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Enhanced Mutagenesis of UV-Irradiated Simian Virus 40 Occurs in Mitomycin C-Treated Host Cells Only at a Low Multiplicity of Infection

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Treatment of monkey kidney cells with mitomycin C (MMC) 24 h prior to infection with UV-irradiated simian virus 40 (SV40) enhanced both virus survival and virus mutagenesis. The use of SV40 as a biological probe has been taken as an easy method to analyse SOS response of mammalian cells to the stress caused by DNA damage or inhibition of DNA replication. The mutation assay we used was based on the reversion from a temperature-sensitive phenotype (*ts*A58 mutant) to a wild-type phenotype. The optimal conditions for producing enhanced survival and mutagenesis in the virus progeny were determined with regard to the multiplicity of infection (MOI). Results showed that the level of enhanced mutagenesis observed for UV-irradiated virus grown in MMC-treated cells was an inverse function of the MOI, while enhanced survival was observed at nearly the same level regardless of the MOI. For the unirradiated virus, almost no increase in the mutation of virus progeny issued from MMC-treated cells was observed, while a small amount of enhanced virus survival was obtained. These results show that enhanced virus mutagenesis and enhanced virus survival can be dissociated under some experimental conditions. Enhanced virus mutagenesis, analogous to the error-prone replication of phages in SOS-induced bacteria, was observed, at least for SV40, only when DNA of both virus and host cells was damaged and when infection occurred with a small number of viral particles. We therefore hypothesize that an error-prone replication mode of UV-damaged templates is observed in induced monkey kidney cells.

DNA viruses have been proposed for use as biological probes for studying error-prone repair or replication pathways in both procaryotes and eucaryotes (8). UV-irradiated phage is repaired and replicated in UV-irradiated bacteria by an error-prone pathway, leading to a high mutation frequency in the phage progeny (26). This earliest observation was the beginning of a series of experiments leading to the hypothesis of the SOS repair mode (15, 27). The SOS regulatory network has now been very well studied and understood in *Escherichia coli* (18, 24), in which a series of different genes are under the genetic control of the *recA* and *lexA* gene products. The SOS genes are sequentially induced by agents which either damage cellular DNA or interfere with normal DNA replication. Among these genes, the induction of the *umuDC* locus is necessary for mutagenesis (25).

Treatment of mammalian cells with various DNA-damaging agents enhances the survival of UV-irradiated animal virus. This result has been found consistently with several single-stranded or double-stranded DNA virus and various host cells (for reviews, see references 8, 16, and 19). Since enhanced survival of UV-irradiated DNA virus has been proposed as a part of inducible functions in mammalian cells in an analogous way to that in *E. coli* (22), mutagenesis was carefully measured to determine whether enhanced virus survival is associated with enhanced virus mutagenesis. Although it has been shown that UV-induced DNA lesions are mutagenic per se without treating the host cell (3, 7, 20), enhanced mutagenesis of UV-irradiated DNA virus is detectable if the host cell is irradiated by UV prior to infection. Indeed, several investigators have reported the existence of such enhanced mutagenesis with UV-irradiated herpesvirus (6, 13), UV-irradiated simian virus 40 (SV40) (20, 21) or UV-irradiated parvovirus (5). These results have been obtained by treating host cells with UV light, or with various chemical carcinogens in the case of SV40 (19, 21). However, other investigators did not find any enhanced mutagenesis either with UV-irradiated adenovirus (7), UV-irradiated SV40 (4, 23), or UV-irradiated herpesvirus (13, 14), although in the latter study, enhanced mutagenesis was found at high multiplicity of infection (MOI).

To understand the reasons behind these conflicting results, we carefully analyzed the different experimental protocols used in various studies and decided to look in detail at the effect of the MOI of infected samples on the level of virus mutagenesis. In this study we used the reversion of an early temperature-sensitive mutant of SV40 (*ts*A58) to a wild-type phenotype at the restrictive temperature of 41°C as the mutation system (20). We found that a decrease of MOI leads to an increase of the mutation rate for both unirradiated and UV-irradiated SV40. Enhanced survival of unirradiated and UV-irradiated virus was observed when host cells were pretreated with mitomycin C (MMC), regardless of MOI level. Enhanced mutagenesis was only detected for UV-irradiated virus after an infection with a low MOI in MMC-treated cells.

