



Air Pollution Exposure And Altered Immune Response To Respiratory Viral Infection

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Why could what we breathe affect viral infections?

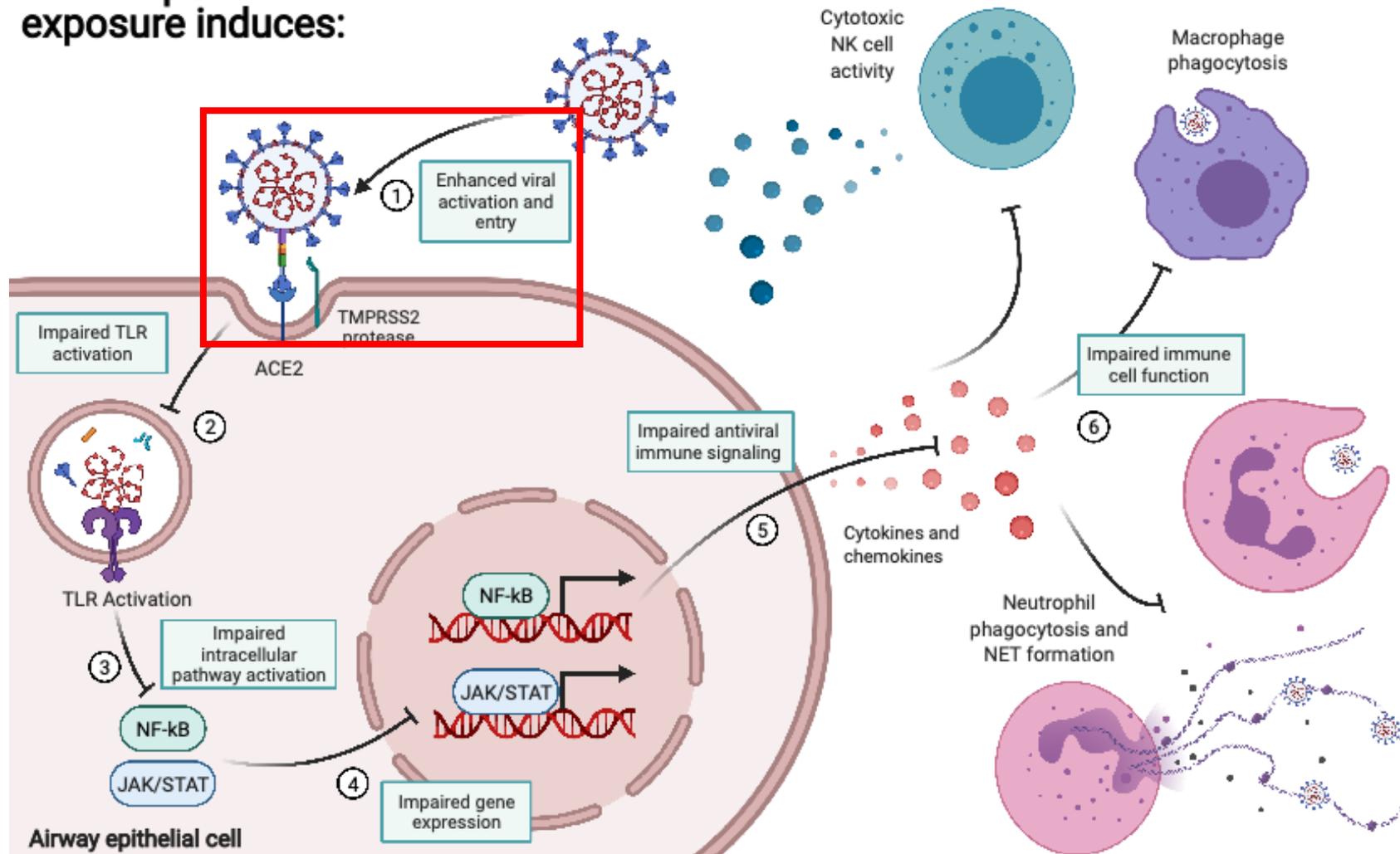
- **Concurrent exposures:**
 - We breathe over 12,000 Liters of air per day – contains both infectious pathogens and air pollutants
- **Target the same tissue**
 - Respiratory epithelium is the primary target for both viral pathogens and inhaled pollutants
- **Rely on similar host defense functions**
 - Innate immune cells are the primary and initial response for pollutants and viral infections

