

# Necroptosis Signaling Promotes Inflammation, Airway Remodeling, and Emphysema in Chronic Obstructive Pulmonary Disease

Zhe Lu<sup>1</sup>, Hannelore P. Van Eeckhoutte, Gang Liu, Prema M. Nair, Bernadette Jones, Caitlin M. Gillis, B. Christina Nalkurthi, Fien Verhamme, Tamariche Buyle-Huybrecht, Peter Vandenabeele, Tom Vanden Berghe, Guy G. Brusselle, Jay C. Horvat, James M. Murphy, Peter A. Wark, Ken R. Bracke, Michael Fricker, and Philip M. Hansbro

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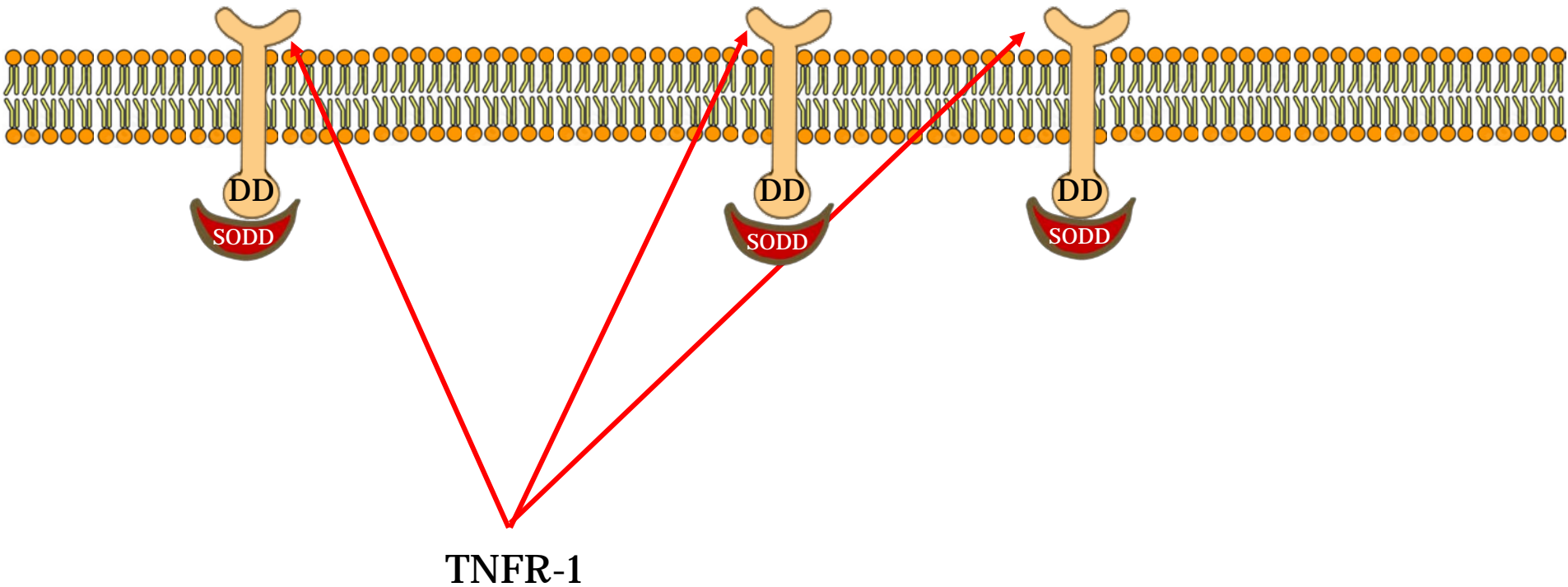
# Presentation Structure

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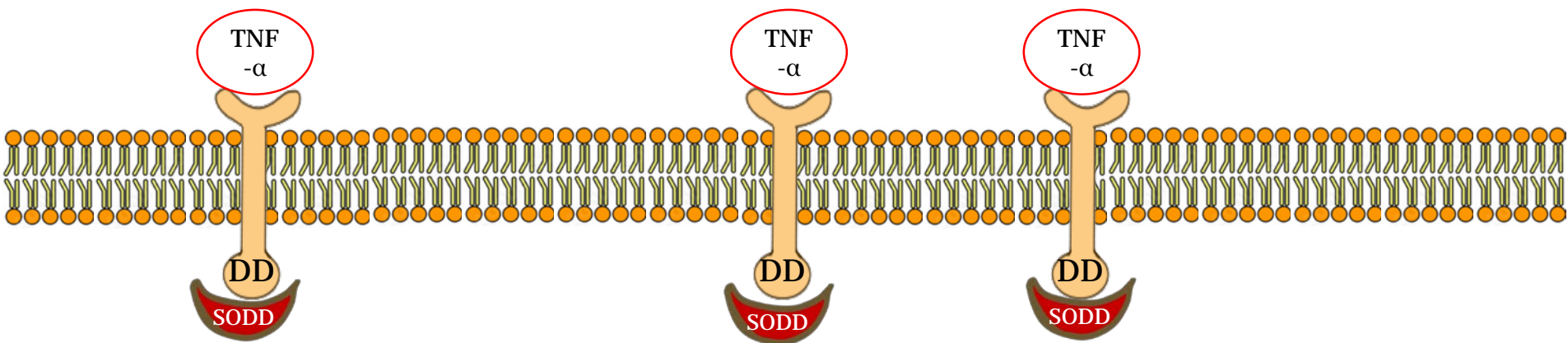
2) Results

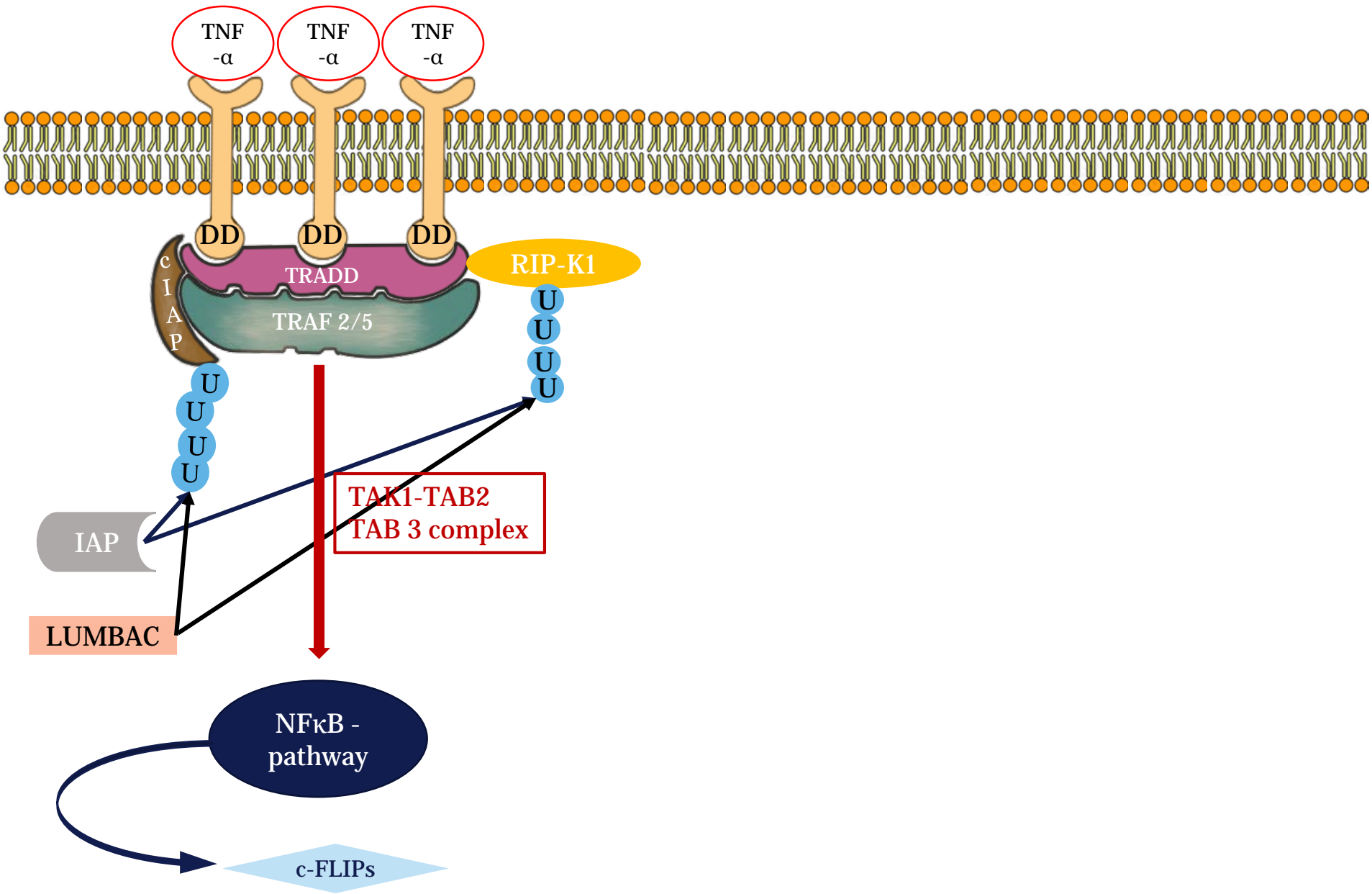
3) Take-Home Messages

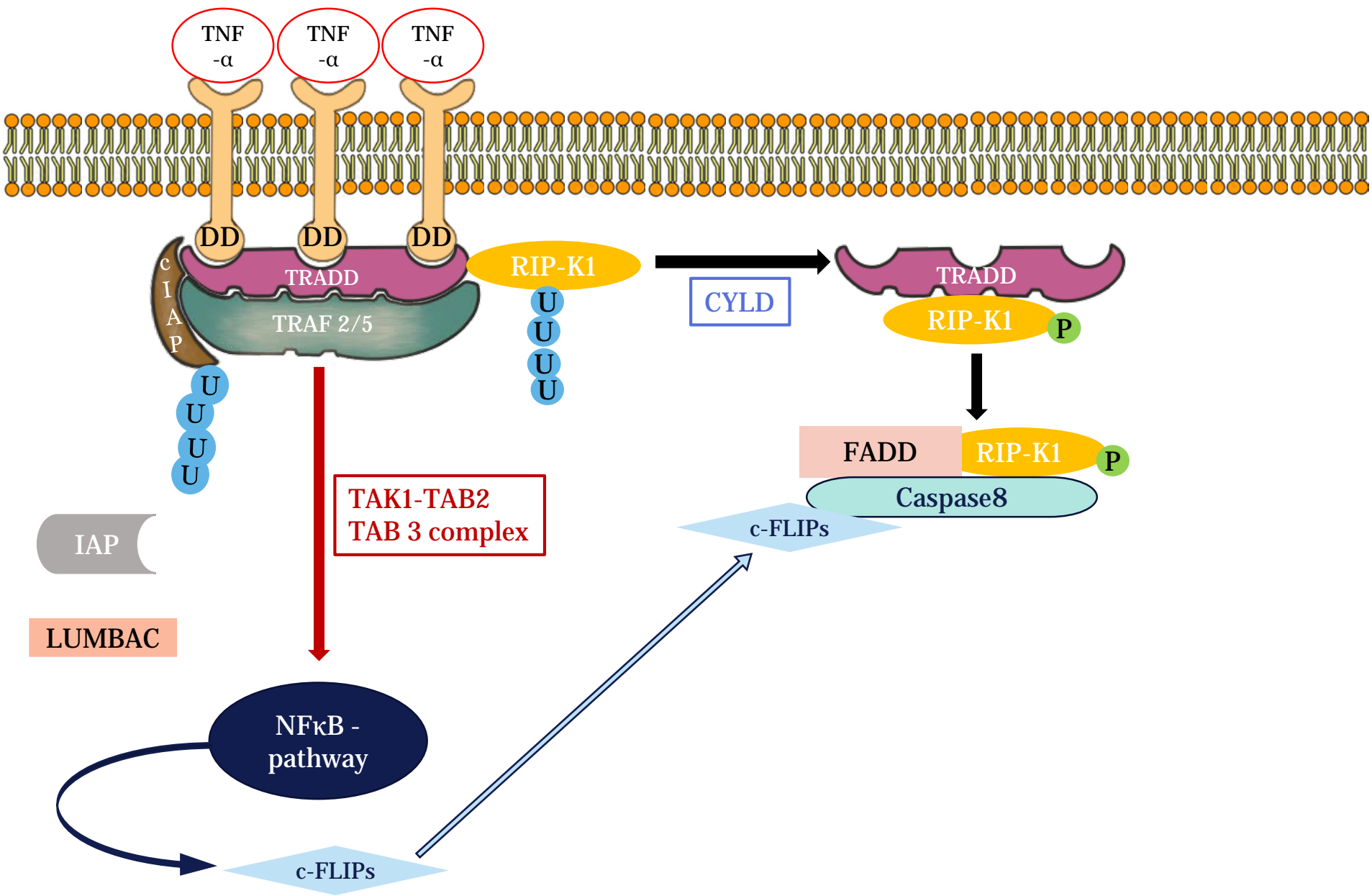
4) Discussion

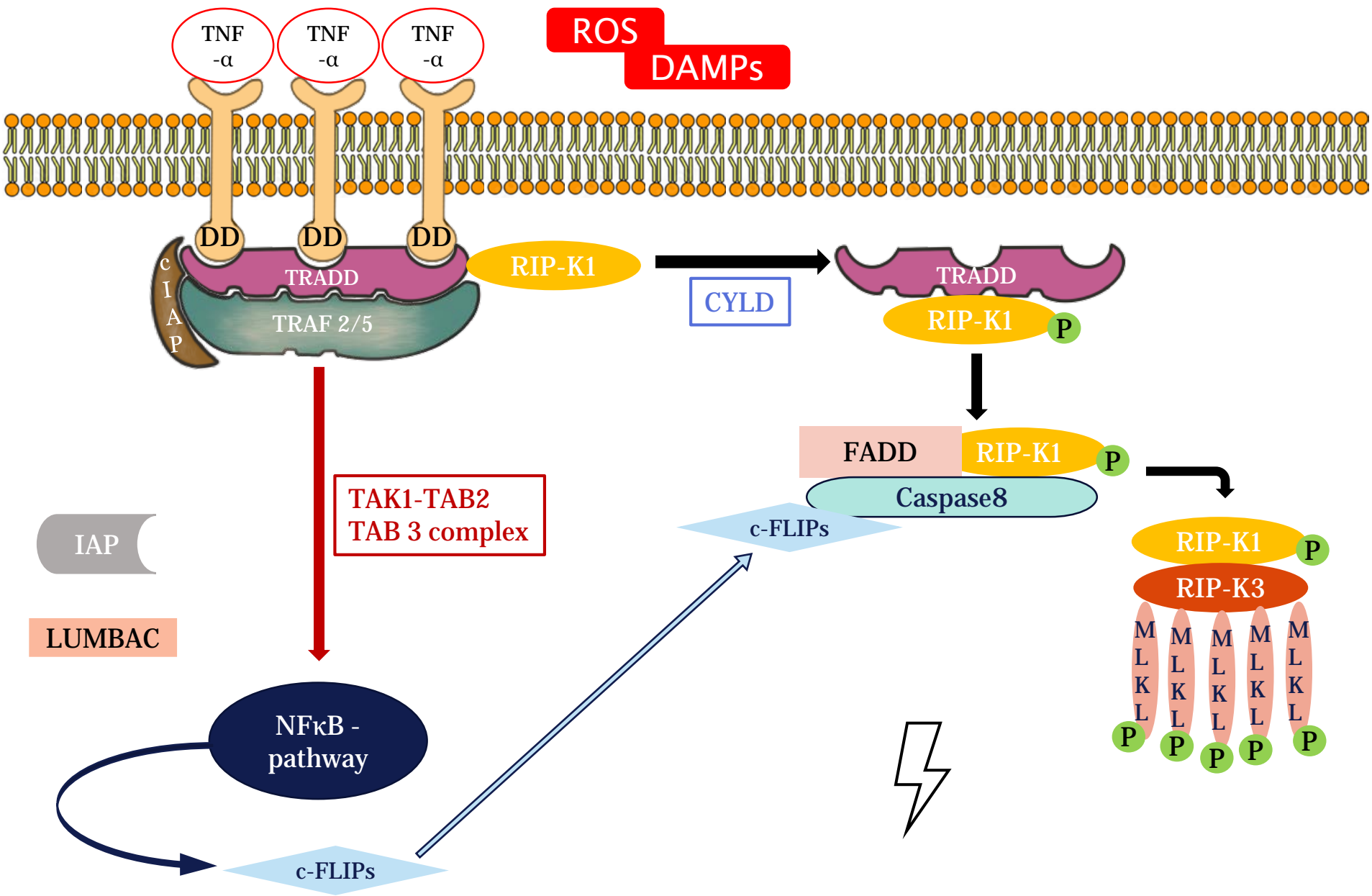


**„Necroptosis Signaling Promotes Inflammation, Airway Remodeling, and Emphysema in Chronic Obstructive Pulmonary Disease“**









