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Co-methylation analysis in lung tissue identifies pathways for fetal origins of COPD

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Study of fetal and adult lung tissue DNA methylation networks reveals pathways of lung disease that may be primed during *in utero* development and with maternal smoke exposure, supporting early-life origins of COPD https://bit.ly/2yzFkds

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ABSTRACT COPD likely has developmental origins; however, the underlying molecular mechanisms are not fully identified. Investigation of lung tissue-specific epigenetic modifications such as DNA methylation using network approaches might facilitate insights linking *in utero* smoke (IUS) exposure and risk for COPD in adulthood.

We performed genome-wide methylation profiling for adult lung DNA from 160 surgical samples and 78 fetal lung DNA samples isolated from discarded tissue at 8–18 weeks of gestation. Co-methylation networks were constructed to identify preserved modules that shared methylation patterns in fetal and adult lung tissues and associations with fetal IUS exposure, gestational age and COPD.

Weighted correlation networks highlighted preserved and co-methylated modules for both fetal and adult lung data associated with fetal IUS exposure, COPD and lower adult lung function. These modules were significantly enriched for genes involved in embryonic organ development and specific inflammation-related pathways, including Hippo, phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), Wnt, mitogen-activated protein kinase and transforming growth factor-β signalling. Gestational age-associated modules were remarkably preserved for COPD and lung function, and were also annotated to genes enriched for the Wnt and PI3K/AKT pathways.

Epigenetic network perturbations in fetal lung tissue exposed to IUS and of early lung development recapitulated in adult lung tissue from ex-smokers with COPD. Overlapping fetal and adult lung tissue network modules highlighted putative disease pathways supportive of exposure-related and age-associated developmental origins of COPD.