# Metabolic and proteomic impacts of fine particulate matter on the bronchial epithelium

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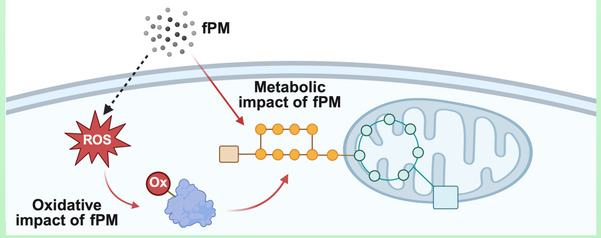
## Background

Fine particulate matter (fPM) is a class of air pollutant known to increase the risk of pulmonary diseases, including lung cancer, through mechanisms such as the epithelial-to-mesenchymal transition (EMT)[1]. The bronchial epithelium, one of the first internal tissues to interact with fPM upon exposure, acts as an important physicochemical barrier to protect proximal and distal lung tissues and against secondary effects on other organs.

Deleterious cellular phenotypes, such as metabolic reprogramming and oxidative stress, have been observed with fPM exposure[2]. Oxidation not only affects protein structure and function, but also has cascading effects on signaling, proliferation, and metabolism. While several individual cellular pathways have been implicated after fPM exposures, these isolated effects are insufficient to account for the complexities of fPM-induced stress responses. Given these limitations, we propose an interdisciplinary systems biology approach to better understand the landscape of fPM exposure.




## Methods

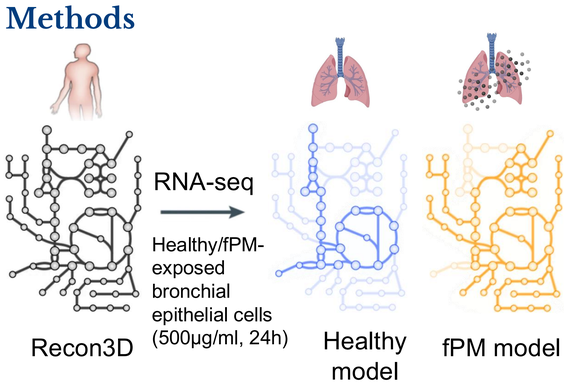



Figure 1: Generation of metabolic network models[3]. Using XomicsToModel[4], models are generated by layering RNA-seq[5], media metabolite concentrations, and bibliomic data onto Recon3D[6]

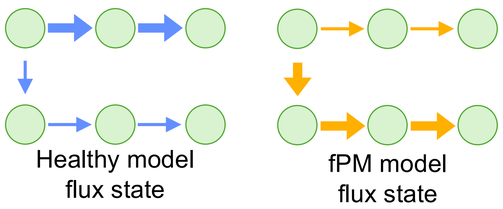



Figure 2: Quantitative analysis of metabolic network models. Metabolic fluxes (described in units of mmol/g dry weight/h) are calculated for reactions in each model to simulate the rate of metabolic substrate turning into product

## Results

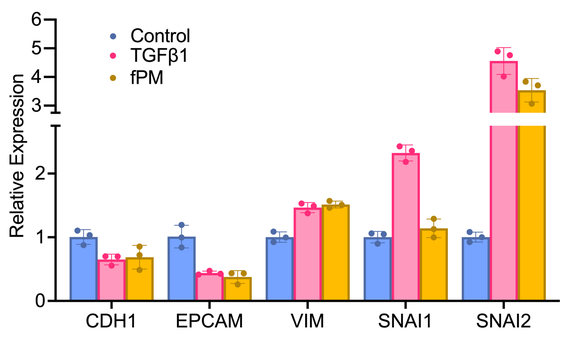



Figure 3: qPCR of EMT markers in bronchial epithelial cells treated with fPM (NIST SRM 2786, 500 µg/ml, 24 h) and TGFβ1 (positive control). Increased EMT observed after fPM exposure

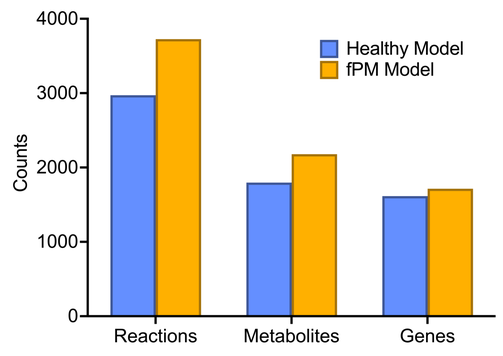



Figure 4: Topology of metabolic network models. fPM model contains more reactions, metabolites, and genes compared to healthy model