MATERIALS AND METHODS

Cells. The established CV-1P and MA-134 lines of African green monkey kidney cells were obtained from P. Berg (Department of Biochemistry, Stanford University, Stanford, Calif.). They were grown on plastic dishes (Becton Dickinson Labware, Oxnard, Calif.) in Dulbecco modified Eagle medium (GIBCO Laboratories, Grand Island, N.Y.) containing 5% fetal calf serum (Flow Laboratories, Inc., McLean, Va.) in a CO_2 incubator at 37°C. Treatment of CV-1P cells was

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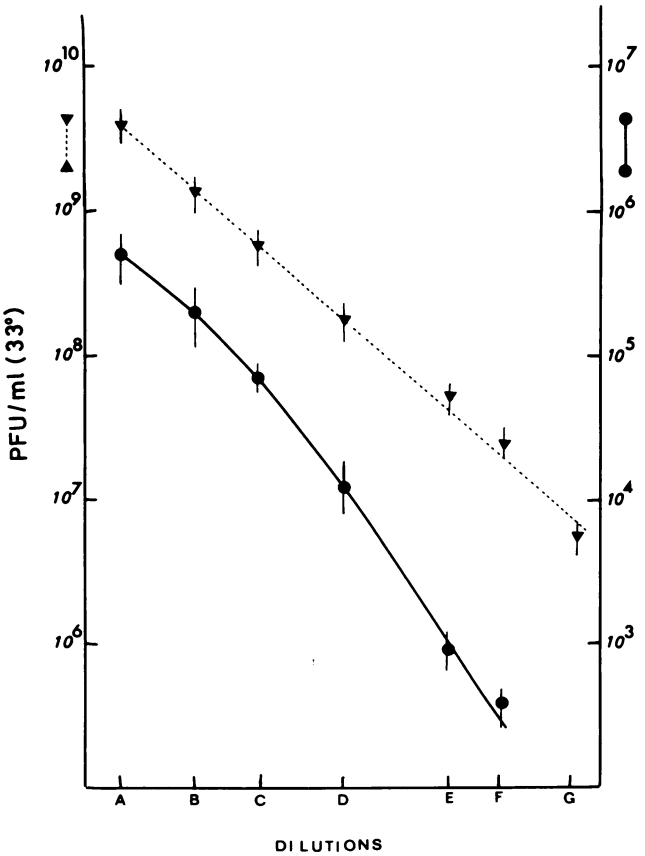

FIG. 1. Titers of *ts*A58 virus at dilutions used for subsequent enhanced reactivation and enhanced mutagenesis studies. Unirradiated (▼) and 1,330-J/m^2 UV-irradiated (●) *ts*A58 SV40 stock (A) was diluted out by a factor of about three several times (dilutions B to G) and plated on untreated cells so that the virus titer could be measured at the permissive temperature by plaque assay on CV-1P cells. The threefold dilutions were made for dilutions A to B, B to C, C to D, and F to G, while a dilution by four for dilution D to E and by two for dilution E to F were made for technical reasons. Dilution A corresponds to 4×10^9 PFU/ml for the unirradiated stock virus and 5×10^5 PFU/ml for the UV-irradiated virus. The error bars correspond to the standard error of the mean from three independent experiments.

made on confluent monolayers. MMC (Sigma Chemical Co., St. Louis, Mo.) dissolved in sterile phosphate-buffered saline (1 mg/ml) was added at various concentrations in cell medium without serum and buffered with 1% HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) buffer (pH 7.9). After a 2.5-h treatment in the dark at 37°C, cells were washed twice with phosphate-buffered saline, and regular medium with 2% serum was added. Cells were always infected after 24 h at 37°C after chemical treatment.

Virus. Temperature-sensitive SV40 mutant *ts*A58, obtained from P. Berg (Department of Biochemistry, Stanford University), was plaque purified and grown on MA-134 cells at 10^{-3} PFU per cell at 33°C. Virus stock was made by the freeze-thawing technique and then purified on a CsCl step gradient as described by Estes et al. (10). Virus suspensions (dilution A) were UV irradiated at 0°C, just before infection, with 1,330 J/m^2 from a germicidal lamp (mainly at 254 nm) at an incident dose rate of 3.2 J/m^2 per s. The dose rate was calibrated with a J-260 Radiometer (UV-Products, Inc.). Virus survival was determined on CV-1P cells by the plaque assay technique as described previously (20). Plaques were counted after 10 days at 41°C and after 20 days at 33°C. The MOI was determined as the number of infectious particles (PFU) per cell. Particularly for UV-irradiated SV40, the MOI was calculated after UV irradiation of the virus suspension, although the same number of virus particles was present in UV-irradiated and unirradiated stock virus.

