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Effect of Ultraviolet Irradiation on the Survival of Simian Virus 40 Functions in Human and Mouse Cells

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The relative sensitivities to ultraviolet light of various simian virus 40 (SV40) functions were studied in human and mouse cells. Transformation appeared to be less ultraviolet (UV)-sensitive than either T or V antigen when all functions were compared in the same cell. However, the time course of both T- and V-antigen appearance was delayed with UV-irradiated virus, so that the survival curves of these functions changed with time. Mouse and human cells which were transformed by UV-SV40 all contained SV40 T antigen. Infectious virus could be recovered from many more transformants than would be expected from the infectivity in African green monkey kidney cells of the irradiated virus. The results suggest that human and mouse cells are capable of reactivating UV-damaged SV40.

Many deoxyribonucleic acid (DNA)-containing tumor viruses are defective for cytocidal interaction in the species in which they induce transformation, although they replicate well in other species. Polyoma transforms hamster cells in tissue culture but kills mouse cells. Adenoviruses produce transformation in rat cells but are highly lytic in human embryonic kidney. With simian virus 40 (SV40), transformation is induced in mouse and hamster cells in tissue culture without any detectable cytocidal effect (6). African green monkey kidney (AGMK) cells, on the other hand, are killed by the virus. SV40 has also been shown to produce transformation of human fibroblast cell strains in culture (14, 19). In this system, however, there is some infectious virus production. Acutely infected human cells synthesize both T antigen, an early virus-specified cellular antigen, and virus capsid (V) antigen, a late viral function associated with the virus particles. The latter is never detected when nonpermissive mouse cells are infected with SV40.

In human cells it was possible to study the relative sensitivities to ultraviolet (UV) irradiation of three SV40 functions (T antigen, V antigen, and transformation) in the same cell. The UV target sizes for transformation and V antigen (infectivity) could, therefore, be compared under identical conditions rather than in separate species under different culture conditions and at very different virus multiplicities (4, 5, 7, 9, 12, 15, 16). The results suggest that host cell reactivation of UV-damaged virus is an important factor in UV-target size determination.

MATERIALS AND METHODS

Cell culture. Cultures were grown in Dulbecco's modification of Eagle's medium supplemented with 10% unheated calf serum (Colorado Serum Co.) in 50-mm plastic petri dishes (Falcon Plastics) and were subcultured with 0.1% trypsin in phosphate-buffered saline. A human fibroblast strain derived from the skin biopsy of an adult (L.S.) was used within the first 20 generations in tissue culture. The continuous line of mouse embryo cells, BALB/3T3 (3), was also used. Primary AGMK cells were obtained from Microbiological Associates.

Virus. A single pool of the small plaque variant (SV-S) of SV40 (20), titering 5×10^8 plaque-forming units (PFU) per ml was grown under conditions which minimize the number of "defective" virions (22, 23).

UV-inactivation. Samples (3 ml) of SV40 in uncovered 100-mm plastic petri dishes were exposed to UV for different amounts of time at room temperature under conditions of constant agitation of the fluid. The ultraviolet light source was a General Electric germicidal lamp. The dose rate at the surface of the sample, 18 cm from the light source, was around 24 erg per mm^2 per sec at a wavelength of 253.7 nm measured by an ultraviolet dosimeter (Ultraviolet Products, Inc.). Each sample, including the control virus which had been exposed to white light for as long as the longest UV dose, was reconstituted to its original volume with sterile distilled water.

SV40 T and V antigen. SV40 T and V antigens were stained by the indirect fluorescent-antibody method (17). Hamster T antibody was kindly supplied by W. P. Rowe (NIH). Hamster V antibody was obtained from K. Takemoto (NIH). Fluorescein-conjugated goat antihamster globulin was obtained from the Resources and Logistics Section of the National Cancer Institute. At least 200 positives or more than 20,000 total cells were scored for each point. In experiments in which low fractions of positive cells (less than around 1%) were found, more than one cover slip was scored.