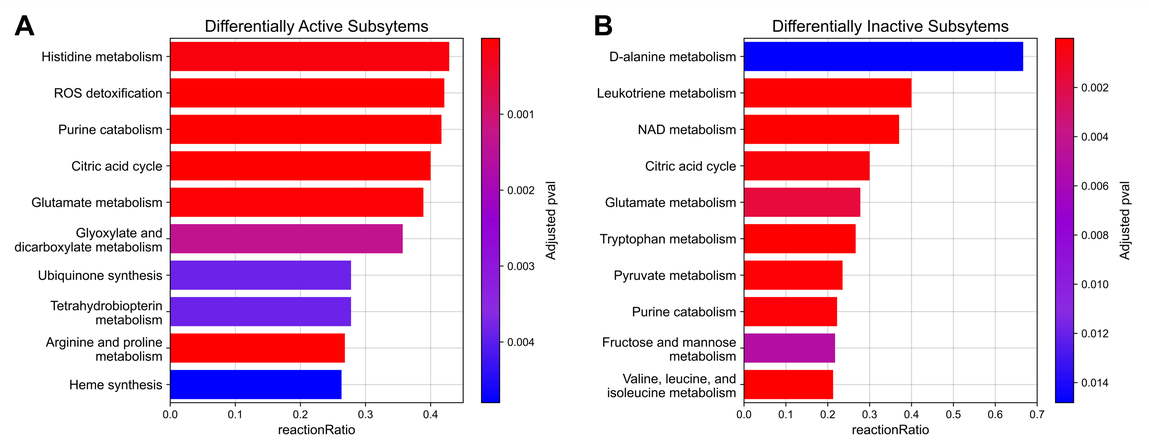



Figure 5: Metabolic subsystem enrichment analysis[7] of differentially (A) active and (B) inactive reactions after fPM exposure. Hypergeometric test using a flux fold change ≥10 and p-value ≤0.05

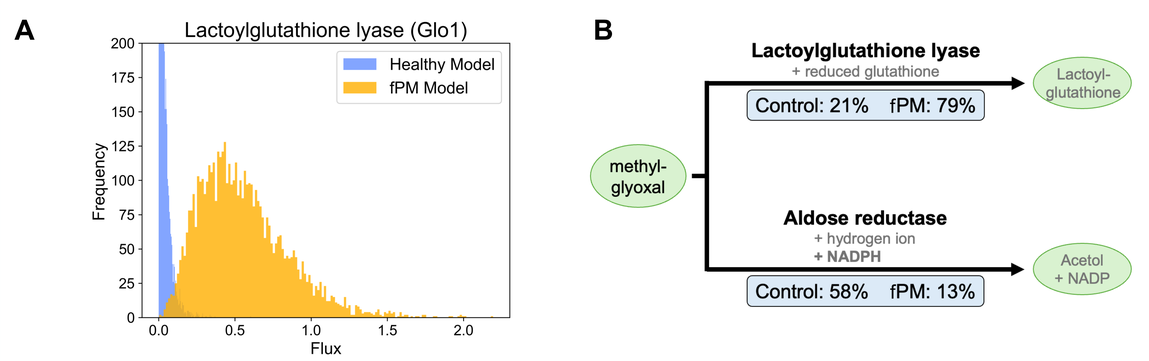



Figure 6: Changes in methylglyoxal breakdown after fPM exposure. (A) Flux distribution for lactoyl-glutathione lyase (Glo1) reaction. Increased flux observed in the fPM model. (B) Differential breakdown of methylglyoxal. fPM model preferentially uses the energy-independent reaction, with an increased percent flux through Glo1 over aldose reductase

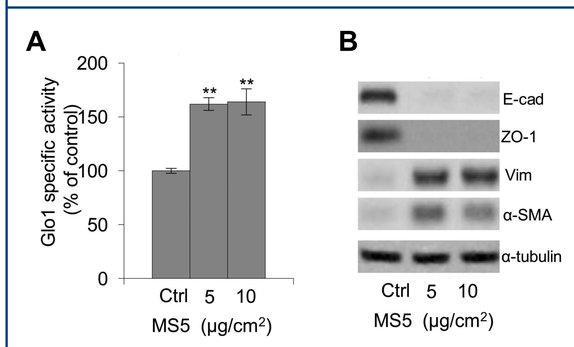



*Figure 7: Effects of crystalline silica (MS5) on bronchial epithelial cells. (A) Increased Glo1 activity and (B) EMT phenotype. (Figure adapted from Antognelli et al., Free Radic Biol Med, 2016[8])

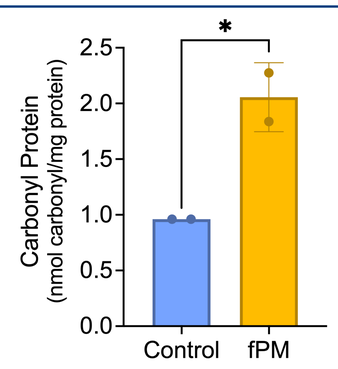


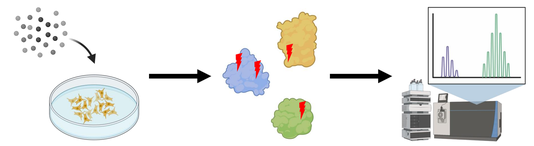

Figure 8: Increased levels of oxidized proteins (carbonylated proteins) measured after bronchial epithelial cells were exposed to fPM

## Conclusions

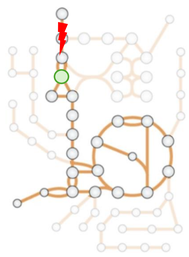
- fPM exposure induces EMT in bronchial epithelial cells
- fPM exposure in bronchial epithelial cells results in metabolome-wide effects, including changes in sugar, nucleotide, and amino acid metabolism
- Cells exposed to fPM preferentially use energy-independent mechanisms of methylglyoxal breakdown
- Increased levels of oxidized proteins can be observed with fPM exposure

## Future Directions

- Validate specific metabolic pathways, such as methylglyoxal breakdown, using $^{13}$C-fluxomics
- Identify proteins oxidized as a result of fPM exposure by redox proteomics



- Simulate protein oxidation in metabolic network models, and identify potential therapeutics using media supplementations



- Investigate the interplay between protein oxidation, metabolic activity, and EMT *in vitro*, and whether supplementation can restore fPM-induced effects

## Acknowledgments

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