Experimental design. For each value, 10 Petri dishes (10 cm in diameter) of MMC-treated or untreated CV-1P monkey cells were infected with unirradiated or UV-irradiated *ts*A58 stock virus at various MOIs. The *ts*A58 SV40 mutant is defective in the initiation of viral DNA replication at 41°C because of a single base-pair substitution (G:C to A:T) in the large T antigen gene (2). After one lytic cycle at the permissive temperature of 33°C (i.e., 92 h), virus progeny is recovered by freeze-thawing and survival is measured by plaque assay on untreated confluent CV-1P cells at 41 and 33°C (20). We have already shown that all plaques growing at 41°C are composed of genotypic revertants, which allows us

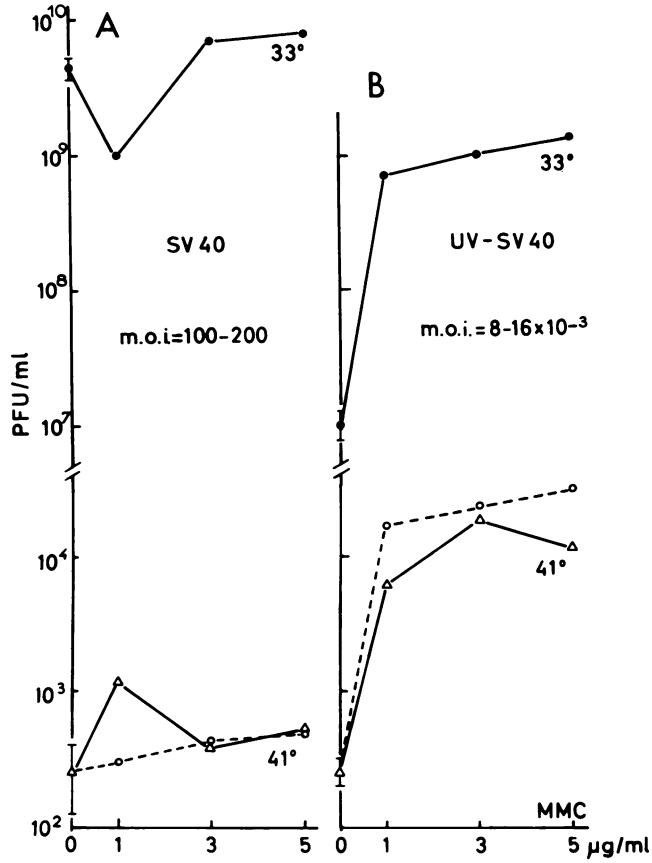

FIG. 2. Titer of progeny of unirradiated and UV-irradiated SV40 grown at a high MOI as a function of host cell treatment. Dilution A of untreated stock virus (A) (MOI between 100 and 200 PFU per cell) and UV-irradiated stock virus (B) (MOI between 8 and 16×10^{-3} PFU per cell) were used to infect control or MMC-treated cells for one lytic cycle at the permissive temperature. CV-1P confluent monolayers were treated with various amounts of MMC (between 1 and 5 µg/ml) 24 h prior to infection. The titer of progeny virus was measured both at 33°C (●) and 41°C (△). The dotted line represents the theoretical curve that should be expected for the survival at 41°C if no enhanced mutagenesis occurs. The MOI indicated in all figures corresponds to the number of surviving virus (measured in PFU) to the number of infected cells.

to measure the absolute number of mutants in the progeny virus. Then, the mutation frequency is defined for a given experimental virus dilution as the ratio of progeny titer at 41°C to progeny titer at 33°C.

