Rhinovirus Inhibits Antigen-Specific T Cell Proliferation through an Intercellular Adhesion Molecule-1–Dependent Mechanism

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To determine whether binding of human rhinovirus (HRV) to intracellular adhesion molecule-1 might disrupt airway immune processes, effects of a major HRV group, HRV-16, on T cell proliferation and cytotoxicity were defined. HRV (1–10 TCID50/cell) significantly inhibited T cell proliferation induced by antigen but not proliferation secondary to mitogens, interleukin-2, or an irradiated allogeneic T cell line. Noninfectious (UV-irradiated) HRV had similar effects. Inhibition of T cell proliferation was dependent on HRV binding to intercellular adhesion molecule-1 on monocytes, indicating that the virus interferes with lymphocyte activation indirectly through effects on antigen-presenting cells. In addition, HRV inhibited T cell cytotoxic responses but not NK cell activity. If these effects also occur in vivo, the resulting disturbance in local airway immunity could increase the chances of successful viral replication, and might also be a factor in the pathogenesis of secondary viral or bacterial respiratory tract infections.

Many viruses, including respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, measles, and poxviruses, have evolved means to enhance replication and subsequent transmission by suppressing antiviral immune responses [1, 2]. A by-product of local or systemic immune suppression by these viruses is an increased susceptibility to secondary bacterial or viral infections.

Human rhinovirus (HRV), one of the most successful pathogens, causes ~30%–50% of upper respiratory infections worldwide [3] and is also associated with local infectious complications, such as otitis media and sinusitis [4–7]. Factors that contribute to the abundance of HRV infections include a remarkable degree of antigenic variation and a fast replicative cycle typical of most RNA viruses [8]. Another interesting feature of HRV is that 90% of the >100 serotypes must bind to intracellular adhesion molecule-1 (ICAM-1) to replicate within host cells [9–11]. Although HRV replication has been documented in only a few cell types, ICAM-1 may be expressed on the surface of many different cells, including those that are active in respiratory immune responses, such as monocytes and airway macrophages [12–14], dendritic cells [15], airway eosinophils [16], mast cells [17], B lymphocytes [18, 19], and activated T lymphocytes [18].

The natural ligand for ICAM-1 is lymphocyte function–associated antigen (LFA-1) [20], designated CD11a/CD18. Although ICAM-1/LFA-1 interactions are important in mediating cellular adhesion [21], it is also clear that interaction of these surface receptors generates costimulatory signals, which include activation of CD4 T cells [22–25], cytotoxicity mediated by T cells and lymphokine-activated killer cells [26–29], and T cell–dependent B cell activation [18]. The binding sites on the ICAM-1 molecule for LFA-1 and HRV overlap [30], and as a result, HRV can block ICAM-1–dependent interactions between T cells and cytokine-treated dermal fibroblasts [31].

It has been hypothesized that HRV may also interfere with ICAM-1/LFA-1 binding on leukocytes and, thus, disrupt immune responses that are dependent on this interaction. An important consequence of these effects could include disruption of local airway immunity and inhibition of anti-HRV responses, which would increase the chance of productive viral replication. To test this hypothesis, the following experiments were done to determine the effects of HRV on T cell proliferative and cytotoxic responses.

Materials and Methods

Reagents and cells. Stimuli used in the T cell proliferation assay included tetanus toxoid (Connaught, Swiftwater, PA), varicella antigen (VZ; Russell Tomar, Department of Pathology, University of Wisconsin), streptokinase, (KabiVitrum, Stockholm), ragweed and Candida extracts (Hollister-Stier, Elkhart, IN), phytohemagglutinin and concanavalin A (ConA; Sigma, St. Louis), and recombinant human interleukin (IL)-2 (R&D Systems, Minneapolis), TK6 cells (American Type Culture Collection, Rockville, MD) or peripheral blood mononuclear cells (PBMC) from a healthy unrelated donor were irradiated (50 Gy) and then frozen at −70°C for use as stimulators of allogeneic T cell proliferation. Anti-
ICAM-1 monoclonal antibody (MAb; C78.4A) [32] was provided by Jeffrey Greve (Miles Laboratories, New Haven, CT). WIN 54954, a peptide that binds to the canyon region of HRV and blocks binding to ICAM-1 and subsequent uncoating of the virus [33], was provided by Dan Pevear (Sterling Winthrop, Collegeville, PA).