Air Pollution and SARS-CoV2 – Epidemiological Studies from around the World

- During the SARS outbreak in 2002, SARS patients coming from areas of high air pollution were more than twice as likely to die from the disease (Cui et al., 2003)
- Long-term exposure to air pollution was associated with increased COVID-19 severity (Conticini et al., 2020)
- Higher historical PM_{2.5} exposures are positively associated with higher county-level COVID-19 mortality (Wu et al., 2020)
- Environmental factors (air quality index) are associated with daily number of COVID-19 cases (Ma et al., 2021)

Potential Interactions Between Air Pollutants and SARS-CoV2

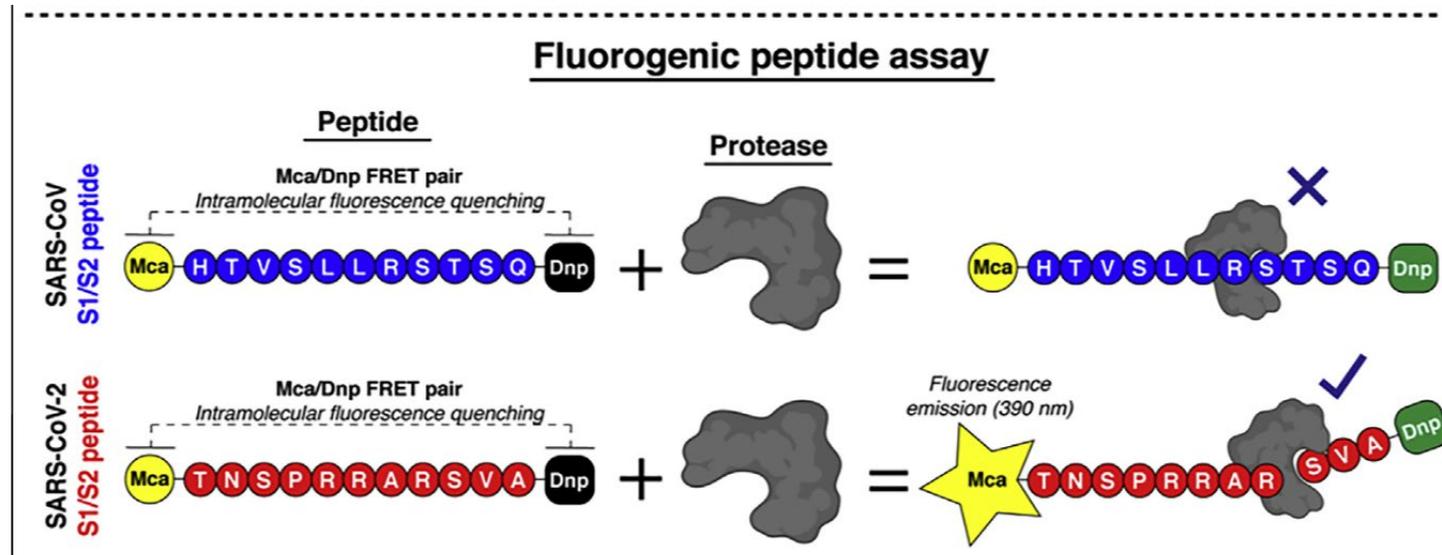
Inhaled pollutant exposure induces:



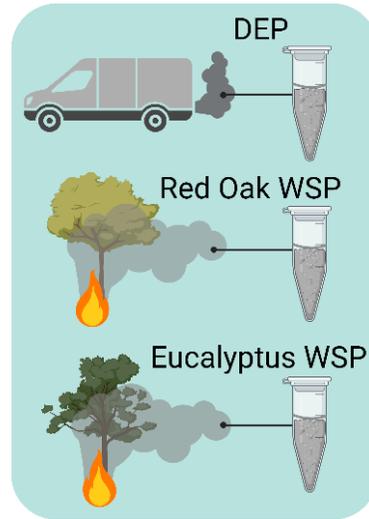
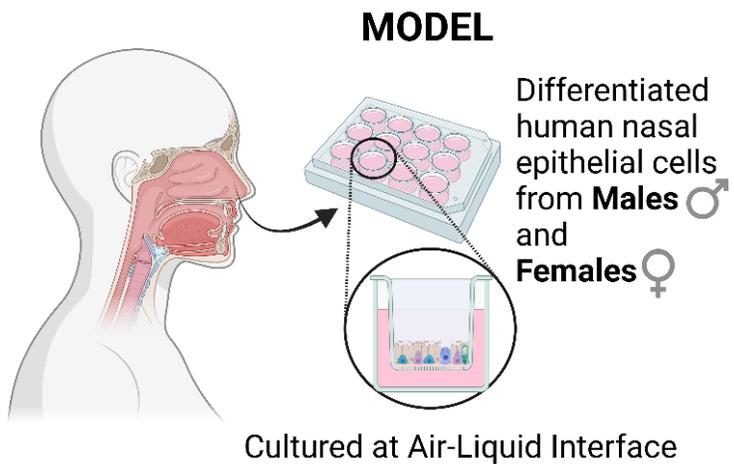
Pollutant-induced Modification of Viral Receptors/Proteolytic Activation

- Proteolytic Cleavage/Activation of SARS-CoV2 requires proteases, such as TMPRSS2, furin, cathepsins, etc.
- Exposure to diesel exhaust increased expression of ACE2 and TMPRSS2 in human pluripotent stem cell-derived alveolar epithelial cells and alveolar organoids (Kim et al., 2020)
- Expression of ACE2 and TMPRSS2 might be regulated by several consensus motifs for binding of the aryl hydrocarbon receptor (AhR), a common pathway activated by ambient air pollutants (Watzky et al., 2020; Lawal 20217)
- Exposure to ozone increases secreted levels of TMPRSS2 and decreases levels of SLPI (antiprotease), which was linked to increased viral entry of influenza virus (Kesic et al., 2012)

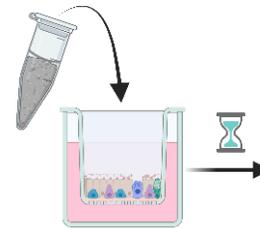
Internally Quenched Fluorescent Peptides to Assess Cleavage Activity



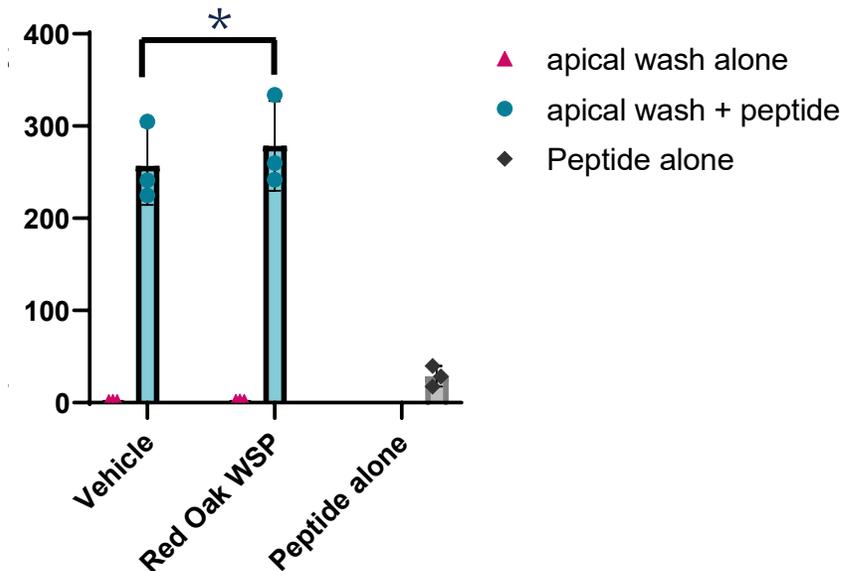
WSP Enhance Cleavage of SARS-CoV2 Peptide



