Epidermal Growth Factor Receptor Signaling to Erk1/2 and STATs Control the Intensity of the Epithelial Inflammatory Responses to Rhinovirus Infection*

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Rhinovirus infection is the most common cause of acute exacerbations of inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease, where it provokes steroid refractory and abnormally intense neutrophilic inflammation that can be life threatening. Epidermal growth factor receptor (EGFR) expression correlates with disease severity and neutrophil infiltration in these conditions. However, the role of EGFR signaling in rhinovirus infection is unknown. We measured the key determinants of neutrophilic inflammation interleukin (IL)-8 and ICAM-1 in rhinovirus (RV16 serotype)-infected bronchial epithelial cells, BEAS-2B. RV16 infection stimulated IL-8 and ICAM-1 expression, which was further elevated (2-fold) by transient up-regulation of EGFR levels. Detection of viral RNA by quantitative real time PCR confirmed that enhanced expression was not associated with increased viral replication. EGFR ligands (epiregulin, amphiregulin, and heparin-binding epidermal growth factor) were induced by RV16 infection, and inhibition of metalloproteases responsible for ligand shedding partially suppressed this response. The EGFR inhibitor AG1478, completely blocked IL-8 and ICAM-1 expression to basal levels, as did the specific Erk1/2 inhibitor U0126. The p38 mitogen-activated protein kinase inhibitor SB203580 blocked IL-8 secretion but not ICAM-1 expression, whereas the PI3K inhibitor wortmannin was ineffective in both responses. Kinase inactive K721R EGFR, which is selectively deficient in STAT signaling, reversed RV16 responses associated with EGFR overexpression. In conclusion, RV16 infection rapidly promotes induction of EGFR ligands and utilizes EGFR signaling to increase IL-8 and ICAM-1 levels. These results suggest that targeting EGFR may provide a selective therapy that dampens neutrophil-driven inflammation without compromising essential antiviral pathways mediated by pathogen recognition receptors such as TLR3.

Although great advances have recently been made in understanding the nature of innate immunity at epithelial barriers, little is understood of the molecular rheostats that control the intensity of these responses. An identical infectious agent can trigger benign or pathogenically intense inflammation in different individuals. Chronic inflammatory lung diseases, such as asthma and COPD2 are at epidemiologic levels globally and afflict more than 1 billion people. Individuals with these conditions are particularly susceptible to acute exacerbations triggered by respiratory tract infection (1–3). Because it is known that these exacerbations are associated with inflammation that is much more intense, often life threatening, we reasoned that epithelial defects known to occur in these conditions might provide fundamental insights into mechanisms regulating the nature of mucosal responses to pathogens.

Respiratory viruses are frequently identified in exacerbations. The use of sensitive PCR-based detection methods has identified viruses in the majority of childhood and adult asthma exacerbations (55–80%) (4–6). Similar detection rates are observed in COPD exacerbations, with detection being more prominent in events requiring hospitalization (7–10). Of these viruses, rhinoviruses (RV) are the most common pathogens detected during an asthma or COPD exacerbation, with at least half of viral triggered episodes being associated with RV (4, 8, 9). The major group of RV including the RV16 strain uses the intercellular adhesion molecule (ICAM-1) as a receptor to infect the respiratory epithelium (11). Because rhinovirus is not itself cytopathic, the intensity of inflammation during the host immune response is thought to be a critical determinant of exacerbation severity (2). Accordingly in healthy humans RV16 infection produces a trivial inflammatory response, but asthmatics and COPD patients mount a more intense reaction to infection (12, 13).

A common and striking molecular feature of the asthmatic and COPD airway is the induction of receptor tyrosine kinase epidermal growth factor receptor (EGFR). Because EGFR and its associated ligands regulate cellular proliferation, differentiation, survival, and migration, this receptor can coordinate repair of damaged epithelium (14). EGFR is normally confined to the intercellular lateral junctions of columnar and basal cells in the bronchial epithelium (15). In contrast, the asthmatic airway displays increased uniform staining throughout the epithe-
lumen including the luminal surface (16, 17) and correlates with increasing severity of asthma (16). Chronic smoke exposure also promotes epithelial irritation (18), and EGFR is up-regulated in COPD (16, 17, 19–21). Furthermore, the polarization of apical expression of EGFR ligands, which are normally separated from basolateral expression of EGFR, is lost. Also, proteases able to liberate membrane-bound latent EGFR ligands are induced; thus the receptor comes into proximity to the milieu of growth factor ligands secreted apically in response to damage mediated by infection. Thus EGFR signaling contributes to inflammation because EGFR ligands directly promote steroid refractory production of the major neutrophil chemokine, interleukin-8 (IL-8), in primary epithelial cultures (22). A strong correlation between EGFR, IL-8, and submucosal neutrophils in asthmatic bronchial biopsies has also been demonstrated (22).