PBMC were obtained by ficoll separation of heparinized whole blood obtained from normal volunteers. Plasma was centrifuged to remove platelets and then used in proliferation experiments. After two washes with PBS and 0.02% EDTA, the cells were resuspended in RPMI with 25% autologous serum, 50 U/mL penicillin, and 50 µg/mL streptomycin. Cell viability, as estimated by staining with trypan blue, was consistently >95%.

HRV suspensions. HRV-16 and HRV-49 were grown in the Ohio strain of HeLa cells. Culture medium with HeLa cells was inoculated with virus and grown in rolling bottles at 33°C. Growth was allowed to continue until cytopathic effects were well advanced. The resulting fluids were centrifuged (2000 rpm for 30 min at 20°C) to remove cellular debris. Aliquots of virus with infectivity of 10^7–10^9 TCID₅₀/mL, as measured by inoculating serial dilutions of virus suspension in HeLa (HRV-16) or WI-38 (HRV-49) cells, were stored at −70°C until needed. Supernatant from uninfected HeLa cell cultures was also frozen in aliquots to be used as a negative control in some experiments.

The HRV-16 suspension was partially purified [34] for some experiments to remove ribosomes and soluble factors of HeLa cell origin. HRV-16 suspension, as described above, was treated with 20 µg/mL RNase A (Sigma) at 35°C for 20 min, and then 1% sodium sarcosyl and 1 µg/mL 2-mercaptoethanol were added. This mixture (27 mL) was transferred to a 30-ml ultracentrifuge tube, underlaid with 3 mL of a solution containing 20 mM TRIS acetate, 1 M NaCl, and 30% (wt/vol) sucrose, and then centrifuged (25,000 rpm at 16°C) for 5 h to pellet the virus. The supernatant was discarded, and the pellet was resuspended in medium, which was then frozen at −70°C until needed.

Noninfectious HRV-16 or HRV-49 suspensions were prepared by irradiating the virus suspension with UV light. To accomplish this, HRV suspension was placed into a plastic petri dish so that the depth was ≤5 mm. An 8-W UV lamp (254 nm) was positioned 10 cm from the virus suspension, and the suspension was irradiated for 15 min while being gently agitated every 4–5 min. This procedure yielded virus that was noninfectious in HeLa cell cultures, but it could induce proliferation of PBMC or HRV-specific T cell clones.

**T cell proliferation assays.** Human PBMC (10^5/well) were added to 96-well microtiter plates (Coming Lab Sciences, Coming, NY) in the presence of either 0.04 IU/mL tetanus toxoid, 125 U/mL streptomycin, 1:100 dilution of varicella zoster antigen, 5 × 10^6 irradiated allogeneic PBMC or TK6 cells, or 100 U/mL IL-2 for 6 days in the presence or absence of live or UV-irradiated HRV-16 (10 TCID₅₀/cell). For experiments involving T cell clones, irradiated monomacrophages cells functioning as antigen-presenting cells (APCs, 10^5 cells/well) were incubated for 48 h along with T cell clones specific for HRV-49 (1–2 × 10^6 cells/well) and antigen (1 TCID₅₀/cell UV-irradiated HRV-49) in the presence or absence of live or UV-irradiated HRV-16 (10 TCID₅₀/APC), purified HRV-16 (10 TCID₅₀/APC), or anti–ICAM-1 MAb (20 µg/mL).

To quantify thymidine incorporation into DNA, [³H]thymidine (1 µCi/well) was incubated with each sample for an additional 18 h, the samples were transferred onto glass paper by use of an automated harvester (Skatron, Lier, Norway), and counts per minute (cpm) were measured in a scintillation counter (Packard, Meriden, CT). Mean cpm were determined for triplicate or quadruplicate wells, and the stimulation index (SI) was calculated by dividing the mean cpm of an antigen or mitogen-stimulated sample by the mean cpm of cells incubated with medium alone. Significant proliferation was defined as SI ≥ 2 for PBMC and SI ≥ 3 for T cell clones. Samples of PBMC that proliferated to HRV-16 alone were not included in subsequent analyses because virus-specific proliferation would have obscured the inhibitory effect of the virus on proliferation due to other stimuli.

**Cytotoxicity assays.** NK cell activity and T cell cytotoxicity were determined using chromium release assays according to standard protocols [35]. In brief, the NK cell assay was done by incubating (37°C) PBMC with ⁵¹Cr-labeled K562 cells (10^5/well) at 4 different effector-to-target cell ratios in the presence of partially purified HRV-16 (5 × 10⁵ TCID₅₀/mL) or medium alone. After a 4-h incubation, free ⁵¹Cr in cell culture supernatants was quantitated in a gamma counter, and lytic units per 10⁶ cells were calculated according to the formula 10^(-3.4) [(E:T)₉₅], where E:T₉₅ is the effector-to-target cell ratio producing 20% lysis, and t is the number of target cells per well.

