Cell, Vol. 56, 849–853, March 10, 1989, Copyright © 1989 by Cell Press

A Cell Adhesion Molecule, ICAM-1, Is the Major Surface Receptor for Rhinoviruses

Donald E. Staunton,* Vincent J. Merluzzi,† Robert Rothlein,† Randall Barton,† Steven D. Marlin,† and Timothy A. Springer*
* The Center for Blood Research
and Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115
† Boehringer Ingelheim Pharmaceuticals
Ridgefield, Connecticut 06877

Summary

Rhinoviruses, which cause common colds, possess over 100 serotypes, 90% of which (the major group) share a single receptor. Lymphocyte function associated molecule 1 (LFA-1) mediates leukocyte adhesion to a wide variety of cell types by binding to intercellular adhesion molecule 1 (ICAM-1). We demonstrate identity between the receptor for the major group of rhinoviruses and ICAM-1. A major group rhinovirus binds specifically to purified ICAM-1 and to ICAM-1 expressed on transfected COS cells, and binding is blocked by three ICAM-1 monoclonal antibodies (MAb) that block ICAM-1–LFA-1 interaction, but not by an ICAM-1 MAb that does not block ICAM-1–LFA-1 interaction. This suggests that the ICAM-1 contact site(s) for LFA-1 and rhinoviruses is proximal or identical. In addition, ICAM-1 MAb block the cytopathic effect in HeLa cells mediated by representative major but not minor group rhinoviruses. ICAM-1 is induced by soluble mediators of inflammation, suggesting that the host immune response to rhinovirus may facilitate spread to uninfected cells.

Introduction

Rhinoviruses are the etiologic agent in approximately 50% of all cases of the common cold (Sperber and Hayden, 1988). A vaccine to prevent the common cold has not been possible, because there are over 100 immunologically non-crossreactive rhinovirus serotypes (Couch, 1985). However, 90% of rhinovirus serotypes (the major group) share a single receptor on the surface of human cells. Competition between different rhinovirus serotypes for binding to cellular receptors (Abraham and Colonno, 1984) and inhibition with an anti-receptor MAb (Colonno et al., 1986), have shown that 78 serotypes bind to a single receptor for the "major group," while 10 serotypes bind to a second receptor for the "minor group." The major receptor, as characterized with a MAb that inhibits virus attachment and cytopathic effect, is a 90 kd single chain glycoprotein with a diffuse band in SDS–PAGE and a broad distribution on epithelial, fibroblast, and B lymphoblastoid lines (Tomassini and Colonno, 1986). The ICAM-1 molecule has an identical molecular mass and similar tissue distribution (Rothlein et al., 1986; Kishimoto et al., 1989). ICAM-1 was originally defined with MAb that inhibit lymphocyte adhesion. ICAM-1 is a member of the immunoglobulin (Ig) supergene family and functions as a ligand for the leukocyte molecule LFA-1, a member of the integrin family (Dustin et al., 1988b). LFA-1/ICAM-1 mediated adhesion is important in a wide variety of immune interactions, and induction of ICAM-1 expression by cytokines in inflammation appears to be important in regulating leukocyte localization in inflammatory sites.

We demonstrate that the major rhinovirus receptor (Tomassini and Colonno, 1986) is identical to ICAM-1, as shown with purified ICAM-1, ICAM-1 transfected cells, and ICAM-1 monoclonal antibody (MAb) inhibition of virus binding and infection of cells in vitro. Of potential interest for host–virus interaction, the LFA-1/ICAM-1 adhesion pathway is important in T lymphocyte–mediated cytolysis of virally infected cells. Furthermore, ICAM-1 surface expression is highly induced by lymphokines and monokines, and thus the immune response to rhinovirus is predicted to lead to increased expression of virus receptor.

Results

To test for identity between ICAM-1 and the major rhinovirus receptor, a representative human rhinovirus (HRV) major group serotype, HRV14, was labeled with [^{35}S]methionine, purified, and the kinetics of binding to transfected COS cells was measured (Figure 1A). [^{35}S]HRV14 bound to COS cells expressing ICAM-1 but not to mock-transfected cells. Binding reached a level of 20% by 60 min. Presence in the assay of the ICAM-1 MAb RR1/1 inhibited binding to the level seen with mock-transfected COS cells.