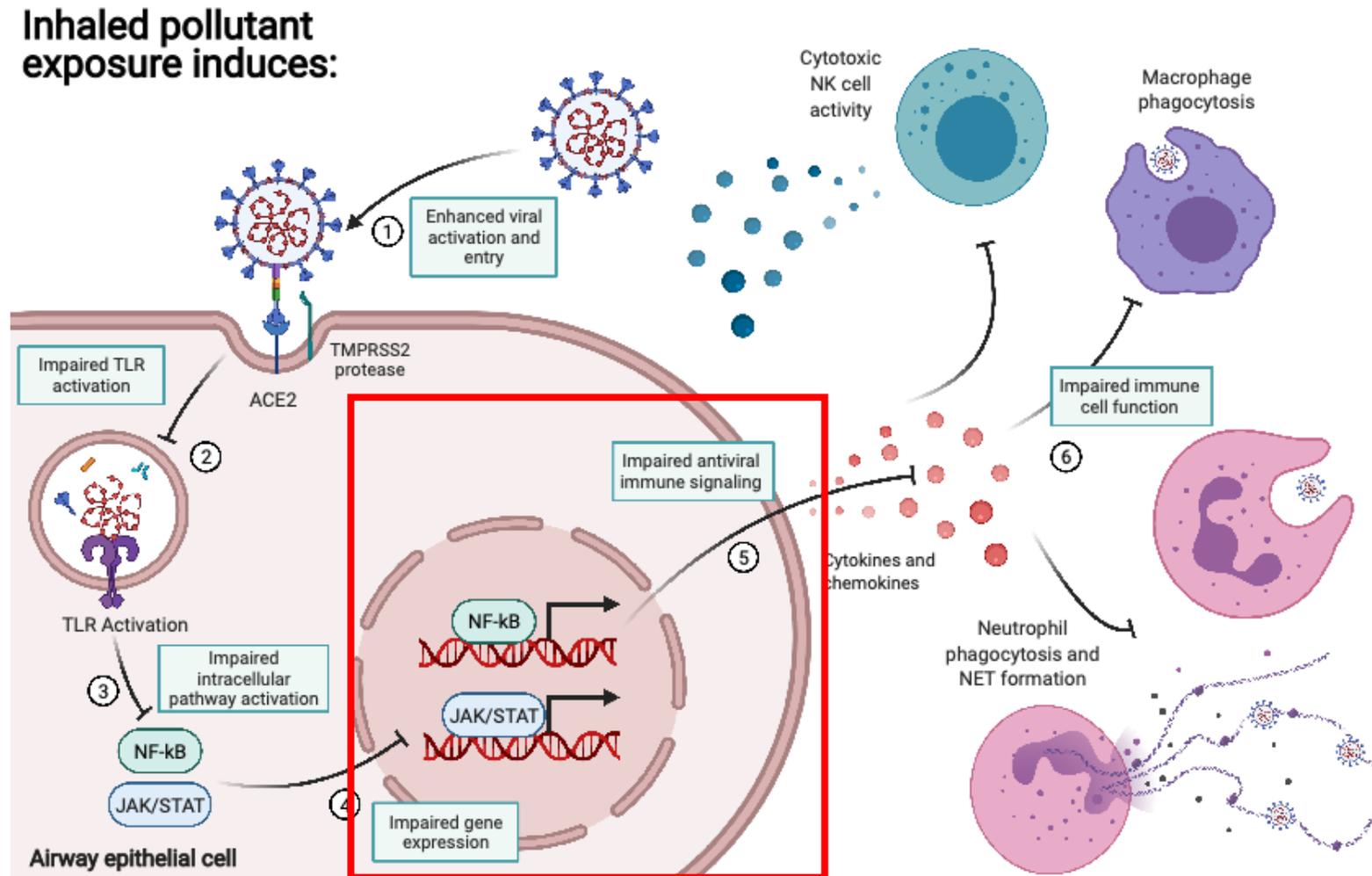
22 $\mu\text{g}/\text{cm}^2$
particulate
suspension
(or vehicle)