For T cell cytotoxicity, PBMC (2 × 10⁶/mL) were sensitized by incubation (6 days, 37°C, 5% CO₂) with irradiated (10,000 rads) allogeneic Epstein-Barr virus–transformed B cells (10⁵ cells/mL). After being washed, sensitized cells were incubated (4 h, 37°C) in round-bottomed 96-well plates along with ⁵¹Cr-labeled target cells (2.5 × 10⁵ cells/well) at different effector-to-target cell ratios in the presence of either partially purified HRV-16 (5 × 10⁵ TCID₅₀/mL) or medium alone. Chromium release was converted into lytic units as described above.

**Incubation of isolated T cells and monocytes with HRV-16.** T cells were isolated from PBMC by use of a T cell enrichment column (R&D Systems), yielding 75%–95% CD³⁺ cells, 5%–24% CD56⁺CD³⁺ cells, and <1% CD14 or CD20 cells. Monocytes were isolated by incubating (4 h, 37°C) 100 µL of PBMC (2 × 10⁶ cells/mL in RPMI) in flat-bottomed 96-well plates. Nonadherent cells were removed by vigorous pipetting with PBS. The T cells and monocytes were then incubated separately overnight with either HRV-16 (10 TCID₅₀/cell) or medium alone. After bound virus was washed away, the cells were recombined and stimulated with tetanus toxoid (0.04 LU/mL). [³H]Thymidine was added on day 6, and incorporation into DNA was measured on day 7.

**Use of WIN 54954 to inhibit HRV-16–ICAM-1 binding.** In preliminary experiments, WIN 54954 inhibited HRV-16–ICAM-1 binding on HeLa cells, as determined by measuring ICAM-1 receptor occupancy by flow cytometry (table 1). HeLa cells were incubated (16 h, 37°C) with HRV-16 (10 TCID₅₀/cell) or medium alone in the presence of 0–20 µg/mL WIN 54954. HeLa cells had a high baseline expression of CD54, but binding of labeled CD54 antibody was blocked by incubation with HRV, as indicated by a reduction in the median channel fluorescence (from 50.8 to 7.1). WIN 54954 at concentrations of 2–20 µg/mL, which had no direct effects on CD54 expression, blocked the HRV-mediated reduction in CD54 binding.

On the basis of the preliminary data and previously published reports [33, 36], WIN 54954 was used as a specific inhibitor of...
HRV–ICAM-1 binding. To accomplish this, HRV-16 was preincubated for 1 h with either WIN 54954 (40 μg/mL) or medium alone. PBMC (10⁵ cells/well in 200 μL final volume) were incubated with RPMI plus 25% autologous plasma and 0.04 LfU/mL tetanus toxoid in a 96-well microtiter plate. Either HRV-16 (2 TCID₅₀/ cell), HRV-16 plus WIN 54954 (10 μg/mL final concentration), or medium alone was then added to the wells. The plate was pulsed with [³H]thymidine on day 6, incubated overnight, and harvested on day 7.

Results

Effect of HRV on T cell proliferation. To determine if a major group HRV could interfere with T cell proliferation, we stimulated PBMC with mitogens, IL-2, allogeneic T cells, or one of four different antigens (tetanus toxoid, VZ, ragweed extract, or streptokinase) in the presence or absence of HRV-16. HRV-16 significantly inhibited T cell proliferation to tetanus, VZ, and ragweed antigens, and it also tended to reduce streptokinase-induced proliferation (figure 1). In contrast, HRV-16 had no effect on proliferative responses to phytohemagglutinin, ConA, or IL-2. The effect on allogeneic T cell proliferation was varied: HRV-16 had no effect on proliferation induced by the TK6 lymphoblastic cell line but tended to reduce proliferation stimulated by irradiated allogeneic PBMC. To determine if the inhibition was dose-dependent, increasing amounts of HRV-16 were incubated with VZ-activated PBMC. As the dose of HRV was increased from 0.1 to 10 TCID₅₀/cell, VZ-induced T cell proliferation progressively diminished (figure 2).

