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CIGARETTE SMOKE EXPOSURE ACTIVATES THE cGAS-STING PATHWAY AND INTERFERON SIGNALING PATHWAY IN MICE

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SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is the third cause of death and the sixth cause of disability for all ages worldwide. Acute Exacerbation of COPD (AECOPD) is the main driver for the accelerated progression of COPD. AECOPD can be triggered by a virus or bacterial infection, leading to severe inflammation and defective lung tissue repair. Several studies show that interferon (IFN) signaling is defective in COPD. However, there is limited information on how IFN signaling is disrupted after cigarette smoke exposure. cGAS-STING signaling is one of several pathways that can activate IFN signaling.

The present study aimed to investigate the effect of smoke exposure on IFN signaling and its relationship with lung repair using multi-omics (RNA-Seq, ATAC-Seq, proteomic) and organoid models. The multi-omics data and organoids were generated from Epcam+ cells isolated from mice chronically exposed to cigarette smoke (CS). The CS-treated organoid model sourced from healthy murine Epcam+ cells, was used to study the relationship between IFN and lung repair.

The RNA-Seq and proteomic analysis from Epcam+ progenitor cells indicate that the cytosolic DNA detector cGAS-STING pathway, an IFN I activator, was activated in those cells derived from CS-treated mice. This activation is denoted by significantly higher expression of *Sting1* and *Zbp1*. Intriguingly, no IFN mRNA transcripts were observed in the RNA-Seq or proteomics data from CS-derived samples. Additionally, there is a noticeable correlation between the high-level activation of IFN I regulator pathway and reduced differentiation of alveolar organoids. However, cGAS, STING, and TBK1 inhibitors failed to rescue the organoid growth in the in vitro CS-treated organoid model.

Taken together, our data suggest that cGAS-STING pathway is not the sole route that potentially activates the IFN I signaling in chronic CS exposure. Consequently, blocking the cGAS-STING may activate different activator cascades. Another possible explanation is that the IFN I signaling activation does not negatively affect tissue regeneration.