Measles Virus Infection of B Lymphocytes Permits Cellular Activation but Blocks Progression through the Cell Cycle†

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Received 5 May 1987/Accepted 5 August 1987

Measles virus infection of unstimulated B lymphocytes suppresses both proliferation and differentiation into immunoglobulin-secreting cells. However, mitogenic stimulation of these infected cells results in cell volume enlargement, rapid RNA synthesis, and the expression of cell surface activation antigens 4F2, HLA-DS, and transferrin receptor. The cellular genes c-myc and histone 2B are induced during early G1 and S phase of the cell cycle, respectively, and viral RNA synthesis can be detected during this interval. However, total RNA synthesis is decreased at 48 h after stimulation, and the histone 2B RNA steady-state level at 48 h is fivefold less than that in uninfected cells. This sequence of events defines an arrest in the G1 phase of the cell cycle in measles virus-infected B cells.

Virus-induced immunosuppression is currently a topic of substantial biomedical interest. A number of viruses have been demonstrated to infect lymphocytes, alter their functions, and establish persistent infection (for a review, see reference 17). However, the mechanisms by which viruses disrupt immune-mediated host defenses and cause disease remain elusive. It is evident that these mechanisms are in part a consequence of the replication strategy of the virus in a particular host cell. For example, measles virus is lymphotropic, yet it cannot replicate in lymphocytes unless they are stimulated by a mitogen (11, 26). One consequence of this restriction is that viral RNA persists in unstimulated lymphocytes (11). Subsequent mitogenic stimulation of infected lymphocytes results in efficient viral replication but suppression of lymphocyte proliferation and differentiation (2). Infected lymphocytes are not lysed during productive infection. In pokeweed mitogen-stimulated cultures, the suppression of immunoglobulin secretion by measles virus is due to infection of B lymphocytes, not T lymphocytes, monocytes, or natural killer cells (16). Infection of T lymphocytes and monocytes does not decrease the secretion of B-cell growth and differentiation factors or cause the production of suppressive factors. Infected B lymphocytes do not proliferate or secrete immunoglobulins.

After stimulation by a mitogen, B lymphocytes undergo a process of activation, proliferation, and differentiation in response to growth and differentiation factors (for a review, see reference 12). Cellular activation and progression through G1 can be observed by increases in cell volume, RNA synthesis, and expression of cell surface activation antigens. The present experiments address the question of when in the B-cell cycle measles virus acts to block immunoglobulin secretion, during activation and progression through G1 or later during the stages of proliferation and differentiation.

† Publication no. 4729-IMM from the Department of Immunology, Research Institute of Scripps Clinic, La Jolla, CA 92037.

