Specific Viral Antigens in Rat Cells Transformed by Herpes Simplex Virus Type 2 and in Rat Tumors Induced by Inoculation of Transformed Cells

Joan C. M. Macnab, L. Visser, A. T. Jamieson, and J. Hay

Medical Research Council Virology Unit, Institute of Virology, Church Street, Glasgow, G11 5JR Scotland

ABSTRACT

A rat cell line, RE1, oncogenically transformed by a herpes simplex virus type 2 ts mutant (ts 1), has been demonstrated to contain herpes simplex virus type 2-specific thymidine kinase activity, as have two of four tumors induced in rats by inoculation of these transformed cells.

A high proportion of sera from tumor-bearing rats (5 of 11) have detectable antibody against herpes simplex virus thymidine kinase, and there is a correlation between enzyme activity in a tumor and antibody in "tumor sera." A proportion of tumor sera possess neutralizing activity for herpes simplex virus infectivity.

Immunofluorescence studies indicate that the transformed cells express antigens which are probably induced early in herpes simplex virus type 2-productive infection.

INTRODUCTION

It is well established that herpesviruses are capable of cell transformation and tumor induction. The first transformation by HSV was described by Munyon et al. (17) (mouse L-cells) and by Duff and Rapp (5) (hamster embryo cells), using virus inactivated by UV irradiation. Subsequent studies using temperature-sensitive mutants (12–14), photodynamically inactivated virus (11) sheared DNA (21), and specific HSV restriction fragments (3) have extended these results to confirm both the transforming and tumor potential of HSV. The continuing expression of HSV information in these cells has been monitored in several cases by immunofluorescence.

Collard et al. (4) detected 10 to 13% of the HSV-2 sequences transcribed during lytic infection to be present in transformed cells, while Frenkel et al. (6) described the presence of between 8 and 32% of the HSV genome in 1 to 3 copies in the same cells.

Macnab and Timbury (15) have shown, using complementation of HSV-2 ts mutants, that a HSV-2-transformed cell line (RE1) must express several viral functions, but no evidence was obtained on their identity.

This paper investigates the presence and location of viral antigens in transformed cells and in tumors by screening for virus-specific enzyme activities, for virus-neutralizing antigens, and for polypeptides synthesized early in lytic virus infection.

MATERIALS AND METHODS

Viruses. HSV-1 strain 17 syn* (1), HSV-2 strain HG52 (19), and pseudorabies virus strain Kaplan (18) were grown and titrated in BHK 21/C13 cells.

Cells. The cells used in this study were the continuous cell line BHK 21/C13 of BHK fibroblasts (16); rat embryo primary cells prepared from approximately 17-day-old embryos from highly inbred colonies of Lister hooded rats and continuous lines cultured from these primaries [Hood cells (14)]; and a transformed rat embryo cell line [RE1 cell line (12–14)], obtained by infection of rat embryo cells with HG52, ts 1 (7, 19) at the nonpermissive temperature.

Media. The Eagle's growth medium (2) used was ETC0. Streptomycin (100 µg/ml), penicillin (100 units/ml), and the antimycotic agent n-butyl p-hydroxybenzoate (0.2 µg/ml) were added to the Eagle's growth medium.

Chemicals. Unless otherwise stated, all chemicals were purchased from Sigma, London, England.

Antisera. Anti-HSV-2 antiserum (4741/L), derived from a rabbit immunized with an extract of rabbit kidney (RK 13) cells infected at nonpenmissive temperature with HSV-2 ts 1 (8), was obtained from Dr. M. C. Timbury of this Institute and fractionated as described below.

Anti-HSV-1 antiserum, derived from mice immunized with a cell extract of HSV-1-infected BHK cells, was prepared by Dr. A. Cross of this Institute. This antiserum was shown by immunoprecipitation to consist of antibodies to HSV-specific and -induced polypeptides. The antiserum reacted with HSV-infected BHK cells but not with mock-infected cells.

