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Abstract Title

B-Raf Kinase Blockade with Dabrafenib Ameliorates Lung Inflammation in Respiratory Syncytial Virus Infection

Authors

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Background

Respiratory syncytial virus (RSV) is the leading cause of hospitalization for acute bronchiolitis in children under 2 years old, resulting in 200,000 deaths annually worldwide. Currently, there are no effective antiviral therapies or clinically approved RSV vaccines for children. We recently demonstrated that B-Raf kinase, an important protein for various cellular functions, is involved in RSV replication, and that the B-Raf kinase inhibitor, dabrafenib, decreases both viral replication and inflammatory signalling in airway epithelial cells in vitro.

Objective

Thus, we hypothesized that B-Raf kinase blockade using dabrafenib may be a novel antiviral approach to treat RSV infection.

Methods

BALB/c female mice (6-7 weeks old) were treated with saline, vehicle, or dabrafenib four hours prior to mock (saline) or RSV intranasal infection (5×10^6 PFU/animal). Animals were weighed every day, and at 5 days post-infection, bronchoalveolar lavage (BAL) was collected to perform differential cell counting using Giemsa staining. Lung tissues were used to measure peribronchial and perivascular inflammation scores by histopathological grading systems, infectious viral load by plaque assay, and Cxcl1, Tnf- α , Il-6, and Il-1 β mRNA expression through RT-qPCR.

Results

RSV-infected mice lost weight up to 3 days post-infection and exhibited significantly increased lung inflammation when compared to the saline-treated and -infected mice. Dabrafenib treatment did not protect animals against RSV-induced weight loss, and no differences in lung viral loads were observed. The treatment reduced immune cell infiltration and significantly reduced lung inflammation scores compared to vehicle-treated RSV-infected mice. Perivascular and peribronchial scores were reduced by nearly 50%. Additionally, dabrafenib significantly decreased mRNA levels of Cxcl1 and Il-6 by 6-fold and 8-fold, respectively.

Conclusion

B-Raf kinase blockade reduces RSV-induced lung inflammation in mice, demonstrating dabrafenib's potential as an alternative approach against RSV infection. For this reason, we will continue to investigate alternative dabrafenib regimens and dosages.