To confirm findings obtained using PBMC and to define the relevant mechanisms, we next examined the effect of HRV-16 on proliferation of a T cell clone (49.19) that is activated by serotype-specific epitopes of a minor group HRV serotype, HRV-49, but does not proliferate in response to HRV-16 (unpublished data). When HRV-16 was added to a culture of clones in the presence of antigen (irradiated HRV-49) and APCs, there was a reduction in antigen-specific T cell proliferation, and this effect was similar to that produced by ICAM-1 MAb (figure 3). HRV-16 that was partially purified to remove products of HeLa cell origin also significantly inhibited T cell proliferation.

To determine if viral replication was required to inhibit T cell proliferation, an aliquot of HRV-16 was divided and half of the viral suspension was UV-irradiated to produce nonreplicative virus particles. Both live and UV-inactivated virus inhibited antigen-specific proliferation of either PBMC (figure 4A) or T cell clone 49.19 (figure 4B) to a similar degree.

Effect of incubating monocytes versus T cells with HRV-16. To determine if HRV-16 inhibits T cell proliferation through effects on APCs (monocytes) or T cells, we prepared cell suspensions enriched for monocytes or T cells and incubated the purified cells separately with HRV-16 or medium alone. After the cells were washed to remove unbound virus, T cells were added back to the monocytes, and the mixture was stimulated with tetanus toxoid. Tetanus toxoid–driven lymphocyte proliferation was inhibited when monocytes alone or both monocytes and lymphocytes were preincubated with HRV-16 (figure 5). In contrast, proliferation was not inhibited when T lymphocytes alone were preincubated with HRV-16.

Blocking HRV effects with WIN 54954. To determine if HRV-16 inhibited T cell proliferation through an ICAM-1–dependent mechanism and to verify that the effect of the HRV suspension was caused by the virus and not by a HeLa cell product, we used WIN 54954 to block attachment of HRV-16 to ICAM-1. As shown previously, tetanus toxoid–induced proliferation was inhibited by HRV-16; however, WIN 54954 completely blocked the inhibitory effect of HRV-16 (figure 6).

Effect of HRV on LPS-induced cytokine secretion. Poliovirus, a closely related picornavirus with a replicative cycle nearly identical to that of HRV, may dramatically inhibit host cell transcription within hours of binding to the cell [8]. To determine whether HRV could inhibit monocyte cytokine secretion, an important costimulatory signal for T cell proliferation, monocytes were activated with LPS in the presence of medium alone, HRV-16, or UV-inactivated HRV-16. TNF-α secretion was not inhibited by either live or inactivated HRV-16, and TNF-α levels tended to be higher in virus-inoculated samples (figure 7). Additional experiments revealed that IL-1 secretion was also unaffected by HRV-16 (data not shown).

Effects of HRV-16 on T cell and NK cell cytotoxicity. To determine if HRV-16 could inhibit lymphocyte responses other than T cell proliferation, T cell and NK cell cytotoxicity assays were done using PBMC obtained from 5 healthy subjects in
Mitogens

Tetanus

U5

VZ

Ragweed

SKSD

IL-2 TK6

PBMC

Figure 1. Effect of human rhinovirus (HRV)-16 on proliferation of peripheral blood mononuclear cells (PBMC). HRV-16 significantly inhibited T cell proliferation triggered by tetanus toxoid (n = 7, *P < .005), varicella antigen (VZ; n = 7, **P < .001), and ragweed (n = 4, *P < .05) but had no effect on proliferation secondary to mitogens (combined data represented for phytohemagglutinin and concanavalin A; n = 4 and n = 2, respectively), interleukin-2 (IL-2; n = 6), or irradiated TK6 cells (n = 7). HRV also tended to inhibit proliferation induced by irradiated allogeneic PBMC (n = 6, P = .07) and streptokinase (n = 4, P = .2). Dose of HRV-16 was 1 TCID50/cell for experiments using ragweed and streptokinase and 10 TCID50/cell for all other experiments. Data are expressed as stimulation index (SI) of cultures incubated with indicated stimulus and medium from uninfected HeLa cells (C) or HRV-16. * = geometric mean SIs for each set of experiments.

Figure 2. Dose-response effect of human rhinovirus (HRV)-16 on varicella-induced proliferation. Peripheral blood mononuclear cells were incubated with varicella antigen for 7 days in presence of increasing concentrations of HRV-16. Proliferation was significantly inhibited by 1 and 10 TCID50/cell HRV-16 (*P < .01, n = 6; **P < .001, n = 8).