"Tumor antisera" were sera of rats bearing tumors (12–14) found after s.c. injection of RE1 cells, and normal rat sera were sera of uninoculated control rats from the same inbred colony. One of the tumor antisera and the normal rat sera were dialyzed at 4°C for 24 hr against 3 changes of 10 µl phosphate buffer, pH 6.8.

Mouse anti-Hood antiserum was obtained from mice immunized with an extract of Hood cells and supplied by Dr. A. Cross.

Antiserum against early HSV-2 polypeptides (9) was prepared by infecting primary or secondary Lister hooded rat embryo cells with HSV-2 (10 to 20 PFU/cell) in the presence of cycloheximide (50 µg/ml). After 7 hr, the cycloheximide was removed, the cells were washed 3 times, and incubation was continued for a further 3 hr. Antigens (both HSV induced and

1 To whom requests for reprints should be addressed.
2 On leave from the Agricultural University, Wageningen, The Netherlands.
3 Deceased.
4 Present address: Department of Microbiology, Uniformed Services University School of Medicine, Bethesda, Md. 20034.
5 The abbreviations used are: HSV, herpes simplex virus; HSV-2, herpes simplex virus type 2; HSV-1, herpes simplex virus type 1; BHK, baby hamster kidney; ETC0, Eagle's medium (Gloucester modification) supplemented (v/v) by 10% calf serum and 10% tryptose phosphate broth; PFU, plaque-forming units; i.d., intradermally; RT, rat tumor.

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HSV specific) present in such preparations typically consist of "immediate early" and "early" HSV-2 polypeptides with very small quantities of "late" material. The infected cells were harvested, disrupted, mixed with Freund's complete adjuvant (Difco Laboratories, Detroit, Mich.), and injected (half i.d. and half i.m.) into Lister hooded rats. After 3 identical boosts at 10-day intervals, the animals were bled out 10 days later. Goat anti-rat fluorescent conjugate was obtained from Nordic Laboratories, Maidenhead, United Kingdom.

Fractionation of Antiserum. One volume of saturated ammonium sulfate was slowly added to 1 volume of antiserum and stirred at 4°C. When this solution had been stirred for another 15 min, it was centrifuged at 25,000 rpm (Spinco A1 40 rotor) for 10 min. The pellet was then resuspended in one-fifth of the original antiserum volume; the resuspended pellet was dialyzed for 24 hr against 2 changes of 10 mM phosphate buffer, pH 7.5, containing 5 mM 2-mercaptoethanol and 5 mM thiourea (0.2 ml/dish). The cells were then resuspended in 10 mM Tris-HCl, pH 7.5, containing 5 mM β-mercaptoethanol and 5 μM thymidine (0.2 ml/dish) and disrupted by ultrasonic vibrations for 10 sec with the Dawe probe sonicator or for 4 × 30 sec with the Cole Parmer bath sonicator. The resulting sonicate was centrifuged at 1500 × g for 5 min at 1000 rpm, and the supernatant fraction was used in enzyme assays.

Preparation of Herpes-infected Cell Extracts. Cells were seeded at 8 × 10⁶ cells/90-mm dish and incubated overnight. Before confluence (i.e., 2 × 10⁶ cells/dish) was reached, the cells were infected at a multiplicity of infection of 10 PFU/cell in 0.2 ml ETC₁₀. The virus was allowed to absorb for 1 hr; then 10 ml ETC₁₀ were added, and incubation was continued. Cells used for thymidine kinase assays were scraped off into the medium 6 hr after infection, and incubation was continued. Cells used for thymidine kinase assay were incubated for 1 hr against 2 changes of 10 mM phosphate buffer, pH 6.8, and then centrifuged at 1500 × g for 10 min. The supernatant fraction was used in enzyme assays.

Preparation of Mock-infected Cell Extracts. Mock-infected cell extracts without virus were essentially prepared as described above. Cells were harvested before they reached confluence and were resuspended in 0.2 ml/90-mm dish.