In a second set of experiments, the binding of HRV14 to purified ICAM-1 was determined. ICAM-1 was purified from hairy leukemia cells by immunoaffinity chromatography as described previously (Marlin and Springer, 1987). The binding of [^{35}S]HRV14 to plastic-bound purified ICAM-1 increased to 40% of input by 90 min (Figure 1B). During the 90 min binding period no significant increase in HRV14 binding to plastic-bound bovine serum albumin (BSA) was observed above initial background levels of 0.5%. In the presence of 20 μg/ml of ICAM-1 MAb, specific HRV14 binding to ICAM-1 was completely abrogated. The presence of a negative control LFA-3 MAb did not inhibit binding at 60 min (data not shown). Thus HRV14 binding to purified ICAM-1 is specific and blocked by an ICAM-1 antibody.

The specificity of HRV14 binding to ICAM-1 was examined with four different ICAM-1 MAb (Figure 2). Three different MAb (RR1/1, R6.5, and LB-2) which bind to at least two different ICAM-1 epitopes (Makgoba et al., 1988a) block HRV14 binding to ICAM-1 transfectants to the level obtained with mock-transfected cells. In contrast, a fourth MAb (CL203) (Matsui et al., 1987) binds equally well and specifically to ICAM-1 transfectants, defining it as an ICAM-1 MAb (not shown), yet it does not significantly block

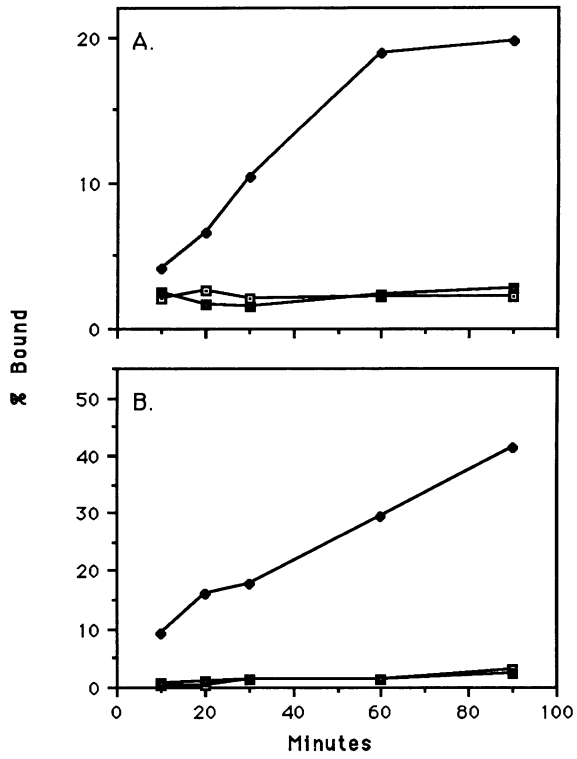

Figure 1. Binding of HRV14 to ICAM-1 Expressed on Transfected COS Cells and to Purified ICAM-1

(A) Transfectants were incubated with [^{35}S]HRV14 for varying times: COS cells transfected with an ICAM-1 cDNA-expression vector construct (◆); mock-transfected COS cells (■); ICAM-1-transfected COS cells in presence of ICAM-1 MAb (□).

(B) [^{35}S]HRV14 incubated in microtiter wells coated with BSA (■) or with purified ICAM-1 in the absence (◆) or presence (□) of ICAM-1 MAb.

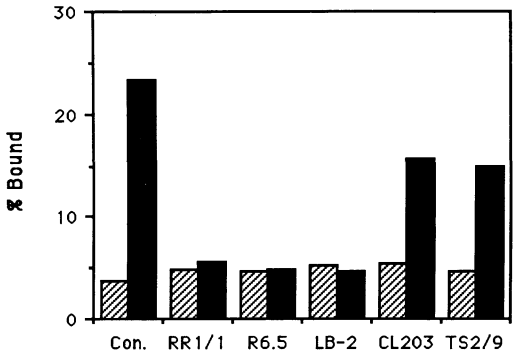

Figure 2. MAb Inhibition of HRV14 Binding to Transfected COS Cells

[^{35}S]HRV14 was incubated with COS cells transfected with ICAM-1 cDNA (solid bars) or mock-transfected COS cells (hatched bars) for 1 hr as described in Experimental Procedures in the presence of 3 μg/ml of purified ICAM-1 MAb RR1/1, R6.5, LB-2, or CL203, or LFA-3 MAb TS2/9.

