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Class I Major Histocompatibility Proteins as Cell Surface Receptors for Simian Virus 40

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Class I major histocompatibility complex proteins appear to be the major cell surface receptors for simian virus 40 (SV40), as implied by the following observations. Adsorption of SV40 to LLC-MK_2 rhesus monkey kidney cells specifically inhibited binding of a monoclonal antibody (MAb) against class I human lymphocyte antigen (HLA) proteins. Conversely, pretreatment of LLC-MK_2 cells with anti-HLA MAbs inhibited infection by SV40. The ability of anti-HLA to inhibit infection was greatly reduced when the order of addition of the anti-HLA and the virus was reversed. Infection was also inhibited by preincubating SV40 with purified soluble class I protein. Finally, human lymphoblastoid cells of the Daudi line, which do not express class I major histocompatibility complex proteins, were infected at relatively low levels with SV40 virions. In a control experiment, we found that pretreatment of cells with a MAb specific for the leukocytic-function-associated antigen LFA-3 actually enhanced infection. This finding may also support the premise that class I major histocompatibility complex proteins are receptors for SV40.

Virus infection begins with the attachment of the virus to a specific receptor on the surface of a susceptible cell. Although cellular receptors are important determinants of virus tropism and pathogenesis, the receptors of only a few viruses have been identified (7). In this report we present evidence which strongly implies that class I proteins encoded by the major histocompatibility complex (MHC) (human lymphocyte antigens [HLA] in humans) serve as specific cell surface receptors of simian virus 40 (SV40).

Our original purpose in this study was to measure the effect of SV40 infection on the expression of cellular class I MHC proteins. Our initial findings in this effort led us to consider the possibility that SV40 uses class I MHC proteins as specific cell surface receptors. In brief, we used radioimmunassay to monitor class I MHC antigens on the surfaces of SV40-infected LLC-MK_2 rhesus monkey kidney cells. (Note that the rhesus monkey is the natural host of SV40 and that infection of rhesus kidney cells results in a stable carrier system with little if any cytopathology [15, 16, 23]). Our ability to detect surface class I MHC antigens was decreased at 7 days postinfection. In contrast, we measured increasing amounts of SV40-specific T antigen at the cell surface. Passaging the cultures restored our ability to detect the MHC antigens. These results suggested that progency virions might be accumulating at the cell surface, perhaps bound to class I MHC proteins, thereby specifically blocking the binding of the anti-HLA monoclonal antibody (MAb). We confirmed that SV40 virions accumulate at the cell surface, as shown by radioimmunassay using a MAb (pAb 597) which recognizes the major virus capsid protein VP1 (data not shown). This is in agreement with our earlier finding that SV40 tends to remain cell associated in this system (15).

We next asked whether preadsorption of SV40 to LLC-MK_2 cells (in the cold to prevent internalization of the virus) might block binding of anti-HLA (BB7.7) to the cells. We began by measuring the binding of 10-fold serial dilutions of the anti-HLA to untreated cells. We then assayed the ability of undiluted SV40 (2×10^8 PFU/ml) to block the most dilute sample of the anti-HLA which saturated the untreated cells (Fig. 1). Our procedure was to suspend monolayer cultures in buffer (2% phosphate-buffered saline, 0.02% bovine serum albumin, Tween 20 [pH 7.4]) in borosilicate glass tubes (5×10^5 cells per tube) and incubate them at room temperature for 0.5 h. The tubes were then centrifuged, and the pellets were suspended in 100 μl of virus or buffer and incubated for 2 h at 4°C. The cells were then incubated with 100 μl of anti-HLA for 0.5 h at 4°C. The cells were next washed three times with buffer and incubated with 100 μl of ^{125}I-labeled goat anti-mouse immunoglobulin G for 0.5 h at 4°C. The tubes were then centrifuged, and the pellets were washed three times with phosphate-buffered saline. Bound counts per minute were measured in a gamma counter.