# Presentation Structure

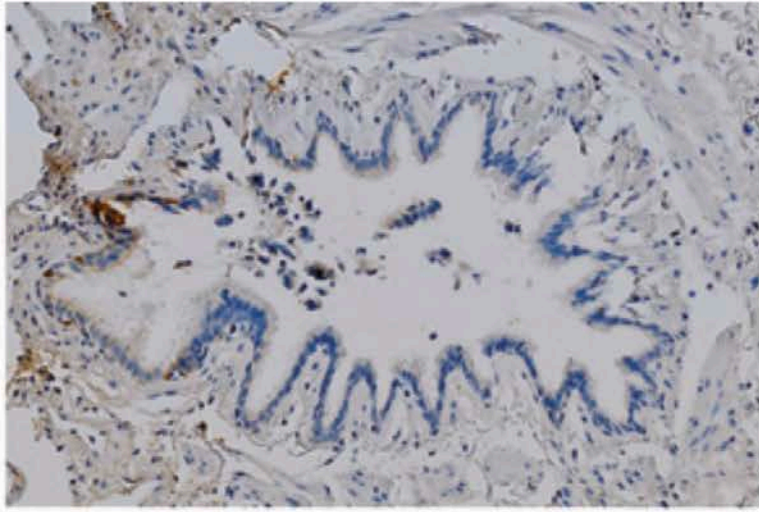
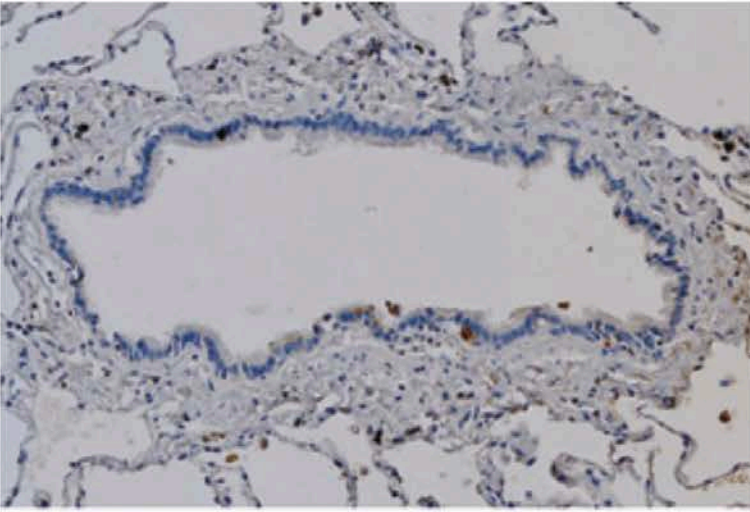
- 1) Introduction
- 2) Results**
- 3) Take-Home Messages
- 4) Discussion



# 1. Levels and Activation of RIPK3 and MLKL in Lung Resections from Patients with COPD?

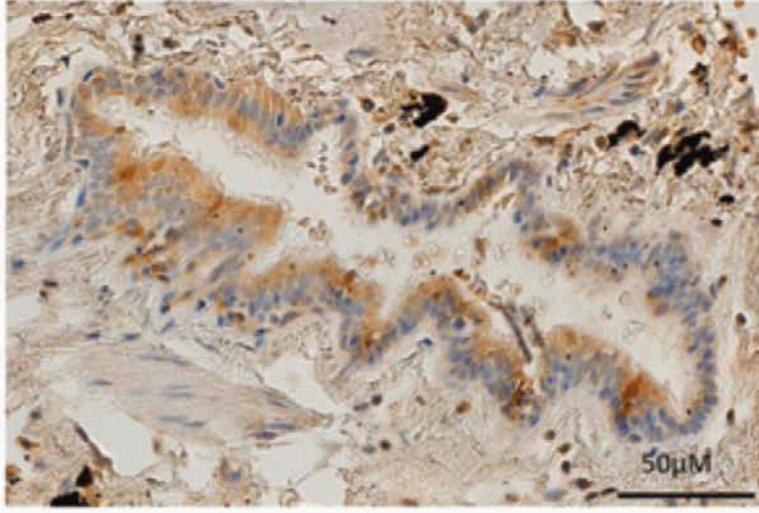
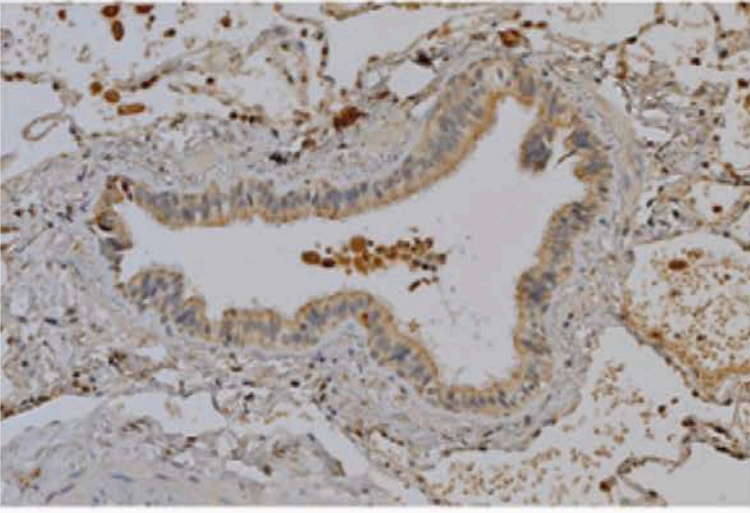
**A**

Never smoker

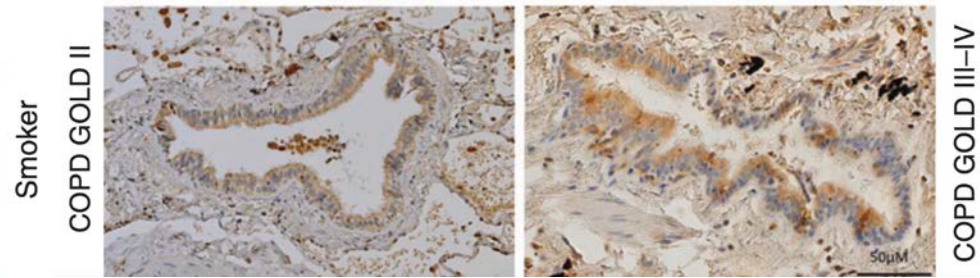
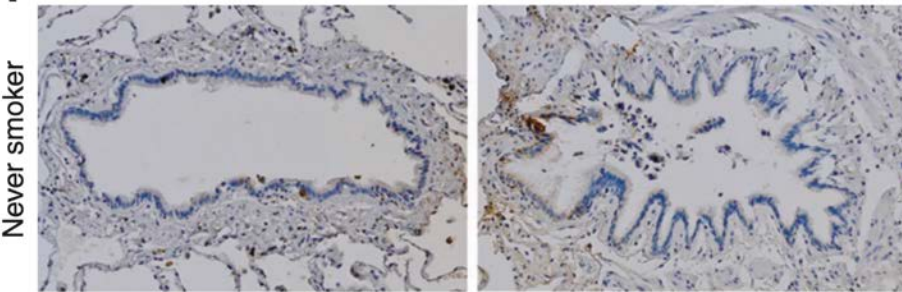
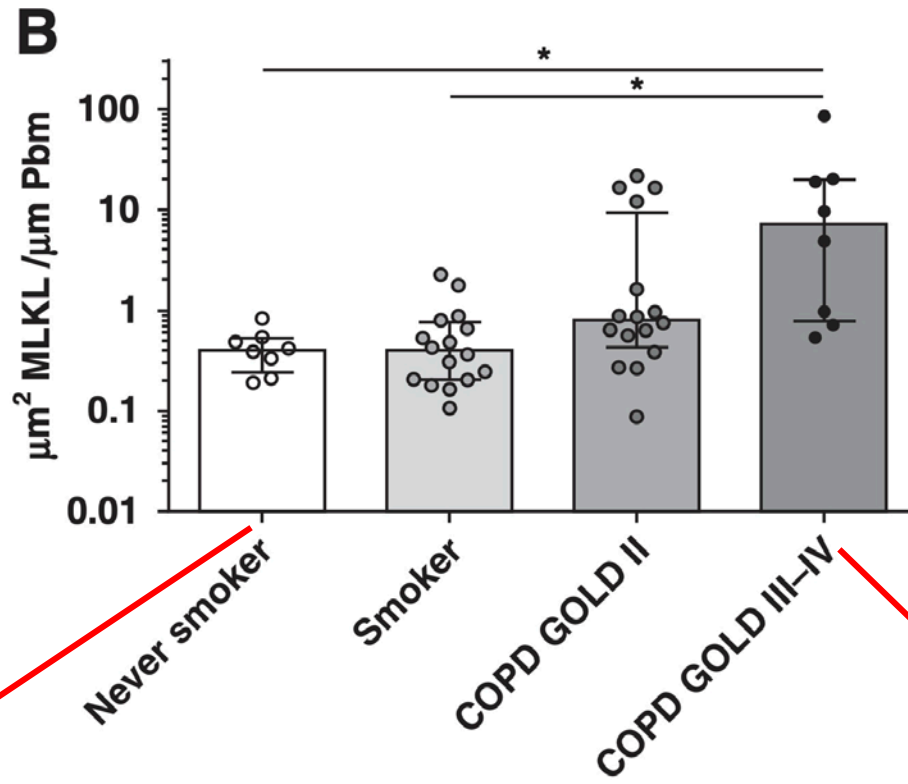


Smoker

COPD GOLD II

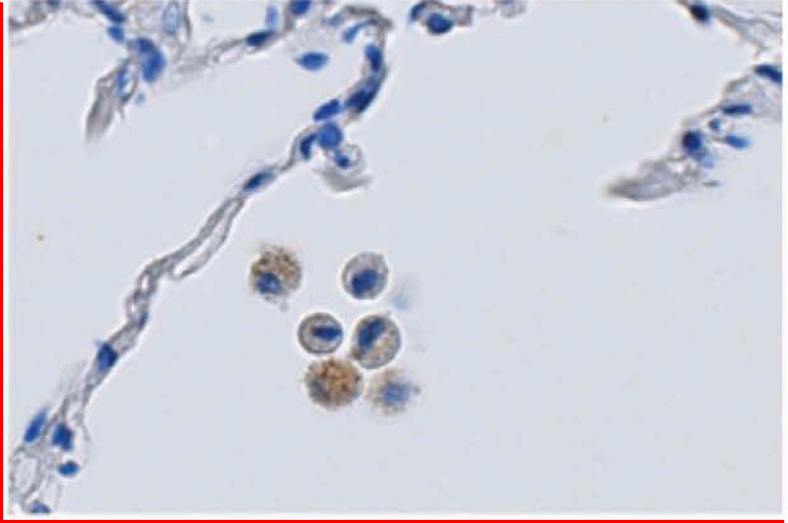
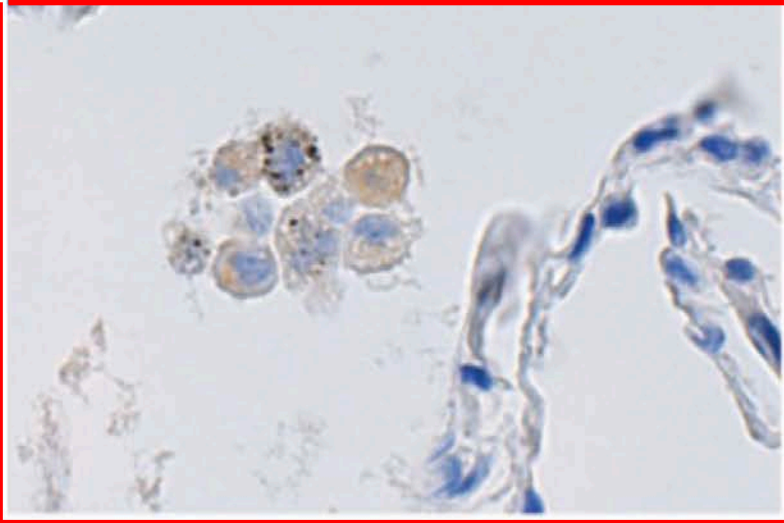


COPD GOLD III-IV



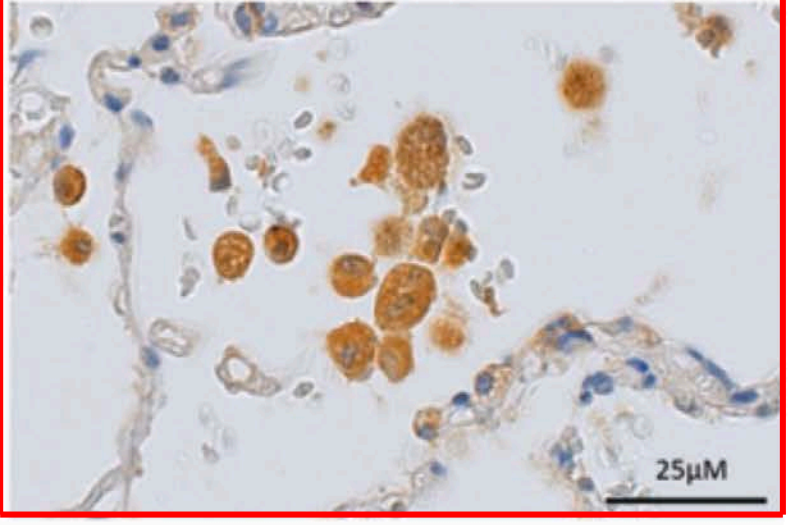
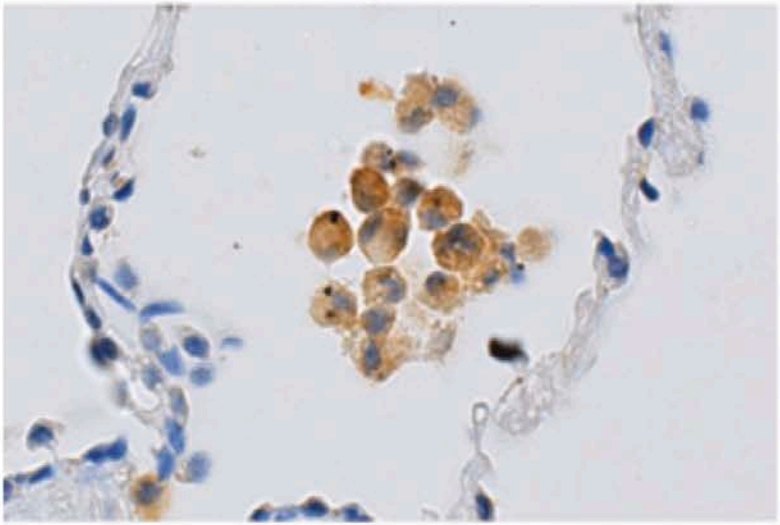
C