HRV14 binding. The CL203 MAb differs from the other three ICAM MAb (Marlin and Springer, 1987; Makgoba et al., 1988a; Rothlein et al., 1988) in that it does not block ICAM-1/LFA-1 interaction as shown by lack of inhibition of JY cell homotypic adhesion (M. L. Dustin and T. A. Springer, unpublished data), and binds to a different site on ICAM-1 (D. E. Staunton, unpublished data). These findings suggest that LFA-1 and HRV14 bind to similar regions of the ICAM-1 molecule. As a further control, the TS2/9 LFA-3 MAb did not block HRV14 binding yet binds at high levels to simian LFA-3 on COS cells.

A critical test of identity of ICAM-1 with the rhinovirus receptor is the ability of ICAM-1 MAb to inhibit rhinovirus infection of cells in vitro as measured by the cytopathic effect on HeLa cell monolayers (Figure 3). ICAM-1 MAb R6.5 and RR1/1 inhibited alone or together the cytopathic effect of two representative major group rhinovirus serotypes, HRV54 (Figure 3A) and HRV4 (Figure 3B), while a control MAb had no effect. In contrast, ICAM-1 MAb had no effect on the cytopathic effect mediated by two representative minor group rhinovirus serotypes, HRV49 and HRV2 (Figures 3C and 3D). Thus, ICAM-1 fulfills all criteria for the major rhinovirus receptor, and is clearly distinct from the minor receptor. In addition, Coxsackie A13, A18, and A21 serotypes bind to the same receptor as the major group of rhinoviruses (Colonno et al., 1986), which indicates that they also bind to ICAM-1.

Discussion

We have demonstrated identity between a cell adhesion molecule, ICAM-1, and the major rhinovirus receptor. This brings together important information about these molecules. ICAM-1 has a polypeptide chain backbone of 55 kd, and variation in complex N-linked carbohydrate processing results in molecular mass heterogeneity of 76 to 114 kd depending on the cell type (Dustin et al., 1986; Dustin et al., 1988b). ICAM-1 has been cloned and sequenced and has an N-terminal extracellular domain with 5 Ig-like domains, a single transmembrane domain, and a short C-terminal cytoplasmic domain (Simmons et al., 1988; Staunton et al., 1988). ICAM-1 shows greatest similarity in the Ig superfamily to two other five-domain adhesion molecules that function in the nervous system, myelin-associated glycoprotein, and neural cell adhesion molecule. Rhinoviruses are members of Picornaviridae, small RNA-containing protein-encapsidated viruses that include Coxsackie virus, foot-and-mouth disease virus, hepatitis A virus, Mengo (encephalomyocarditis) virus, and poliovirus (Couch, 1985). The structures of the last two viruses and rhinovirus HRV14 have been solved by X-ray crystallography (Rossmann et al., 1985; Hogle et al., 1985; Luo et al., 1987). The viruses have icosahedral symmetry with 60 copies of each capsid protomer. There is a "canyon" in rhino and polio viruses that has been proposed to contain the receptor binding site, and which forms a "moat" around the 5-fold axis; in Mengovirus there are instead five "pits." In HRV14 the antigenic regions have been mapped to hypervariable regions outside the canyon. The rhinovirus canyon (12–30 Å wide, 25 Å deep) is too narrow to admit an Fab fragment (35 Å) (Rossmann et al., 1985). The canyon hypothesis proposes that picornaviruses "can accept