We therefore tested the hypothesis that overexpression of EGFR is a fundamental determinant of epithelial responses to RV16 using IL-8 and ICAM-1 as inflammatory response indices. We dissected the nature of the amplifying effect of EGFR pharmacologically and by genetic manipulation of EGFR. Our findings show that the EGFR/Erk pathway regulates RV16 induction of IL-8 and ICAM-1, and overexpression of EGFR augments their release in a STAT-dependent manner. Thus targeting EGFR may offer an effective therapy that reduces the inflammatory burden associated with asthma and COPD exacerbations, which operates independently of the antiviral defenses of the hosts.

MATERIALS AND METHODS

Cell Culture—Human BEAS-2B cells were obtained from ATCC (Manassas, VA) and were cultured in a 1:1 mixture of keratinocyte serum-free medium supplemented with 50 mg/ml of bovine pituitary extract and 5 μg/ml of epidermal growth factor, and minimum essential medium supplemented with 10% FCS, 2 mM L-glutamine, 1.0 mM sodium pyruvate, 0.1 mM nonessential amino acids, and 1.5 g/liter sodium bicarbonate and antibiotics (5 μg/ml gentamycin, 100 μg/ml penicillin, 100 μg/ml streptomycin). HeLa cells of the Ohio strain were a gift from Dr. Reena Ghildyal (Department of Medicine, Monash University, Melbourne, Australia) and were cultured in minimum essential medium supplemented with 10% FCS, 2 mM L-glutamine, and 25 μg/ml gentamycin. All of the cell culture medium and supplements were purchased from Invitrogen.

Viral Stock Preparation—RV16 (gift from Dr. Ghildyal, Monash) was cultured in Ohio-HeLa cells. Stock viruses were inoculated onto HeLa cells until a cytopathic effect was observed. Supernatant was collected, and the cell debris was cleared by centrifugation. RV16 was titrated by diluting stock virus (10^-1 to 10^-8) and then inoculating HeLa cells in 96-well plates. Upon observation of cytopathic effect, TCID_50 (50% tissue culture infectious dose) was determined by the Reed-Muench method.

Transient Expression of EGFR cDNA—Human EGFR cDNA and the kinase inactive EGFR mutant (K721R) cloned into the mammalian expression vector pcDNA1 (Invitrogen) have been previously reported (23). BEAS-2B cells were plated out in 6-well multidishes for 24 h prior to transfection using the Effectene reagent (Qiagen). Transfections were carried out in Dulbecco’s modified Eagle’s medium supplemented with 5% FCS together with 5 μg/ml gentamycin, and the cells were infected with RV 24 h post-transfection.

Cell Infection and Inhibitors—The cells were infected with RV16 (multiplicity of infection of 2) for 1 h on a rocker at 37 °C and subsequently replenished with fresh maintenance medium (Dulbecco’s modified Eagle’s medium with 1% FCS). In some experiments, prior to infection, the cells were exposed to selective inhibitors for 30 min. The EGFR blocker AG1478 (10 μM; Biomol, Plymouth Meeting, PA), the Erk1/2 inhibitor U0126 (10 μM; Cell Signaling Technology, Beverly, MA), the p38 inhibitor SB203580 (10 μM; Cell Signaling Technology), the broad spectrum protease inhibitor GM6001 (10 μM; Biomol), and tumor necrosis factor proteinase inhibitor-1 (10 μM; Merck) were used. At specified time points cell pellets were harvested, archived at −70 °C, and subsequently subjected to Western analysis and quantitative real time PCR (QPCR) as detailed below.

Quantification of IL-8, EGFR, and ICAM-1 Protein—Cell-free supernatants were collected, and IL-8 concentration was measured using commercially available paired antibodies and standards, following the manufacturer’s instructions (BD Pharmingen). Western blotting was performed to quantify EGFR, ICAM-1, and tubulin levels as previously described (24). Primary antibodies (Cell Signaling) were incubated overnight at 4 °C and visualized by autoradiography using chemiluminescence (ECL Plus; Amersham Biosciences). Densitometry was performed using Kodak EDAS one-dimensional image analysis software.