RESULTS

Determination of MOI. To allow a reproducible and measurable MOI, we used a CsCl-purified *ts*A58 stock virus. Part of this purified stock virus was UV irradiated in vitro at 1,330 J/m^2, and then serial dilutions by a factor of about three were carried out. The titer of progeny from each dilution was measured independently for unirradiated and for UV-irradiated stock virus, and the MOI is defined in both cases as the ratio of the number of infecting PFU (determined from the plaque formation assay on untreated CV-1P cells) to the number of host cells. The survival of the two stock virus measured by direct plaque assay at the permissive temperature is shown in Fig. 1. The survival of unirradiated virus

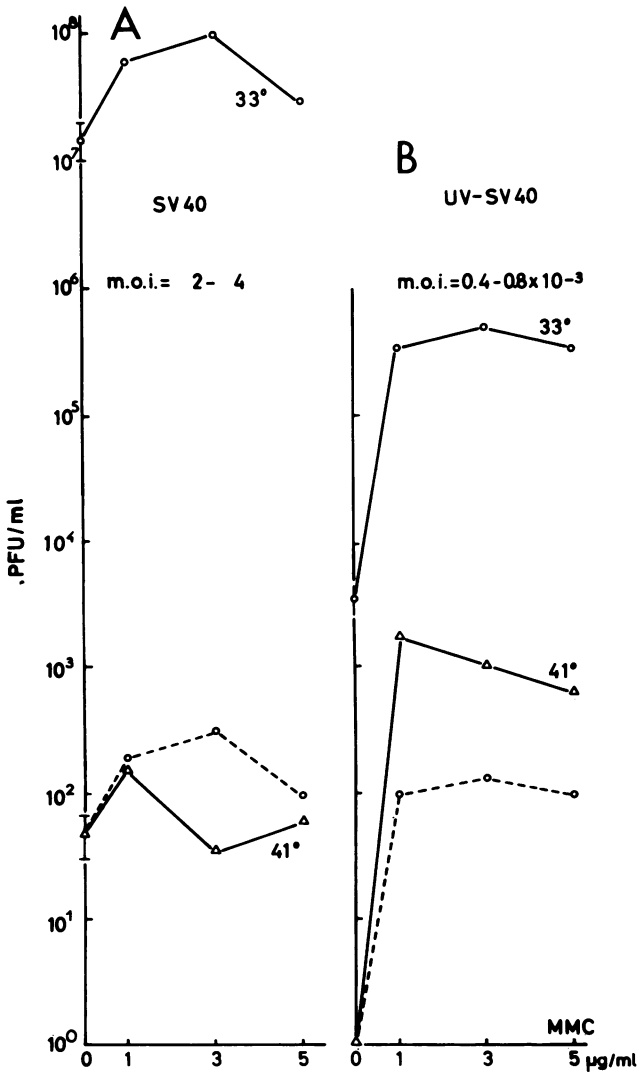

FIG. 3. Progeny titers of unirradiated and UV-irradiated SV40 grown at a low MOI as a function of host cell treatment, as described in the legend to Fig. 2 but with dilution D of unirradiated stock virus (MOI between 2 and 4 PFU per cell) and UV-irradiated stock virus (MOI between 0.4 and 0.8 × 10^{-3} PFU per cell).