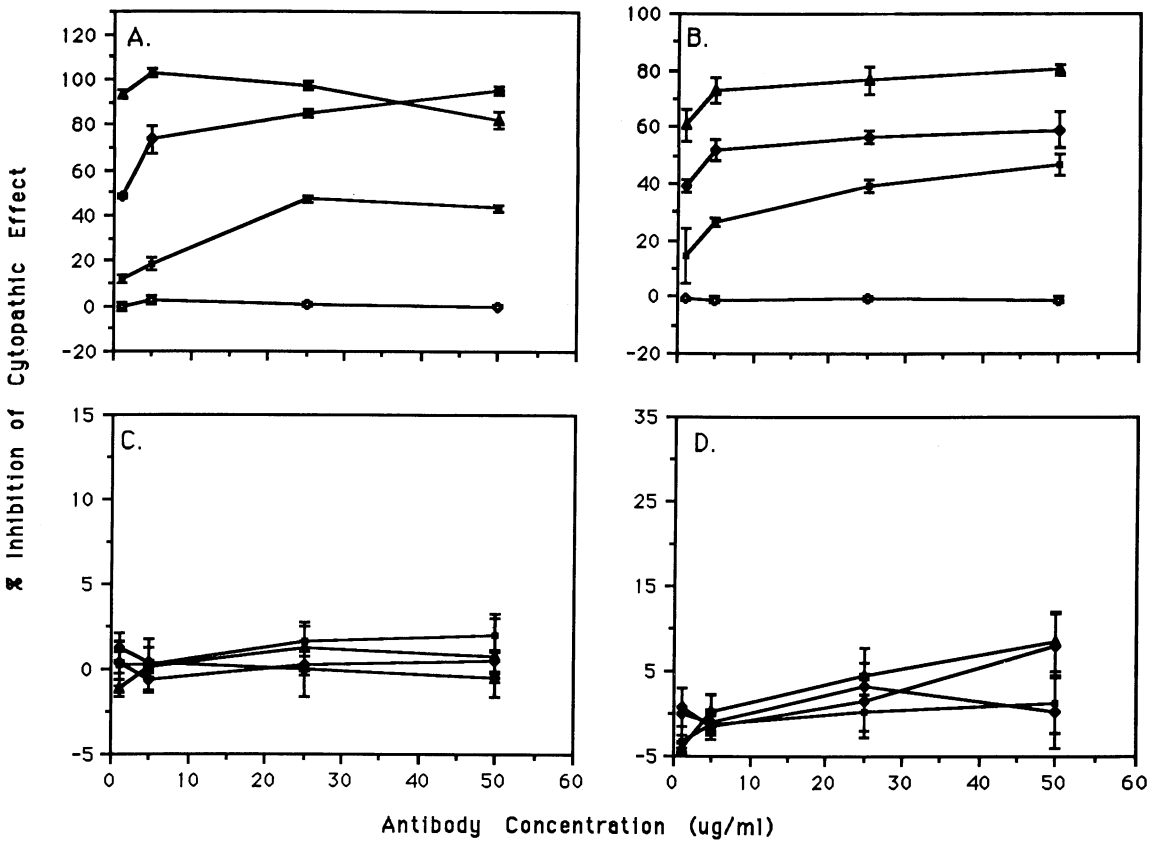

Figure 3. ICAM-1 MAb Inhibit Cytopathic Effect of Rhinovirus Major but Not Minor Group Serotypes

HeLa cells in the presence of purified ICAM-1 MAb R6.5 (◆), ICAM-1 MAb RR1/1 (■), or R6.5 and RR1/1 (▲), or as a control LFA-1 MAb R3.1 (◇) at the indicated concentrations were infected with major rhinovirus serotypes HRV54 (A) and HRV4 (B) or minor rhinovirus serotypes HRV49 (C) and HRV2 (D), and cytopathic effect was determined 4 days later.

mutations on the hypervariable surface, thereby escaping the host's immune system, while maintaining a more constant receptor attachment site which is physically inaccessible to antibodies" (Rossmann and Palmenberg, 1988). Fab fragments contain paired Ig domains; ICAM-1 with 5 Ig domains must contain at least one unpaired domain. A single Ig domain is of approximately the correct size to fit within the canyon. ICAM-1 is the first picornavirus receptor for which we know the amino acid sequence and host biological function; other picornavirus receptors may also be in the Ig superfamily and function in adhesion. A recently defined poliovirus receptor (Shepley et al., 1988) is similar in size to ICAM-1 and, like ICAM-1 (Katz et al., 1984), its gene maps to chromosome 19; however, it is distinct in tissue distribution. Poliovirus does not bind to ICAM-1 (unpublished data), in agreement with virus crosscompetition assays showing that the rhinovirus and poliovirus receptors are distinct (Abraham and Colonno, 1984).