Enzyme Assay. Thymidine kinase assay was assayed essentially by the method of Jamieson et al. (10). The assay contained, in a final volume of 100 μl, 20 μM [³H]thymidine (15 to 30 μCi/μmol; The Radiochemical Centre, Amersham, England); 10 μM thymidine; 10 mM ATP; 10 mM MgCl₂; 0.2 mM potassium phosphate buffer, pH 6; 15 μM enzyme fraction; and varying volumes of antiserum (0 to 35 μl). The difference in volume was compensated by 10 mM phosphate buffer, pH 6.8. Enzyme fraction and antiserum were preincubated for 20 min at room temperature (20°C). After addition to the reagents, tubes were shaken and incubated at 37°C for 15 min. The reaction was stopped by immersing the mixture in a boiling water bath for 2 min. Distilled water (100 μl) was added to each tube, and the mixture was centrifuged for 15 min at 1500 rpm. Fifty μl of the supernatants were spotted in duplicate onto Whatman DE81 or SB2 paper squares, which were washed once in 4 mM ammonium formate and 10 μM thymidine at 37°C for 7 min, once in 4 mM ammonium formate at 37°C for 7 min, and once in distilled water at room temperature for 5 min. The discs were dried and counted in a scintillation counter using 0.5% (w/v) PPO in toluene.

Immunofluorescence. This was carried out essentially by the indirect method of Mac nab (12) using fixed and unfixed cell preparations.

Virus Neutralization Tests. These were performed as follows. Stock virus was diluted to give approximately 1.5 × 10⁵ PFU/ml, and an equal volume of antiserum was added. The mixture was shaken gently for 30 min at 37°C, and 4 × 10⁶ BHK cells were added to 0.2 ml of the mixture. After 45 min of further shaking at 37°C to allow absorption, the cells were plated on 50-mm Petri plates, and the resulting monolayer was incubated for 2 to 3 days at 37°C and scored for plaque formation.

RESULTS

Inhibitory Activity of Tumor Antisera on Virus-induced Thymidine Kinase Activity. Tumor antisera from tumor-bearing animals were tested for ability to inhibit specifically HSV-2 thymidine kinase activity, as expressed in HSV-2-infected BHK cells. As a control, the thymidine kinase activity detected in the extracts of these infected cells was tested with anti-HSV-2 antiserum and compared with the effect on extracts of HSV-1-infected and mock-infected cells. Dose-response curves showed that, after prior incubation with 35 μl antiserum, the activity of HSV-2-infected cell extracts was only 25% of the activity of infected extracts which were not treated with HSV antiserum (Table 1). However, HSV-1-infected and mock-infected cell extracts showed 75 and 140% thymidine kinase activity, respectively, when incubated in the presence of 35 μl anti-HSV-2 antiserum. Extracts not incubated with antiserum were defined as containing 100% activity (Table 1). A tumor antiserum, RT10, tested in the same experiment as the anti-HSV-2 antiserum showed a smaller but significant inhibition of thymidine kinase activity of HSV-2-infected cell extracts. Mock-infected cell extracts showed 75 and 140% thymidine kinase activity, respectively, when incubated in the presence of 35 μl anti-HSV-2 antiserum.

Table 1

<table>
<thead>
<tr>
<th>Sera (tumor marker)</th>
<th>HSV-2</th>
<th>HSV-1</th>
<th>Mock-infected cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2 antiserum with anti-thymidine kinase activity</td>
<td>25</td>
<td>75</td>
<td>140²</td>
</tr>
<tr>
<td>Tumor A² (RT8)</td>
<td>65</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Tumor D² (RT6)</td>
<td>62</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Tumor H² (RT10)</td>
<td>39</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Tumor J² (RT16)</td>
<td>65</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Tumor K² (RT15)</td>
<td>62</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Tumor B² (RT14)</td>
<td>96</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Tumor C² (RT12)</td>
<td>98</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Tumor E² (RT8)</td>
<td>98</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Tumor F² (RT11)</td>
<td>99</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Tumor G² (RT13)</td>
<td>99</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Tumor F (RT17)</td>
<td>99</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Rat embryo control sera</td>
<td>110⁴</td>
<td>110⁴</td>
<td></td>
</tr>
</tbody>
</table>

² Normal rat serum and mock-infected cells cause a nonspecific stimulation of activity on incubation resulting in figures above 100%. Extracts not incubated with antiserum were defined as 100% for the purposes of thymidine kinase calculations.