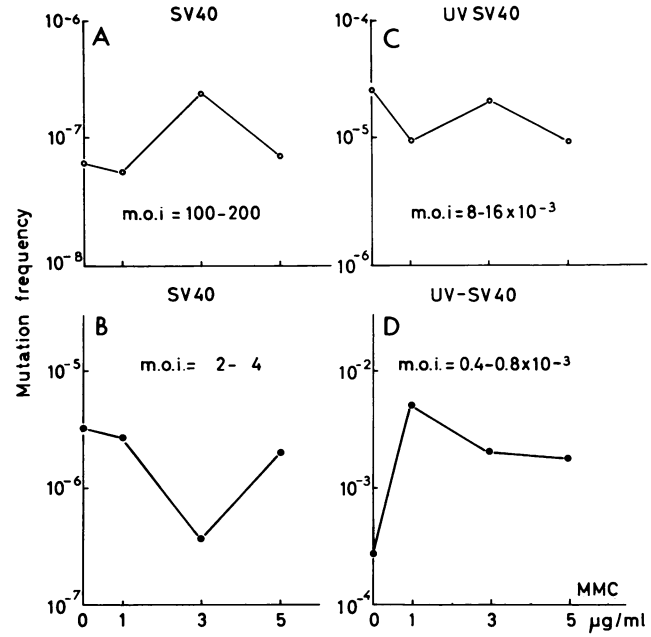

FIG. 4. Mutation frequency of untreated and UV-irradiated virus as a function of host cell treatment. The mutation frequency was calculated as the ratio of the number of plaques growing at 41°C (representing genotypic revertants) to the number of plaques growing at 33°C for each progeny produced after one lytic cycle at the permissive temperature. (A and B) Mutation frequency of unirradiated virus grown at a high MOI. (Dilution A, panel A) and a low MOI (dilution D, panel B). (C and D) Mutation frequency of 1,330-J/m^2 UV-irradiated virus grown at a high MOI (dilution A, panel C) and a low MOI (dilution D, panel D). Results were obtained by using data from Fig. 2 and 3.

was directly proportional to the dilution factor as expected, while the survival of UV-irradiated SV40 decreased much more rapidly at a low MOI, indicating that multiplicity reactivation may occur in cells infected with UV-damaged templates at a high MOI. The exact MOIs used in this study were calculated from the virus titers reported in Fig. 1.

Survival and mutagenesis of unirradiated SV40 growing in MMC-treated or control host cells. For each dilution (A to F [see legend to Fig. 1]) of unirradiated stock virus, the survival of the progeny virus made after one lytic cycle in control or MMC-treated cells was determined at 33 and 41°C. Complete results are shown in Fig. 2 and 3 for only two dilutions (A and D). At a high MOI (dilution A), there were no significant differences between the progeny titers from control or MMC-treated cells, whatever the temperature at which the plaques were grown. This implies that the mutation frequency does not significantly increase in the progeny from treated cells (Fig. 4). At lower MOIs (dilution D), progeny titers increased at 33°C but not at 41°C when cells were treated with MMC (Fig. 3), which indicates the presence of enhanced capacity for virus production but the absence of enhanced mutagenesis (Fig. 4). From the plot of mutation frequency as a function of MOI, two interesting points were observed (Fig. 5). First, the mutation frequency for unirradiated virus increases strongly from 2 × 10^{-8} to roughly 10^{-6}, and then a plateau is reached. Second, no significant difference is observed between mutation frequency of virus progeny obtained in control or MMC-treated cells (Fig. 5). The ratio of mutation frequency of progeny from MMC-treated cells to mutation frequency of progeny

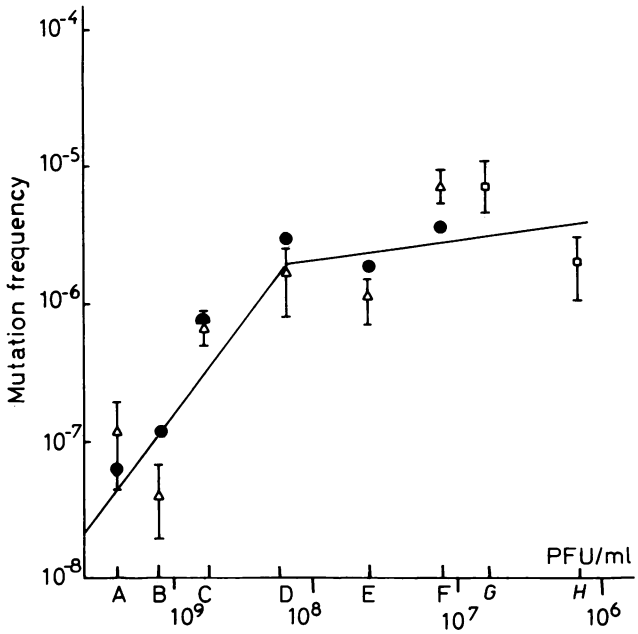

FIG. 5. Mutation frequency of untreated virus as a function of growth at different MOIs. The mutation frequency was calculated as described in the legend to Fig. 4 for each threefold dilution (from dilution A to H, with the viral titer of the infectious samples expressed in PFU/ml) of untreated stock virus in progeny obtained in host cells that were untreated (●) or treated with 3 μg of MMC per ml (△ or □). Error bars correspond to the standard error of the mean from three independent determinations.