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MATERIALS AND METHODS

Reagents. Staphylococcus aureus Cowan 1 was a suspension of Formalin-fixed S. aureus cells (Bethesda Research Laboratories, Inc., Gaithersburg, Md.). Anti-mu antibody was the F(ab')2 fragment of goat anti-human heavy chain-specific immunoglobulin M (IgM) (Tago, Inc., Burlingame, Calif.). B-cell growth factor (BCGF), with lectin removed and free of interleukin-2 (IL-2) and interferon activity, was purchased from Cellular Products, Inc. (Buffalo, N.Y.). 12-O-Tetradecanoylphorbol-13-acetate (TPA) (Sigma Chemical Co., St. Louis, Mo.) was dissolved at 1 mg/ml in 95% ethanol and diluted in culture medium before use. The Ca2+ ionophore A23187 (Boehringer Mannheim Biochemicals, Indianapolis, Ind.) was dissolved in dimethyl sulfoxide at 5 mg/ml and diluted in culture medium before use. Recombinant IL-2 (lot no. LP210) was obtained from Cetus Corp. (Emeryville, Calif.). Actinomycin D (Calbiochem-Behring Diagnostics, La Jolla, Calif.) was dissolved at 1 mg/ml in water. Mouse monoclonal antibody anti-4F2 was prepared as described previously (10). The monoclonal antibodies, anti-HLA-DS (Leu-10) and anti-transferrin receptor, were purchased from Becton Dickinson Monoclonal Center, Inc. (Mountain View, Calif.). The fluorescein conjugate of a goat F(ab')2 anti-mouse IgG (Tago, Inc.) was used as the second antibody. Plasmids containing cDNA clones of the measles virus nucleoprotein gene (cloned in pBR322; donated by Robert Fujinami, Department of Pathology, University of California, San Diego) (9), human c-myc (pHSR-1; American Type Culture Collection, Rockville, Md.), and histone 2B (cloned in pSp62; donated by Jay Nelson, Department of Immunology, Research Institute of Scripps Clinic) (28) were prepared by standard methods. The full-length inserts of the measles virus nucleoprotein and the histone 2B clones and the EcoRI-ClaI fragment of the c-myc clone were used as templates to prepare 32P-labeled cDNA probes of high specific activity by a method of primer extension with mixed-sequence hexadeoxynucleotides (Pharmacia, Inc., Piscataway, N.J.) (7).
Cell preparations. Human tonsils were obtained surgically from patients with chronic tonsillitis, and single-cell suspensions were prepared as described previously (29). T-lymphocyte depletion was accomplished by two cycles of rosetting with 2-aminoethylisothiouronium bromide-treated sheep erythrocytes (6). Tonsil B lymphocytes were size fractionated by counterflow centrifugal elutriation (Beckman model J-6B; Beckman Instruments, Palo Alto, Calif.) as previously described (20) or by density centrifugation on discontinuous gradients of Percoll (Pharmacia, Uppsala, Sweden) (5). For the elutriation method, cell fractions with a mean cell volume of between 150 and 175 μm³ were pooled as small B cells. For the method of cell density separation with Percoll, gradients of 20, 45, 50, 55, and 60% were made, and cells at the 50 to 55% and 55 to 60% interfaces were pooled as small B cells. With either method, the small B cell population was >95% viable, and there was minimal spontaneous proliferation as determined by [3H]thymidine uptake at 72 h of culture (1,000 cpm).

Measles virus infection of B lymphocytes. The Edmonston strain of measles virus (American Type Culture Collection) passed and plaque on Vero cells was used to infect lymphocytes at a multiplicity of infection of 3, as previously described (10). Virus stocks were titrated and mycoplasma tested as by Hoechst 33258 stain (Serva Feinbiochemica, Heidelberg, Federal Republic of Germany) (3). Measles virus antigens were detected in infected cells by direct immunofluorescence using a rhodamine-conjugated IgG preparation from the serum of a patient with subacute sclerosing panencephalitis (2).

Culture conditions and assays for RNA and DNA synthesis. For all experiments, cells were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (Dutchland Laboratories, Inc., Denver, Colo.; or HyClone, Logan, Utah), 2 mM glutamine (Flow Laboratories, Inc., McLean, Va.), gentamicin (50 μg/ml), or penicillin (50 U/ml) and streptomycin (50 μg/ml). Cells (10⁴) were cultured in 0.2 ml of medium in 96-well flat-bottom plates (Costar, Cambridge, Mass.) at 37°C in 5% CO₂. The final concentrations of mitogens used for all experiments were: S. aureus Cowan 1, 2% (vol/vol) of a stock suspension in RPMI 1640; anti-mu, 25 μg/ml; BCGF, 10%; TPA, 1 or 30 ng/ml; and the Ca²⁺ ionophore (A23187), 125 ng/ml. Preliminary titrations established that 1 ng of TPA per ml plus 125 ng of Ca²⁺ ionophore per ml were synergistically mitogenic for small B lymphocytes. When indicated, a supernatant of phytohemagglutinin-stimulated T-lymphocyte cultures, called PHA supernatant, was used at 25% (vol/vol). To measure RNA synthesis, cultures were pulsed with [3H]uridine (38.9 Ci/mM; New England Nuclear Corp., Boston, Mass.) with 1 μCi per well for 8 h before harvest on fiberglass filters. Cellular RNA synthesis was suppressed by greater than 95% with actinomycin D (5 μg/ml) for a 1- or 2-h pulse before addition of [3H]uridine for some experiments. DNA synthesis was measured by [3H]thymidine uptake (6.7 Ci/mM; New England Nuclear Corp.) by using 1 μCi per well for 18 h before harvest on fiberglass filters. The filters were processed on a multichannel automated cell harvester (Skatron; Flow Laboratories) and counted in a liquid scintillation beta counter (Searle Analytic, Des Plaines, Ill.).

