### SUPPLEMENTARY MATERIAL

# Inhaled Ozone (O<sub>3</sub>)-Induces Changes in Serum Metabolomic and Liver Transcriptomic Profiles in Rats

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**SI Figure 1:** Heatmaps of liver gene expression for cytokine network in rats exposed to  $O_3$  (A: immediately after 1-day 6-hr air or  $O_3$ , 0-hr time point; B. immediately after 2-day 6-hr air or  $O_3$ , 2-day, 0-hr) and C. 18-hr after 2-day 6-hr air or  $O_3$ ; 2-day, 18-hr) exposure.

Figure 1A



Figure 1B

Air Ozone chemokine C-X-C motif ligand 13

Figure 1C



Functional gene lists were generated by NetAffx queries at the Affymetrix website (<u>www.affymetrix.com</u>) and identified from differentially expressed genes (DEGs) list for each time point (air vs  $O_3$ ) based on the query term, "cytokines". Genes were then median centered with average linkage, hierarchically clustered using Cluster 3.0 and displayed through Java Treeview. Heat map of DEGs with significant  $O_3$  effect were identified separately at each time point. Red indicates genes that have high expression values across both groups, green indicates genes that have low expression values across both groups, and black indicates median expression.

**SI Figure 2:** Heatmaps of liver gene expression showing differentially expressed genes (air versus O<sub>3</sub>) for apoptosis network in rats exposed to O<sub>3</sub> (A-D, exposed for 6hr/day; immediately after 1-day; E, immediately after 2-day, F, 18-hr after 2-day time point).

Figure 2A



## Figure 2B

Air	Ozone	
		protein_disulfide_isomerase_family_A_member_4
		GTP_cyclonydrolase_1
		myotrophin rabaptin RAB GTPase binding effector protein 1
		sphingosine-1-phosphate_lyase_1
		SRY sex_determining_region_Y-box_4
		THAP_domain_containing_apoptosis_associated_protein_3
		histone_deacetylase_5
		retinoblastoma 1 – chemokine C-X-C motif ligand 12 stromal cell-derived factor 1
		chemokine_C-X-C_motit_ligand=12_stromal_cell-derived_tactor_1
		neuropilin T
		hing_finger_and_FXVE_like_domain_containing_protein
		solute carrier family 29 nucleoside transporters member 1
		adducth 3 gamma'
		GTP_cvclohydrolase_1
		inhibitor, of kappa tight polypeptide_gene_enhancer_in_B-cells_kinase_bet
		ATE-pinding_cassette_sub-tamily_B_MRB-TAE_member_1A
		ALP-pinding_cassette_sub-family_B_MDR-LAP_memper_1A ATP-binding_cassette_sub-family_B_MDR-TAP_member_1A
		suppression of tumorigenicity 13
		ubiquitin specific peptidase 28 intersectio 1 SH3 domain protein
		similar to RikEN cDNA 1700023003
		nuclear receptor subfamily 3 group C_member_1
		CREB_binding_protein
		peptid%proly[_1somerase_Dcyclophilin_D PRKC_apoptosis_WT1_regulator
		interleukin_33
		heat_shock_protein_90kDa_alpha_cytosolic_class_B_member_1
		activity A receptor type I
		heat_shock_protein_90_alpha_cytosolic_class_A_member_1
		catenin_cadherin_associated_protein_alpha_1
		CSE1_chromosome_segregation_1-like A kinase_PBKA_anchor_protein_T3
		Homeodomain_Interacting_protein_kinase_2
		similar to chromosome 16 open reading frame 5
		endothelin_receptor_type_A
		protein_phosphatase_2_formeriy_2A_regulatory_subunit_B_beta_isoform cardiolipin_synthase_1
		cardiolipin_synthase_1 programmed cell death 4
		cAMP_responsive_element_modulator
		X-box binding protein 1 Pho dualing Protein 1
		activity A receptor type I