Figure 3. Effect of human rhinovirus (HRV)-16 on proliferation of antigen-specific T cell clones. Antigen-induced proliferation of HRV-49-specific T cell clones was significantly inhibited by either 10 TCID50/cell HRV-16 (HRV16, *P = .02, n = 4), same dose of partially purified HRV-16 (pHRV16, **P = .04, n = 3), or 20 µg/mL anti–intracellular adhesion molecule-1 monoclonal antibody (ICAM-1) (#P = .02, n = 4). Data represent geometric means ± SEs.

Discussion

Our data demonstrate that HRV-16 inhibits both antigen-specific T cell proliferation and cytotoxicity through an ICAM-1-dependent mechanism. Although HRV inhibits antigen-spe-
cific T cell proliferation to antigens, such as tetanus toxoid, VZ, ragweed, and Candida species, it had no effect on T cell proliferation mediated by phytohemagglutinin, irradiated TK6 cells, or IL-2. Since antigens differ from the latter stimuli in that they require processing and major histocompatibility complex—restricted presentation to the T cell, these data suggest that HRV inhibits T cell proliferation through effects on the APC. The normal proliferative responses to IL-2 and mitogen also indicate that HRV is not directly toxic to T lymphocytes, and this was confirmed by the finding that T cells incubated separately with HRV and then recombined with APCs proliferated vigorously after stimulation with antigen. In contrast, separate incubation of HRV-16 with monocytes inhibited the subsequent ability of these cells to activate T cells, indicating that HRV indirectly exerts its effects on T cell proliferation through effects on the APC. Furthermore, inhibition of APC function was dependent upon HRV binding to ICAM-1 because WIN 54954, which blocks HRV-16–ICAM-1 binding, also blocked the effects of HRV-16 on T cell proliferation.

The effect of HRV-16 on antigen-specific proliferation varied with the dose of virus and the individual antigen. Likewise, previous reports have found that the requirement for antigen-independent interactions, such as ICAM-1/LFA-1 for T cell

Figure 4. Effect of UV-inactivated human rhinovirus (iHRV-16) on T cell proliferation. iHRV-16 was as potent as live human rhinovirus (HRV)-16 in inhibiting antigen-specific proliferation of peripheral blood mononuclear cells (PBMC) stimulated with either tetanus toxoid, varicella antigen, ragweed extract, or Candida skin test antigen (*P < .005, **P < .05, n = 10) (A) or HRV-49–specific T cell clones (†P = .01, ††P < .05, n = 4) (B). Data represent geometric means ± SEs.

Figure 5. Effect of preincubating monocytes vs. lymphocytes with human rhinovirus (HRV)-16 on antigen-specific proliferation. Monocytes and T cells were purified from peripheral blood mononuclear cells and then incubated overnight separately with either 10 TCID50/cell HRV-16 (+) or medium alone (−). Cells were then washed, recombined, and stimulated with tetanus toxoid (0.64 LFU/mL). Preincubation of either monocytes (*P = .03, n = 7) or monocytes and T cells (**P = .02, n = 7) with HRV-16 significantly decreased T cell proliferation. In contrast, incubating only T cells with HRV-16 did not significantly affect tetanus toxoid–induced proliferation. Data, which were not normally distributed, are represented as box plot, with 25–75 percentiles within box; median is horizontal line, and error bars indicate 10th and 90th percentiles.

Figure 6. Effect of WIN 54954 (WIN) on human rhinovirus-16 (RV)–induced inhibition of T cell proliferation. Peripheral blood mononuclear cells were stimulated with tetanus toxoid in presence of 2 TCID50/cell human RV or human RV that was preincubated for 1 h with 10 μg/mL WIN. WIN prevented human RV-mediated suppression of T cell proliferation (*P = .02, n = 4). WIN compound alone had no effect on tetanus toxoid–induced proliferation. Data represent geometric means ± SEs. tet = tetanus antigen.
tended to block proliferation induced by allogeneic PBMC but not by TK6 cells. The difference in these two responses to HRV may be due to differences in surface molecules, because T cell lines, such as TK6, would express relatively little ICAM-1 but abundant HLA-DR compared with monocytes and B cells in peripheral blood. These factors would tend to reduce the susceptibility of TK6 cells to the effects of HRV-16.