Since SV40 can grow to a limited extent in human cells, the medium for all SV40-infected human cultures was supplemented with 0.5% (v/v) calf SV40 antiserum (BBL). This concentration was capable of neutralizing between 10^5 and 10^6 PFU in 1 hr at 37 C; under these conditions, supernatant fluids from human cultures infected with SV40 and then maintained in the presence of antiserum contained little or no infectious virus (less than 100 PFU/ml).

Plaque assay. Monolayers of AGMK cells were exposed to appropriately diluted 0.2-ml samples of virus for 3 hr at 37 C. Cultures were then washed once and overlaid with 4 ml of Eagle's medium containing 0.9% (w/v) Noble agar (Difco). Additional overlays of 3 ml were made at 4, 7, and 10 days; at 12 days, an overlay containing 0.5% neutral red was added. SV-S plaques were scored at 14 days (20).

SV40 transformation assay. Logarithmically growing cells were inoculated with 0.5 ml of virus and incubated at 37 C for 3 hr with frequent gentle agitation. SV40-infected human cultures were transferred to new petri dishes within 24 hr of infection at 10^4 and 5×10^4 cells per plate for the transformation assay. They were continually maintained in the presence of SV40 antiserum. For the transformation assay with BALB/3T3, cells were subcultured within 24 hr after infection to petri dishes at 10^2, 10^3, and 10^4 cells per plate. Transformed colonies were scored at 24 days for human cells and at 21 days for BALB/3T3 by methods reported earlier (2, 3).

Cell fusion technique. The methods followed for cell fusion have been previously described (21). Briefly, around 5×10^6 transformed and 5×10^6 AGMK cells were suspended in 0.9 ml of medium and mixed with 0.1 ml of UV-inactivated Sendai virus (UV-SeV) containing 6,000 hemagglutinating units. The mixture was kept in an ice bath for 10 min with intermittent shaking and then placed in a water bath at 37 C for 1 hr. The cells were inoculated into 75-cm^2 tissue culture flasks (Falcon Plastics) in Dulbecco's medium containing 5% agamma globulin serum (Grand Island Biological Co.). At 10 days, each culture was frozen and thawed three times, and the fluids were assayed for plaque formation on AGMK cells.

RESULTS

Dose response curves for SV40 viral functions in human and mouse cells. The dose response curves for different SV40 functions in mouse and human cells were studied with unirradiated virus. With human cells the number of T and V antigen-containing cells was proportional to the amount of virus added for multiplicities as high as 300 PFU/cell (Fig. 1A). The T- and V-antigen values were very similar at each virus dose. The dose response curve for transformation in human cells was parallel to those for T and V antigen, but at a level about 100-fold lower. Similarly in mouse cells (Fig. 1B), the number of T-antigen positives and the number of transformants were proportional to the amount of virus added until plateau levels were reached at high virus multiplicities (over 300 PFU/cell). A virus multiplicity of 200 PFU/cell was chosen for subsequent experiments since it resulted in a high value in the linear portion of the dose response curve for each function.

UV inactivation of SV40 functions in human cells. Human cultures were exposed to unirradiated SV40 or to equal amounts of virus which had been exposed to UV for different time intervals. The curves for transformation, T antigen, and V antigen are adequately described as exponentially decreasing functions with time (Fig. 2). A slight shoulder in the curve for transformation was disregarded for the analyses in the present report. The inactivation of plaque formation