Never smoker

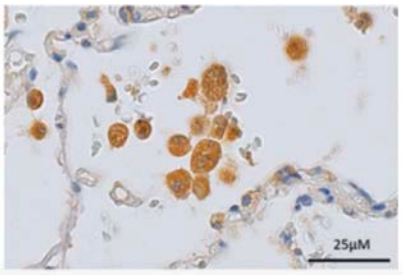
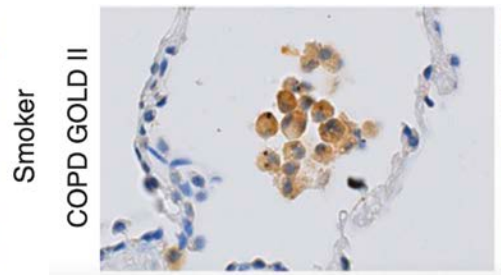
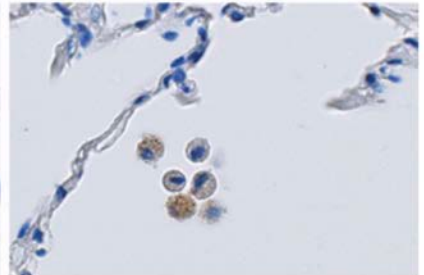
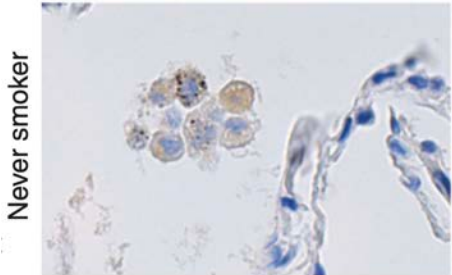
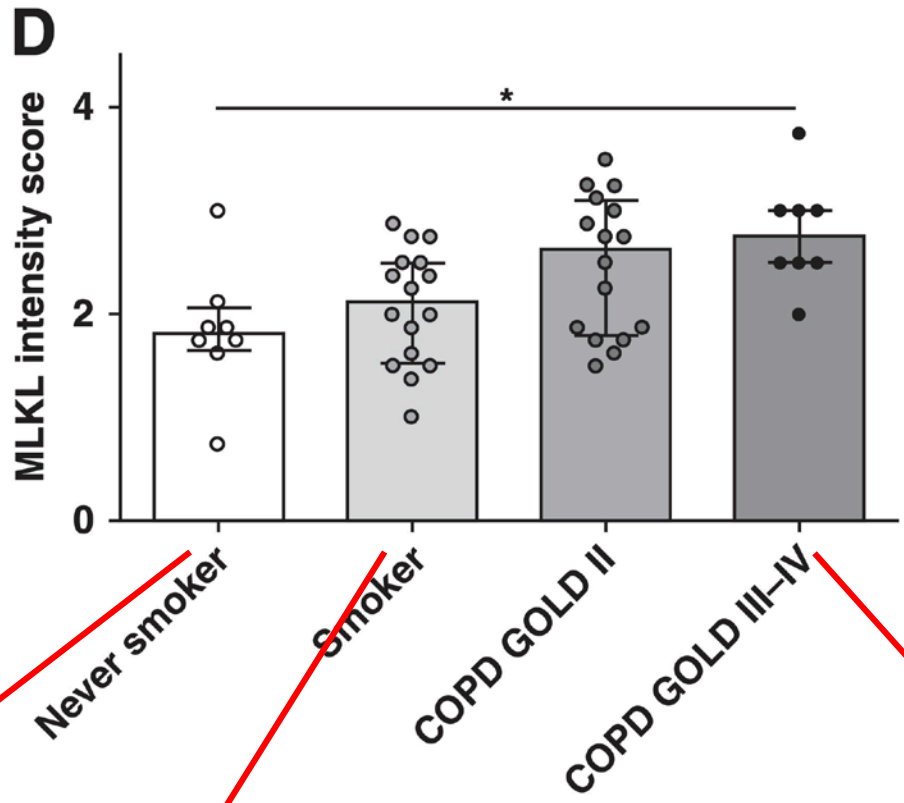


Smoker

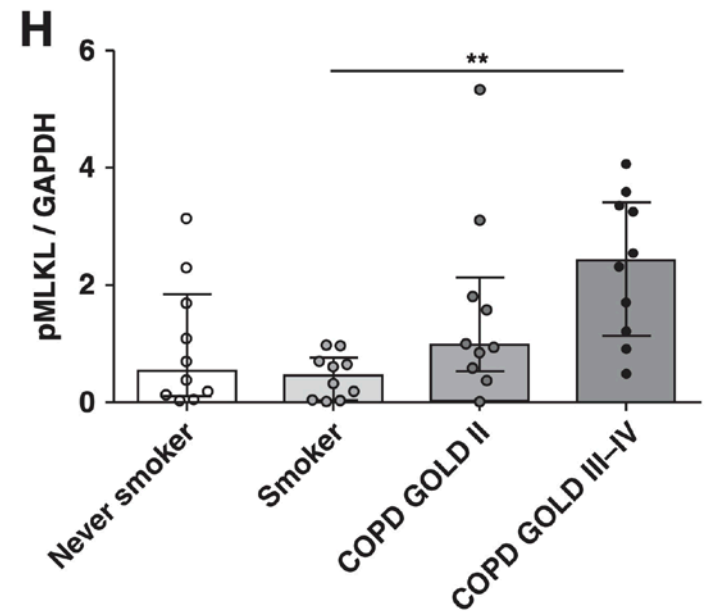
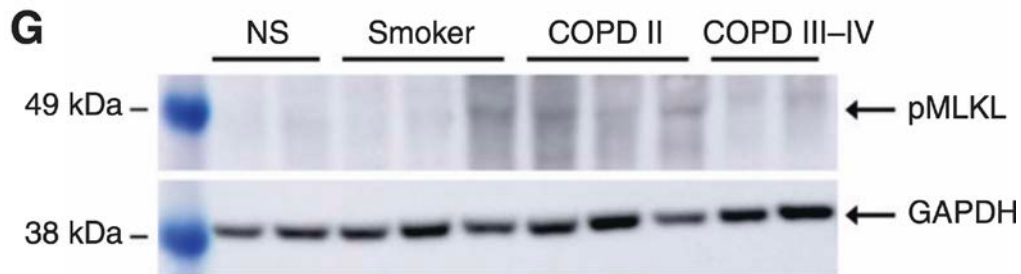
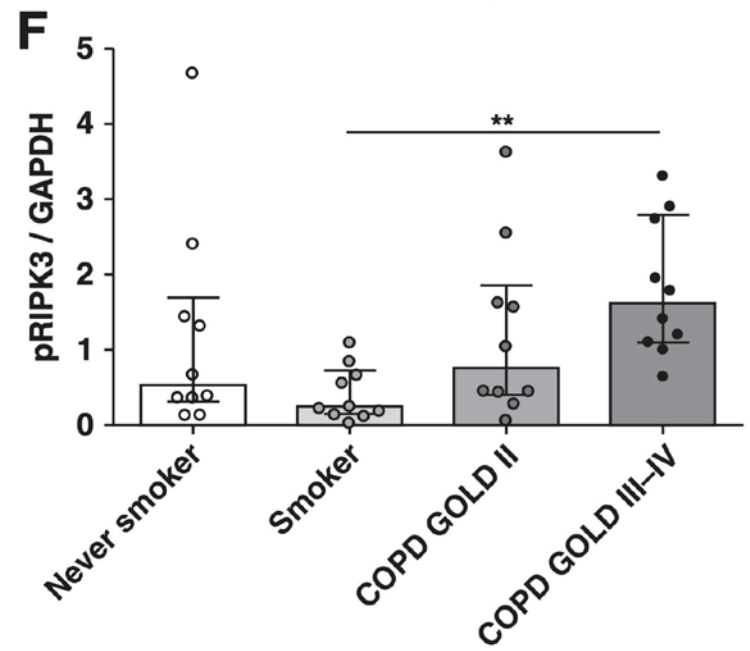
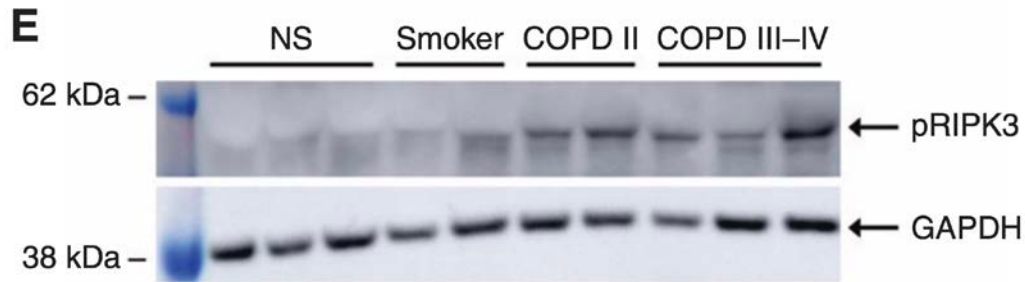
COPD GOLD II

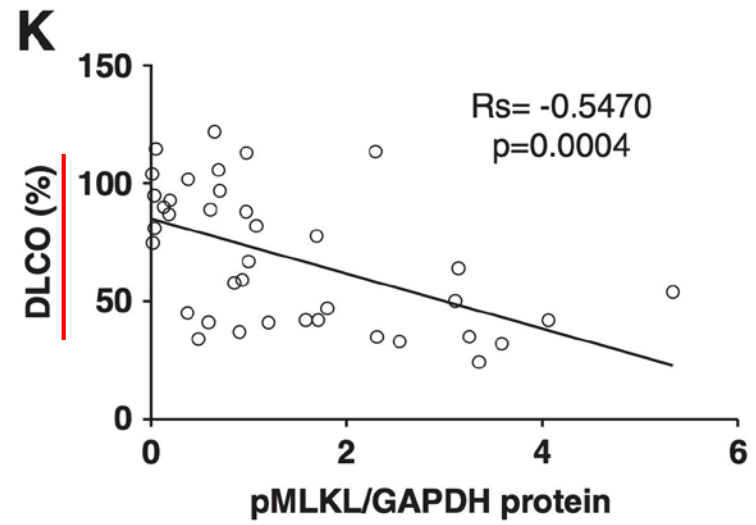
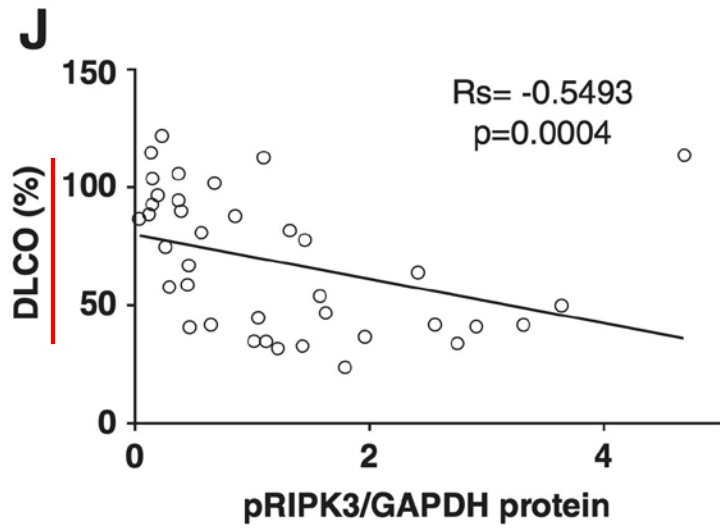
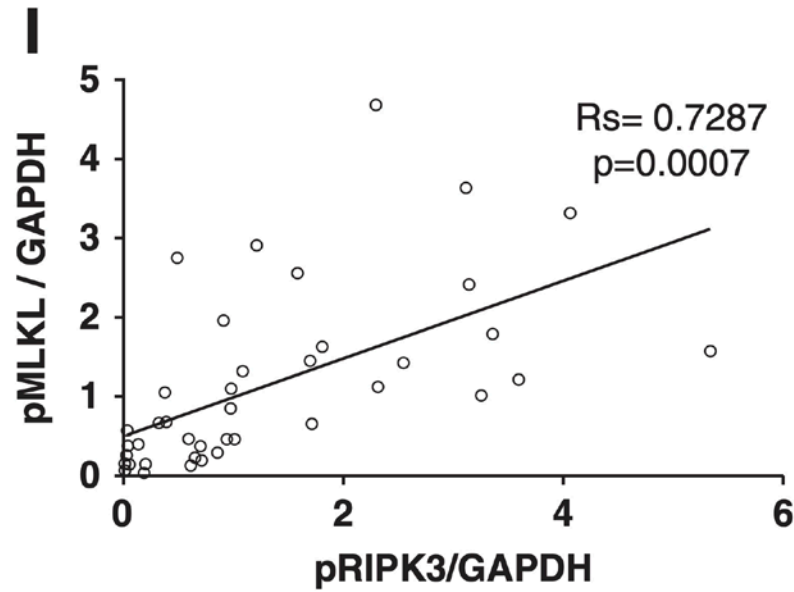