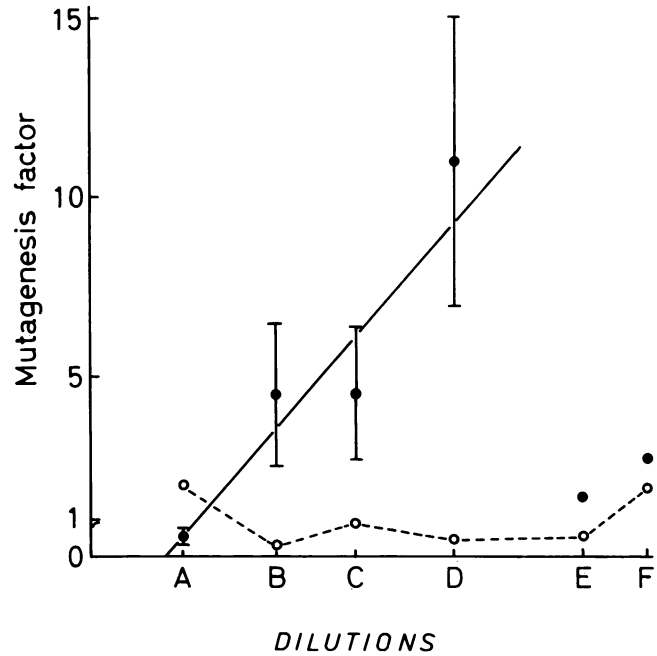

FIG. 6. Mutagenesis factor of unirradiated and UV-irradiated virus as a function of growth at different MOIs. The mutagenesis factor was calculated as the ratio of the mutation frequency of progeny issued from MMC-treated cells (3 μg/ml) to that from untreated cells. Results are computed from Fig. 5 for untreated virus (○) and from Fig. 8 for UV-irradiated virus (●). The values for UV-irradiated virus at dilutions E and F are not taken into account because no plaques were detected at 41°C for the progeny issued from untreated cells because of the low number of PFU. Error bars correspond to the standard error of the mean from three independent determinations. A mutagenesis factor >1 indicates the presence of enhanced mutagenesis.

from control cells defines a mutagenesis factor which is close to 1, indicating the absence of enhanced mutagenesis for the untreated stock virus (Fig. 6). However, the same ratio for survival measurements which quantifies the reactivation factor was almost always greater than 1, indicating an enhanced production of progeny by unirradiated virus in MMC-treated cells (Fig. 7).

Survival and mutagenesis of UV-irradiated SV40 growing in MMC-treated or control host cells. The same protocol was used for the *ts*A58 mutant irradiated with UV at 1,330 J/m^2 as for the unirradiated virus. Figures 2 and 3 show that at a high MOI (dilution A), as well as at a low MOI (dilution D), the survival of progeny from MMC-treated cells at 33°C is much higher than survival of progeny from control cells. Figure 7 shows that the reactivation factor varies from 20 to 100 because of MMC-treatment and is relatively independent of the MOI. The titer of virus progeny at 41°C is higher for MMC-treated cells compared with that for control cells only at low MOIs (Fig. 2 and 3, dilution D versus dilution A). This result implies that mutation frequency is higher for the progeny issued from MMC-treated cells as compared with that from controls only at low MOIs (Fig. 4). In fact, the mutagenesis factor increases almost linearly with a decrease in the MOI logarithm (Fig. 6). The evolution of mutation frequency for progeny issued from untreated or MMC-treated cells as a function of growth at different MOIs is plotted in Fig. 8. The shape of the two curves is roughly comparable with those for untreated virus. A rapid increase in mutation frequency was observed from high to low MOIs. For the untreated cells, a plateau in the mutation frequency was rapidly reached, while for the MMC-treated cells the mutation frequency increased almost linearly as a function of the logarithm of the MOI decrease (Fig. 8).