Cellular volume analysis. The size distribution of B lymphocytes was determined using a bead-calibrated Coulter Channelizer, model H4 (Coulter Electronics, Inc., Hialeah, Fla.). The cells were suspended in lysis buffer (20 mM K₂HPO₄, 0.15 M NaCl, 0.1% sodium dodecyl sulfate) and analyzed with the following settings: amplification, 1; aperture, 100; current, 1; lower threshold, 10; upper threshold, 100. Data were analyzed by an on-line computer and x/y plotter.

Cellular RNA hybridization. Total cellular RNA was extracted from lymphocytes by the method of Chirgwin et al. (4), followed by centrifugation through a 5.7 M cesium chloride cushion (8). RNA was quantitated by ethidium bromide staining of ribosomal 28 and 18S bands on 1% agarose nondenaturing gels, and the RNA content of all samples was adjusted to 5 μg. RNA blotting onto nitrocellulose filters and hybridization with cDNA probes were performed by a standard procedure (18). Briefly, RNA samples were denatured in 6× SSC (1× SSC is 0.15 M sodium chloride and 0.015 M sodium citrate, pH 7.0) and 7.4% formaldehyde at 65°C for 15 min. Serial fivefold dilutions of samples were applied to nitrocellulose filters ( pore size, 0.45 μm) (BA85-SB; Schleicher & Schuell, Inc., Keene, N.H.) using a slot blot apparatus (Minifold II, Schleicher & Schuell). Filters were dried in a vacuum oven at 80°C for 2 h. Filters were prehybridized in sealed bags at 42°C for 6 h in a solution of 50% deionized formamide, 5× SSC, and 2.5× Denhardt (20× Denhardt is 0.4% bovine serum albumin, 0.4% Ficoll, 0.4% polyvinylpyrrolidone). Boiled, sonicated salmon sperm DNA was added to a concentration of 0.1 μg/ml. Blots were hybridized for 18 h at 42°C with 2 × 10⁶ cpm of 32P-labeled probe. After hybridization, filters were washed three times in 2× SSC-0.1% sodium dodecyl sulfate at 37°C for 5 min and then twice in 0.1× SSC-0.1% sodium dodecyl sulfate at 50°C for 15 min. Washed filters were exposed against Kodak XAR-5 film with an intensifying screen (Cronex Lightning-Fast; E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.) at −70°C for indicated periods of time. To remove bound probe from filters for subsequent rehybridization, filters were washed twice in boiling 0.1× SSC-0.1% sodium dodecyl sulfate for 15 min and then exposed to film for 18 h or longer to confirm removal of 32P label.

Immunofluorescence. Surface immunofluorescent staining of lymphocytes was performed by standard techniques as specified by the manufacturer of the monoclonal antibodies utilized. Immunofluorescence was quantitated on a fluorescence-activated cell sorter (FACS IV; Becton Dickinson Immunocytometry Systems, Mountain View, Calif.) as previously described (16). Lymphocytes were gated by forward and side light scatter with wide margins to include both large and infected cells in the stimulated populations.

Measurement of secreted immunoglobulins. Supernatants of B-cell cultures were harvested and stored at 0°C. Total IgG and IgM were quantitated by an enzyme-linked immunosorbent assay as previously described (15).

RESULTS

B-cell activation. (i) Increase in cell volume. When tonsil B lymphocytes were infected in vitro with measles virus, mean cell volume did not increase at 12, 24, or 48 h after infection, suggesting that infection did not directly activate these cells. However, infection followed by stimulation of the cells with S. aureus Cowan 1 or TPA plus Ca²⁺ ionophore resulted in a significant increase in cell volume (Table 1 and Fig. 1). Infected cells responded as well as uninfected cells did to the mitogens; that is, mean cell volumes and kinetics of the response were similar in both groups of cells. The increase in cell volume with stimulation was detected in un fractionated tonsil B lymphocytes but was clearer when small B cells had been fractionated by elutriation or on Percoll gradients (Fig. 1). As documented previously (12), this event coincides with entry of cells into G₁ of the cell cycle.
TABLE 1. Increase in cell volume after measles virus infection and stimulation of B lymphocytes

<table>
<thead>
<tr>
<th>Cells</th>
<th>S. aureus Cowan 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cell volume * (µm) poststimulation</td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Uninfected</td>
<td>-</td>
<td>210 ± 15</td>
<td>188 ± 38</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>275 ± 17</td>
<td>324 ± 58</td>
</tr>
<tr>
<td>Infected</td>
<td>-</td>
<td>216 ± 9</td>
<td>187 ± 33</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>284 ± 33</td>
<td>308 ± 43</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation of four experiments.

