchange induction or chromosomal rearrangements. However, viral probes may also be used and the recombination between genomes of several viruses infecting the same cell simultaneously may be an indicator of recombinational activity in the cell. When cells are infected at high multiplicity of infection with UV-damaged viruses, it is a well-known fact that multiplicity reactivation occurs [29]. The mechanism of multiplicity reactivation is not yet well understood, but it seems to require a recombination event. On the other hand, a cell may be treated with a compound to be tested and then infected with two viruses having different genetic markers, and finally recombinants between two markers may be detected after a lytic cycle.

Some experiments have been carried out with UV-irradiated mutants of Herpes simplex viruses, either thermosensitive [30] or mutated on the gene for thymidine kinase [31]. These experiments show that the UV irradiation of virus increases the recovery of recombinants, indicating that blockage of the replication fork by a pyrimidine dimer could give rise to intermediates which could be used as a substrate by host recombination enzymes. The recombination frequency between thermosensitive mutants of adenoviruses was also studied using normal human fibroblasts and fibroblasts obtained from patients with either xeroderma pigmentosum, Bloom's syndrome, or Fanconi's anemia. All these cells were shown to be recombination proficient to a certain extent [32].

SV40 genome segments having homologous overlapping terminis [33] and SV40 temperature-sensitive mutants [34] were also used to analyze recombination activity in monkey kidney cells. In the former experiments, it was shown that SV40 genomes recombine to give viable viral particles at a frequency of approximately 10^{13}. In the work by Dubbs and co-workers [34], it was shown that recombination occurs between two mutants of the same complementation group at a frequency of about 2×10^{-4}. This recombination frequency is increased by either

transfection with viral DNA instead of virus infection, UV irradiation of the virus, or treatment of infected cells with Ara C which interrupt DNA synthesis. In these experiments no significant effect of UV irradiation of the host cells on the recombination frequency has been reported. Although this list is not exhaustive, it seems to us that no extensive work has been carried out with host cells treated with either physical or chemical carcinogens prior to infection with either intact or DNA-damaged viruses. Furthermore, this kind or experiment is actually in progress in our laboratory using various SV40 mutants as a probe for demonstrating recombination activity in mammalian cells.

We have provided in this paper some evidence showing that it is possible to investigate, at the molecular level, the events leading to the modification of genetic expression in mammalian cells using relatively simple experimental protocols. We have shown that viral DNA replication is blocked at the first pyrimidine dimer encountered during its progression and that carcinogen treatment of host cells induces a mutagenic replication mode of UV-irradiated virus, and finally we have proposed an experimental protocol for the study of inducible recombination using SV40 genetic markers.

The use of small DNA viruses as molecular probes for studying inducible error-prone repair functions in mammalian cells is more satisfactory than the use of larger viruses such as Herpes viruses or adenoviruses, since the virus-coded enzymatic systems and their large genomes could mask cellular functions and produce conflicting results which are difficult to interpret.

In recent experiments it has been shown that virus induction and UV-reactivation are two processes having parallel kinetics in SV40-transformed hamster cells [35, 36]. These functions present a tight homology with the bacterial lysogenic induction and with Weigle's reactivation. The mechanism of this induction of latent tumor virus in mammalian cells is still a matter of speculation; however, it is possible that this process would take place in a coordinately controlled SOS system in mammalian cells.

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