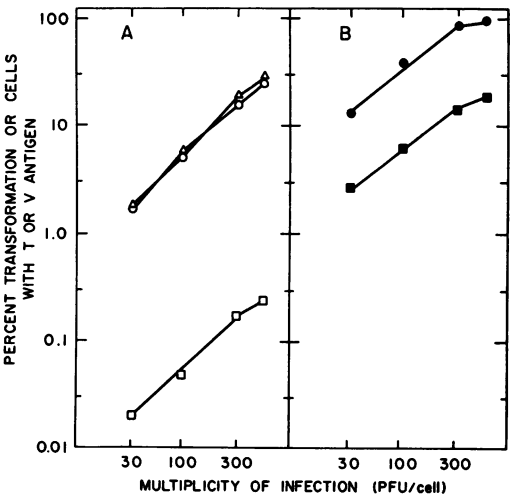

FIG. 1. *Cultures containing ca. 5×10^5 cells were exposed to SV40 at different multiplicities of infection for 3 hr and then transferred to new petri dishes with cover slips for the T- and V-antigen assay and to regular petri dishes for the transformation assay. Human cells were maintained in medium supplemented with 0.5% SV40 antiserum. (A) Human fibroblast strain L.S. T and V antigen were assayed at 72 hr, and transformed colonies were scored at 24 days. (B) Mouse BALB/3T3 cells. T antigen was assayed at 48 hr. and transformed colonies were scored at 21 days.*

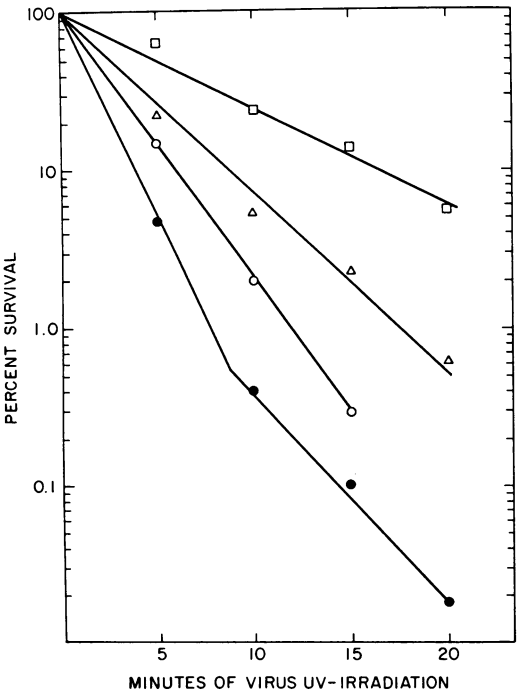

FIG. 2. *Effect of UV irradiation on the survival of SV40 functions in human cells. T and V antigen were determined at 72 hr and transformation frequency at 24 days. The results are the average of three experiments. For unirradiated SV40, the transformation frequency (□) was 0.09%; the percentage of T antigen-positive cells (△) was 9.9%; the percentage of V antigen-positive cells (○) was 9.5%; and the PFU values (●) in AGMK cells were 1.1 × 10⁸ PFU.*

on AGMK cells showed two components, a UV-sensitive and a resistant one. Similarly shaped curves have been reported for UV inactivation of infectivity of polyoma (5) and adenovirus 1 (12). Whether the resistant component is due to the presence in the virus stock of a minority of relatively UV-resistant virions, to imperfect mixing during UV-irradiation of virus, or to multiplicity reactivation is not clear. However, since the titration of plaque formation with even the most UV-damaged virus was linear with dilution, the last possibility appears unlikely.

Transformation appeared to be the most resistant of the three viral functions measured in the human cell. Its survival curve had a slope of around one-half that of T antigen and one-third that of V antigen (Table 1). T-antigen induction was more resistant than V antigen as would be expected for an early versus late viral function. Carp and Gilden (8) found somewhat larger differences in the UV sensitivities of T antigen

TABLE 1. *Comparison of the ultraviolet (UV) survival of simian virus 40 functions in mouse and human cells*[a]

Simian virus 40 function	Human	Mouse
Transformation	0.23	0.28
T antigen	0.43	0.92
V antigen	0.61	—[b]
Infectivity[c]	1.0	1.0

[a] Data is presented as the ratio of the slope of the UV-survival curve for each viral function measurable in human or mouse cells to the slope for UV inactivation of plaque formation in African green monkey kidney cells in the sensitive portion of its inactivation curve. T- and V-antigen survivals were determined at 3 days.

[b] Not applicable.

[c] Plaque-forming units.

and plaque formation when these functions were compared in the monkey cell.

The fact that the transforming function of SV40 appeared to be more resistant than T antigen to UV irradiation was somewhat unexpected. T antigen is normally present in SV40-transformed cells including those induced by virus exposed to large amounts of UV (10). If the UV-target size for transformation were truly smaller than the target size for T antigen, then virus exposed to a large enough UV dose should induce a class of T antigen-negative transformants.

