Title

Respiratory virus-induced EGFR activation suppresses IRF1-dependent Interferon-λ and antiviral defense in airway epithelium

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Authors

Ueki, Iris F
Min-Oo, Gundula
Kalinowski, April
et al.

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EGFR Inhibition Suppresses Respiratory Viral Infection In Vitro And In Vivo

J. Koff[1], G. Min-Oo[2], E. Ballon-Landa[3], A. Kalinowski[1], I. Ueki[2], L. Lanier[2], J. A. Nadel[4],
[1]Yale University, New Haven, CT, [2]University of California, San Francicso, San Francisco, [3]University of California, Irvine, Irvine, [4]

Rationale: Respiratory viruses cause pneumonia and exacerbations of chronic lung diseases, such as asthma and COPD. To date limited therapies are available to treat viral infections. Viruses induce epithelial production of IL-8, a neutrophil chemokine, via EGFR activation. Because there is no role for neutrophil recruitment in anti-viral responses, we hypothesized that: 1) virus-induced EGFR activation is important for infection, and 2) EGFR inhibition decreases viral infection.
Objective: Evaluate the effect of EGFR inhibition on respiratory viral infection in vitro and in vivo.
Methods: NHBE cells were infected with Influenza (Flu) H1N1 virus and Rhinovirus (RV) -1b and -16 with or without a selective EGFR inhibitor (AG 1478), and cytokine production was measured by ELISA. The effect of EGFR inhibitors [AG 1478, Gefitinib (Iressa ®)] on viral infection was measured by standard TCID50%, plaque assays, and flow cytometry in epithelial (MDCK, HeLa, and BEAS-2b) cell lines infected with Flu, RV1b, and RV16. C57BL/6 female mice infected with intranasal PR8/34 Flu were treated with Gefitinib or vehicle by gavage. 48 and 72 h after infection BAL and lungs were collected. Viral infection was measured in lung by plaque assay, and cytokines in BAL were measured by ELISA.
Results: Flu-, RV1b-, and RV16-stimulated NHBE cells increased IL-8 production compared to vehicle alone. The addition of AG 1478 decreased virus-induced IL-8 production significantly. EGFR inhibitors (AG 1478 and Gefitinib) suppressed Flu infection of MDCK cells, and RV infection in HeLa cells measured by TCID50% assay. An airway epithelial (BEAS-2b) cell line infected with each virus showed suppressed viral infection with the addition of Gefitinib by plaque assay. In vivo experiments confirmed that Gefitinib decreased Flu infection and MIP-2 production at 48 h. We found that EGFR inhibition does not affect internalization of Flu and RV infection in NHBE cells. Instead, EGFR inhibition increased epithelial production of IL-29.
Conclusions: EGFR inhibition decreases Flu- and RV-induced IL-8 production in NHBE cells. In addition, EGFR inhibition suppresses Flu and RV infection in vitro, and Flu infection in vivo. While this effect does not involve viral internalization, it may be mediated by an increase in IL-29 production, an important anti-viral mediator. Ongoing experiments will explore these mechanisms in detail.

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