Under these conditions, SV40 inhibited binding of the anti-HLA by 62% (Fig. 1). To establish a control, we asked whether the same preadsorption of virus might block the binding of antibodies specific for other cell surface proteins. These proteins included leukocytic-function-associated antigen LFA-3, which is involved in T-cell adhesion and activation (see below), and the vitronectin receptor (VNR), which adheres to extracellular matrix vitronectin. Again, we used the most dilute sample of each MAb which saturated untreated cells. We measured some inhibition of binding of both anti-LFA-3 (TS2/9*) and anti-VNR (Telios; a rabbit MAb detected with ^{125}I-labeled goat anti-rabbit serum), but that inhibition (22% in each instance) was much less than the inhibition of the anti-HLA. In this regard, note that LFA-3 was present in much lower amounts than class I MHC antigens (13). Our radioimmunoassays also showed lower levels of VNR than class I MHC proteins at the cell surface. Thus, one would expect SV40 to more readily saturate LFA-3 and VNR than class I MHC antigens, presuming that the virus has an equal affinity for each. Our finding that SV40 blocks the binding of anti-HLA more readily than that of anti-LFA-3 or anti-VNR therefore implies that the interaction of SV40 with class I MHC proteins is specific.

In the converse of the above experiment, we asked whether pretreatment of LLC-MK_2 cells with anti-HLA might block infection by SV40, as scored by indirect immu-

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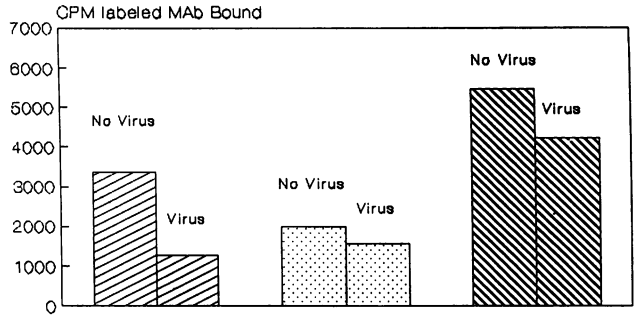

FIG. 1. Inhibition of binding of MAbs to LLC-MK_2 cells by preadsorption of SV40. Symbols: ▨, SV40 versus anti-class I MHC; ▧, SV40 versus anti-VNR; ▩, SV40 versus anti-LFA-3.

nofluorescence staining of the cultures for nuclear SV40 T antigen (Fig. 2). Our procedure was to incubate cells growing (approximately 70% confluent) on Lab-Tek eight-well culture slides with 100 μl of a dilution series of anti-HLA, anti-LFA-3, anti-VNR, anti-fibronectin receptor (Telios), or nonspecific ascites fluid for 45 min at 37°C. Cells were then incubated with SV40 at an input of 1 PFU per cell for 1 h at 37°C. At 2 days postinfection, the cells were fixed in cold acetone, and infected cells were identified by indirect immunofluorescence staining for the SV40 T antigen (16).

Pretreatment with anti-HLA indeed blocked infection in relation to the amount of MAb used (Fig. 2). In contrast, pretreatment of the cells with anti-VNR at dilutions of 1:10, 1:50, 1:100, and 1:1,000 had no effect whatsoever on infection (Fig. 2), even though the cells could be saturated with the anti-VNR at a dilution of 1:100 (not shown). A similar result was obtained with anti-fibronectin receptor (not shown). Pretreatment of the cultures with nonspecific ascites fluid was also without effect.

Pretreatment of the cells with anti-LFA-3 actually enhanced infection (Fig. 2). Although this result was not expected, it may actually support our assertion that class I MHC proteins are receptors for SV40 (see below).

A variation of the infection inhibition experiment in which the order of addition of the anti-HLA and the virus was reversed was done. Cells were first infected (1 PFU per cell for 1 h at 37°C) and then incubated with anti-HLA (undiluted; 45 min at 37°C). Cultures were fixed and stained at 2 days as described above. Adding anti-HLA after the virus resulted in a 30% inhibition of infection, whereas adding anti-HLA before the virus resulted in 85% inhibition (Fig. 3). This shows that the predominant effect of anti-HLA occurs at a stage very early in infection. However, anti-HLA may affect a later stage as well. Further experiments will be required to test this possibility.

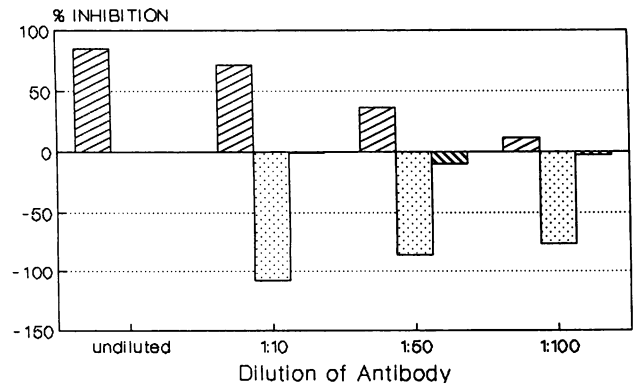

FIG. 2. Inhibition of infection of LLC-MK_2 cells by preadsorption of MAbs. Infection inhibition is expressed relative to that of cells treated with nonspecific ascites fluid. Symbols: ▨, anti-class I MHC; ▩, anti-LFA-3; ▧, anti-VNR.