Like the use of the CD4 T lymphocyte adhesion molecule as a receptor by the human immunodeficiency virus, the use of the ICAM-1 adhesion molecule as a receptor by rhinovirus has important implications for the interaction between virus infection and the host immune response. ICAM-1 is strongly induced on epithelial cells, fibroblasts, and endothelial cells by lipopolysaccharide and cytokines secreted by T lymphocytes and monocytes including IFN-γ, TNF-α and β, and IL-α and β (Dustin et al., 1988b; Kishimoto et al., 1989). After induction ICAM-1 becomes a major surface component, expressed in up to 1.8×10^6 sites/epidermal keratinocyte and 3.5×10^6 sites/endothelial cell (Dustin et al., 1988a; Dustin and Springer, 1988). The CD2/LFA-3 and LFA-1 pathways of lymphocyte adhesion vary in relative importance depending on the cell to which the lymphocyte adheres; the relative strength of interaction of LFA-1 with ICAM-1 and with a ligand distinct from ICAM-1 also varies (Rothlein et al., 1986; Makgoba et al., 1988b; Shaw and Luce, 1987; Dustin and Springer, 1988). Rhinoviruses infect the nasal epithelium; it is of interest that epitheloid lines, including epidermal keratinocytes, A431, and HeLa, demonstrate exclusively the LFA-1/ICAM-1 pathway (Dustin et al., 1988a; Makgoba et al., 1988a). Rhinovirus binding to ICAM-1 may inhibit or alter T lymphocyte-mediated cytotoxic and helper cell interactions with infected cells. T lymphocyte responses to antigen in cutaneous sites, as well as intradermal injection of the cytokines γ-IFN and TNF, induce strong expression of ICAM-1 on epithelial cells and endothelial cells (Wantzin et al., 1989; Munro et al., 1989). Although similar studies on mucosal epithelia remain to be done, the response to rhinovirus infection of nasal epithelium (Couch,

1985) should, like other immune inflammatory responses studied to date, result in induction of ICAM-1 expression. Thus the rhinovirus appears to turn the host response to its own advantage to induce its receptor. Cytokine-induced ICAM-1 expression on uninfected cells neighboring the infected site is predicted to facilitate spread of rhinovirus infection.

Finally, since 90% of rhinovirus serotypes (the major group) use ICAM-1 as their receptor, purified soluble ICAM-1 may have utility in neutralizing or inhibiting virus infection as a therapeutic agent for preventing the common cold.

Experimental Procedures

MAb

ICAM-1 MAb RR1/1 (Rothlein et al., 1986), R6.5 (Rothlein et al., 1988), LB-2 (Clark et al., 1986), and CL203 (Matsui et al., 1987), LFA-3 MAb TS2/9 (Sanchez-Madrid et al., 1982) and LFA-1 MAb R3.1 (Rothlein et al., 1988) have been described, and were used as Protein A–sepharose purified IgG, except for CL203 used as ascites.

Binding of [^{35}S]HRV-14 to ICAM-1 on Transfected COS Cells and to Purified ICAM-1

HeLa cells infected with HRV14 were labeled with [^{35}S]methionine, and [^{35}S]HRV14 was purified by sucrose gradient sedimentation (Sherry et al., 1986); virus was used at 2.6×10^5 cpm (1.2×10^8 pfu) /ml RPMI 1640. COS-7 cells were transfected with CDM8 (Seed, 1987) containing the SalI–KpnI 1.8 kb ICAM-1 coding region fragment (Staunton et al., 1988) with DEAE-dextran (Kingston, 1987) (2 μg DNA/10 cm 50% confluent plate), or were mock-transfected without plasmid DNA. Two days after transfection cells were trypsinized and transferred to 24-well culture plates and assayed near confluency 1 day later. ICAM-1 purified from hairy leukemia spleen cells with MAb-Sepharose (Marlin and Springer, 1987) (50 ng in 40 μl PBS) was incubated in Immulon (Dynatech) microtiter wells overnight at 4°C. These and control wells were blocked with 100 μl of 1% BSA in PBS for 1 hr at 24°C and washed 2× with RPMI 1640. [^{35}S]HRV14 was added (50 or 100 μl) with or without 1 μg of purified RR1/1 ICAM-1 MAb (Rothlein et al., 1986) and incubated at 24°C for the indicated times on a rocker. Media was aspirated and after one wash with 100 μl of RPMI 1640 bound [^{35}S]HRV14 was eluted with 100 μl of 1% SDS in PBS and scintillation counted.