(ii) New RNA synthesis. Small tonsil B lymphocytes stimulated with S. aureus Cowan 1 were tested for RNA synthesis by [3H]uridine uptake at 24 and 48 h of culture. Uninfected B cells responded to stimulation with increased RNA synthesis at 24 and 48 h (Fig. 2). RNA synthesis by stimulated infected B cells also increased but not significantly more than that by the uninfected cells at 24 h. At 48 h after stimulation, there was a 20 to 50% decrease in RNA synthesis by infected compared with uninfected cells. The amount of RNA synthesis in stimulated infected cells that could be attributed to viral replication was not detectable using this assay. Measles virus RNA synthesis is relatively resistant to actinomycin D (1, 30). Stimulated infected cells pulsed with 5 µg of actinomycin D per ml before the [3H]uridine pulse took up no more 3H than the unstimulated control amount, i.e., there was no measurable uptake of actinomycin D-resistant [3H]uridine (Fig. 2).

In RNA blot hybridization experiments, the steady-state level of measles virus nucleoprotein RNA was compared with the levels of two cellular mRNAs induced at different times in the cell cycle. Transcription of the cellular gene c-myc is markedly elevated 1 h after mitogen stimulation of lymphocytes (14, 28), and then the steady-state level falls gradually through the cell cycle. The amount of histone 2B mRNAs, however, is greatly increased in S phase (23). Total cellular RNA was extracted from uninfected or measles virus-infected B lymphocytes at various times after stimulation with TPA plus Ca2+ ionophore. RNAs blotted onto nitrocellulose were hybridized sequentially with probes specific for histone 2B (autoradiograph exposure, 4 days), c-myc (exposure, 4 days), and measles virus nucleoprotein (exposure, 4 h). There were major increases in hybridization signal with infected-cell RNA for measles nucleoprotein, c-myc, and histone 2B at 48, 2, and 48 h, respectively (Fig. 3). Comparing infected- with uninfected-cell RNA, there was less hybridization for c-myc at 2 h but nearly equal hybridization at 48 h. The increase above base-line signal for histone 2B at 48 h was approximately fivefold less with infected-versus uninfected-cell RNA. Other minor differences in hybridization between uninfected- and infected-cell RNA, as well as the hybridization of uninfected-cell RNA at 48 h with measles nucleoprotein, were not reproducible in other experiments.

(iii) Cell surface antigen expression. The third parameter of B-cell activation we examined was the expression of the cell surface antigens 4F2, HLA-DS, and transferrin receptor. The first, 4F2, is a glycoprotein induced after stimulation of a wide variety of cells (10). Second, the major histocompatibility complex class 2 antigen HLA-DS, considered to be the human homolog of the murine IA antigen, is present on a majority of resting B lymphocytes, but the amount of antigen and the number of antigen-positive cells increase after stimulation (13). The third activation antigen, the

FIG. 1. Increase in cell volume 48 h after stimulation of uninfected or measles-infected small B lymphocytes. Cells were prepared by counterflow centrifugal elutriation and then infected and cultured as described in Materials and Methods. x/y plots of Coulter volume measurements are recorded. Unstimulated cells; ——, cells stimulated with S. aureus Cowan 1.