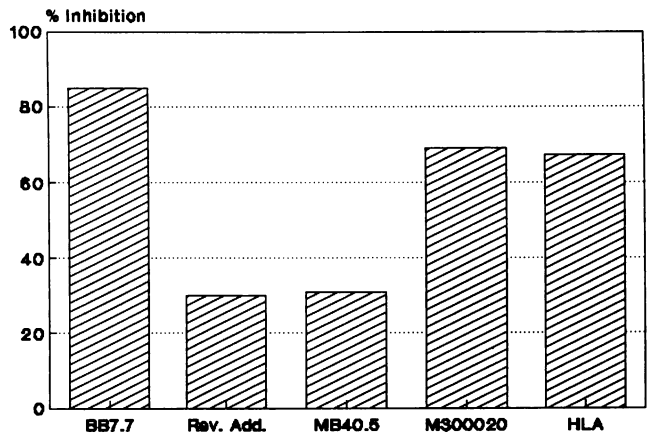

FIG. 3. Inhibition of infection of LLC-MK_2 cells by treatment with anti-MHC MAb BB7.7 before infection versus after infection (reverse addition [Rev. Add.]), by pretreatment of cells with anti-HLA MAbs MB40.5 and M300020, and by preincubation of virus with purified class I MHC (HLA) proteins.

We used anti-HLA MAb BB7.7 in the experiments described above. This antibody recognizes a combinatorial determinant between the HLA heavy chain and the B2 microglobulin. We also tested the abilities of anti-HLA MAbs M300020 (Olympus Immunochemicals) and MB40.5 (American Type Culture Collection) to block infection. Each of these MAbs recognizes a monomorphic determinant on the HLA heavy chain. Pretreatment of the cultures with the highest dilutions of MAbs BB7.7, M300020, and MB40.5 which saturated untreated cells resulted in inhibitions of infection of 85, 69, and 31%, respectively (Fig. 3). Thus, not unexpectedly, the ability of an anti-HLA MAb to block infection by SV40 depends on the particular epitope recognized by the MAb.

We also attempted to demonstrate a direct interaction between SV40 and class I MHC protein by testing the ability of purified class I protein to block infection. Purified virus (40 μg) was preincubated with soluble purified HLA class I protein (40 μg) in phosphate-buffered saline for 2 h at 4°C. Cells were then incubated with the mixture for 1 h at 37°C and were fixed and stained for SV40 T antigen at 2 days postinfection. Preincubation of virus with the soluble class I protein resulted in a 68% inhibition of infection relative to that achieved with the control, for which the virus was preincubated in phosphate-buffered saline (Fig. 3).

All of the experiments described above were done with LLC-MK_2 rhesus monkey kidney cells. We chose those cells because the rhesus monkey is the natural host of SV40 and because the kidney is a known site of SV40 latency in vivo (23). Since productive SV40 infection is usually studied in more permissive cell lines derived from green monkey kidneys, we asked whether anti-HLA would also block infection of highly permissive CV-1 cells. At an input of about 1 PFU per cell, 80% of the untreated CV-1 cells became infected, whereas only 26% of the cells pretreated with undiluted BB7.7 became infected. Pretreatment with the nonspecific ascites fluid again had no effect.

We next attempted to infect human lymphoblastoid cells of the Daudi line, which do not express class I MHC antigens (because of a defect in B2 microglobulin expression [19]). In our first experiment, exposure of the Daudi cells to SV40 virions at an input of 50 PFU per cell did not result in any T-antigen-producing cells. In contrast, we were able to obtain some T-antigen-producing Daudi cells by transfecting with SV40 DNA. We then compared the plating efficiency of SV40 on Daudi cells with that on Raji cells, another human lymphoblastoid cell line which expresses large amounts of class I MHC proteins (17). In this experiment the Daudi cells were less susceptible to infection than were the Raji cells, but they nevertheless were infected (although at very low levels). For example, at an input of 10 PFU per cell, 0.5% of the Daudi cells were infected, whereas 1.5% of the Raji cells were infected. At an input of 100 PFU per cell, 2.5% of the Daudi cells were infected and 7.5% of the Raji cells were infected. Of the parallel CV-1 cells, 100% were infected at both input multiplicities.

