Lung Retinoid Metabolism in Sexually Dimorphic Susceptibility to Environmental Exposure

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Biological sex influences susceptibility and responses to environmental pollutant-induced lung injury, however the molecular mechanisms underlying these sex-specific responses remain incompletely understood. Retinoids (vitamin A and its metabolites) are essential regulators of lung development, homeostasis, and repair following injury. We hypothesized that sex-specific differences in retinoid metabolism contribute to divergent responses to environmental pollutant exposure. High-performance liquid chromatography (HPLC) was used to assess lung retinoid metabolites, while flow cytometry was employed to sort retinoid-containing lung cell populations and characterize using single-cell RNA sequencing (scRNA-seq). scRNA-seq datasets from healthy male and female murine lungs were analyzed to identify cell type-specific transcriptional differences. Furthermore, publicly accessible scRNA-seq datasets of human lungs were analyzed to assess the translational relevance of our findings. Differential gene expression and pathway enrichment analyses were conducted on lipid and retinoid metabolic pathways. Integrated single-cell transcriptomic analyses identified robust sex-specific transcriptional programs across lung endothelial cells, epithelial cells, fibroblasts, and macrophages. When compared with males, female mouse and human lungs demonstrated pathway enrichment of the "Retinol metabolism", "Response to retinoic acid", and associated lipid metabolic pathways, including "PPAR signaling", "Fatty acid metabolism", and "Lipid transport". These pathway-level differences were driven by increased expression of key retinoid metabolic genes, including *CYP26B1, LRAT, RDH10, ALDH1A2, ALDH1A3,* and *CRABP2,* alongside increased expression of lipid metabolism-associated genes, including *GPIHBP1, LPL,* and *CD36*. These findings provide a framework for understanding sex-specific differences in lung retinoid metabolism and establish a foundation for future investigations on how retinoid metabolism and associated lipid metabolic pathways contribute to sexually dimorphic susceptibility and responses to environmental pollutant exposure. Supported by NIH R25ES020721.