Mark products (RT10)

This antiserum was from a rat bearing a tumor induced by REHSV-2-333 cells (13, 14). Antiseras A, B, C, D, E, F, H, I, J, and K were from rats bearing tumors induced by RE1 cells.

Table 2

<table>
<thead>
<tr>
<th>% of residual thymidine kinase activity after incubation with HSV-2- and HSV-1-infected cell extracts</th>
</tr>
</thead>
</table>

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HSV-2-specific thymidine kinase activity and no detectable inhibition of HSV-1-coded thymidine kinase activity. In a further experiment, in which 8 µl of HSV-2- or HSV-1-infected cell extract were assayed in the presence of 42 µl of this tumor antiserum, RT10, the inhibition of the HSV-2-infected cell extract was 61% as opposed to only 8% for the HSV-1-infected cell extract (Table 1). Additional experiments reproduced essentially the same effects. Of 10 additional tumor antisera tested against HSV-2- and HSV-1-infected cell extracts, 4 [RT5, RT6, RT15, RT16 (Chart 1; Table 1)] gave a substantial specific inhibition of the activity of HSV-2-infected cell extracts but not of the HSV-1-infected cell extract (Chart 1; Tables 1 and 2); the remainder were all negative. All the tumor antisera which showed specific inhibition were obtained from nonimmunosuppressed animals (13, 14); similar antisera from immunosuppressed animals were all negative (Table 4). The types of immunosuppression used were described in detail by Macnab (14). Briefly, animals were divided into 3 classes. In Class 1, immunosuppression consisted of thymectomy combined with X-irradiation and further suppression with antilymphocytic serum or antithymocytic serum; Class 2 animals were immunosuppressed only by treatment with either antilymphocytic serum or antithymocytic serum; and Class 3 animals were given injections between birth and 48 hr of age. Tumor formation in Class 1 was observed in the region of 12 weeks after injection of transformed cells, in Class 2 a latent period of approximately 40 weeks elapsed before tumor formation, and in Class 3 a latent period of up to 2 years could elapse between injection of transformed cells and subsequent tumor formation. Tumors arose at the site of injection and contained HSV antigens as detected by immunofluorescence studies. To exclude the possibility that sera of the highly inbred colony of rats contain a factor which inhibits HSV thymidine kinase activity specifically (and which is not induced by injection of RE1 cells and tumor formation), 2 sera of different healthy control rats were tested. The normal rat sera did not show any inhibition of HSV-2- or HSV-1-specific thymidine kinase activity. The dose-response curve for one of these 2 sera is shown in Chart 1B and Table 1.

Because of the small amounts of tumor antiserum available, preparation of immunoglobulins from the sera could not be attempted. However, after dialysis against 10 mM phosphate buffer, pH 6.8, of one of the tumor antisera and the 2 normal sera, no change from the previously obtained dose-response curves (Chart 1) was detected. This further reduces the possibility that dialyzable, highly specific nonimmunoglobulin molecules were responsible for the inhibition patterns observed.

**Thymidine Kinase Activity in a Transformed Cell Line and in Primary Rat Tumors.** Extracts were made from 4 primary tumors and from the RE1 cell line, grown in the presence and absence of 5 µM thymidine as a potential enzyme inducer. In these assays, use was made of an antiserum with activity specifically against both HSV-1 and HSV-2 thymidine kinase. This had been prepared using HSV-1-infected cell extracts. Both preparations of RE1 cells and 2 of the 4 tumor extracts (RT6 and RT10) clearly contained thymidine kinase activity inhibited by the virus-specific antiserum (Chart 2; Table 2). As controls, uninfected normal rat cell thymidine kinase (Hood cells) and pseudorabies virus thymidine kinase were tested and were not affected by the HSV antiserum. In addition, a mouse anti-normal rat cell antiserum failed to inhibit the RE1 cell thymidine kinase activity (data not shown). Addition of thymidine to cell lines had no apparent inducing effect. Two other HSV-2-transformed rat lines (RE7 and REHSV-2-333) tested in similar experiments did not contain HSV thymidine kinase activity (data not shown).