We asked whether the low, but real, infectivity of the Daudi cells might be due to the expression of some class I MHC heavy-chain proteins on those cells. We measured class I MHC expression by fluorescence-activated cell scanning analysis in which the primary antibodies were MAbs BB7.7 (which recognizes a combinatorial determinant of the HLA A, B, and C heavy chains and B2 microglobulin) and W6/32 (which recognizes monomorphic determinants on the HLA A, B, and C molecules). No class I MHC expression above background levels (secondary antibody only) could be detected on the Daudi cells when either MAb was used. In contrast, we readily detected class I MHC expression on the Raji cells when either MAb was used (data not shown). It is not likely that class I MHC antigens are expressed on Daudi cells below our level of detectability. Instead, we interpret these results to mean that SV40 is also able to infect cells in a way not mediated by class I proteins. Note that human immunodeficiency virus is also able to infect cells which do not express its specific receptor (4).

When several of the findings described above are considered together, they strongly imply that class I MHC proteins are the major cell surface receptors for SV40. First, we find that preadsorption of SV40 to cells inhibits binding of anti-HLA. Second, we find that pretreatment of cells with anti-HLA inhibits infection by SV40. Third, we find that the ability of anti-HLA to block infection is much reduced when it is added after virus adsorption. This shows that the major effect of the antibody must be on an early stage of infection. Fourth, we find that preincubating SV40 with purified HLA inhibits infection of cells. This suggests that the class I proteins, rather than some other proteins associated with them at the cell surface, are the actual receptors. The recent report (5) that SV40 binding to Vero cells is not inhibited by treatment of cell surfaces with trypsin or chymotrypsin whereas SV40 binding is significantly reduced by treatment of cells with papain is also consistent with our premise, since HLA proteins are insensitive to trypsin or chymotrypsin but are cleaved near the cell surface by papain.

We noted above that the enhanced levels of infection resulting from pretreatment of cells with anti-LFA-3 might also be consistent with our premise that class I MHC proteins are the major receptors for SV40. Foreign antigens are recognized by cytotoxic T lymphocytes (CTLs) only when associated with appropriate class I proteins on the target cell surface, a phenomenon known as MHC restriction (29). However, CTLs also recognize other proteins on the target cell surface, including LFA-3 (24). CD2 on the CTL is the natural ligand of LFA-3 on the target cell. It was suggested that the interaction of CD2 with LFA-3 might affect the manner in which MHC antigens are presented on the target cell membrane (B. Bierer, D. Golan, C. Brown, S. Herrmann, and S. Burakoff, personal communication). In support of this premise, treating cells with anti-LFA-3 (to model the CD2–LFA-3 interaction) specifically immobilized MHC class I proteins in the cell membrane (Bierer et al., personal communication). It was suggested that the interaction of CD2 (or anti-LFA-3) with LFA-3 might in turn make MHC class I proteins more accessible to the T-cell receptor. Similarly, in explanation of our findings, anti-LFA-3 may be making MHC class I proteins more accessible to SV40.

The normal cellular roles of viral receptors are known for only a few viruses (7). The likelihood that class I MHC proteins are major cell surface receptors for SV40 is particularly interesting at this time, since three other viruses were recently shown to also use immunoglobulin superfamily proteins as their receptors. These viruses are the human immunodeficiency virus, which uses CD4 as its receptor (8, 12); the rhinoviruses, which use ICAM-1 (11, 22); and poliovirus, which uses an unidentified immunoglobulin superfamily protein (14). Thus, an enveloped retrovirus, two nonenveloped picornaviruses, and a small DNA tumor virus may use immunoglobulin superfamily proteins as their receptors. Note that other known virus receptors, such as that of influenza (26), are not immunoglobulin superfamily members. Also note that polyomavirus does not use the same receptor as SV40 (5).

Immunoglobulin superfamily members show sequence and structural similarities to immunoglobulins (28). They have many different functions, but in all cases they have a recognition or binding role at the cell surface. For instance, CD4 is the T-cell surface glycoprotein that interacts with class II MHC molecules on the surfaces of antigen-presenting cells (9). The role of MHC class I proteins in the interaction between target cells and CTLs was noted above.