Apical washes from
particle exposed and
unexposed hNECs for
cleavage assay

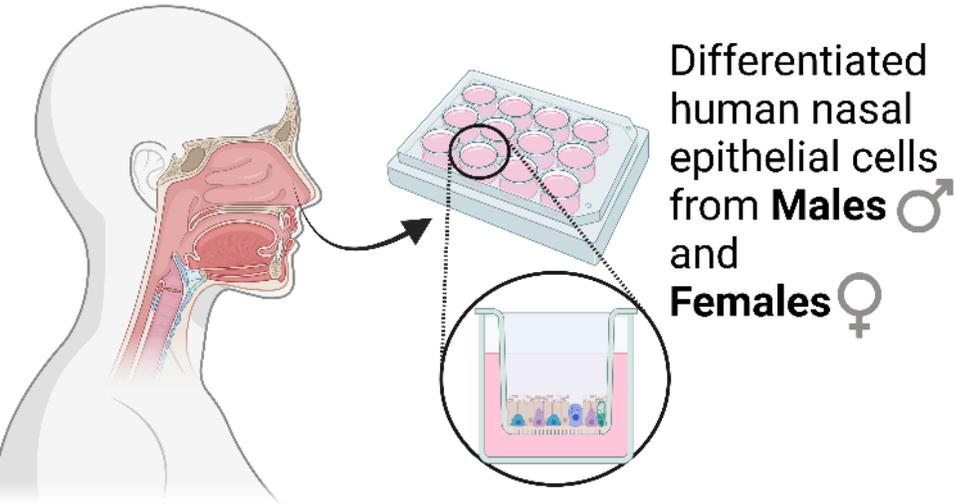


Potential Interactions Between Air Pollutants and SARS-CoV2

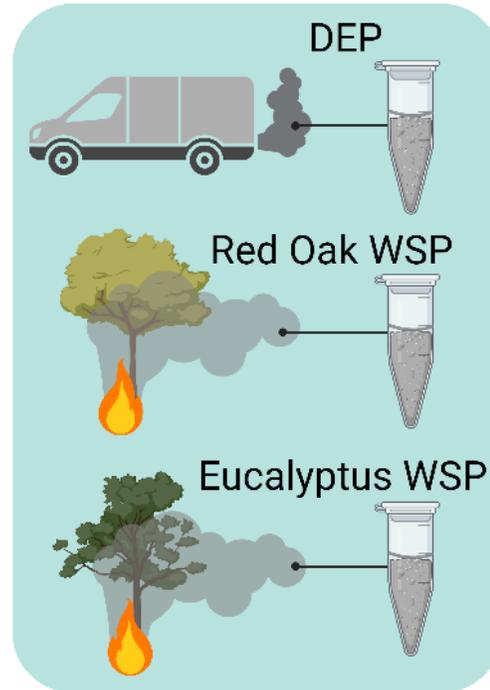


Experimental Outline

MODEL

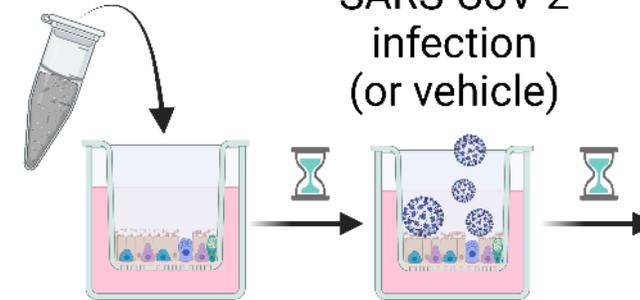


Cultured at Air-Liquid Interface

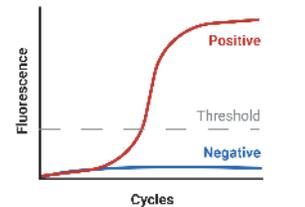


22 $\mu\text{g}/\text{cm}^2$
particulate
suspension
(or vehicle)