RNA Extraction and QPCR—Total RNA was isolated from individual samples, according to the manufacturer’s instructions, using the RNeasy kit (Qiagen). The purified RNA was used as a template to generate first-strand cDNA synthesis using SuperScript III (Invitrogen) as previously described (25). QPCR was performed using the ABI PRISM 7900HT sequence detection system (Applied Biosystems). For IL-8 and ICAM-1, TaqMan probe/primer combinations were used. A total volume of 10 μl was used for TaqMan PCR using AmpliTaq Gold polymerase and universal master mix (Applied Biosystems). EGFR ligands primers listed in Table 1 (EGF, HB-EGF, transforming growth factor α, epiregulin, and amphiregulin) were designed using the Primer Express software (Applied Biosystems), and the reactions were performed using SYBR green master mix (Invitrogen). Default PCR thermal profiles were

### TABLE 1

| Target                  | Sequence                                   |
|-------------------------|--------------------------------------------|
| Transforming growth factor α | Sense 5'-TGTTGCTGTTGCTCCCATGCTT
                                 | Antisense 5'-GTCACCTCCAGGGAACCAAA
| EGFR                    | Sense 5'-GTCACCTCCAGGGAACCAAA
                                 | Antisense 5'-AAATGACATCTGCGAATTCCTTGAG
| HB-EGF                  | Sense 5'-CGTTGCGGGCACCATG
                                 | Antisense 5'-GGAGAAGACTGCGACGGAAAG
| Amphiregulin            | Sense 5'-ACCTGGCCTGAGGACATTATAGT
                                 | Antisense 5'-CCCTTCCCCAGAAGTAACTGCTCA
| Epiregulin              | Sense 5'-TCTCTTCTCTACTGAGACGATCGAT
                                 | Antisense 5'-CCCCCTCATTAGCTGAACTTCTT
| IR8                     | Sense 5'-CCGCGCTTGAAGTAACTTCTT
                                 | Antisense 5'-TTGCAAACTGTTCTTCTGTC
| RV16                    | OL26 5'-GCACTCTCTGTTCTTCCCTCC
                                 | OL27 5'-CGAGACCCAAAGGTTAGGC
used as previously described (25). The threshold cycle numbers were calculated using the \( \Delta \Delta C_T \) relative value method using 18S rRNA as the housekeeping gene. RV16 viral RNA detection was achieved with the OL26 and OL27 primers listed in Table 1. Viral RNA was detected only in RV16-infected cells, present at the early 3-h time point and increasing over the 40-h kinetic study, indicating productive viral replication. At the indicated time points, cell-free supernatants from vehicle-, diluent-, and RV16-treated cells were assayed for secreted IL-8 by ELISA. *, \( p < 0.05 \) by \( t \) test (\( n = 4 \)).

RESULTS

IL-8 Expression Is Augmented in RV16-infected Cells Overexpressing EGFR—RV16 infection of BEAS-2B cells led to rapid viral RNA production within 3 h, increasing over the 40-h incubation period as assessed by detection of viral RNA using QPCR (Fig. 1A). Although a previous study did not detect RV14 virus within 4 h of BEAS-2B infection (27), the serial titers methodology used in that study is markedly less sensitive than QPCR-based approaches (28). RV16 infection stimulated IL-8 secretion that was significantly greater than diluent-treated cells. IL-8 production occurred within 3 h of infection, and the levels remained significantly elevated over the 40-h time course (Fig. 1B). The early induction of IL-8 is consistent with early detection of viral RNA production in infected cells.

BEAS-2B cells express low endogenous EGFR levels that are at the lower limit of detection by Western analysis. Cells transfected with EGFR cDNA displayed markedly higher EGFR levels (Fig. 2A), and the protocol was standardized to reproducibly increase receptor levels by about 10–15-fold. Importantly, cells overexpressing EGFR secreted 2-fold more IL-8 in supernatants collected at the indicated time points (Fig. 2B). To assess whether IL-8 levels were being transcriptionally regulated,
Role of EGFR in Rhinovirus Infection

 FIGURE 3. EGFR overexpression enhanced RV16-mediated ICAM-1 levels. A, endogenous ICAM-1 levels were measured at the indicated time points by QPCR over a 40-h time course in vehicle- or diluent-treated and RV16-infected cells. B, ICAM-1 protein levels were assessed in untransfected (open bar) and EGFR-transfected (closed bar) cells 40 h after RV16 infection by Western analysis (inset, representative blot). The blots were subjected to densitometry and presented as a fold increase above untransfected/vehicle treated cells. *, p < 0.05 by t test (n = 5).

mRNA expression was analyzed by QPCR. Like protein secretion, RV16 infection induced IL-8 transcript, and this was further enhanced 2-fold in EGFR-overexpressing cells (Fig. 2C). Elevated EGFR levels also promoted an increase in basal IL-8 mRNA expression (Fig. 2C), which is consistent with the significant correlation between EGFR and IL-8 expression in asthmatic bronchial biopsies (22).