Both live and UV-irradiated (nonreplicative) HRV-16 effectively inhibited T cell proliferation, providing evidence that viral replication is not required for HRV to inhibit APC function. Furthermore, we [41] and others [42] have been unable to detect HRV replication in PBMC. Purified HRV and virus in HeLa cell supernatant were equally effective in inhibiting T cell proliferation, ruling out the possibility that this was caused by a factor synthesized by infected HeLa cells. Anti-ICAM-1 MAb also inhibited T cell proliferation, as previously noted, although the MAb tended to be less effective than HRV. This raises the possibility that, in addition to blocking ICAM-1/LFA-I interactions, HRV may also have additional inhibitory effects on APC function, such as inhibiting antigen uptake or processing. We found no evidence, however, that decreased cell proliferation was the result of reduced monocyte cytokine secretion. In addition, although HRV sometimes reduced rates of thymidine incorporation to levels below baseline (SI < 1), HRV does not adversely affect the in vitro survival of monocytes [41] or lymphocytes (unpublished data).

The inhibitory action of HRV was dose dependent, and significant inhibition of T cell proliferation occurred when virus concentrations exceeded 0.1 TCID_{50}/cell, or 5 × 10^{4} TCID_{50}/mL. High titers of HRV (10^{5}–10^{6} TCID_{50}/mL) may be found in nasal lavage fluid of infected individuals during the first 3 days of a cold [3], and considering that the nasal secretions are typically diluted in 5–10 mL of normal saline, the amount of HRV in nasal secretions appears to be sufficient to affect ICAM-1–dependent processes in the airway or possibly in regional lymph nodes, where respiratory viruses may be trans-

**Figure 7.** Effect of human rhinovirus (HRV)-16 on lipopolysaccharide (LPS)-induced monocyte tumor necrosis factor (TNF)-α secretion. Monocytes were stimulated with LPS in presence of medium alone, 10 TCID_{50}/mL HRV-16, or equivalent amount of UV-inactivated HRV-16 (iHRV-16). TNF-α secretion was not inhibited by HRV-16 and tended to be greater at all doses of LPS. Data represent geometric means of 2 experiments.

**Figure 8.** Effect of human rhinovirus (HRV)-16 on T cell- and NK cell–mediated cytotoxicity. A, HRV-16 significantly inhibited cytotoxic T cell responses to Epstein-Barr virus–transformed allogeneic B cells (P < .01, n = 5). B, In contrast, NK cell activity, as measured by lysis of K562 cells, tended to be slightly enhanced by HRV-16, although this trend was not statistically significant (P = .12, n = 5). CTL = cytotoxic T lymphocyte.
ported by afferent lymphoid vessels [43]. It is unlikely, however, that HRV infection, which is localized to the respiratory tract, would inhibit systemic immune responses through this mechanism.

In addition to effects on T cell proliferation, cytotoxic T cell responses were also inhibited by HRV-16. Since proliferation and virus-specific cytotoxicity both contribute to the clearance of respiratory viral infections [44], inhibiting T cell immune responses may therefore give major group HRVs a competitive advantage in the kinetic race between viral replication and the clearance of virus-infected cells by the immune system. The net result may be prolonged or enhanced HRV replication, producing greater viral shedding and thus an increased likelihood of virus transmission to another host [45]. In contrast to effects on T cells, HRV did not inhibit NK cell responses, despite the fact that ICAM-1/LFA-1 binding can contribute to NK activity under some conditions [46].

Another possible effect of modulating local immune responses may be to increase the chances of coinfection with other agents. Rhinovirus upper respiratory infections can lead to secondary bacterial infections of the middle ear or sinuses [4–7], and coinfections with HRV and bacteria may be particularly difficult to treat. For example, Sung and et al. [7] studied 71 patients with combined viral and bacterial otitis and found that the presence of HRV was associated with a higher incidence of therapeutic failure than were respiratory syncytial, parainfluenza, or influenza viruses. Though local tissue swelling, which causes impaired drainage of the sinuses and middle ear, undoubtedly contributes to the high incidence of secondary bacterial and viral infections [47], inhibition of lymphocyte function may also predispose to local infectious complications.

In summary, major group HRVs, such as HRV-16, can inhibit antigen-specific T cell proliferation, T cell cytotoxicity, and potentially other processes that are dependent on ICAM-1/LFA-1 binding. This inhibition is likely to occur in the local airway environment, where high titers of HRV may be found during an acute infection. Modulation of ICAM-1–dependent immune responses may give the virus a competitive advantage with the immune system, leading to enhanced viral replication and transmission, and also contribute to the high incidence of other respiratory infections that follow HRV infections.

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References

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