With human cells a much larger number of cells synthesize both T and V antigen acutely and then go on to become transformed. The ratio of T antigen-positive cells to eventual transformants is about 200 to 1 (reference 2; see also Fig. 1). The great majority of T antigen-positive cells is presumably either killed by the virus or eventually cured. The highest UV dose to the virus (20 min) decreased the T-antigen/transformation ratio to about 20 to 1. The technical difficulties in measuring very low levels of T antigen and transformation made it difficult to study whether at a higher UV dosage, the ratio would ever become less than one. Such a ratio would imply the existence of a class of T antigen-negative transformants. To search for such a class, the nonpermissive mouse cell line, BALB/3T3, was used.

UV-inactivation of viral functions in BALB/3T3. With BALB/3T3, around 10 to 15% of cells that make T antigen in response to SV40 infection go on to become transformed (Fig. 1). It was, therefore, more feasible in this system to test whether UV inactivation of virus resulted in the production of a class of transformants lacking T antigen. With BALB/3T3, the percentage of T antigen-containing cells is normally maximal

at 48 hr and was scored at that time (3). The UV-survival curves are shown in Fig. 3. As with human cells, transformation appeared less UV-sensitive than T antigen in the mouse cell. T-antigen survival best fits a two component curve. Its slope in the more sensitive portion of the curve was almost as steep as that of plaque formation in AGMK cells.

In Table 1, the UV sensitivities of each viral function are compared to the survival of infectivity (PFU in AGMK). The UV sensitivity of transformation in either mouse or human cells was around one quarter that of infectivity. Similar findings with other oncogenic viruses have previously been interpreted to mean that transformation requires much less of the viral genome than infectivity (4, 5, 7, 12). The slopes of the survival curves for transformation in the mouse and human cells differed from each other by only around 20%. In human cells where V antigen (infectivity) and transformation could be compared at the same virus multiplicity, V antigen was 2.8 times as UV-sensitive as transformation.

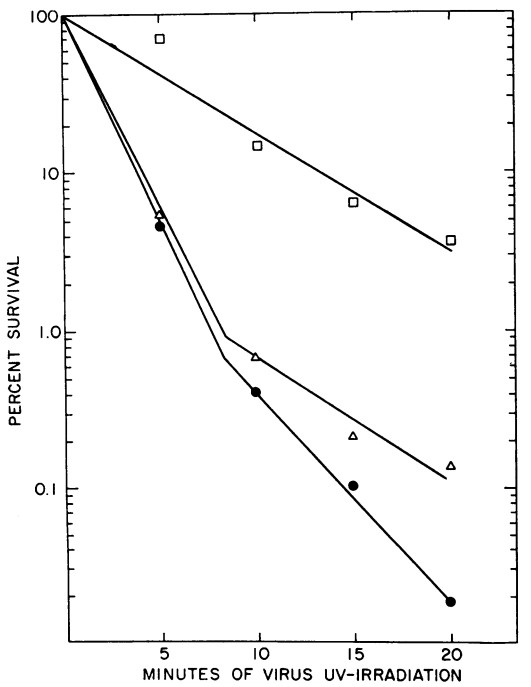

FIG. 3. *Effect of UV irradiation on the survival of SV40 functions in mouse cells. T antigen was measured at 48 hr and transformation frequency at 21 days. The results are the average of three experiments. For unirradiated SV40, the transformation frequency (□) was 9.3%; the percentage of T antigen-positive cells (△) was 55%; and the PFU values (●) in AGMK cells were 1.1 × 10^8 PFU.*

Presence of SV40 T antigen in UV-SV40 transformed clones. When the fraction of BALB/3T3 cells containing T antigen at 48 hr was compared to the actual percentage of cells that grew into transformed colonies, the ratio of T-antigen positives to the number of transformants became smaller than one for SV40 preparations exposed to UV for 5 min or more. For example, with SV40 which was UV-treated for 5 min, T antigen was detected in 3% of the cells acutely; yet 4.3% of the cells went on to become transformed. This indicated that only around 70% of the transformed colonies should be T antigen-positive. For higher UV doses, the ratio of T-antigen positives to transformants should be even smaller.

