ADDITIONAL MATERIALS AVAILABLE ON THE HEI WEBSITE

Research Report 201

Understanding the Functional Impact of VOC–Ozone Mixtures on the Chemistry of RNA in Epithelial Lung Cells

Contreras et al.

Additional Materials 3: Appendix C. Review of Toxicogenomic Studies of Exposed Models to Environmental Agents

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Appendix C. Summary of toxicogenomic studies of exposed models to environmental agents

CHEMICAL	CONCENTRATION	OMIC	NO. SIGNIFICANT TARGETS	TISSUE/CELL	PATHWAYS AFFECTED	REFERENCE
Transcriptomics						
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	50 mg/kg of bodyweight NNK three times per week for 8 weeks	RNA-seq	926	Gprc5a(−/−) mice (C57BL/6 x 129 sv)	Response to oxidative stress, inflammation and immune regulation	Kantrowitz et al. 2018
Arsenic	0 or 100 nM for 7 weeks	mRNA array	644	Immortalized human keratinocytes (HaCaT)	Cell cycle/cell cycle regulation	Al-Eryani et al. 2017
Beta-chloroprene	0.3, 3, 13, and 90 ppm for mice; 5, 30, 90, and 200 ppm for rats	mRNA microarray	725	Female B6C3F1/Crl mice and female F344/NCrl rats	Glutathione biosynthesis and metabolism	Thomas et al. 2013
Carbon nanotubes (CNTs)	4 mg/kg body weight	RNA-seq	6026	Common inbred strains (BALB/c, C57Bl/6, DBA/2, and C3H/He) of mice	Inflammation, lung damage, immune cell recruitment and cell survival; NF-Kbeta signaling, p38 MAPK signaling and dendritic cell maturation, TLR signaling and TREM1 signaling	Frank et al. 2017
Cigarette smoke	6 d/wk in a whole-body chamber (Teague TE 10z, TSP 100–200 mg/m3) for 6 months	mRNA microarray	69	Two different wild-type murine strains (C57BL/6 and NZW/LacJ) and two genetic models with mutations in COPD genome-wide association study genes (HHIP and FAM13A)	Xenobiotic metabolisms signaling and NRF2 mediated oxidative stress response	Yun et al. 2017
Cigarette smoke	0.8 mg nicotine and 10 mg tar per cigarette for 2 hours	lnRNA and mRNA array	119	C57BL/6 mice	Immune response, defense response and cell chemotaxism cytokine-cytokine receptor	Wang et al. 2014

	twice daily, 6 days per week for 4 weeks				interaction and chemokine signaling pathway	
Cigarette smoke	Healthy never smoker and current smokers without cancer; current and former smokers with cancer and without cancer	RNA-seq	20573	Bronchial airway epithelial cell brushings	Xenobiotics metabolisms retinol metabolism, and oxidoreductase activity; smokers with lung cancer: chemokine signaling, cytokine-cytokine receptor, cell adhesion	Beane et al. 2011
Cigarette smoke	2R4F University of Kentucky reference cigarettes; dilute as 1/50 smoke:air (vol/vol) for 1 hour	mRNA microarray	5355	Primary lung cells (tracheobronchial epithelium)	Xenobiotic metabolism, oxidant/antioxidant balance; DNA damage and repair; downregulation of the factor – beta pathway	Maunders et al. 2007
Cigarette smoke	23 never smokers, 34 current smokers and 18 former smokers	mRNA microarray	97	Bronchial airway epithelial cell from smokers and non-smokers	Induces xenobiotic and redox-regulating genes and several oncogenes and decreases expression of several tumor suppressor genes and genes that regulate airway inflammation; several genes, including potential oncogenes and tumor suppressor genes, failed to revert to never-smoker levels years after cessation of smoking	Spira et al. 2004
Cigarette smoke and electronic cigarette	3R4F reference cigarettes; e-cigarettes (Lounge model designed with 2.8 Ω coil and 3.6 V power supply); ISO 3308:2012 regime (35 mL puff volume, 2 s draw, 60 s puff inter-val)	RNA-seq	2394	Human bronchial epithelial cell (BEAS-2B)	Downregulation of oxidative stress response and cell death	Anthérieu et al. 2017
Copper oxide nanoparticles	3.3 mg/m3 and 13.2 mg/m3	mRNA array	1000	Adult male (8-week-old) Wistar Unilever outbred rats (strain HsdCpb:WU)	Cell proliferation, survival and inflammation	Costa et al. 2018
Dichloroethane (DCM)	0, 100, 500, 2000, 3000 and 4000 ppm DCM for 90 days	mRNA microarray	224	Female B6C3F1 mice	Cellular metabolism and circadian clock	Andersen et al. 2017