ICAM-1 MAb Inhibition of HRV Cytopathic Effect in HeLa Cells

HeLa cells (American Type Culture Collection CCL2) maintained in RPM1 1640/10% FCS/0.5% gentamycin were plated at 2.5×10^4 cells/microtiter well. After 1 day, medium was replaced with MAb (50 μl) for 30 min at 37°C, then 100 TCID of virus was added (50 μl), both in RPMI 1640/5% FCS/0.5% gentamycin/20 mM $MgCl_2$, and plates were incubated for 4 days at 33°C. Medium was removed, 50 μl of 0.5% crystal violet in 20% methanol was added for 3 min, then plates were vigorously washed with tap water and read at 570 nM to measure the number of viable cells left in the culture well. Percent inhibition of cytopathic effect = 100 × [OD (MAb + virus) − OD (+ virus)]/[OD (− virus) − OD (+ virus)]. ODs without and with virus ranged from 0.837 to 1.228 and 0.005 to 0.113, respectively, in different plates and with the four different HRV. Each experimental point was in triplicate.

Acknowledgments

This work was supported by National Institutes of Health Grant CA31798 and by Boehringer Ingelheim. We thank D. Leippe of Dr. R. Rueckert's lab for kindly providing labeled HRV14, M. Dustin for generously contributing purified ICAM-1, and Drs. J. Greve and A. McClelland of Molecular Therapeutics, Inc., New Haven, CT, for information in advance of publication.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 8, 1988.

References

Abraham, G., and Colonno, R. J. (1984). Many rhinovirus serotypes share the same cellular receptor. J. Virol. *51*, 340–345.

Clark, E. A., Ledbetter, J. A., Holly, R. C., Dinndorf, P. A., and Shu, G. (1986). Polypeptides on human B lymphocytes associated with cell activation. Hum. Immunol. *16*, 100–113.

Colonno, R. J., Callahan, P. L., and Long, W. J. (1986). Isolation of a monoclonal antibody that blocks attachment of the major group of human rhinoviruses. J. Virol. *57*, 7–12.

Couch, R. B. (1985). Rhinoviruses. In Fields Virology, B. N. Fields, D. M. Knipe, J. L. Melnick, R. M. Chanock, B. Roizman, and R. E. Shope, eds. (New York: Raven Press), pp. 795–816.

Dustin, M. L., and Springer, T. A. (1988). Lymphocyte function associated antigen-1 (LFA-1) interaction with intercellular adhesion molecule-1 (ICAM-1) is one of at least three mechanisms for lymphocyte adhesion to cultured endothelial cells. J. Cell. Biol. *107*, 321–331.

Dustin, M. L., Rothlein, R., Bhan, A. K., Dinarello, C. A., and Springer, T. A. (1986). Induction by IL-1 and interferon, tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). J. Immunol. *137*, 245–254.

Dustin, M. L., Singer, K. H., Tuck, D. T., and Springer, T. A. (1988a). Adhesion of T lymphoblasts to epidermal keratinocytes is regulated by interferon gamma and is mediated by intercellular adhesion molecule-1 (ICAM-1). J. Exp. Med. *167*, 1323–1340.

Dustin, M. L., Staunton, D. E., and Springer, T. A. (1988b). Supergene families meet in the immune system. Immunol. Today *9*, 213–215.

Hogle, J. M., Chow, M., and Filman, D. J. (1985). Three-dimensional structure of poliovirus at 2.9 A resolution. Science *229*, 1358–1365.

Katz, F. E., Parkar, M., Stanely, K., Murray, L. J., Clark, E. A., and Greaves, M. F. (1984). Chromosome mapping of cell membrane antigens expressed on activated B cells. Eur. J. Immunol. *15*, 103–106.

Kingston, R. E. (1987). Introduction of DNA into mammalian cells. In Current Protocols in Molecular Biology (New York: Greene Publishing Associates), pp. 901–996.

Kishimoto, T. K., Larson, R. S., Corbi, A. L., Dustin, M. L., Staunton, D. E., and Springer, T. A. (1989). The leukocyte integrins: LFA-1, Mac-1, and p150,95. Adv. Immunol., in press.

Luo, M., Vriend, G., Kamer, G., Minor, I., Arnold, E., Rossmann, M. G., Boege, U., Scraba, D. G., Duke, G. M., and Palmenberg, A. C. (1987). The atomic structure of Mengo virus at 3.0 A resolution. Science *235*, 182–191.

Makgoba, M. W., Sanders, M. E., Luce, G. E. G., Dustin, M. L., Springer, T. A., Clark, E. A., Mannoni, P., and Shaw, S. (1988a). ICAM-1: definition by multiple antibodies of a ligand for LFA-1 dependent adhesion of B, T and myeloid cells. Nature *331*, 86–88.