COPD GOLD III-IV



COPD GOLD III-IV



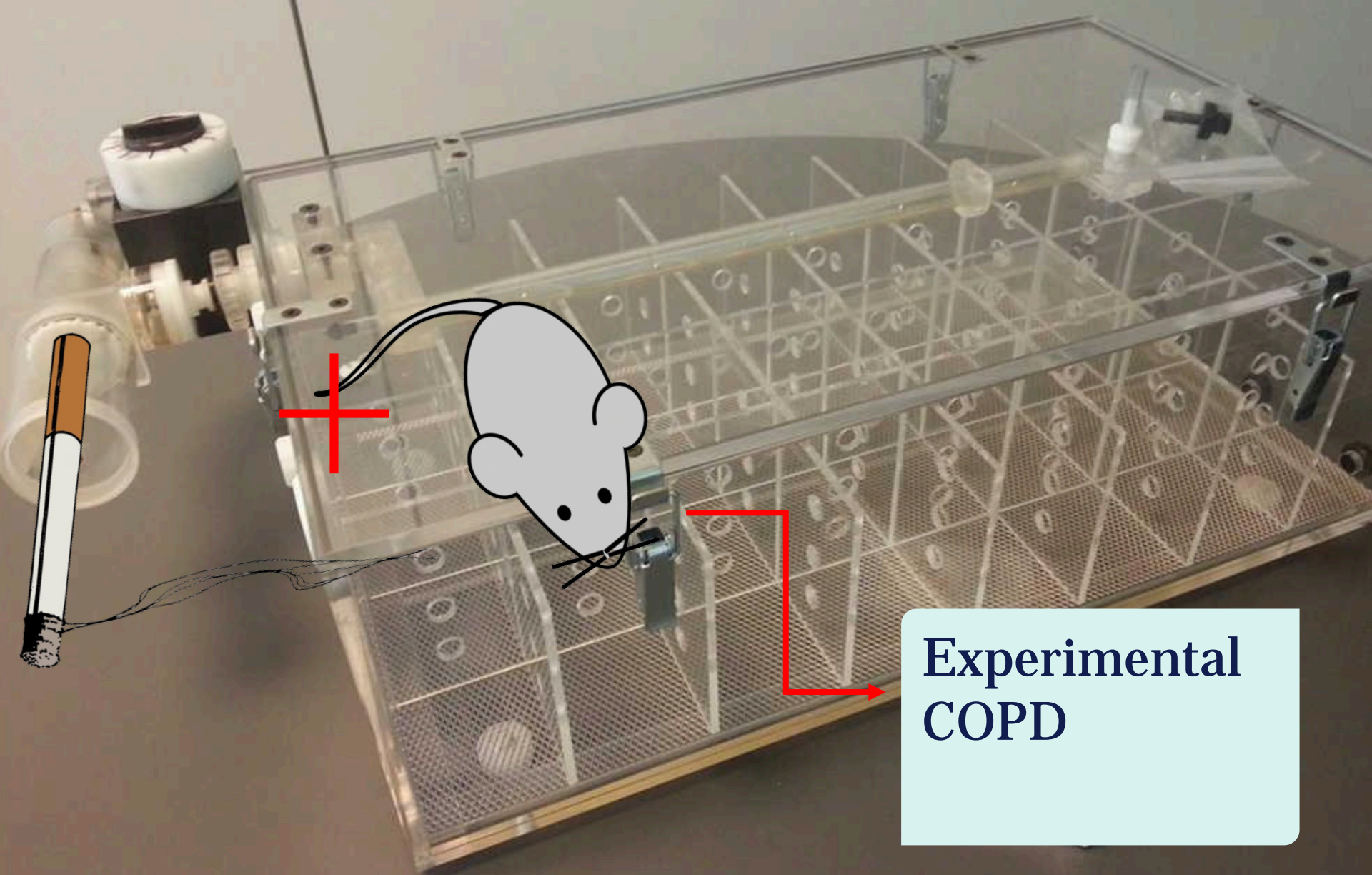


# 1. Levels and Activation of RIPK3 and MLKL in Lung Resections from Patients with COPD?

→ Elevated expression and activation of necroptosis proteins are associated with increasing COPD severity.

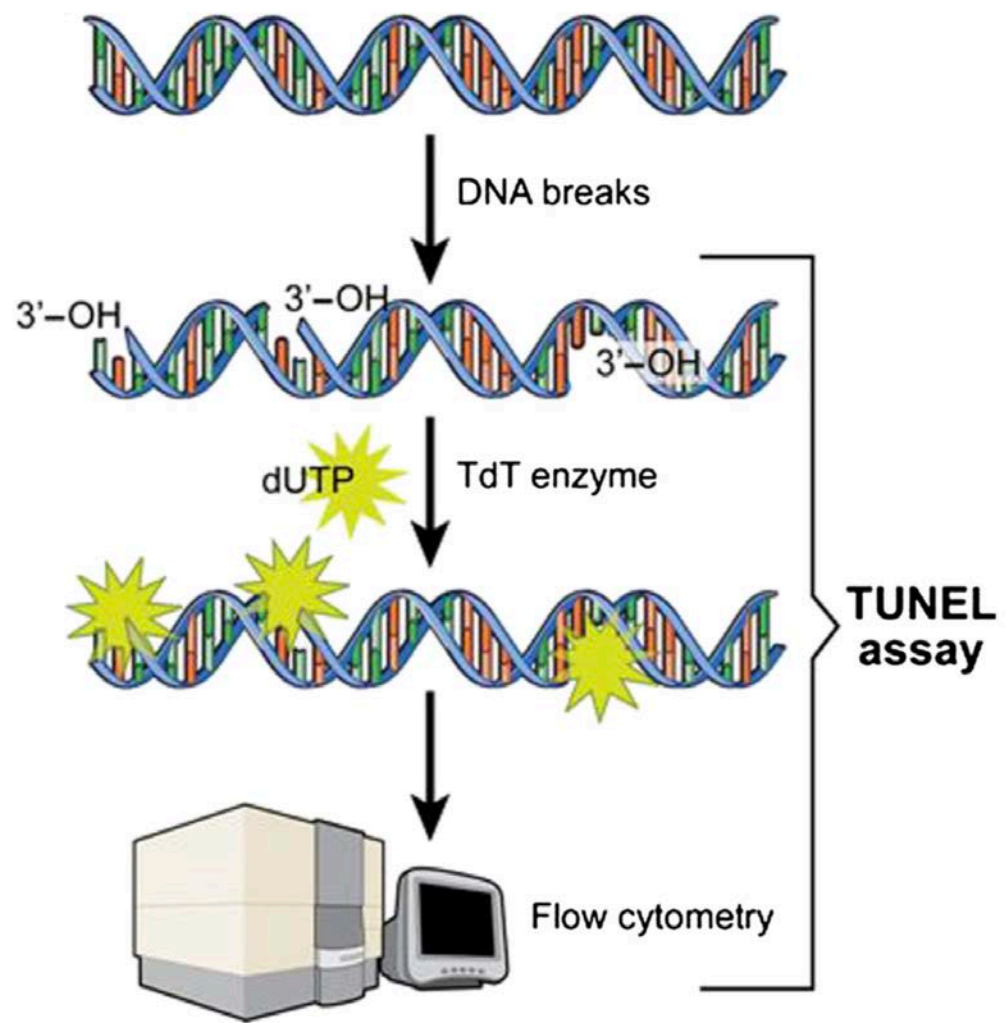


## 2. Is there an upregulation of necroptosis-related mRNA and proteins in the lung in experimental COPD?

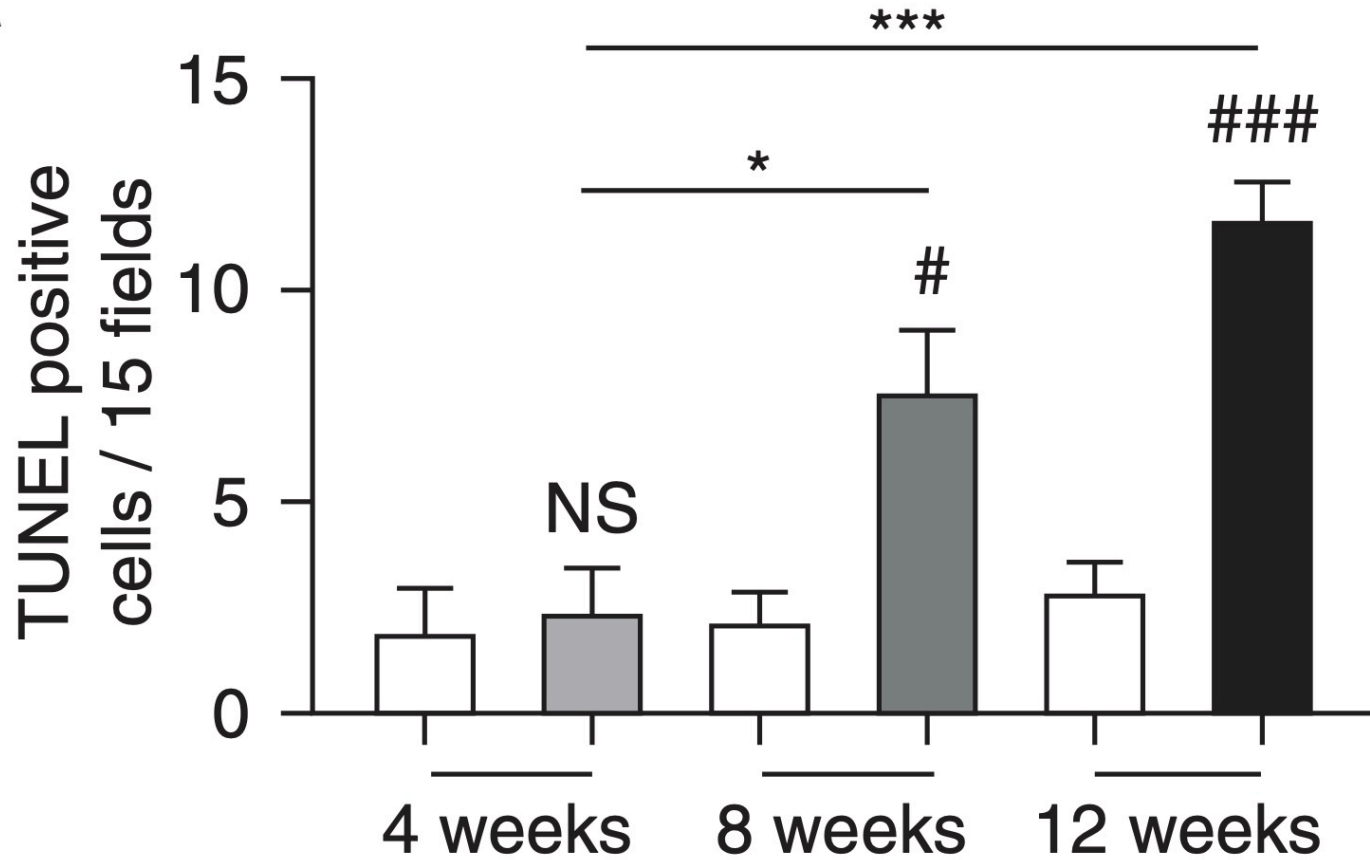


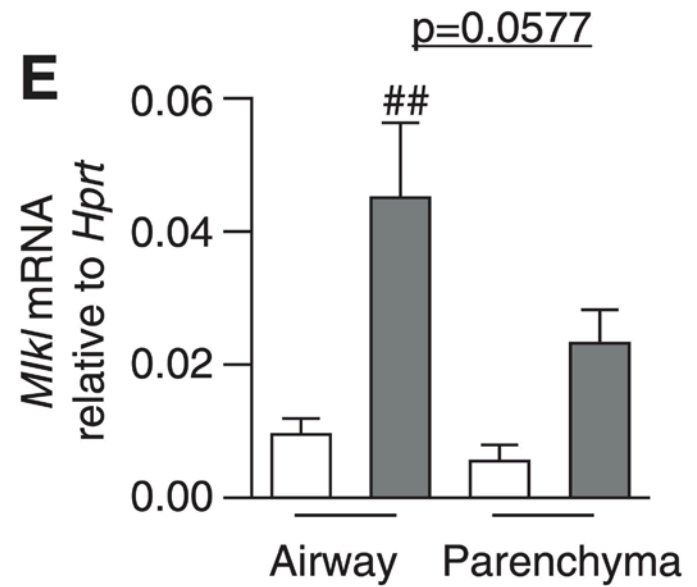
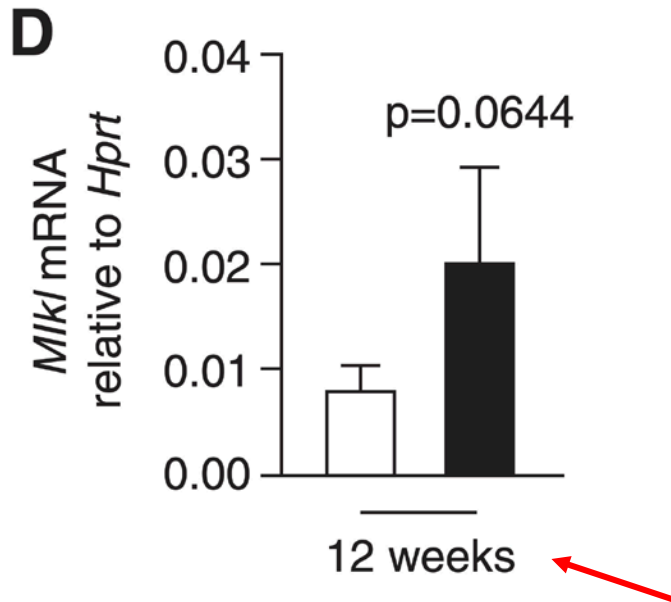
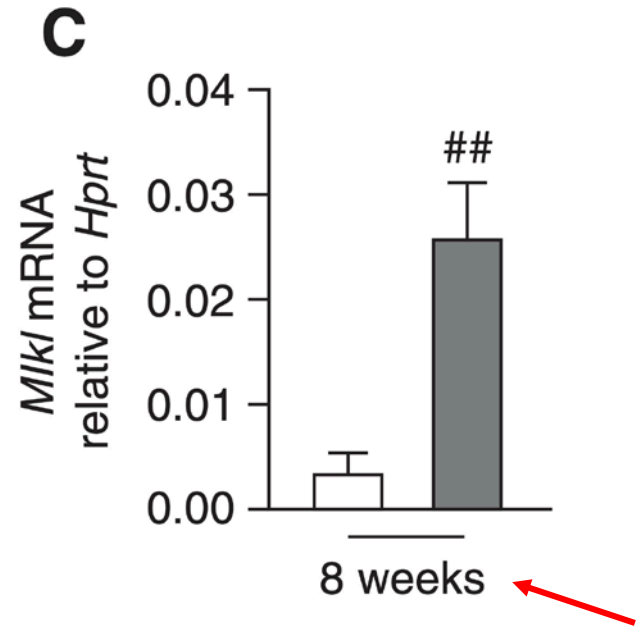
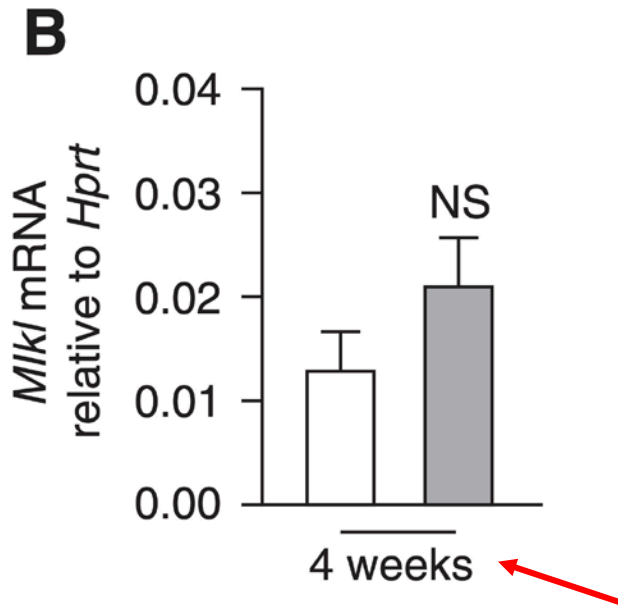
**Experimental  
COPD**