Formaldehyde	0 to 0.5 mM for 6 h and 0 to 0.1 mM for 96 h	RNA-seq	654	Human bronchial epithelial cells (BEAS-2B) and human nasal cell (RPMI2650)	Chronic myeloid leukemia signaling; decreased in acetylation of the N-terminal tail of cytosolic histones important for chromatin assembly	Chen et al. 2017
PM2.5	0.1 mg/ml of total isoprene-derived SOA mixture	mRNA array	84	Human bronchial epithelial cell (BEAS-2B)	Oxidative stress, NRF2 mediated oxidative stress response	Arashiro et al. 2018
PM2.5	Water and organic phase PM2.5 for 48 hours	mRNA and miRNA microarray	2501	Human alveolar epithelial cell (A549)	Responses to nutrients, positive regulation of biosynthetic processes, positive regulation of nucleic acid metabolic processes; cell cycle process, the M phase, and the cell cycle check point	Jeong et al. 2017
PM2.5	6.25, 12.5, 25, 50,100, 200 and 400 μg/mL of PM2.5	mRNA microarray	1636	Human bronchial epithelial cell (BEAS-2B)	Gene transcription, signal transduction, cell proliferation, cellular metabolic processes, immune response, etc.	Li et al. 2017
PM2.5	Seed aerosols ~100μg/m3, 200 ppbv NO and 3.5 ppm isoprene	mRNA array	29	Human bronchial epithelial cell (BEAS-2B)	NRF2 mediated oxidative stress response	Lin et al. 2017
PM 2.5	PM2.5 concentrations: 73.5± 61.3 μg/m3 in the unfiltered chamber and 19.8 ±9.0 μg/m3 in the filtered chamber	RNA-seq	54	Pregnant Sprague Dawley rats	Circadian rhythm disorder; molecular clock genes expression in rodent lung	Song et al. 2017
PM2.5	10 mg/cm2 PM2.5 for 24 hours	mRNA microarray	983	Human bronchial epithelial cell (BEAS-2B)	Oxidative stress, inflammation and DNA damage responses; PM affected genes and proteins related to inflammation responses, cancer development, extracellular matrix remodeling and cytoskeleton organization	Longhin et al. 2015

Styrene monomer	1, 5, 10, 20, 40 and 120 ppm for 24 hours	mRNA microarray	1917	Male mice (the parental C57BL/6 strain, a CYP2F2(−/−) knock out and a CYP2F2(−/−) transgenic containing human CYP2F1, 2A13 and 2B6)	Cell cycle, mitotic M-M/G1 phases, DNA-synthesis and metabolism of lipids and lipoproteins	Andersen et al. 2017
VOC and NOX mixture, plus Synthetic Urban Mix	2 ppm carbon Synthetic Urban Mix and 0.2 ppm NOX for 4 hours	mRNA array	709	Human alveolar epithelial cell (A549)	miRNA expression levels within lung cells	Rager et al. 2011
Proteomics						
Aerosolized JP-8 jet fuel	1000 and 2500 mg/m3 for 1 h/day for 7 days	Proteomics	42	Male Swiss-Webster mice	Impaired protein synthetic machinery, toxic/metabolic stress and detoxification systems, ultrastructural damage, and functional responses to CO2 handling, acid-base homeostasis and fluid secretion	Witzmann et al. 1999
Arsenic, cadmium, chromium, mitomycin C, or nickel	3 µM Cd(II) (as cadmium chloride), 10 µM Cr(VI) (as sodiumdichromate), 3 µg/cm2 Ni(II) (as nickel subsulfide), 5 µM or 50 µM As(III) (as sodium arsenite),or 1 µM MMC for 4 hr	Proteomics	291	Human bronchial epithelial cell (BEAS-2B)	Transcription factors, inflammatory cytokines, kinases, and DNA repair proteins	Andrew et al. 2003
Carbon heated tobacco product version 1.2 (CHTP1.2)	5 µg/l, 23 µg/l and 50 µg/l	Proteomics	966	Female Sprague-Dawley rats	Inflammatory and cellular stress responses, lower lipid concentrations in serum	Titz et al. 2018