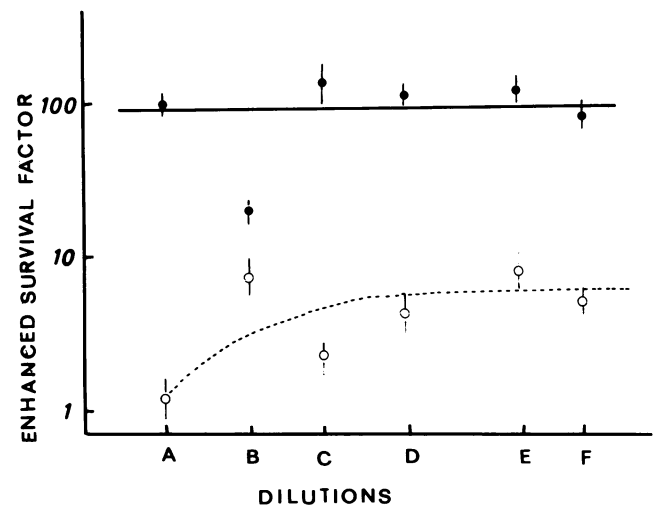

FIG. 7. Enhanced survival factor of unirradiated and UV-irradiated virus as a function of MOI. The enhanced survival factor was calculated as the ratio of the titer of progeny issued from MMC-treated cells (3 μg/ml) to that from untreated cells, for untreated virus (○) and UV-irradiated virus (●). An enhanced reactivation factor >1 indicates the presence of enhanced virus survival.

DISCUSSION

Several lines of evidence indicate that inducible genes and functions exist in yeast (17) and mammalian (16, 19) cells as a response to treatment which inhibits DNA replication. Because of the lack of defective mammalian cell mutants, however, the analysis of physiological responses analogous to *E. coli* SOS functions has been very difficult and has led to conflicting interpretations (16, 19, 23). Thus, the analysis of enhanced mutagenesis of DNA-damaged animal virus represents one way to characterize inducible repair functions in mammalian cells. Since the reported results concerning enhanced virus mutagenesis were conflicting, even with a presumed similar experimental protocol, we considered that variations in the number of infecting particles could explain variations in the results. In particular, it is known that the number of viral particles in 1 PFU can greatly vary from one laboratory to another, depending on the preparation of stock virus, the cell type used, and the growth temperature.

Our results show that changes in the MOI lead to important changes in either spontaneous or UV-induced mutation frequencies. It is important to provide a reminder here that we used an MOI that corresponded to the number of surviving particles per infected cell. The shape of the mutation frequency curve in Fig. 5 is not due to an inhibiting growth of revertants at a high MOI, since we have already shown that *ts*A58 mutants and phenotypic revertants have identical growth characteristics at the permissive temperature (20). The increase of spontaneous mutations with the decrease of MOI has also been reported with bacteriophage T4 (9) and, to a lesser extent, with parvovirus H_1 (5). The exact interpretation of this result is not quite clear, although at a low MOI one can assume that the infecting molecules will be replicated much more often than at a high MOI since the replicative pool should be smaller. The probability to acquire point mutations during DNA replication should increase for each replication cycle. In the case of unirradiated SV40, treatment of the host cell with MMC does not significantly increase the mutation frequency of progeny, indicating that in the treated cells the replication complex is not particularly error prone on undamaged templates. In the case of UV-irradiated SV40, the picture is different, although all mutation frequencies increase while the MOI decreases (Fig. 8). At a high MOI no significant differences were observed in the mutation frequency of progeny, regardless of the cell treatment used. However, the decrease in MOI led to a significantly greater increase in mutation of progeny grown in MMC-treated cells compared with those grown in control cells. The difference in mutation frequency was very clear and could be explained by the greater error proneness of replication of UV-irradiated SV40 in MMC-treated cells. Under nonselective conditions for carrying out the lytic cycle, the greatest number of mutations was obtained only when both viral DNA and host cells were treated with DNA-damaging agents and when the number of infecting damaged molecules was the lowest.