Since several dissimilar viruses appear to use immunoglobulin superfamily proteins for their receptors, it is interesting to ask whether this is merely a coincidence or, instead, has some deeper significance. Immunoglobulin superfamily proteins are plentiful on cell surfaces, and they presumably evolved to serve recognition functions. This would seem to make them particularly suitable receptors for viruses. In addition, it was suggested that the nature of the interaction between the immunoglobulin superfamily proteins and the receptor-binding sites on the viruses might enable the viruses to escape the host immune response (14, 22, 27). The receptor-binding sites, at least in the case of picornaviruses, are too small (1.2 to 3 nm wide, 2.5 nm deep) to permit entry of a Fab fragment (3.5 nm) (6, 20, 21). In contrast, the immunoglobulinlike domains of the receptors are just about the right size (approximately 2 nm) to penetrate the receptor-binding sites. Thus, the receptor-binding sites are nonimmunogenic and may be highly conserved. However, mutations elsewhere on the hypervariable surface of a virion, which do not affect receptor binding, may allow the virion to escape neutralization by antibodies against the parent strain. Consistent with the results described above, human immunodeficiency virus appears to recognize a loop on CD4 containing as few as 12 amino acids (1). Studies on the interactions of other viruses with their receptors (immunoglobulin superfamily or otherwise) will be necessary to test the generality of these findings and hypotheses.

Since MHC class I proteins play a crucial role in the cellular immune response, SV40 attachment to them might

have further consequences in vivo. The accumulation of virions at the cell surface, bound to class I MHC proteins, might block attack by SV40-specific CTLs. (Note that SV40-specific CTLs respond to surface T antigen in an MHC-restricted manner [2, 3, 10, 18, 25].) MHC-bound extracellular virions might then promote viral persistence, which is characteristic of the interaction of SV40 with its natural host, the rhesus macaque (15). Experiments to test the effect of bound virions on target cell recognition and destruction by CTLs are in progress.