ICAM-1 Induction by EGFR Overexpression—ICAM-1 has previously been reported to be induced by RV16 infection (29), and likewise we observed a 2-fold increase in ICAM-1 mRNA that was only significant at the early time points (Fig. 3A). Consistent with transcript levels at 40 h, RV16 infection did not significantly alter ICAM-1 protein expression above vehicle-treated cells, as assessed by Western blotting (Fig. 3B). In contrast, RV16 infection significantly increased ICAM-1 levels in cells overexpressing EGFR. There was a small and nonsignificant trend toward increased ICAM-1 expression in vehicle- or diluent-treated cells transfected with EGFR cDNA. To assess whether increased inflammatory markers were associated with greater RV16 replication, viral RNA levels were measured in cells expressing endogenous and elevated EGFR. As shown in Fig. 4, no difference in viral RNA quantity was observed over 40 h, thus implicating alternate mechanisms for IL-8 and ICAM-1 amplification.

Mechanisms of EGFR Activation in RV16-infected Cells—Autocrine production of EGFR ligands in response to epithelial damage is associated with wound repair mechanisms (14); however ligand production in response to RV16 infection has not been investigated. Hence, we measured a panel of EGFR ligands by QPCR in RV16-infected BEAS-2B cells. As shown in Fig. 5, amphiregulin, and HB-EGF was elevated 1.5-fold in RV16-infected cells at the 3-h time point. We also observed a 2-fold induction of epiregulin in response to RV16 infection, again at the early 3-h time point, indicating a direct viral-mediated process for ligand up-regulation. Transforming growth factor α was not significantly altered by RV16, and unaltered C_tr (threshold) values for EGF were only detected at the later cycles (cycles 35–40; data not shown). Like other membrane-anchored growth factors, EGFR ligands exist as transmembrane precursors that are proteolytically cleaved and released to promote receptor engagement (30). Ectodomain shedding is regulated by matrix metalloproteases and the alternate class of metalloproteases known as ADAMs (a disintegrin and metalloproteases). To assess the role of metalloproteases in RV-mediated inflammatory events, we utilized the broad spectrum metalloprotease inhibitor, GM6001. IL-8 production in RV16-infected cells expressing endogenous receptor levels was suppressed with GM6001 by 50% (Fig. 6A). Likewise, enhanced IL-8 production in EGFR-overexpressing cells was blocked with GM6001 by about 50% compared with RV16-infected cells expressing endogenous receptor levels. GM6001 also significantly reduced ICAM-1 expression associated with elevated EGFR levels (Fig. 6B). We also utilized the selective ADAMs inhibitor tumor necrosis factor protease inhibitor-1 and observed no inhibitory effect on RV-mediated IL-8 production (data not shown). Collectively, these results implicate matrix metalloproteases in ectodermal ligand shedding.

EGFR Signaling Pathways Regulating IL-8 and ICAM-1 Expression—Ligand engagement of EGFR promotes formation of homodimeric and heterodimeric complexes with its closely related family member ErbB2/HER2, leading to receptor activation. Upon activation, multiple pathways are engaged and include (i) Ras/Erk MAPK, (ii) PI3K/Akt, and (iii) STAT transcription factors (31). To evaluate these signaling pathways, selective pharmacological inhibitors were used. The EGFR receptor blocker, AG1478 suppressed IL-8 production to base-
line levels (Fig. 7A), implicating EGFR signaling in endogenous and overexpressed systems. The Erk pathway blocker, U0126 also effectively blocked IL-8 production equivalent to AG1478 inhibitor levels. In contrast, the PI3K/Akt pathway inhibitor, wortmannin did not reduce IL-8 expression. The p38 MAPK has previously been shown to regulate cytokine production in response to RV infection, and consistent with this study (32), we observed a significant decline in SB203580 treated cells. Enhanced ICAM-1 expression in EGFR-overexpressing cells was inhibited by AG1478 and U0126 (Fig. 7B). Wortmannin was again ineffective at reducing ICAM-1 induction attributed to EGFR overexpression. In contrast to IL-8, p38 MAPK does not regulate ICAM-1 expression because SB203580 did not alter its expression. We next introduced EGFR kinase inactive K721R cDNA into RV16-infected BEAS-2B cells. This construct is defective in ATP binding and is unique in that it retains its ability to heterodimerize with ErbB2. This interaction is sufficient for activation of Erk and Akt pathways; however, STAT activation is completely absent (23, 33). Here, we observed that IL-8 and ICAM-1 expression attributed to elevated EGFR levels were reversed in EGFR K712R-expressing cells (Fig. 8). Hence, STAT signaling is unconditionally required for induction of inflammatory markers associated with enhanced EGFR expression.