METHOD



0, 24, or 72 h p.i.
sample collection

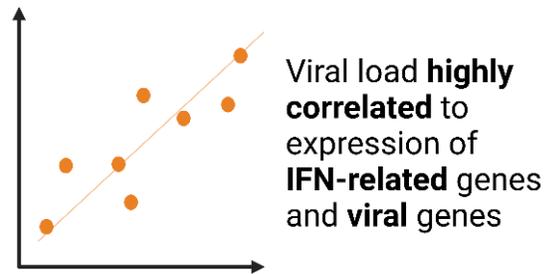
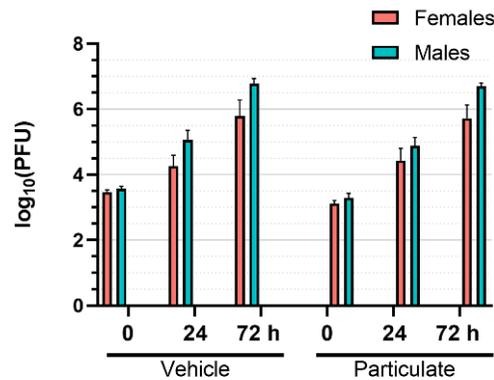


gene expression

WSP Modify SARS-CoV2 Antiviral Gene Expression in a Sex-dependent Manner

RESULTS

Particulate exposure did not affect viral load



SARS-CoV-2 infection alone

Upregulates:

- IFIT1*
- IFITM3*
- IFNB1*
- IFNL1*
- IFNL2*
- MX1*
- CCL3* ♂ > ♀
- CCL5*
- CXCL8*
- CXCL9*
- CXCL10*
- CXCL11*
- IL6*
- TNF*
- IRF7*
- STAT1*
- DDX58*
- ACE2*

Red Oak WSP + SARS-CoV-2 infection

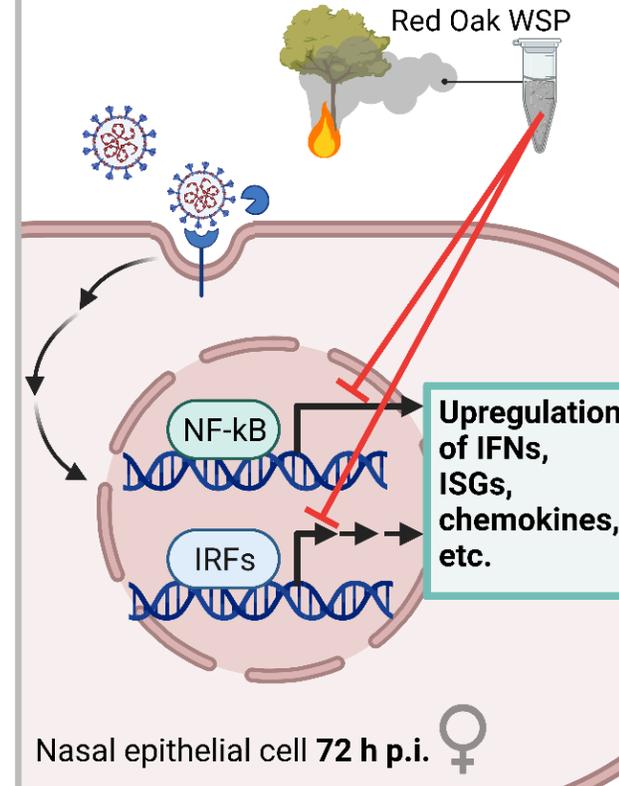
Downregulates:

- IFIT1*
- IFITM3*
- IFNB1*
- MX1*
- CXCL10*
- CXCL11*
- IRF7*
- STAT1*
- DDX58*
- (IFNL1)*
- (IFNL2)*

Downregulates:

- CCL3*
- MMP7*

CONCLUSIONS



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WSP Modify SARS-CoV2 Antiviral Gene Expression in a Sex-dependent Manner

 | Research Article

Woodsmoke particle exposure prior to SARS-CoV-2 infection alters antiviral response gene expression in human nasal epithelial cells in a sex-dependent manner

Stephanie A Brocke, Grant T Billings, Sharon Taft-Benz, Neil E. Alexis, Mark T Heise, and Ilona Jaspers *

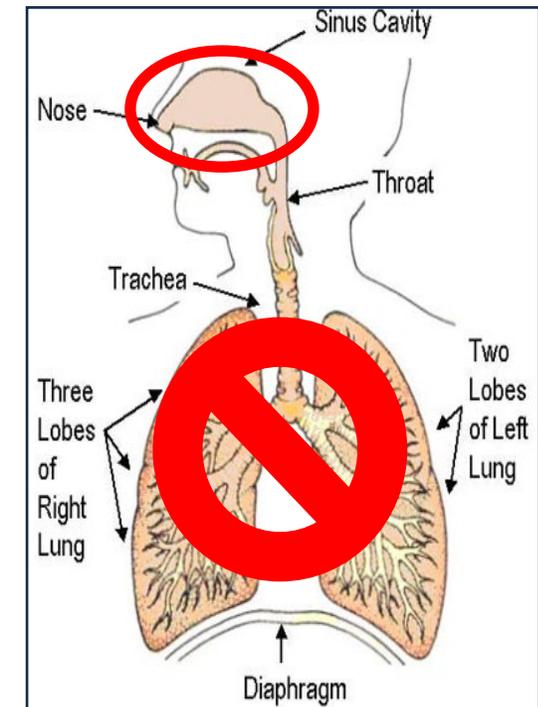
02 FEB 2022 // <https://doi.org/10.1152/ajplung.00362.2021>

Human *in vivo* studies of Influenza Infections

fluMist
Influenza Virus Vaccine
Live, Intranasal



- **FluMist™ is a cold-adapted Live Attenuated Influenza Virus (LAIV) vaccine**
- **“cold-adapted”, thus replication limited to nasal cavity (32°C)**
- **It generates a replicative but self limited viral infection with innate and immune host defense responses**
- **Provides a safe tool to study influenza virus infections *in vivo***



Model Pollutant Exposures and LAIV - Woodsmoke



- PM derived from Woodsmoke is of increasing public health concern in the US and globally
- Healthy study participants were exposed to either 500 $\mu\text{g}/\text{m}^3$ of wood smoke particulate or air for two hours
- LAIV-induced CXCL10 (a critical IFN-inducible chemokine) levels were suppressed in the nasal mucosa of all participants
- An exposure by sex interaction was observed, with males showing greater inflammation-related gene expression, while in females' host-defense related gene expression was mildly decreased

Wood Smoke Exposure Alters Human Inflammatory Responses to Viral Infection in a Sex-Specific Manner

A Randomized, Placebo-controlled Study

Meghan E. Rebuli¹, Adam M. Speen¹, Elizabeth M. Martin^{1,2}, Kezia A. Addo¹, Erica A. Pawlak³, Ellen Glista-Baker³, Carole Robinette³, Haibo Zhou⁴, Terry L. Noah^{1,3,5}, and Ilona Jaspers^{1,3,5}

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Summary

- Both acute and chronic exposure to air pollutants (particulate and gas phase) affect respiratory host defense
- Epidemiological studies suggest a link between pollutant exposure and COVID-19, but more studies are needed to determine whether other co-factors are modifying this effects
- Organotypic *in vitro* models have uncovered plausible mechanisms by which inhaled air pollutants could affect the susceptibility to SARS-CoV2
- Model virus infections combined with controlled acute pollutant exposures have identified pollutant-induced modification of respiratory virus infection; sex is a biological variable that needs to be considered

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Diesel Exhaust Exposure and Nasal Response to Attenuated Influenza in Normal and Allergic Volunteers

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