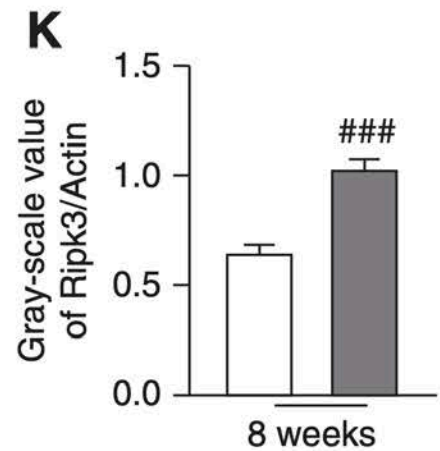
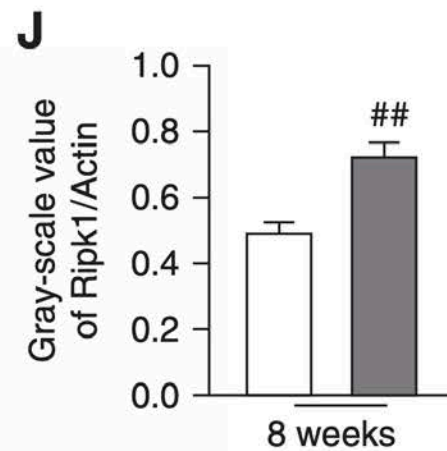
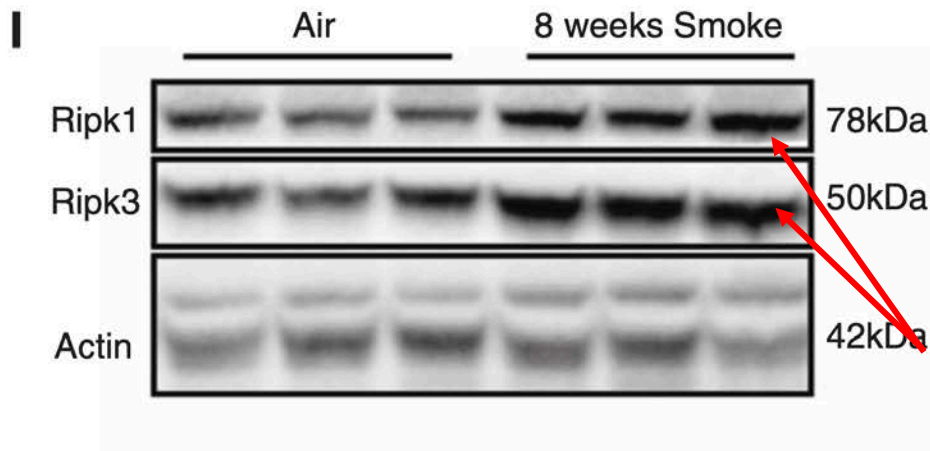
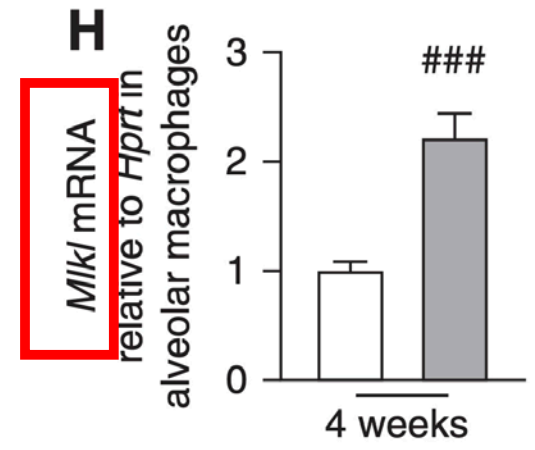
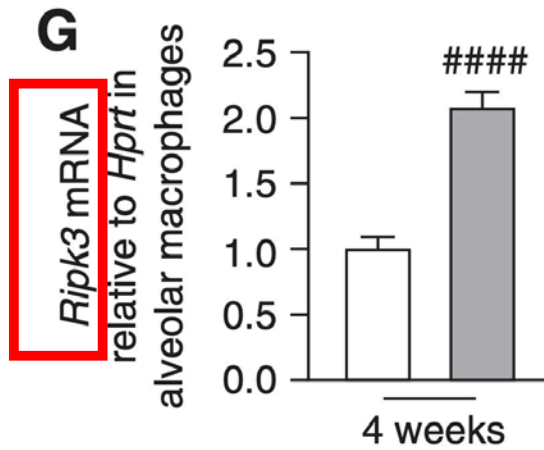
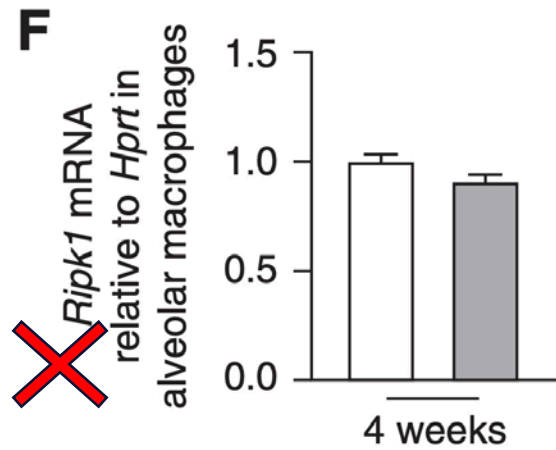
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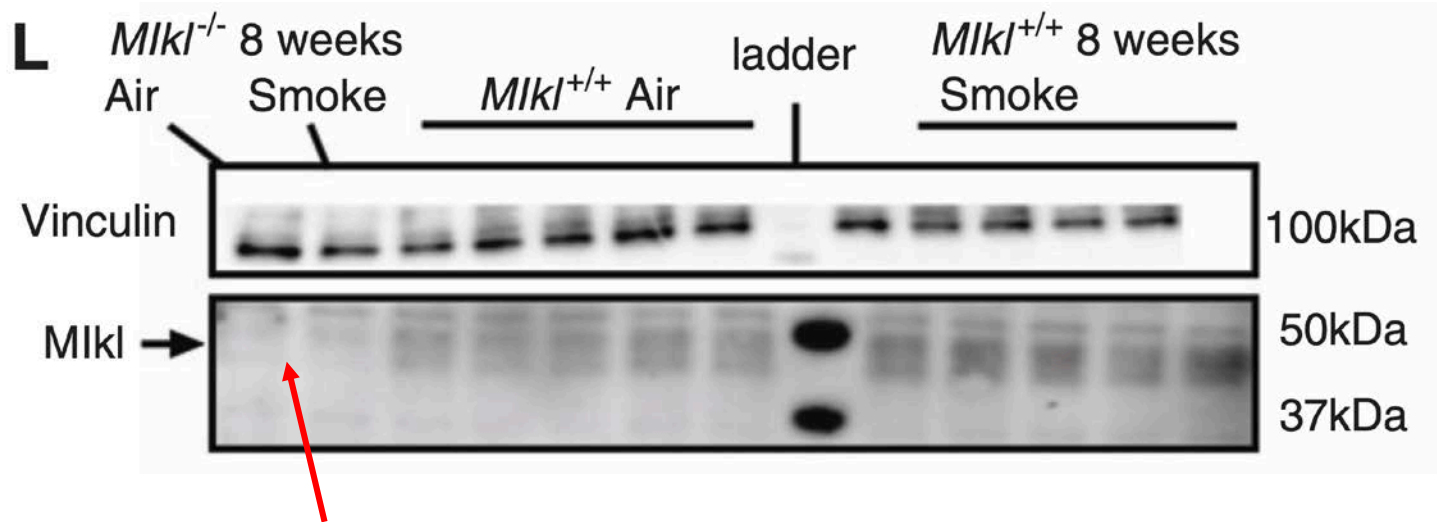