An attempt was made, therefore, to obtain T antigen-negative transformants. Individual colonies of cells transformed by normal SV40 or virus which had been UV irradiated for 5, 10, 15, or 20 min were isolated by the cloning cylinder technique. For each time point, a total of ten individual transformed colonies were examined for the presence of T antigen. T antigen-positive cells were present in every one.

Kinetics of T-antigen induction with normal and UV irradiated SV40. In the above studies, T- and V-antigen levels using UV-irradiated SV40 had been measured at the time of maximal synthesis with normal SV40. It was possible, however, that the time course of T- and V-antigen induction might be altered with the UV-damaged virus. Therefore, the kinetics of T- and V-antigen production were compared in cells infected with normal and UV-irradiated SV40. Cultures were maintained in the logarithmic phase of growth after infection to minimize any selective growth advantage of transformed cells. T-antigen positives were almost never seen in groups of more than two cells before 7 days. At later times, a minority of positives were seen in small clusters, presumably representing early transformed colonies.

In Fig. 4, the time course of T-antigen induction in human cells is shown for unirradiated SV40 and for virus that had been UV irradiated for either 5 or 15 min. The control virus was tested at two multiplicities (200 and 40 PFU/cell). In each case the highest percentage of T-antigen positives was seen at 72 hr, and by 7 days the levels had fallen to less than 40% of the peak values. At lower virus inputs with control virus, the peak in T-antigen synthesis occurred at 3 days also.

The time course of T-antigen synthesis was clearly delayed with UV-treated SV40. The highest fraction of T-antigen positives was seen at times later than 72 hr. With virus that had been

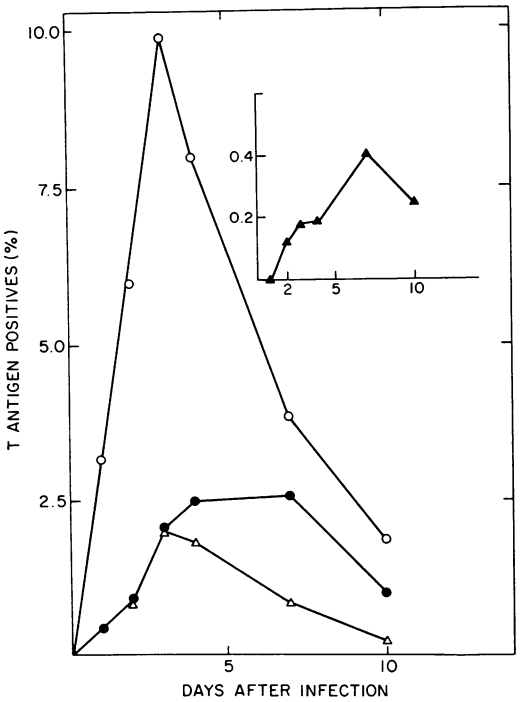

FIG. 4. *Kinetics of T-antigen induction in human cells by unirradiated and UV-irradiated SV40. Symbols: ○, unirradiated; △, unirradiated, 1:5 dilution; ●, UV-irradiated for 5 min; ▲, UV-irradiated for 15 min.*

UV irradiated for 15 min, for example, the fraction of T-antigen positives at 7 days was more than twice that seen at 72 hr. At 7 days, positive cells were usually observed singly rather than in groups, suggesting that SV40 may have remained several days in many cells before expressing T antigen. A similar delay in the kinetics of T-antigen induction was observed with UV-inactivated SV40 in BALB/3T3 cells.

Change in survival curve for T antigen with time. The fact that the kinetics of T-antigen production differed for each virus preparation, depending upon the length of its exposure to UV, made it difficult to arbitrarily select one time point for measurement of UV survival. When the UV survival curves for T antigen at various times after infection (from Fig. 4) were compared to the survival curve for transformation, the slope of T- antigen gradually approached that of transformation (Table 2). In fact, by 7 days the ratio of the slope of T-antigen survival to that of transformation had decreased to one. The actual percentage of T antigen-positive cells at 7 days was still higher by three- to fivefold than the number of transformed colonies eventually detected.