**DISCUSSION**

In the present study we have found evidence that overexpression of EGFR regulates the intensity of rhinovirus induced inflammatory responses. Experimental human models of RV infection in individuals with asthma and COPD have directly demonstrated induction of enhanced inflammatory markers in the airways, an increase in clinical symptoms, and an accelerated decline in lung function (13, 34–37). In vitro, RV promotes expression of important host defense mediators including the neutrophil chemokine IL-8 (27), RANTES (38), inducible nitric-oxide synthase (39), and type 1 interferons (40). These mediators recruit neutrophils and eosinophils to the site of infection to clear damaged/infected tissue and cooperate in conjunction with interferons to limit viral replication. Excessive or persistent leukocyte migration into the airways are, however, thought to be deleterious because of their high protease and reactive oxygen species content. Accordingly, innate immune processes are also normally self-limiting because the initial insult promotes expression of key anti-inflammatory mediators such as IL-10 and SOCS proteins critical to resolution of the responses of the hosts (41). Defects in innate immunity have been identified in asthma and COPD. Bronchial epithelial cells from asthmatic subjects produce less type I and type III (α)}
interferons in response to RV infection, an event associated with increased survival of infected cells and enhanced viral replication (40, 42). Cigarette smoking is the main cause of COPD, and smoke exposure is known to impair antiviral immune responses and humoral host defenses (43). However, the molecular mechanisms responsible for exaggerated and/or persistent host-mediated inflammation that predispose to accelerated lung function decline still remain obscure.

The EGFR is more abundant at sites of airway damage where it coordinates essential wound repair mechanisms; however the chronic nature of lung diseases may contribute to dysregulated EGFR signaling. Also, susceptible chronic smokers display permanent genetic alterations known as somatic mutations induced by cigarette-derived carcinogens. We have previously proposed that somatic mutations associated with EGFR amplification are a major determinant of disease susceptibility and progression (44). Our findings highlight an important role for EGFR in IL-8 and ICAM-1 levels. BEAS-2B cells were transfected with an empty vector control (Vector), EGFR (WT), or kinase inactive EGFR (K721R) that has defective STAT signaling but retains its ability to activate Erk1/2 and Akt. 40 h following RV16 infection, supernatants were retained for IL-8 measurement by ELISA (A) and cell pellets were subjected to Western analysis using specific antibodies to ICAM-1 and α-tubulin (B). Western blots were subjected to densitometry and expressed as a percentage increase above the vector control (inset, representative blots). *, p < 0.05 by t test (n = 4).

Because elevated IL-8 and ICAM-1 expression were not associated with an increase in viral replication, we inferred that EGFR signaling events were contributing to amplified RV16 host defense responses. We demonstrate for the first time that RV16 infection promotes a rapid and transient induction of the EGFR ligands, amphiregulin, epiregulin, and HB-EGF. The early peak in EGFR ligand expression is most likely mediated by RV16 engagement of a pathogen recognition receptor such as TLR3. The concurrent release of antiviral mediators and EGFR ligands may cooperate in clearance of infection and repair of damaged tissue. A secondary consequence of excessive EGFR engagement is persistent inflammatory transcriptome signal-
ing. Consistent with this concept, we found that the specific EGFR inhibitor AG1478 completely blocked IL-8 production in RV16-infected cells to basal levels. Furthermore, elevated ICAM-1 expression caused by EGFR overexpression was reversed by AG1478 treatment. These findings implicate EGFR signaling as an indispensable component in RV-mediated inflammatory events. TLR3 is a unique TLR family member because it exclusively operates in a MyD88-independent manner via the adaptor molecule TRIF. Although MyD88-dependent pathways are classically associated with inflammatory gene induction, cells deficient in MyD88 still display MAPK and NFκB activation (48). Hence, our data favor a model where the initial RV insult promotes induction of selective EGFR ligands that subsequently activate EGFR to initiate inflammatory gene programs. In concordance with our findings, EGFR activation was shown to be essential for lipopolysaccharide- and phorbol 12-myristate 13-acetate-induced IL-8 production in airway epithelial cells (49). The role of ICAM-1 in RV infection of the respiratory epithelium is very well established (50–52), and it will be of interest to determine whether additional benefit could be obtained by combining EGFR blockers with ICAM-1 antagonists or knockdown approaches.