Cigarette smoke	60% concentration of tobacco smoke (11 mg of tar, 1.1 mg of nicotine and 11 mg carbon monoxide per cigarette) for 4 successive weeks	Proteomics	33	Male Sprague-Dawley rats	Xenobiotic metabolic pathways, surfactant secretion, host defense, and the inflammatory response, steroid biosynthesis pathway, amino acid metabolisms, three signaling pathways including the estrogen signaling pathway, the NOD-like receptor signaling pathway, and the PI3K-Akt signaling	Ma et al. 2018
Cigarette smoke	0.1% cigarette smoke condensate for 12 months	Proteomics	3959	Human alveolar epithelial cell (A549)	Metabolism, cell communication, nucleic acid metabolism, enrichment of phagosome maturation, antigen presentation, nuclear factor erythroid 2-related factor 2-mediated oxidative stress response, and cholesterol biosynthesis pathways	Advani et al. 2017
Cigarette smoke	6–7 cigarettes (“Great Gate”) twice a day 30min for 1, 2 and 4 months	Proteomics	28	Wistar rats	Up-regulated expression of two proteins, receptor for advanced glycation endpoints (RAGE) and thioredoxin (Trx)	Zhang et al. 2008
CNTs, crocidolite asbestos, ultrafine carbon black	Suspensions of nanomaterials (40 micrograms per mouse) twice a week for 3 weeks	Proteomics	109	C57BL/6 mice	Two high-sensitivity markers of inflammation including S100a9, abundance of identified lung tissue proteins	Teeguarden et al. 2011
Diacetyl vapor	50 µL of 25 mM (~1000 ppm) for 1 h on days 0, 2, and 4; cells were harvested on day 6	Proteomics	3389	Human primary tracheobronchial epithelial cells	Altered expression of proteins and phosphopeptides, loss of cilia, increased squamous differentiation	Foster et al. 2016
Diesel exhaust particles	6 h exposure 30 µg/ml	Proteomics	71	Rat lung epithelial cell line SV40T2	Drug metabolism, antioxidation, cell cycle/proliferation/apoptosis, coagulation/fibrinolysis	Koike et al. 2004
Ottawa urban dust (EHC-93)	0, 60, 140 and 200 µg/cm2 for 24 hours	Proteomics	206	Human alveolar epithelial cell (A549)	Cell death, proliferation, and inflammatory response; secretion of pro-inflammatory cytokines	Vuong et al. 2017a

PM2.5	24 mg/l and 120 mg/l for 72 h	Proteomics	27	Human alveolar epithelial cell (A549)	Oxidative stress, metabolic disturbances, dysregulation of signal transduction; pathways: cytoskeleton system, oxidative stress, carbohydrate energy metabolism, signal transduction, protein synthesis and degradation, mitochondrial structure, transcriptional regulation, cytoskeleton system	Huang et al. 2013
Silica particles (cristobalite (CR) and Alpha-quartz	0, 60, 140 and 200 µg/cm2 for a 24 h	Proteomics	49	Human alveolar epithelial cell (A549)	Cell death and cell proliferation	Vuong et al. 2017b