TABLE 2. *Change in ultraviolet-survival curve of T antigen with time: comparison to transformation*

Time after infection	Relative slope[a]
days	
1	2.9
2	2.2
3	2.0
4	1.7
7	1.0
10	1.0

[a] Relative slope is the ratio of the slopes of the survival curves for T antigen and transformation.

Kinetics of V-antigen formation with UV-SV40. The time course of V- antigen appearance with normal and UV-irradiated SV40 was studied next. The highest percentage of V-antigen positives with control virus was observed at 3 days (Fig. 5). This was the case for each of several different multiplicities of infection tested, two of which (200 and 70 PFU/cell) are shown in Fig. 4. As with T antigen, the time course of V-antigen appearance was delayed by using UV-irradiated SV40. With virus that had been exposed to UV for 5 min, the highest fraction of V antigen-containing cells was seen at 5 days.

Rescuability of infectious virus from UV-SV40 transformed cells. The delayed time course of V-antigen induction by UV-damaged virus suggested that it might be possible to recover infectious virus from more UV-SV40 transformants than would be predicted from the 3-day survival curve for V antigen or the more UV-sensitive survival curve for infectivity in AGMK cells. SV40-transformed human and BALB/3T3 lines were tested for virus recoverability by the method of cell fusion (21). A transformant was considered negative if it failed to yield virus after co-cultivation with AGMK cells in the presence of UV-SeV on three separate attempts.

Virus was recoverable from 70% of the SV40 human transformants tested that had been transformed by virus exposed to UV for 10 min (Table 3). Yet, this virus contained only 0.4% of its original plaque-forming titer. With the SV40-transformed mouse lines tested, infectious virus could be recovered from three out of six transformants produced by virus containing 0.04% of its initial titer. These results compare favorably with those of previous studies of virus recoverability from UV-SV40 transformed mouse and hamster cells (10, 13).

In the present report, all of the viruses recovered from UV-SV40 transformants had the same plaque morphology as the parent virus

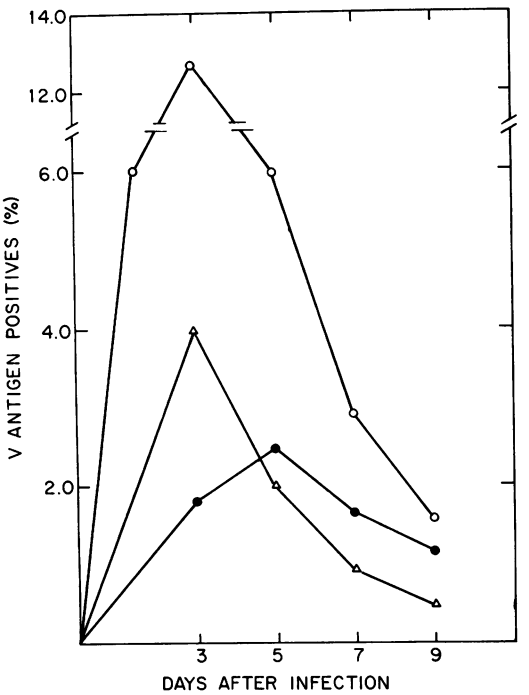

FIG. 5. *Kinetics of V antigen induction in human cells by unirradiated and UV-irradiated SV40. Symbols:* ○, *unirradiated;* △, *unirradiated, 1:3 dilution;* ●, *UV-irradiated for 5 min.*

TABLE 3. *Recoverability of infectious virus from ultraviolet (UV) simian virus 40 mouse and human transformed clones*

UV dose (min)	PFU[a] (per cent of initial titer)	Human transformants[b]		Mouse transformants[b]	
		No. of clones tested	No. of virus yielders	No. of clones tested	No. of virus yielders
0	100	10	10	5	5
10	0.4	10	7	6	2
15	0.1	6	2	4	1
20	0.04	6	0	6	3

[a] Plaque forming units (PFU) assayed in African green monkey kidney cells. The titer of unirradiated simian virus 40 was 5×10^8 PFU/ml.