The Ras/Erk pathway regulates EGFR-mediated gene expression via the AP-1 transcription factor complex consisting of Jun, Fos, and ATF-2 dimers. These AP-1 subunits are regulated both at the transcriptional level and by MAPK-mediated phosphorylation. EGFR transactivation recruits the Grb2/Sos complex to the receptor, which then facilitates activation of Erk1/2 through a series of intermediate kinases (31). Because the selective Erk inhibitor U0126 blocked IL-8 and ICAM-1 expression in an analogous manner to AG1478, Erk kinases represent a critical effector molecule downstream of EGFR. The p38 MAPK is not classically associated with EGFR signaling; however, consistent with our findings, inhibition of p38 potently inhibited IL-8 secretion in BEAS-2B cells infected with RV16 (32). The MyD88-independent/TRIF signaling cascade has previously been shown to promote the delayed activation of p38 and NFκB (53). Hence, activation of TLR3 during RV infection can activate p38 and NFκB, and downstream events that regulate gene expression. The p38 MAPK also regulates post-transcriptional mechanisms responsible for IL-8 mRNA stability and can also control the translational machinery required for IL-8 protein expression (54). Because the p38 inhibitor, SB203580, did not inhibit ICAM-1 expression in EGFR-overexpressing cells, p38 is signaling independently of EGFR in RV-infected cells and differentially regulates IL-8 and ICAM-1.

EGFR transactivation also recruits the p85 subunit of PI3K, where the lipid kinase facilitates activation of key regulatory kinases such as Akt. The PI3K/Akt pathway plays an integral role in cell survival and can activate NFκB in a cell type- and stimulus-specific manner (35). This pathway was found to regulate IL-8 expression in RV39-infected epithelial cells through NFκB transactivation (56). In contrast, we observed no inhibitory effect with the PI3K inhibitor, wortmannin, which may reflect subtle differences in signaling triggered by RV16 versus RV39 serotypes. The PI3K pathway has recently been implicated as an early phase suppressor of TLR signaling via negative regulation of MAPK activity (57), and consistent with this concept we found that inhibition of this pathway augmented RV16-induced IL-8 expression. The conflicting data relating to PI3K/Akt regulation of RV-mediated inflammatory gene expression may reflect the cell and stimulus-specific nature of this pathway and/or altered cellular signaling associated with EGFR overexpression. EGFR transactivation also recruits and activates STAT proteins via a JAK kinase-independent manner, followed by translocation to the nucleus where they promote gene expression (31). Here, we show that the kinase inactive K721R construct deficient in EGFR-associated STAT activation reversed the amplified IL-8 and ICAM-1 inflammatory response associated with elevated EGFR levels.

Our findings identify the EGFR pathway as a key regulator of RV16-mediated induction of IL-8 and ICAM-1 in bronchial epithelial cells. Enhanced EGFR expression augmented inflammatory gene expression via downstream signaling to Erk1/2 and STAT pathways (Fig. 9). Because infectious exacerbations
Role of EGFR in Rhinovirus Infection

of COPD and asthma are commonly triggered by RV infections that are steroid refractory, transient disruption of EGFR signaling may provide an alternative approach to controlling these acute inflammatory events. Recurrent exacerbations accelerate decline in lung function and are the single most important determinant of disease morbidity, hospitalization, and total cost (58). Indeed, most of the health care resources consumed in the management of inflammatory lung diseases derives from the morbidity and mortality associated with these debilitating events (59, 60). Whereas current therapeutic options for treating exacerbations, such as anti-inflammatory glucocorticosteroids and bronchodilators have only modest effects in reducing their frequency and severity (61, 62), targeting the EGFR system may provide a novel therapeutic avenue. EGFR signaling has also been linked to goblet cell metaplasia causing mucus hypersecretion (63). Furthermore, because key antiviral defense programs involving type I interferons can be directly triggered by pathogen engagement of TLR3, inhibition of EGFR may provide a selective therapy that dampens neutrophil-driven inflammatory events without compromising essential antiviral pathways.

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