**Virus-neutralizing Activity in Sera from Tumor-bearing Rats.** The sera from rats bearing tumors induced by RE1 cells and described in Chart 1 and Table 1 were tested for ability to neutralize HSV-2 infectivity. As controls, normal rat sera and pseudorabies virus were used, and HSV-1 neutralization was examined to determine the type specificity of any activity demonstrated. Serum G from a tumor induced by the REHSV-2-333-transformed cell line which lacked HSV thymidine kinase activity was included as an additional control. Virus and serum were mixed and tested by plaque assay as described in "Materials and Methods." Table 3 and Fig. 1 show the results of the experiment. Four sera (Sera B, D, F, and G) contained no neutralizing activity, nor did normal rat serum, while 2 sera (Sera D and I) gave a slight response and 2 sera (Sera C and H) showed a clear inhibition of infectivity. There was considerable cross-reaction with HSV-1 but no cross-reaction with pseudorabies virus. Thus, tumors are capable of expressing viral neutralizing antigens, but only a proportion do so.

**Early Virus-induced Antigens in Transformed Cells.** Antiserum was raised in rats against proteins induced by HSV-2.
cence, almost 100% of the cells showed punctate fluorescence examined at passages 3 to 20. By indirect immunofluorescence, transformed and tumor cell lines whether or not they had HSV-transformed and tumor cell lines as detected by the antiserum against early antigens. Almost 100% of the cells fluoresced.

DISCUSSION

These results indicate that a HSV-2 ts 1-transformed line of rat cells, RE1, expresses HSV-2-specific thymidine kinase activity, virus infectivity-neutralizing antigens, and at least some of the early proteins induced in productive HSV-2 infection. In addition, tumors induced by injection of these cells into rats continue to express, to a variable extent, virus-specific thymidine kinase and neutralizing antigens. Our attempts to date to detect viral thymidine kinase activity in tumor cell lines derived from the HSV-2-induced primary rat tumors have not been successful.

The level of thymidine kinase activity in transformed cells is much lower than that found in productively infected cells; in tumors, there is even less (Table 2). In addition, the ability of the transformed cell line RE1 to express viral thymidine kinase is variable; on occasion, particularly when the cells have grown to high density, little or no virus-specific activity can be demonstrated, and this may suggest that expression of the viral enzyme is enhanced in growing cells. The production of thymidine kinase by tumor cells correlates with the appearance of virus-specific activity in the serum of a tumor-bearing animal. The presence of antibody against the virus thymidine kinase (normally an "internal" nonstructural polypeptide of the in-

Table 2

Residual thymidine kinase activity of transformed cells and tumor extracts after incubation with HSV-specific anti-thymidine kinase antiserum

<table>
<thead>
<tr>
<th>Serum</th>
<th>HSV-2 strain HG52</th>
<th>HSV-1 strain 17</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
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<tr>
<td>D</td>
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<td>E</td>
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<tr>
<td>F</td>
<td>0</td>
<td>0</td>
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<tr>
<td>G</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H</td>
<td>92</td>
<td>81</td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>J</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>K</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*No neutralizing activity against pseudorabies virus was present in any serum.
* Sera were diluted to half-strength.

early in the infectious cycle (9). Immunofluorescence studies were carried out on cells from tumors grown as cell lines and examined at passages 3 to 20. By indirect immunofluorescence, almost 100% of the cells showed punctate fluorescence within the cytoplasm and, to a more intense degree, in the perinuclear area; not all cells, however, showed an equal intensity of fluorescence. This antiserum in other experiments detected principally antigen in the nuclei of cells infected under the same conditions as those used to prepare antigen for inoculation. HSV-specific antigens were detected in all of the transformed and tumor cell lines whether or not they had HSV thymidine kinase activity or viral neutralizing antigen. Fig. 2 shows the typical perinuclear and cytoplasmic fluorescence seen with the RT10 tumor cell line and is typical of all HSV-transformed and tumor cell lines as detected by the antiserum against early antigens. Almost 100% of the cells fluoresced.