[b] Each clone was derived from a single transformed colony. Recoverability of simian virus 40 was tested by cell fusion as described in the text.

(SV-S) and were easily rescued by cell fusion. Kit and co-workers have also detected a class of viruses with a different plaque morphology than the parent strain, suggesting a permanent genetic alteration of the input virus (13).

Since the virus multiplicity used in the above studies was quite high, it was possible that multiplicity reaction (MR) resulted in the delayed expression of viral functions by UV-irradiated SV40. Another mechanism consistent with the above results was host cell reactivation (HCR) of UV-damaged virus. This phenomenon involves the repair of UV-damaged viral DNA by cellular enzymes and has been studied with bacteriophage in certain bacteria (11, 18). The time required for host cell enzymes to repair UV-damaged SV40 might account for the delay in expression of viral functions.

The first possibility was tested by exposing human cells to UV-irradiated SV40 at several virus multiplicities. If MR were involved, the level of production by UV-SV40 of a given viral function might fall more steeply with virus dilution than in a "one hit" titration pattern. A stock of UV-SV40 (5 min) was used; the fraction of T and V antigen-containing cells was determined at two times, 3 and 7 days. Table 4 shows that the percentages of both T and V antigen-positive cells fell linearly with dilution of the UV-irradiated virus. These findings, however, do not exclude the involvement of MR in this system. Since there is known to be a 10^2- to 10^3-fold excess of physical particles over infectious units in SV40 stocks, the contribution of these through complementation toward the expression of virus functions cannot be excluded at the virus dilutions studied. The technical difficulties in scoring very low levels of T or V antigen-positive cells on cover slips prevents accurate analysis at higher virus dilutions.

DISCUSSION

The results presented above show that the UV survival curves of viral functions measured rela-

TABLE 4. *Effect of virus multiplicity on the expression of T and V antigen by ultraviolet (UV)-irradiated simian virus 40*[a]

Virus dilution	Per cent of antigen-positive cells at			
	3 days		7 days	
	T	V	T	V
Concd	2.8	1.8	3.1	2.6
1:3	1.0	0.65	1.1	0.8
1:9	0.25	0.2	0.3	0.4
1:27	0.1	0.1	0.1	0.15

[a] Human cultures were exposed to different dilutions of SV40 previously treated with UV irradiation for 5 min. T- and V-antigen positives were scored at 3 and 7 days after infection.

tively early in infection cannot be meaningfully compared to those of functions measured much later, as demonstrated by the fact that the T-antigen survival curve changes with time after infection. That the slope of the UV-survival curve for T antigen eventually paralleled the slope for transformation is consistent with the observed presence of T antigen in every one of a large number of UV-SV40 transformants examined here and in previous reports (10, 13). These findings support the conclusion that T-antigen and transformation functions are closely related despite the apparent differences in UV-sensitivity of the two functions when T antigen was measured very early in relation to the time transformation was assayed.

In other studies, Uchida and Watanabe (22) have characterized defective SV40 virions that are produced by repeated high multiplicity passage of the virus in monkey cells. These virions induce T but not V antigen and contain only around 85% of the normal amount of DNA (23). Mouse cells transformed by this virus are similar to some of the UV-SV40 transformants described here and elsewhere (10, 13) in that virus cannot be recovered from them (22). These findings all support the concept that the entire SV40 genome is not required for transformation.

The studies presented here are consistent with either the hypothesis that UV-damaged virions complement each other (MR) or that the host cell repairs UV damage to the viral DNA (HCR). In another report, the UV-survival curves for SV40 functions were compared in normal human cells and in cells from patients with xeroderma pigmentosa, a genetic disease associated with impaired capacity to repair UV damage to DNA (3). In analogy to mutant strains of bacteria which lack the capacity of HCR of UV-damaged phage (11, 18), the DNA repair-deficient xeroderma cells allow much less expression than normal cells of UV-SV40 viral functions. These data support the hypothesis that HCR plays a major role in the expression of the viral functions of irradiated SV40 in normal cells.

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