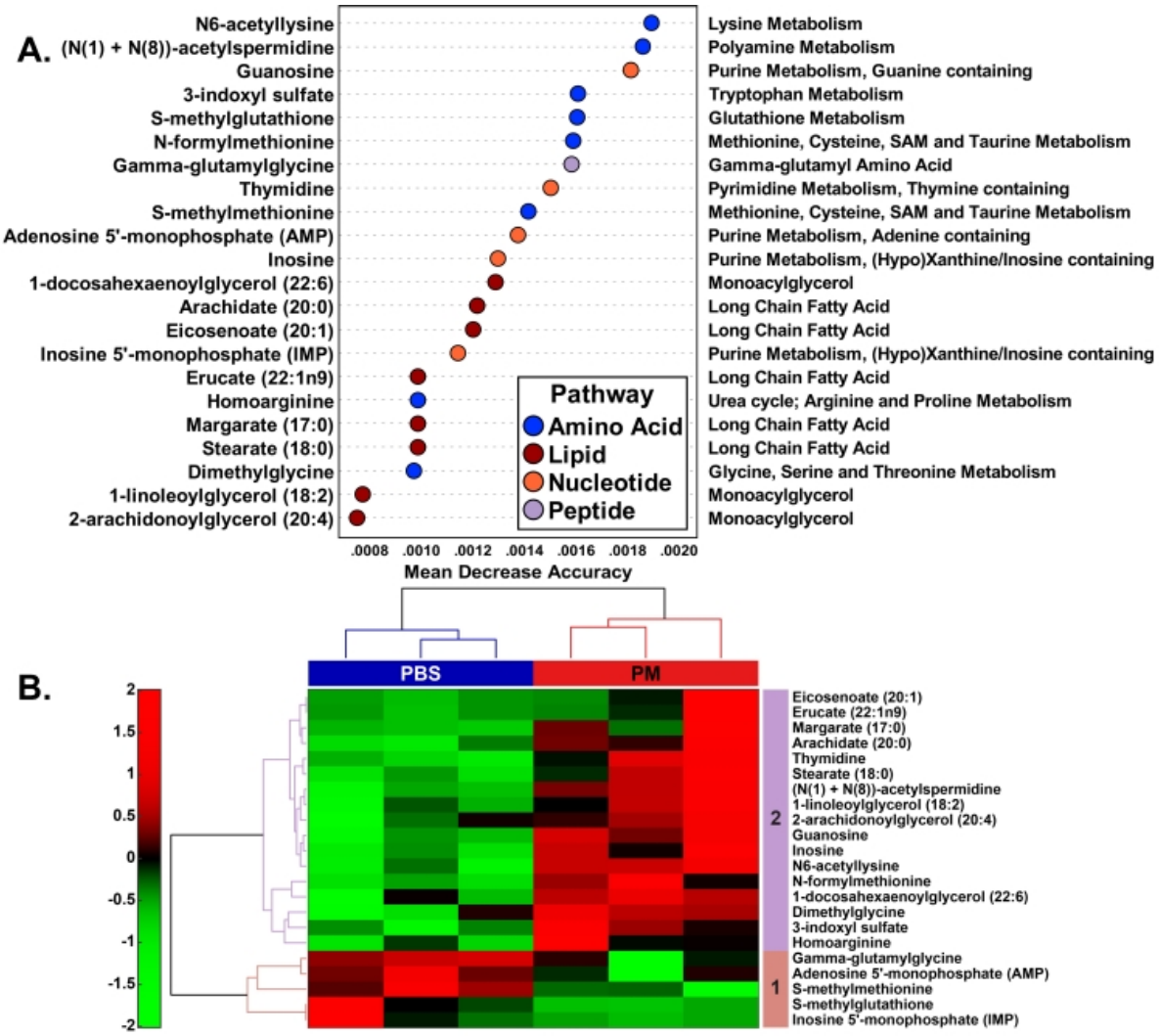
Metabolomics at the Intersection of Murine WTC-PM Exposure and High Fat Diet: A Machine Learning Assessment

G. Crowley[1], E. Caraher[1], A. Veerappan[1], R. Lam[1], S. Haider[1], S. Kwon[1], M. Liu[2], A. Nolan[3]; [1]Medicine, NYU School of Medicine, New York, NY, United States, [2]Population Health and Environmental Medicine, NYU School of Medicine, New York, NY, United States, [3]Medicine, New York University, New York, NY, United States.

Corresponding author's email: george.crowley@nyumc.org

RATIONALE We have previously reported that high fat diet-particulate matter (HFD-PM) co-exposure can induce airway hypereactivity (AHR) in a murine model similar to what is clinically seen in the WTC-exposed firefighter cohort. LPA, a potential pathway that links MetSyn and pulmonary disease, is increased in HFD-PM co-exposure. Echocardiography results indicate that PM exposure in obesity causes subsequent cardiopulmonary dysfunction. To further our understanding of potential pathways involved in vascular and pulmonary remodeling, we assayed the metabolome of HFD and PM co-exposure. METHODS Murine HFD PM Exposure Model. C57Bl/6 wild type (WT) mice (n=8/group), aged 6-8 weeks were fed HFD (60% of calories from lard; D12492i; Research Diets) or normal diet (ND) with 13% of calories from fat. After 12-weeks of HFD and ≥20% weight gain when compared to age matched ND controls, oropharyngeal aspiration of 200µg WTC-PM_{53} or an equal volume of PBS was administered. Metabolomics. 24-hrs after exposure, 100-mg of lung was snap frozen and underwent metabolomics assessment (Metabolon); 3 mice/Group. Qualified/curated metabolites subjected to random forests(RF; randomForest package R3.4.3, R-Project). Refined metabolite profile (top 5% based on mean decrease accuracy) was developed and included in a second model to assess classification performance. Unsupervised, agglomerative, two-way hierarchical clustering (Spearman correlation, average linkage; MATLAB-R2018a) performed for data visualization on refined profile. RESULTS The refined profile of metabolites (n=22) are shown, Figure 1A. Hierarchical clustering of the refined profile revealed differential expression in 2 clusters, Figure 1B. Random forests of the refined profile had 0% estimated classification error. Cluster 1, elevated in PBS-exposed mice, contained metabolites related to dietary protein. Meanwhile, Cluster 2, elevated in PM-exposed mice, included fatty acid metabolites that play a role in inflammation, as well as metabolites of amino acids. CONCLUSIONS Similar to our human population, we observe that fatty acids and acetylated lysine residues are differentially expressed. These metabolites may play a role in WTC-PM-related pathology and implicate epigenetic modulation as a potential result of WTC-exposure and a mechanism of WTC-AHR. Furthermore, elevations in metabolites related to dietary protein have been linked to resistance to WTC-related lung disease, and are seen here to be decreased in response to PM-exposure. Future work will investigate cardiovascular and respiratory remodeling that occurs after PM exposure in the context of high fat diets.



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