The rabbit antiserum 4741/L gave cytoplasmic and perinuclear fluorescence with almost 100% of the HSV-transformed and tumor cell lines. This antiserum was prepared against cells infected with HSV-2 strain HG52 ts 1 at nonpermissive temperature. The mutant ts 1 expresses a greater than wild-type amount of DNA polymerase (B), and it does not switch off the immediate early polypeptides.7

7 J. C. M. Macnab, unpublished results.
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Fig. 1. Neutralizing activity of several rat tumor antisera with HSV-2 (HG52). Left to right: top, virus control HG52, Serum I (RT1T); Serum C (RT12). bottom, a tumor serum control with no virus, Serum D (RT5), Serum H (RT10). Serum C inhibited both plaque number and plaque size.

Fig. 2. HSV-specific fluorescence as detected in a rat tumor cell line, RT10, by HSV-2 antiserum raised in inbred Lister hooded rats against early proteins expressed 0 to 3 hr after release of HSV-2-infected rat embryo cells from a cycloheximide block. The tumor, which is transplantable, was formed by injection of RE1-transformed cells into a newborn rat. Fluorescence which is both cytoplasmic and perinuclear is seen in almost all cells. This fluorescence is typical of all HSV-transformed and tumor cell lines.

It might be conceivable that some other antigen, e.g., cellular thymidine kinase, induced in tumor formation or HSV infection, could cross-react, but the specificity of the sera tested here makes that unlikely. In addition, serum from a rat bearing a tumor to REHSV-2-333 cells which were thymidine kinase negative did not have anti-thymidine kinase activity.

Herpes-neutralizing activity appears to reside in antibody to a small number of virus structural polypeptides (20) and would appear to be distinct from thymidine kinase activity. Only one of the strongly positive neutralizing sera contained anti-thymidine kinase activity; thus, we detect no clear correlation between the expression of these antigens or between neutralizing activity and immunosuppression.

The population of early antigens probably includes little thymidine kinase activity or virus-neutralizing activity and thus constitutes a third class of virus expression in transformed cells. This group of virus proteins is likely to include molecules used by the virus both to regulate at least part of its own protein.
synthesis (9) and to control host cell function. In other host-virus systems, plausible models for viral transformation have been proposed which involve the function of such virus-induced controlling polypeptides. It is less straightforward to propose a role in transformation for neutralizing antigens or indeed for thymidine kinase activity at both permissive and nonpermissive temperatures, indicating that thymidine kinase activity is not essential for the initiation of morphological transformation. Of course, both the thymidine kinase and neutralizing antigen genes may be connected, physically or operationally, to the HSV transforming gene(s). Transformed and tumor cell lines which do not express HSV-specific thymidine kinase activity do express HSV antigens detectable by immunofluorescence and are also tumorigenic. Thus, the expression of HSV thymidine kinase is not essential for maintenance of the transformed state. Since only one HSV-transformed cell line (RE1) expressed HSV-specific thymidine kinase activity, it is possible that the thymidine kinase function continued to be expressed as a result of the specific mutation involved in ts 1 which must have pleiotropic effects on the expression of polymerase and immediate-early antigens accounting for their continuing expression at nonpermissive temperature.

These studies show the continuing expression of HSV genetic information in a HSV-2-transformed rat line RE1 and in 2 of 4 tumors derived after injection of RE1 cells. Although expression of virus-neutralizing activity and thymidine kinase activity is variable from one tumor-bearing animal to another, there is a correlation between the expression of HSV thymidine kinase activity and the immunocompetence of the rat in this small sample of 11 rats tested (Table 4).


correlation between the expression of HSV thymidine kinase activity and the immunocompetence of the rat in this small sample of 11 rats tested (Table 4).

ACKNOWLEDGMENTS

We thank Professor Subak-Sharpe for his interest in this work and for his enthusiastic support. We thank Dr. A. Cross and Dr. M. C. Timbury for kindly supplying antiserum.

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