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LITERATURE CITED

1. **Arthos, J., K. C. Deen, M. A. Chaikin, J. A. Fornwald, G. Sathe, Q. J. Sattentau, P. R. Clapham, R. A. Weiss, J. S. McDougal, C. Pietropaolo, R. Axel, A. Trunch, P. J. Maddon, and R. W. Sweet.** 1989. Identification of the residues in human CD4 critical for the binding of HIV. Cell **57**:469–481.
2. **Bates, M. P., S. R. Jennings, Y. Tanaka, M. J. Tevethia, and S. S. Tevethia.** 1988. Recognition of simian virus 40 T antigen synthesized during viral lytic cycle in monkey kidney cells expressing mouse H-2K^b-transfected genes by SV40-specific cytotoxic T lymphocytes leads to abrogation of virus lytic cycle. Virology **162**:197–205.
3. **Chang, C., R. G. Martin, D. M. Livingston, S. W. Luborsky, C.-P. Hu, and P. T. Mora.** 1979. Relationship between T-antigen and tumor-specific transplantation antigen in simian virus 40-transformed cells. J. Virol. **29**:69–75.
4. **Clapham, P. R., J. N. Weber, D. Whitby, K. McIntosh, A. G. Dalgleish, P. J. Maddon, K. C. Deen, R. W. Sweet, and R. A. Weiss.** 1989. Soluble CD4 blocks the infectivity of diverse strains of HIV and SIV for T cells and monocytes but not for brain and muscle cells. Nature (London) **337**:368–370.
5. **Clayson, E. T., and R. C. Compans.** 1989. Characterization of simian virus 40 receptor moieties on the surfaces of Vero C1008 cells. J. Virol. **63**:1095–1100.
6. **Colonno, R., J. Condra, S. Mizutani, P. Callahan, M. Davies, and M. Mucko.** 1988. Evidence for the direct involvement of the rhinovirus canyon in receptor binding. Proc. Natl. Acad. Sci. USA **85**:5449–5453.
7. **Crowell, R. L., and K. Lonberg-Holm.** 1986. Introduction and overview, p. 1–9. *In* R. L. Crowell and K. Lonberg-Holm (ed.), Virus attachment and entry into cells. American Society for Microbiology, Washington, D.C.
8. **Dalgleish, A. G., P. C. L. Beverly, P. R. Clapham, D. H. Crawford, M. F. Greaves, and R. A. Weiss.** 1984. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature (London) **312**:763–767.
9. **Doyle, C., and J. L. Strominger.** 1987. Interaction between CD4 and class II MHC molecules mediates cell adhesion. Nature (London) **330**:256–259.
10. **Gooding, L. R., and K. A. O'Connell.** 1983. Recognition by cytotoxic T lymphocytes of cells expressing fragments of the SV40 tumor antigen. J. Immunol. **131**:2580–2586.
11. **Greve, J. M., G. Davis, A. M. Meyer, C. P. Forte, S. C. Yost, C. W. Marlor, M. E. Kamarck, and A. McClelland.** 1989. The major human rhinovirus receptor is ICAM-1. Cell **56**:839–847.
12. **Klatzman, D., E. Champagne, S. Chamaret, J. Gruest, D. Guetard, T. Hercend, J. C. Gluckman, and L. Montagnier.** 1984. T lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. Nature (London) **312**:767–768.
13. **Krensky, A. M., F. Sanchez-Madrid, E. Robbins, J. A. Nagy, T. A. Springer, and S. J. Burakoff.** 1983. The functional significance, distribution, and structure of LFA-1, LFA-2, and LFA-3: cell surface antigens associated with CTL-target interactions. J. Immunol. **131**:611–616.
14. **Mendelsohn, C. L., E. Wimmer, and V. R. Racaniello.** 1989. Cellular receptor for poliovirus: molecular cloning, nucleotide sequence, and expression of a new member of the immunoglobulin superfamily. Cell **56**:855–865.
15. **Norkin, L. C.** 1982. Papovaviral persistent infections. Microbiol. Rev. **46**:384–425.
16. **Norkin, L. C., and J. Ouellette.** 1976. Cell killing by simian virus 40: variation in the pattern of lysosomal enzyme release, cellular enzyme release, and cell death during productive infection of normal and simian virus 40-transformed simian cell lines. J. Virol. **18**:48–57.
17. **Norment, A. M., R. D. Salter, P. Parham, V. H. Engelhard, and D. R. Littman.** 1988. Cell-cell adhesion mediated by CD8 and MHC class 1 molecules. Nature (London) **336**:79–81.
18. **Pan, S., and B. B. Knowles.** 1983. Monoclonal antibody to S antigen blocks lysis of cloned cytotoxic T cell line specific for TASA. Virology **125**:1–7.
19. **Rosa, F., H. Berissi, J. Weissenbach, L. Maroteaux, M. Fellows, and M. Revel.** 1983. The B2-microglobulin mRNA in Daudi cells has a mutated initiation codon but is still inducible by interferon. EMBO J. **2**:239–243.
20. **Rossmann, M. G., E. Arnold, J. W. Erikson, E. A. Frankenberger, J. P. Grifith, H. J. Hecht, J. E. Johnson, G. Kamer, M. Luo, A. G. Mosser, R. R. Rueckert, B. Sherry, and G. Vriend.** 1985. Structure of a human common cold virus and functional relationship to other picornaviruses. Nature (London) **317**: 145–153.
21. **Rossmann, M. G., and A. C. Palmenberg.** 1988. Conservation of the putative receptor attachment site in picornaviruses. Virology **164**:373–382.
22. **Staunton, D. E., V. J. Merluzzi, R. Rothlein, R. Barton, S. D. Marlin, and T. A. Springer.** 1989. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell **56**:849–853.
23. **Sweet, B. H., and M. R. Hilleman.** 1960. The vacuolating virus, SV40. Proc. Soc. Exp. Biol. Med. **105**:420–427.
24. **Takai, Y., M. Reed, S. J. Burakoff, and S. Herrmann.** 1987. Direct evidence for a receptor-ligand interaction between T cell surface antigen CD2 and lymphocyte-function-associated antigen 3. Proc. Natl. Acad. Sci. USA **84**:6864–6868.
25. **Tevethia, S. S., D. C. Flyer, and R. Tjian.** 1980. Biology of simian virus 40 (SV40) transplantation antigen (TrAg). VI. Mechanism of induction of SV40 transplantation immunity in mice by purified SV40 T antigen (D2 antigen). Virology **107**: 13–23.
26. **Weiss, W., J. H. Brown, S. Cusack, J. C. Paulson, J. J. Skehel, and D. C. Wiley.** 1988. Structure of the influenza virus hemagglutinin complexes with its receptor, sialic acid. Nature (London) **333**:426–431.
27. **White, J. M., and D. R. Littman.** 1989. Viral receptors of the immunoglobulin superfamily. Cell **56**:725–728.
28. **Williams, A. F., and A. N. Barclay.** 1988. The immunoglobulin superfamily—domains for cell surface recognition. Annu. Rev. Immunol. **6**:381–405.
29. **Zinkernagel, R. M., and P. C. Doherty.** 1981. MHC-restricted cytotoxic T cells: studies on the biological role of polymorphic major transplantation antigens determining T cell restriction—specificity, function, and responsiveness. Adv. Immunol. **27**: 51–177.