FIG. 2. Total RNA synthesis by small B lymphocytes 24 and 48 h after stimulation with S. aureus Cowan 1 (SAC) or S. aureus Cowan 1 followed by actinomycin D (ActD) added 2 h before the [3H]uridine pulse. Data are the means plus one standard deviation of triplicate cultures. ** Uninfected cells; ——, measles virus-infected cells. KCPM, 10^3 cpm.
transferrin receptor, is induced by mitogenic stimulation of cells, and its expression is required for B-lymphocyte proliferation (22). Mock- or measles virus-infected small B lymphocytes were stimulated with *S. aureus* Cowan 1 or TPA plus Ca**2+** ionophore, and surface immunofluorescence staining was done at 24, 48, and 72 h after stimulation. Fluorescence-activated cell sorter analysis of the cells, using unstimulated cells for controls, showed no block in expression of 4F2, HLA-DS, or transferrin receptor on measles-infected cells (Fig. 4). In these experiments, either the mean fluorescence intensity or the modal number of positive cells increased in the stimulated populations, indicating that the majority of cells in the test populations expressed the antigens after stimulation. There were fewer fluorescence-positive cells in the measles-infected populations stained for HLA-DS and transferrin receptor, compared with uninfected cells. 4F2 immunofluorescence was bright at 24 and 48 h after stimulation, and the number of cells positive for HLA-DS increased at 48 h. Optimal expression of transferrin receptor occurred 72 h after stimulation. These kinetics were alike in uninfected and infected cells.

**B-cell proliferation and differentiation: suppression by measles virus**. After small B lymphocytes were infected with measles virus and stimulated with the mitogens *S. aureus* Cowan 1 with and without BCGF, anti-mu with and without BCGF, and TPA with and without Ca**2+** ionophore, proliferation was measured by [3H]thymidine uptake at 72 h after stimulation. In three experiments, proliferation of measles-infected B lymphocytes was reduced by 90% or more compared with that of uninfected cells in response to all the mitogens tested (Fig. 5). However, UV-inactivated measles virus did not suppress the proliferative response (data not shown). In other experiments, B-lymphocyte cultures stimulated with *S. aureus* Cowan 1 for 48 h and then incubated in IL-2 or a PHA supernatant for 72 h were assayed for secretion of IgG and IgM by enzyme-linked immunosorbent assay (Table 2). There was no increase in IgG or IgM secretion by virus-infected B cells with any combination of stimuli.

**Measles virus replication in activated B lymphocytes**. Small B lymphocytes were infected with measles virus at a multiplicity of infection of 3 for 1 h. After a 6-h incubation at 37°C, the cells were stimulated with mitogen. Virus infection of cells was confirmed by immunofluorescence, and viral replication was measured by plaque assay. Of these infected small B lymphocytes, 90 to 95% expressed viral antigen by surface immunofluorescence and flow cytometric analysis at 48 or 72 h after stimulation (data not shown). At those times (Fig. 6), the amount of infectious virus produced in stimu-

![Image](http://jvi.asm.org/)
labeled, infected B-lymphocyte cultures exceeded that in unstimulated cultures by more than $10^5$ PFU/ml.

**DISCUSSION**

These experiments demonstrate the following. (i) Measles virus-infected B lymphocytes undergo the transition from G$_0$ to G$_1$ after mitogenic stimulation. (ii) Infected B lymphocytes do not proliferate or secrete immunoglobulin when stimulated by any of several B-cell mitogens. (iii) Measles virus replication occurs during G$_1$. This is the first report to our knowledge of the effect of a nontransforming virus on a lymphocyte during progression through the cell cycle. Previous reports have shown that measles virus suppresses lymphocyte proliferation (25) and the differentiation of B lymphocytes into immunoglobulin-secreting cells (16). The present experiments were undertaken to define the stage of the cell cycle at which infected B lymphocytes are arrested. After mitogenic stimulation of small resting B lymphocytes, measurable increases in cell volume, RNA synthesis, and cell surface antigen expression during the first 48 h characterize cellular activation and progression through G$_1$ (12). Measles virus infection of B lymphocytes does not itself produce these changes. However, as described here, both infected and uninfected B lymphocytes stimulated by various mitogens increase in cell volume with similar kinetics. Total RNA synthesis by infected, stimulated B lymphocytes is not suppressed at 24 h, but there is a consistent 20 to 50% reduction compared with uninfected cells at 48 h. The component of viral RNA synthesis at these times does not affect evaluation of total RNA synthesis measured by $[^3H]$uridine uptake, because there is no measurable actinomycin D-resistant RNA synthesis. However, we have not examined whether measles virus RNA synthesis in lymphocytes is resistant to actinomycin D, as was reported for viral replication in HeLa and Vero cells (1, 30). The RNA hybridization experiments demonstrate that measles virus RNA synthesis is increased in stimulated cells during the