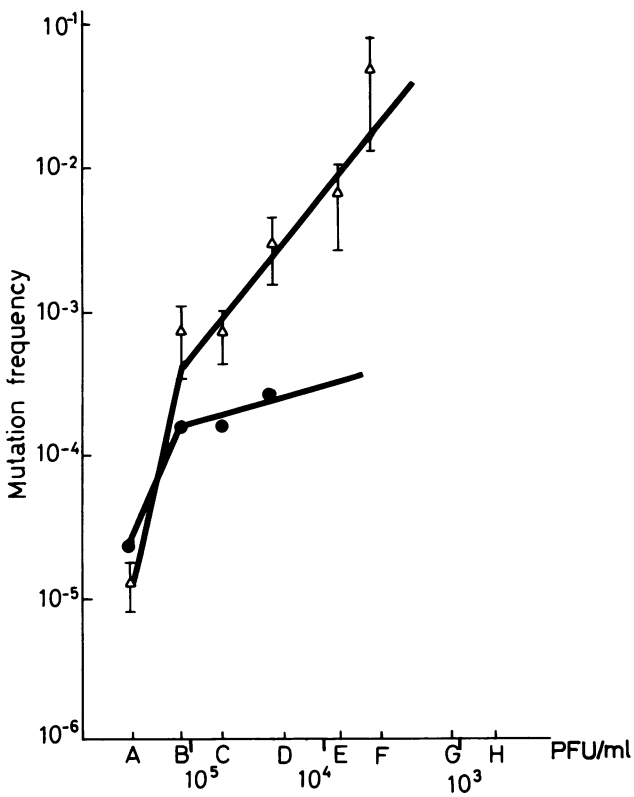

FIG. 8. Mutation frequency of UV-irradiated virus as a function of growth at different MOIs as described in the legend to Fig. 5. Dilutions of UV-irradiated stock virus were grown in untreated cells (●) or cells treated with 3 μg of MMC per ml (△).

At a high MOI it is plausible that other biological processes outside normal DNA replication take place, such as recombination, abnormal replication, or DNA degradation. In that case the effect of cell treatment on mutagenesis may be too small compared with the other biological responses and may not be detected. We were unable to detect enhanced virus mutagenesis in the same viral system after transfection of damaged DNA molecules of SV40 instead of whole-virus particle infection (11). In that system we interpreted the absence of detectable enhanced mutagenesis, although enhanced virus survival was present, by the fact that DNA transfection is more or less equivalent to a high MOI (11). The presence of a large number of damaged DNA molecules in the cell after DNA transfection may render it difficult to detect the error-prone replication pathway. Such variable effects on mutagenesis at a high MOI has also been found with herpes simplex virus, for which a higher mutation rate was obtained (14), and in *E. coli*, in which increased recombination leads to a decrease in mutagenesis (1).

In terms of molecular mechanisms, we have previously shown in the same viral system that UV irradiation gives rise to base-pair substitution within the T-antigen gene located opposite UV-induced DNA lesions (2). In the context of our current study, this suggests that the higher error proneness of MMC-treated cells could be due to a more active error-prone pathway which may likely be due to replication errors made opposite noninstructive DNA lesions by the replication complex. The biochemical mechanisms underlying this process is still unknown, even in *E. coli*, in which most of the genes involved in this process have been isolated (18, 24).

Treatment of cells with DNA-damaging agents, such as MMC, increases the titers of infecting unirradiated and UV-irradiated virus. Since the increase in survival is greater for UV-irradiated virus and is accompanied by mutagenesis under specific experimental conditions, we suggest the existence of two different biological processes that lead to enhanced virus plaque formation. One type, which is observed both with untreated virus and UV-irradiated virus, is not error prone. In this case, we can observe a dissociation between the cell capacity for enhancing plaque formation and virus mutagenesis. We suggest that this process may be

independent of DNA replication and may be due to a more efficient prereplication step of the SV40 lytic cycle in treated cells, such as nucleotide excision repair or T-antigen RNA transcription. The second type observed only with UV-irradiated virus is strongly error prone. Its expression, however, is only detected when a small number of UV-damaged molecules is present in treated cells. We suggest that this process may be dependent on DNA replication on damaged templates and may be due to higher replication errors introduced opposite DNA lesions. The higher efficiency for SV40 replication in treated host cells may be due to the synthesis of cellular factors that allow a better replication of viral molecules either by higher transcription of the T antigen necessary to initiate replication or by a greater availability of replication enzymes or cofactors. Thus, it has been shown that treatment of SV40-transformed cells by DNA-damaging agents induces the amplification of viral sequences because of the recognition of SV40 replication origins, leading to specific replication of integrated viral genomes (12). An identical process in MMC-treated monkey cells may explain the enhanced virus survival. The error-prone component may be explained, as in bacteria, by the induction of cofactors for relaxing the fidelity of the replication complex.

The fact that enhanced viral mutagenesis is only observed under specific experimental conditions allows us to believe that the conflicting results reported on this process either with the same virus or with other viruses could be explained partially by uncontrolled variations from lab to lab in the MOI used, although it is difficult to compare the MOI calculated in various laboratories because of possible changes in the ratio of PFU to physical virus particles. Thus, we conclude that error-prone replication of damaged viral genomes does really happen in treated monkey cells, but the demonstration of its existence needs specific experimental conditions, some of which have been described here.

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