Makgoba, M. W., Sanders, M. E., Ginther Luce, G. E., Gugel, E. A., Dustin, M. L., Springer, T. A., and Shaw, S. (1988b). Functional evidence that intercellular adhesion molecule-1 (ICAM-1) is a ligand for LFA-1 in cytotoxic T cell recognition. Eur. J. Immunol. *18*, 637–640.

Marlin, S. D., and Springer, T. A. (1987). Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function–associated antigen 1 (LFA-1). Cell *51*, 813–819.

Matsui, M., Temponi, M., and Ferrone, S. (1987). Characterization of a monoclonal antibody-defined human melanoma-associated antigen susceptible to induction by immune interferon. J. Immunol. *139*, 2088–2095.

Munro, J. M., Pober, J. S., and Cotran, R. S. (1989). Tumor necrosis factor and interferon–gamma induce distinct patterns of endothelial activation and leukocyte accumulation in skin of papio anubis. Am. J. Pathol., in press.

Rossmann, M. G., and Palmenberg, A. C. (1988). Conservation of the putative receptor attachment site in picornaviruses. Virology *164*, 373–382.

Rossmann, M. G., Arnold, E., Erickson, J. W., Frankenberger, E. A., Griffith, J. P., Hecht, H. J., Johnson, J. E., Kamer, G., Luo, M., Mosser, A. G., Rueckert, R. R., Sherry, B., and Vriend, G. (1985). Structure of a human common cold virus and functional relationship to other picornaviruses. Nature *317*, 145–153.

Rothlein, R., Dustin, M. L., Marlin, S. D., and Springer, T. A. (1986). A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J. Immunol. *137*, 1270–1274.

Rothlein, R., Czajkowski, M., O'Neil, M. M., Marlin, S. D., Mainolfi, E., and Merluzzi, V. J. (1988). Induction of intercellular adhesion molecule 1 on primary and continuous cell lines by pro-inflammatory cytokines. Regulation by pharmacologic agents and neutralizing antibodies. J. Immunol. *141*, 1665–1669.

Sanchez-Madrid, F., Krensky, A. M., Ware, C. F., Robbins, E., Strominger, J. L., Burakoff, S. J., and Springer, T. A. (1982). Three distinct antigens associated with human T lymphocyte-mediated cytolysis: LFA-1, LFA-2, and LFA-3. Proc. Natl. Acad. Sci. USA *79*, 7489–7493.

Seed, B. (1987). An LFA-3 cDNA encodes a phospholipid-linked membrane protein homologous to its receptor CD2. Nature *329*, 840–842.

Shaw, S., and Luce, G. E. G. (1987). The lymphocyte function-associated antigen (LFA-1) and CD2/LFA-3 pathways of antigen-independent human T cell adhesion. J. Immunol. *139*, 1037–1045.

Shepley, M. P., Sherry, B., and Weiner, H. L. (1988). Monoclonal antibody identification of a 100-kda membrane protein in HeLa cells and human spinal cord involved in poliovirus attachment. Proc. Natl. Acad. Sci. USA. *85*, 7743–7747.

Sherry, B., Mosser, A. G., Colonno, R. J., and Rueckert, R. R. (1986). Use of monoclonal antibodies to identify four neutralization immunogens on a common cold picornavirus, human rhinovirus 14. J. Virol. *57*, 246–257.

Simmons, D., Makgoba, M. W., and Seed, B. (1988). ICAM, an adhesion ligand of LFA-1, is homologous to the neural cell adhesion molecule NCAM. Nature *331*, 624–627.

Sperber, S. J., and Hayden, F. G. (1988). Chemotherapy of rhinovirus colds. Antimic. Agents. Chemo. *32*, 409–419.

Staunton, D. E., Marlin, S. D., Stratowa, C., Dustin, M. L., and Springer, T. A. (1988). Primary structure of intercellular adhesion molecule 1 (ICAM-1) demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell *52*, 925–933.

Tomassini, J. E., and Colonno, R. J. (1986). Isolation of a receptor protein involved in attachment of human rhinoviruses. J. Virol. *58*, 290–295.

Wantzin, G. L., Ralfkiaer, E., Avnstorp, C., Czajkowski, M., Marlin, S. D., and Rothlein, R. (1989). Kinetics and characterization of intercellular adhesion molecule-1 (ICAM-1) expression on keratinocytes in various inflammatory skin lesions and malignant cutaneous lymphomas. J. Am. Acad. Dermatol., in press.