**TABLE 2. Immunoglobulin secretion by mock- or measles virus-infected B lymphocytes**

<table>
<thead>
<tr>
<th>Medium</th>
<th>IgG concn (ng/ml)</th>
<th>IgM concn (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mock</td>
<td>Measles virus</td>
</tr>
<tr>
<td>Medium alone</td>
<td>157</td>
<td>128</td>
</tr>
<tr>
<td>Medium + IL-2</td>
<td>1,019</td>
<td>128</td>
</tr>
<tr>
<td>Medium + PHA supernatant</td>
<td>988</td>
<td>161</td>
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</table>

* Following stimulation with *S. aureus* Cowan 1 for 48 h, cultures were incubated with IL-2 (100 U/ml) or a PHA supernatant (25% [vol/vol]) for 3 days. Culture supernatants were tested for IgG and IgM by enzyme-linked immunosorbent assay. Data are means of quadruplicate cultures.

**FIG. 5.** Suppression of DNA synthesis in B lymphocytes infected with measles virus. Small B lymphocytes, uninfected (□□□□□) or virus infected (●●●●●●), were cultured with *S. aureus* Cowan I (SAC) with and without BCGF, anti-mu plus BCGF, or TPA with and without Ca$^{2+}$ ionophore. Cultures were pulsed with $[^3H]$thymidine for 18 h and harvested at 72 h. Data are mean counts per minute of triplicate cultures. KCPM, $10^3$ cpm.

**FIG. 6.** Measles virus replication in stimulated B lymphocytes. Triplicate cultures of infected B lymphocytes, with or without TPA plus Ca$^{2+}$ ionophore, were harvested at indicated times after stimulation. The amounts of infectious virus produced in culture were determined by plaque assay on Vero cell monolayers. For each time point on the x axis, the increase in virus from stimulated cultures compared with unstimulated cultures is recorded on the y axis.
interval of G1 to S phase, as defined by induction of c-myc (14) and histone 2B (23). Interestingly, one cellular RNA, c-myc, is not suppressed in infected cells at 48 h, while another cellular RNA, histone 2B, is. The expression of cell surface activation antigens, another measure of inducible cellular RNA and protein synthesis during G1, is not significantly altered by measles virus infection (Fig. 4). Neither mean fluorescence intensity nor time of expression decreases in infected cells compared with uninfected cells for 4F2, HL-DA-DS, and transferrin receptor, although the number of infected cells expressing HL-DA-DS and the transferrin receptor is slightly decreased relative to uninfected cells. An alternative explanation of these results is that measles virus infection does not block cell cycle progression, but that the infection suppresses proliferation and immunoglobulin secretion independently. However, if measles virus is added to pokeweed mitogen-stimulated cultures after day 3 of a 7-day culture, the suppression of immunoglobulin synthesis progressively decreases (2). Already differentiated functions of lymphocytes are not suppressed by the virus (for a review, see reference 17). With few exceptions, in vitro models of B-lymphocyte differentiation demonstrate an obligatory coupling of proliferation to immunoglobulin secretion. A variety of nonviral agents have been shown to arrest stimulated B lymphocytes in G0 of the cell cycle, including cyclosporin A (19), diterpine forskolin (21), and an antibody reactive with the B1 cell surface protein (22). Usually both proliferation and immunoglobulin secretion are suppressed. Reversible inhibition of B-cell proliferation with aphidicolin also blocks immunoglobulin secretion by murine B cells (24). Measles virus infection of T lymphocytes does not block mitogen-induced secretion of IL-2 or IL-2 receptor expression, but proliferation is suppressed (unpublished data). One might speculate that the cytopathic effect of measles virus in lymphocytes and the mechanism of immunosuppression during infection in vivo are reducible to a common mechanism resulting in cell cycle arrest in G0. The induction or suppression of cellular genes regulating cell proliferation during viral replication in activated lymphocytes is the subject of work in progress.

ACKNOWLEDGMENTS

This work was supported in part by Public Health Service grants AI-07007 and NS-12428 from the National Institutes of Health. M. B. McChesney has a postdoctoral fellowship from the Arthritis Foundation. We are grateful for the advice and assistance of Peter Southern, Lindsay Whitton, Jay Nelson, and Jasodhara Ray, Department of Immunology, Research Institute of Scripps Clinic, and we thank Gay L. Schilling for manuscript preparation.

LITERATURE CITED