**A**







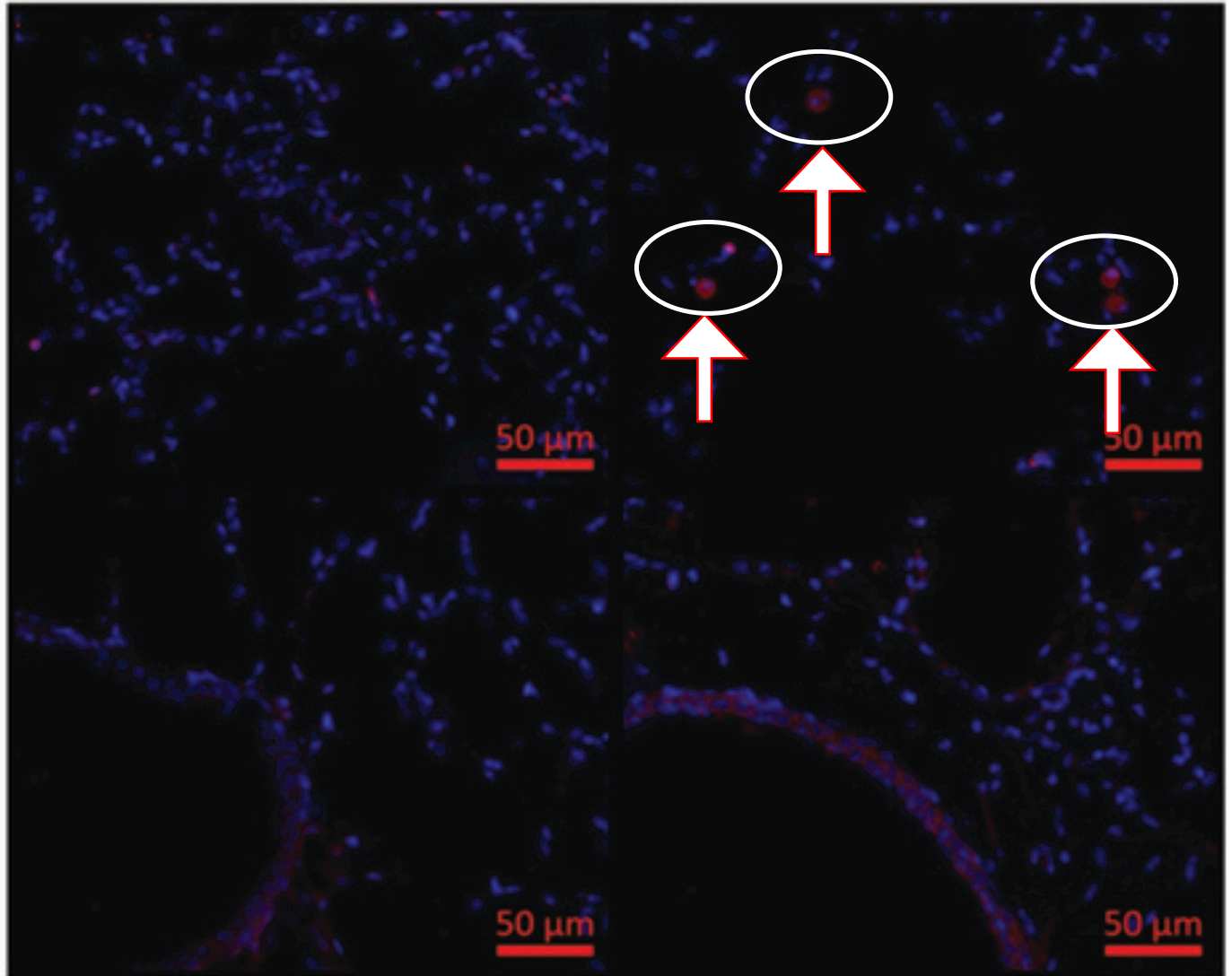


Air

8 weeks Smoke

Parenchyma

Airway

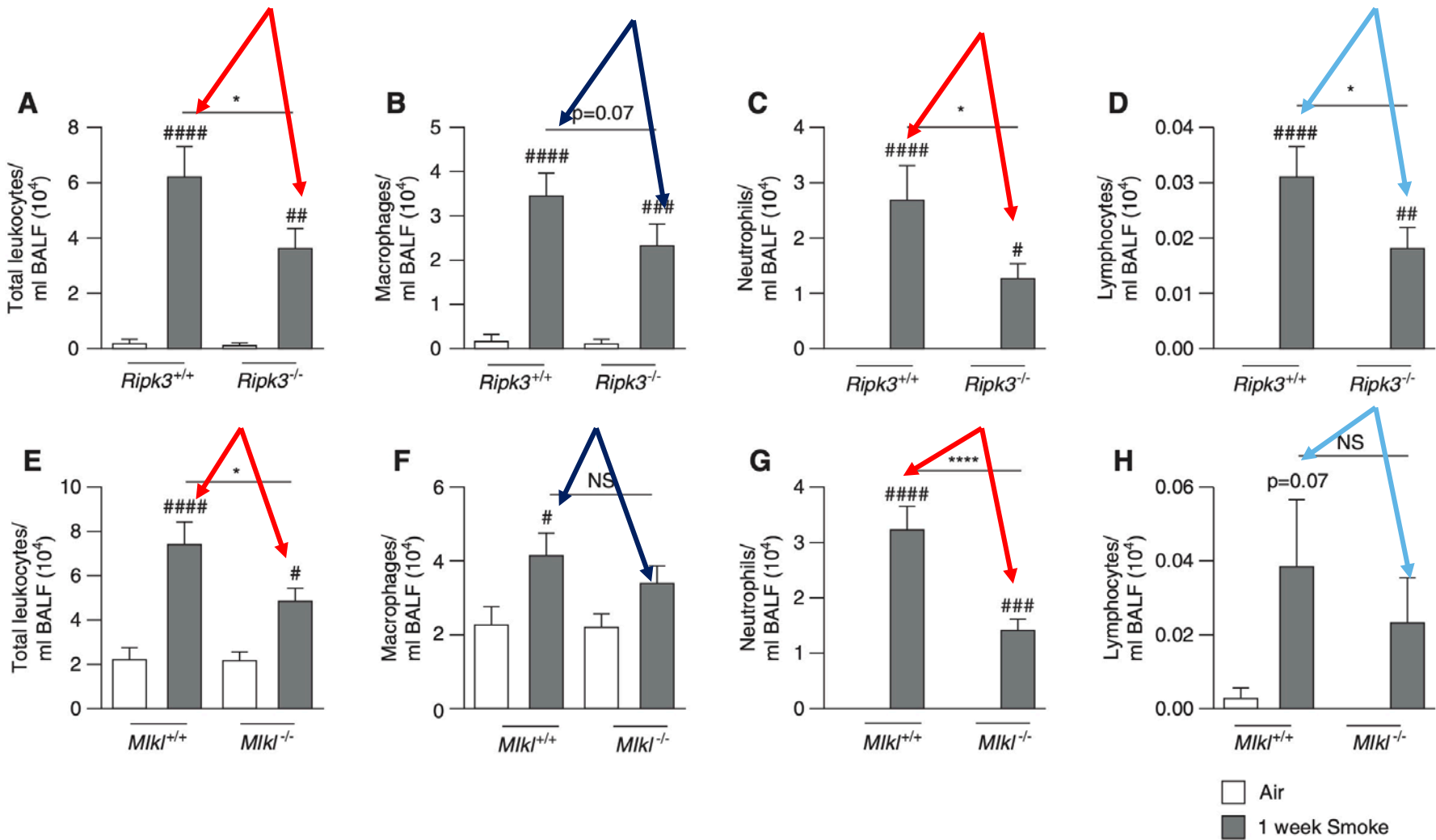


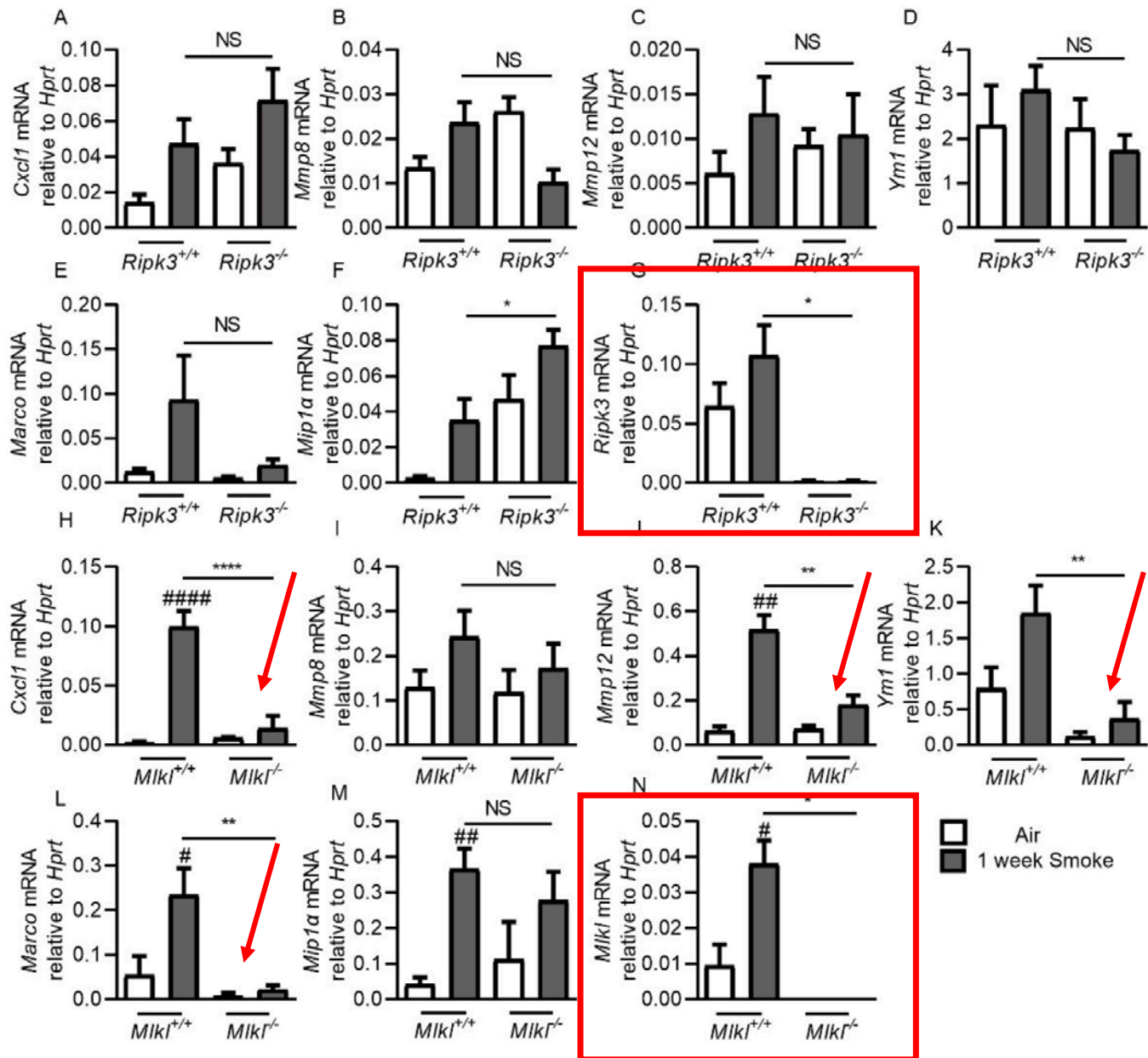


2. Is there an upregulation of necroptosis-related mRNA and proteins in the lung in experimental COPD?

→ Core necrosome components, particularly Mkl1, were increased at the mRNA and protein levels in lung tissue and alveolar macrophages in experimental COPD.

# 3. Role of RIPK3 and MLKL regarding airway inflammation in response to acute CS exposure?

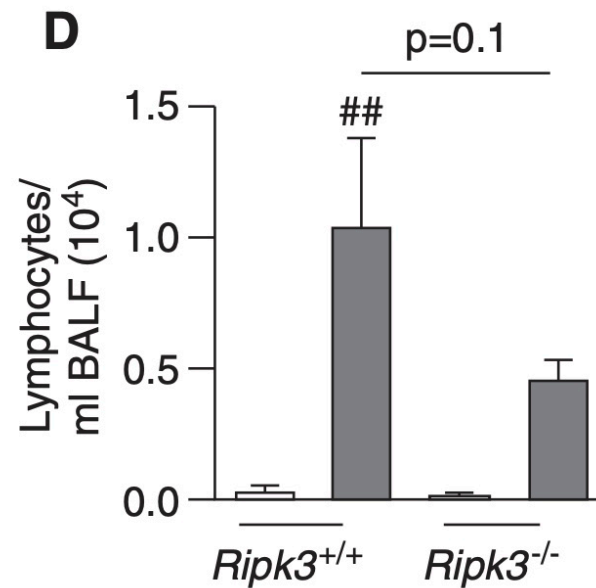
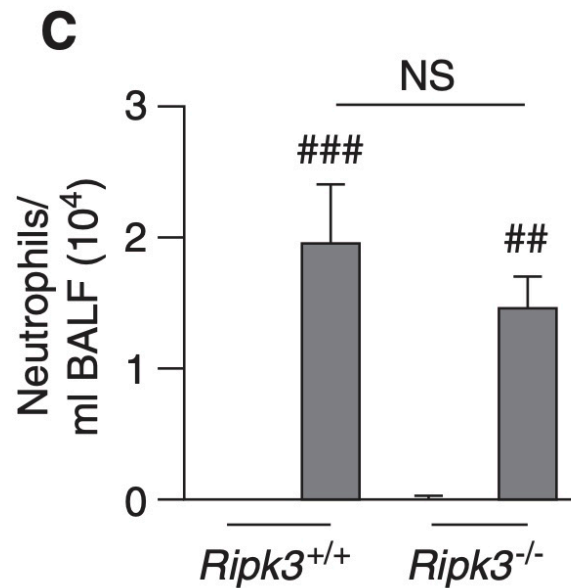
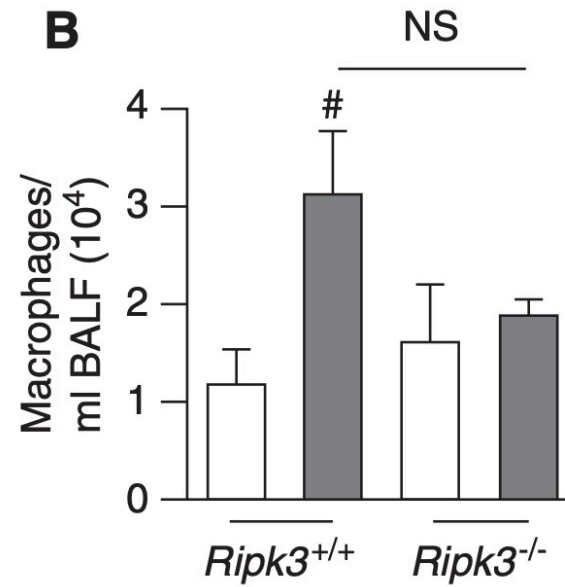
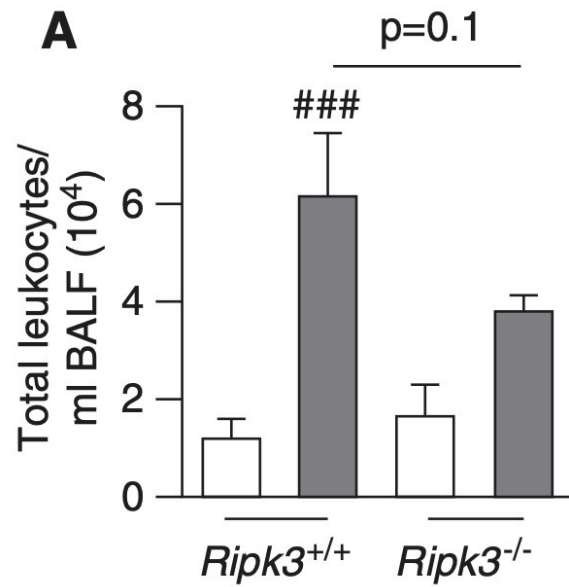


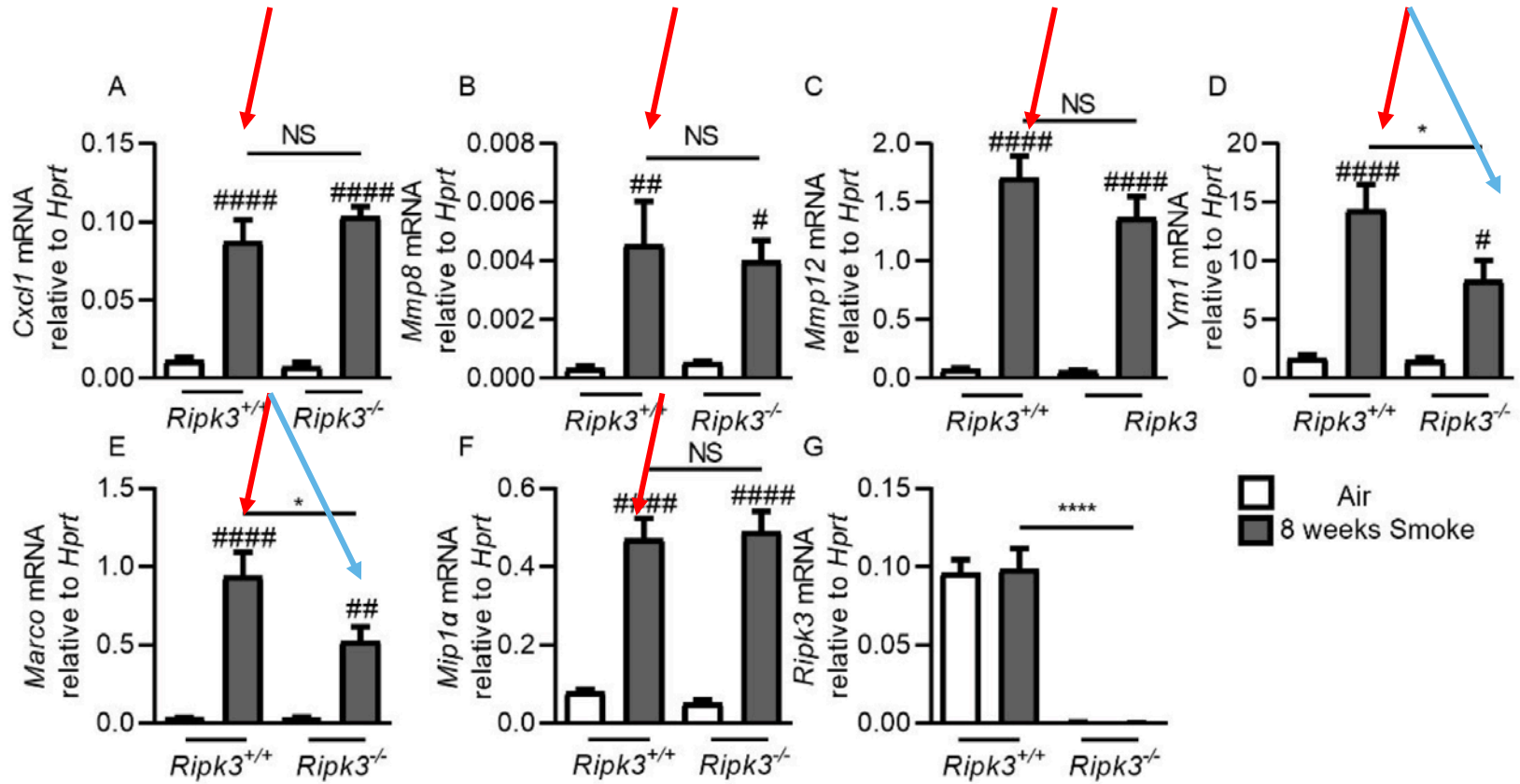


### 3. Role of RIPK3 and MLKL regarding airway inflammation in response to acute CS exposure?

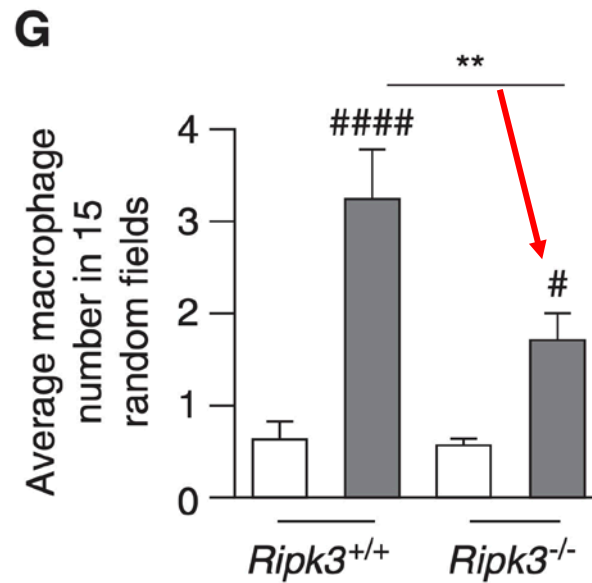
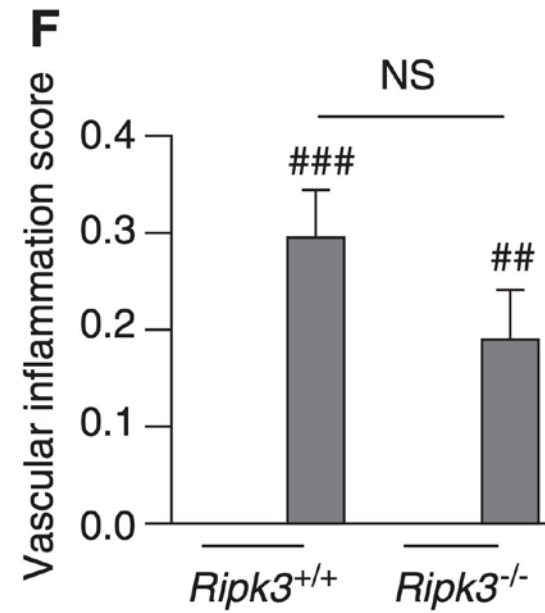
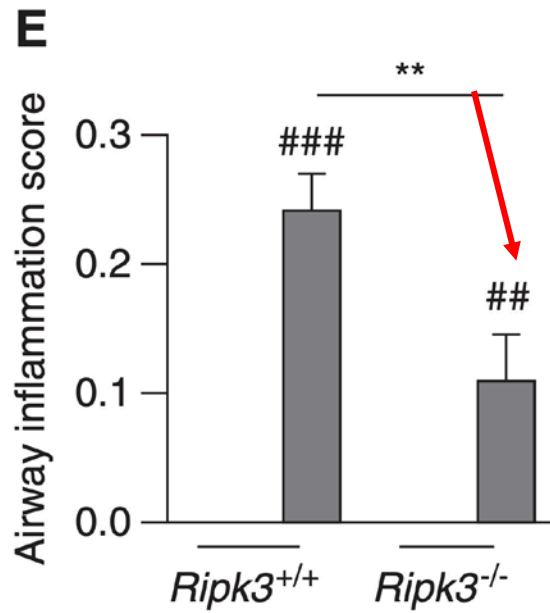
→ It seems RIPK3 and MLKL do drive airway inflammation in response to acute CS exposure

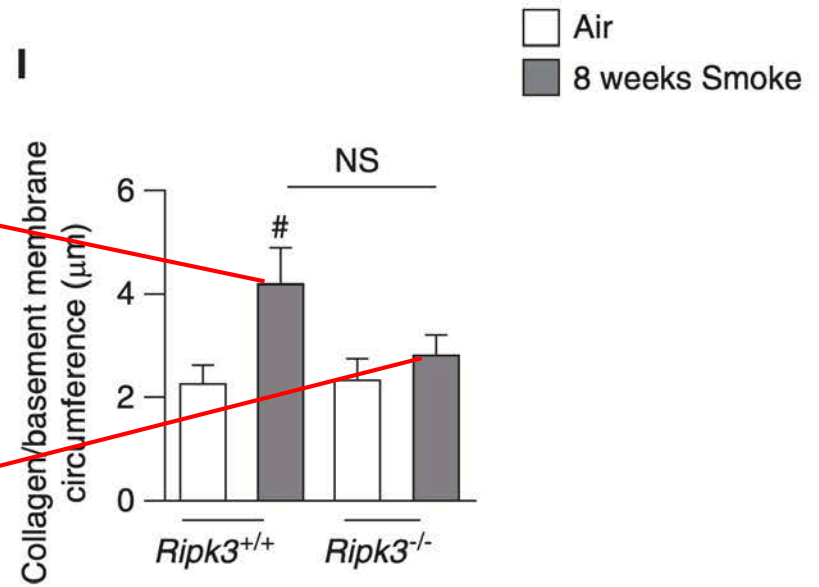
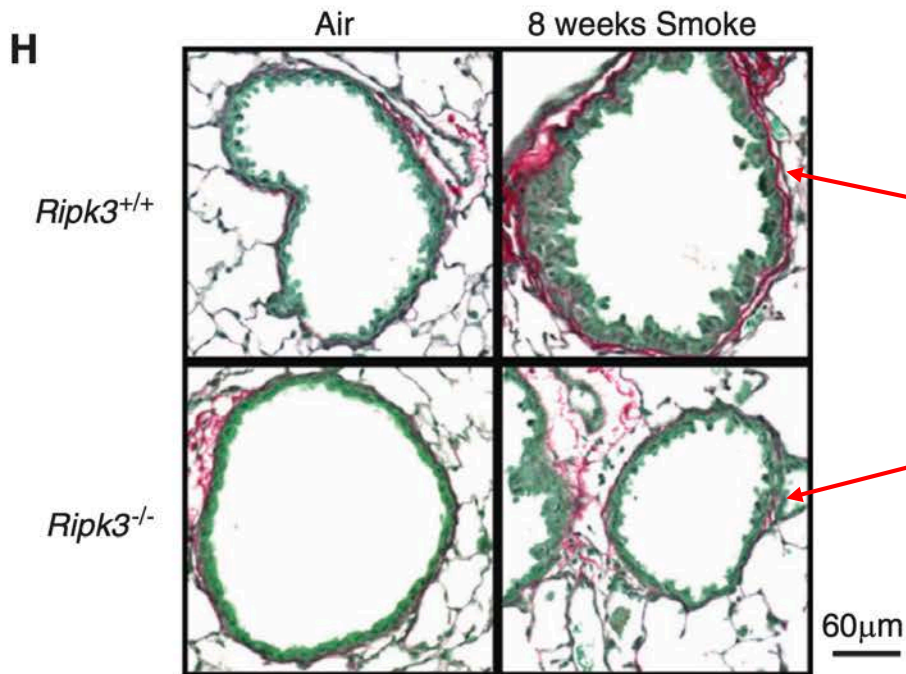
# 4. What is the role of Ripk3 in inflammation and pathology in experimental COPD?

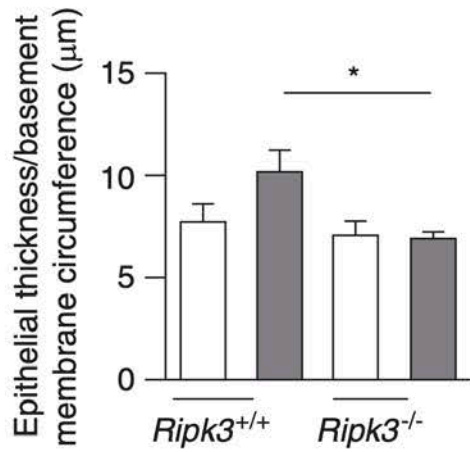
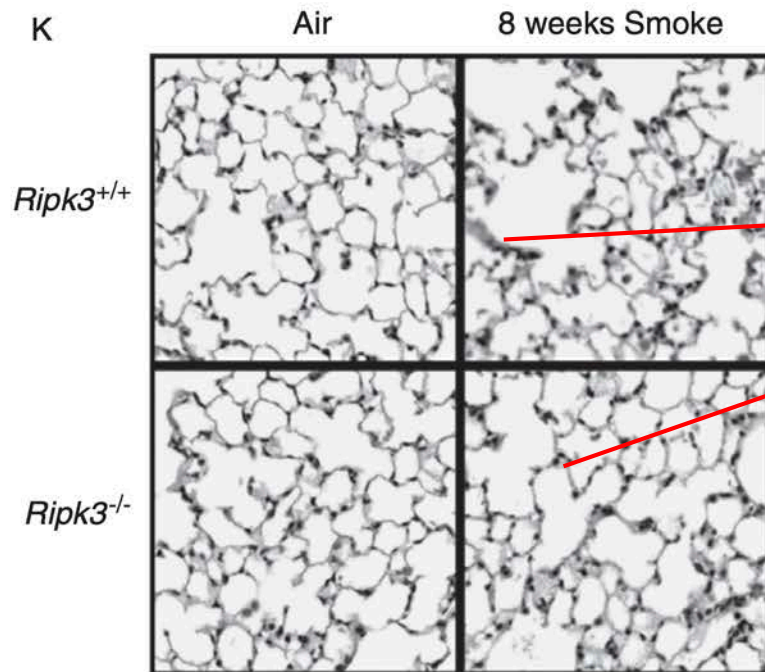
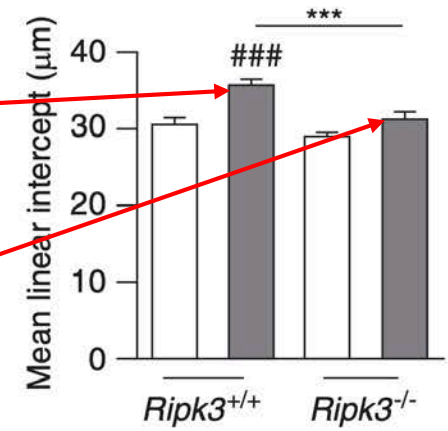








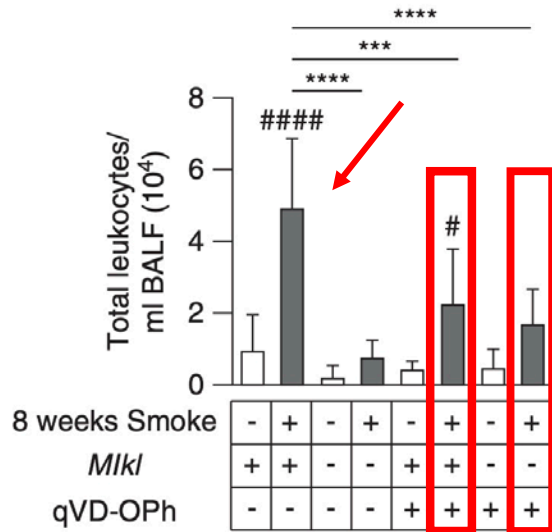
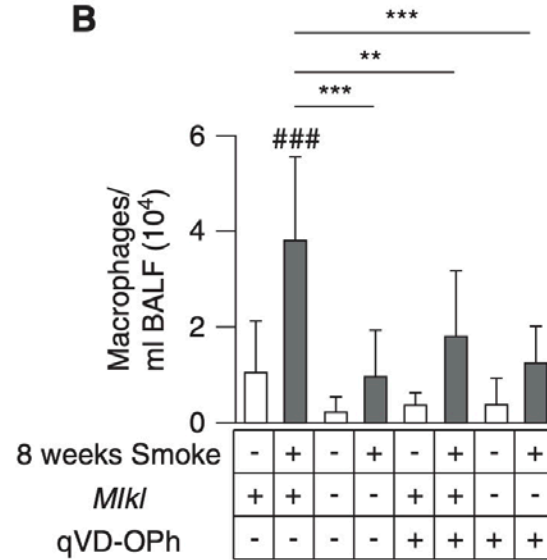
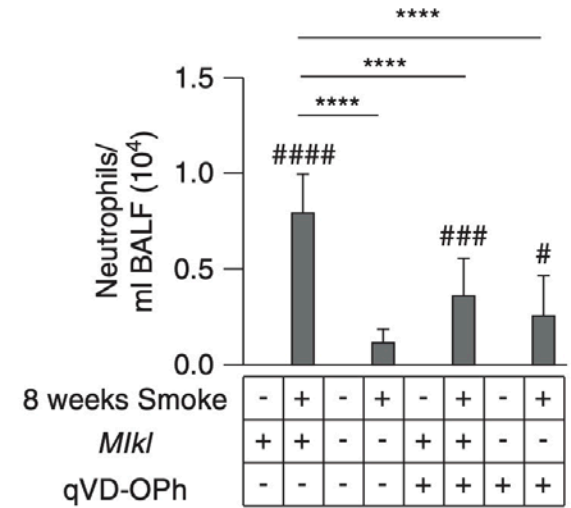
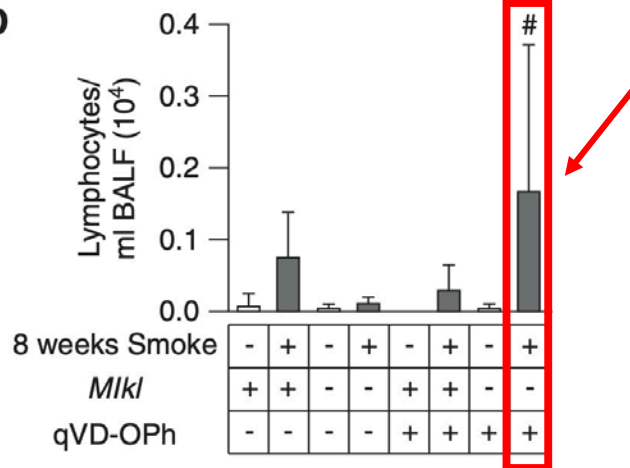


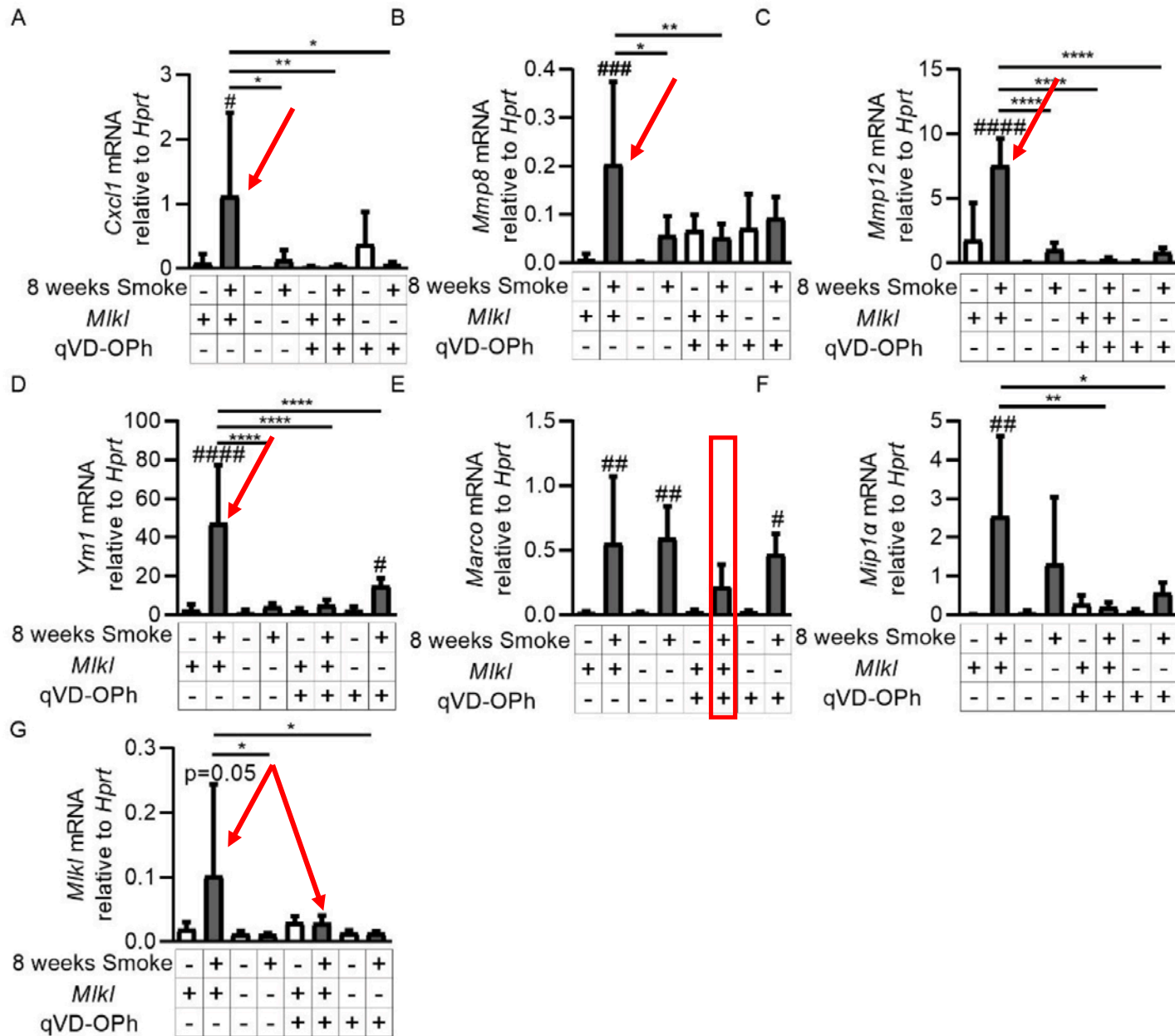
**J****K****L**

## 4. What is the role of Ripk3 in inflammation and pathology in experimental COPD?

→ Ripk3 deficiency reduces airway inflammation, airway remodeling, and emphysema in experimental COPD

# 5. Effects of Mlkl deficiency and combined inhibition of the apoptotic and necroptotic cell death pathways in COPD?

**A****B****C****D**

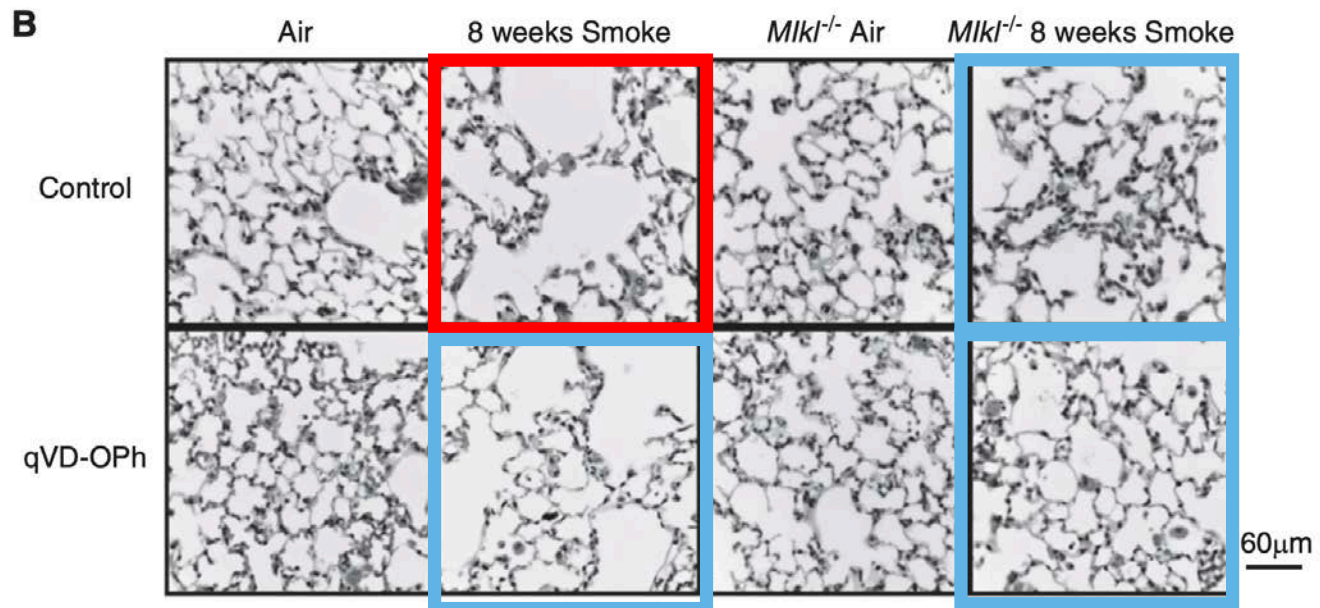
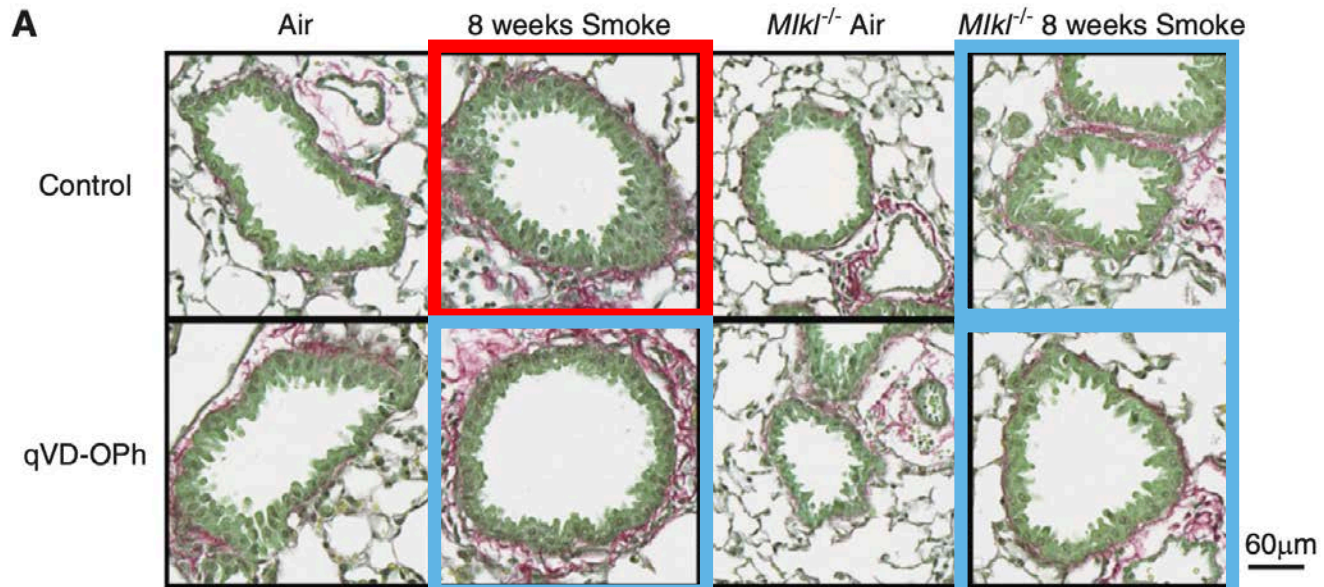


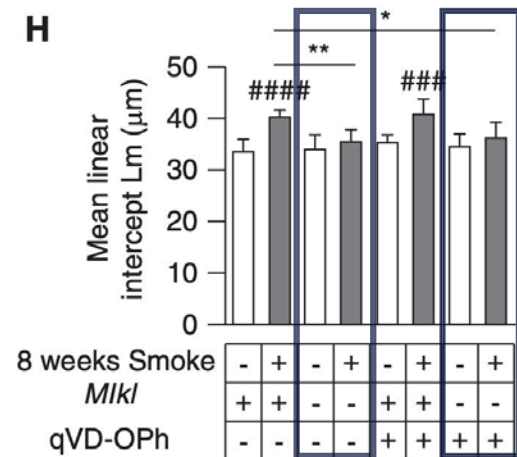
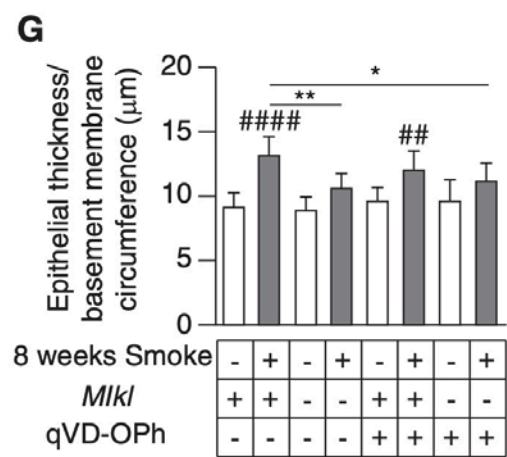
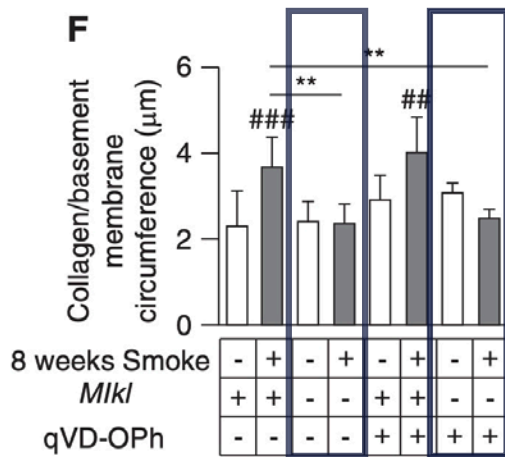
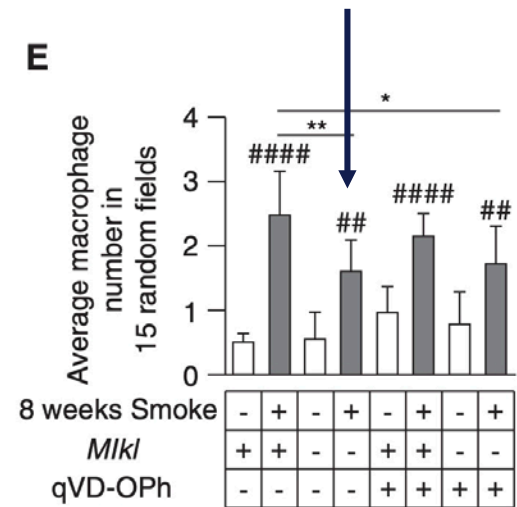
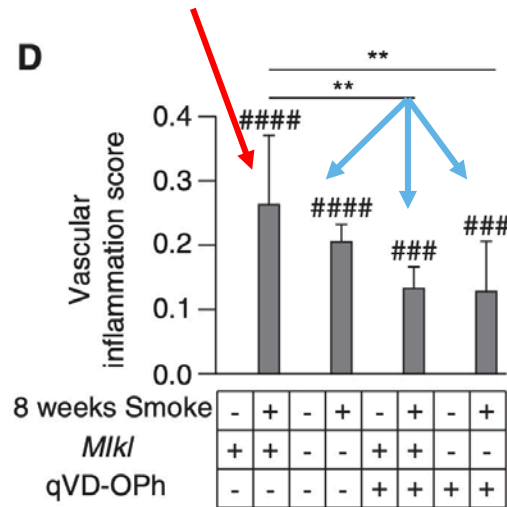
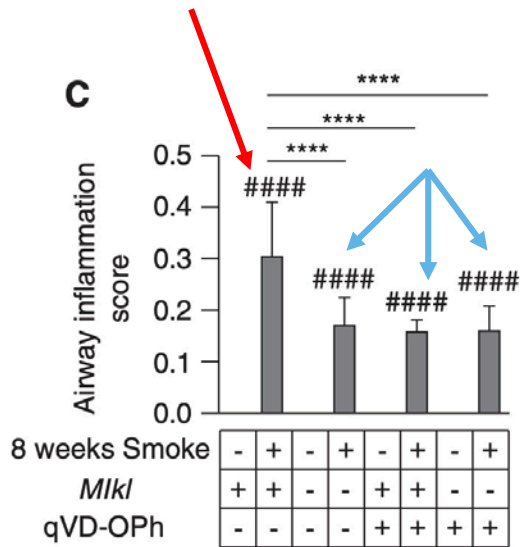
## 5. Effects of Mlkl deficiency and combined inhibition of the apoptotic and necroptotic cell death pathways in COPD?

→ Both Mlkl deficiency and pan-caspase inhibition reduce chronic CS-induced airway inflammation

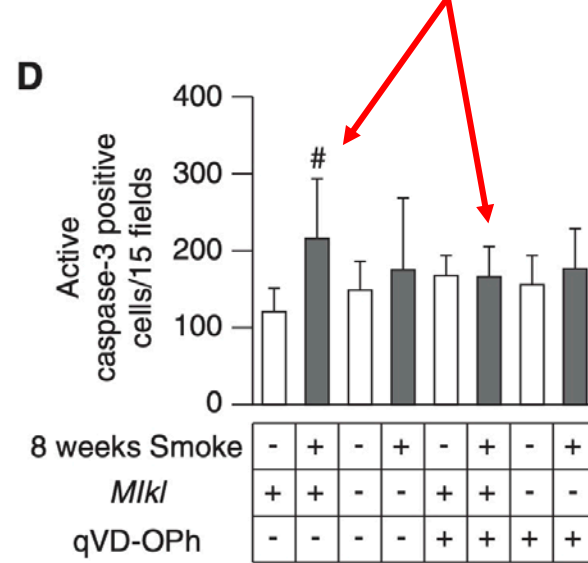
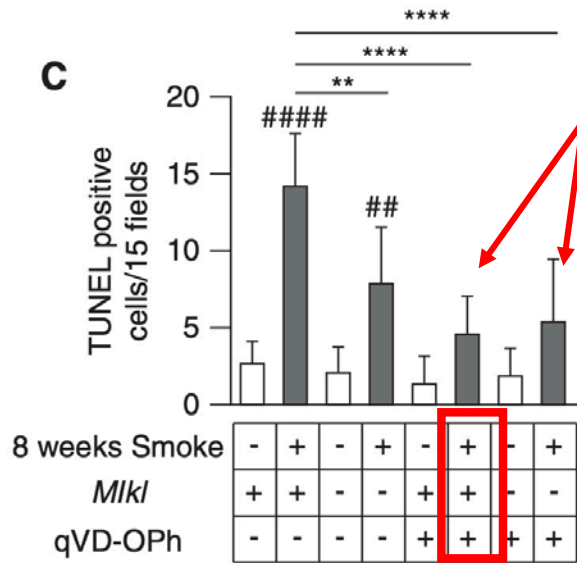
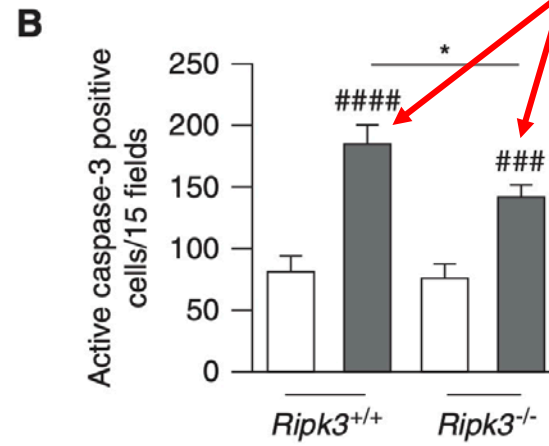
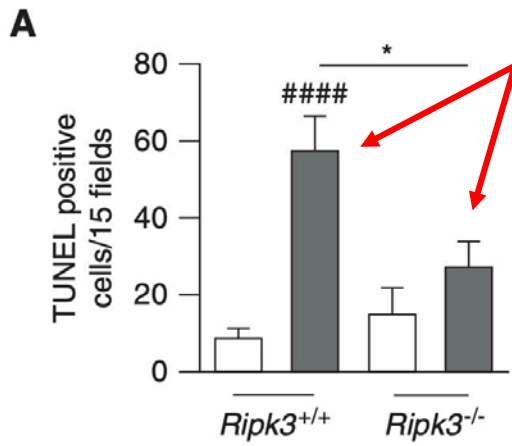


# 6. Differential effects of Mkl deficiency versus caspase Inhibition on experimental COPD pathology





# 7. Effects of Ripk3 and Mlkl deficiency and qVD- OPh treatment on CS-induced lung-cell death in experimental COPD?



□ Air  
■ 8 weeks Smoke

## 7. Effects of Ripk3 and Mlkl deficiency and qVD- OPh treatment on CS-induced lung-cell death in experimental COPD?

→ Ripk3 and Mlkl deficiency and qVD- OPh treatment provide protection from CS-induced lung-cell death in experimental COPD

# Presentation Structure

- 1) Introduction
- 2) Results
- 3) Take-Home Messages**
- 4) Discussion

# Take-Home Messages

- 1) Elevated expression and activation of necroptosis proteins are associated with increasing COPD severity.
- 2) Core necrosome components, particularly Mlkl, were increased at the mRNA and protein levels in lung tissue and alveolar macrophages in experimental COPD.
- 3) RIPK3 and MLKL drive airway inflammation in response to acute CS exposure
- 4) Ripk3 deficiency reduces airway inflammation, airway remodeling, and emphysema in experimental COPD
- 5) Both Mlkl deficiency and pan-caspase inhibition reduce chronic CS-induced airway inflammation
- 6) Ripk3, Mlkl deficiency and qVD-OPh treatment provide protection from CS-induced lung-cell death in experimental COPD



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