# Figure 2C

heme_oxygenase_decycling_1 insulin_receptor_substrate_2 growth_arrest_and_DNA-damage-inducible_beta suppressor_of_cytokine_signaling_3 B-cell_CLL-Imphoma_3 KruppeI-like_factor_10 immediate_early_response_3 nuclear_protein_transcriptional_regulator_1 Macrophage_stimulating_1_hepatocyte_growth_factor-like kininogen_1_kininogen_1-like_1 arginase_liver cell_deafh-inducing_DFFA-like_effector_a connective_tissue_growth_factor retinoblastoma-like_2 peroxisome_proliferator-activated_receptor_gamma_coactivator_1_alpha forkhead_box_01 laminin_gamma_1 wingless-type_MMTV_integration_site_family_member_4 cyclin-dependent_kinase_inhibitor_1A Son_DNA_binding_protein serinite_palmitoyltransferase_1a_liver Ras-related_Gry_ordein serinite_palmitoyltransferase_1a_liver Ras-related_Gry_boxia_inducible_domain_family_member_1A cullin_1 FAST_kinase_domains_2 B-cell_translocation_gene_1_anti-proliferative dynamin_1-like HIG1_hypoxia_inducible_domain_family_member_1A cyclin-cependent_simase_al continue_genetoboxylase_1 cyclin_Cependent_kinase_substrate_1 transforming_growth_factor_beta_regulator_4 HIG1_hypoxia_inducible_domain_family_member_1A cyclin_Ce_somatic family_with_sequence_similarity_82_member_A2 ornithine_decaboxylase_1 cyclin_C1 molecule cyclin_C1 molecule cyclin_C1 molecule cyclin_C1 molecule cyclin_C3 muticar_casein_kinase_and_cyclin-dependent_kinase_substrate_1 transforming_growth_factor_beta_regulator_4 HI3_histone_family_38 mutis_homolog_2 nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 thyroid_hormone_receptor_alpha RNA_binding_motir_RNP1_RRM_protein_3 mution_retire_family_78 mutis_homolog_7 nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 thyroid_hormone_receptor_7_C_elargeneters	Air	Ozone	
insulin_reference_simularity_82_member_42 growth_arrest_and_DNA-damage-inducible_beta suppressor_of_cytokine_signaling_3 B-cell_CLL-iymphoma_3 kruppe-likke_factor_10 immediate_early_response_3 nuclear_proference cell_deaff-inducing_DFFA-likke_effector_a connective_tissue_growth_factor retinoblastoma-likke_1 peroxisome_proliferator-activated_receptor_gamma_coactivator_1_alpha forkhead_box_01 larminin_gamma_1 wingless-type_MMTV_integration_site_family_member_4 cyclin-dependent_kinase_inhibitor_1A cyclin-dependent_kinase_interve dynamin_1-like HiG1_typoxia_inducible_domain_family_member_1A cytochrome_c_somatic family_with_sequence_similarity_82_member_A2 omithine_decarboxylase_1 cyclin_C mitofusin_2 CD24_molecule cyclin_G prohibilin nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 transforming_growth_factor_beta_regulator_4 H3_histone_family_3B mults_homolog_2 nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 thyproid_hormone_receptor_alpha RNA_binding_rowtir_RNP1_RRM_protein_3 mitofushonding_rowtir_RNP1_RRM_protein_3 mitofushonding_rowtir_RNP1_RRM_protein_3			heme oxygenase decycling 1
growth_arrest_and_DNA-damage-inducible_beta suppressor_of_crtokine_signaling_3 B-cell_CLL-hmphoma_3 Kruppel-like_factor_10 immediate_early_response_3 nuclear_protein_transcriptional_regulator_1 Macrophage_stimulating_1 hepatocyte_growth_factor-like kininogen_1_kininogen_1-like_1 arginase_liver cell_deaffi-inducing_DFFA-like_effector_a connective_itsue_growth_factor retinoblastoma-like_2 peroxisome_proliferator-activated_receptor_gamma_coactivator_1_alpha forkhead_box_01 larminin_gamma_1 wingless-type_MMTV_integration_site_family_member_4 cyclin-dependent_kinase_inhibitor_1A Son_DNA_binding_protein serine-threonine_kinase_a lactate_dehydrogenase_A lactate_dehydrogenase_A lactate_dehydrogenase_A camitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_palmitoyttransferase_1a_liver carmitine_decarboxylase_1 cytochrome_c_somatic cytochrome_c_somatic cytochrome_c_somatic cytochrome_c_somatic cytochrome_c_somatic cytochrome_case_1 hibitor_decarboxylase_1 cyclin_C6 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 mitofusin_2 CD24_molecule cyclin_C6 mitofusin_2 CD24_molecule cyclin_C7 muclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 transforming_growth_factor_beta_regulator_4 H3_histone_family_38 mults_homolog_2 nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1 thyvroid_hormone_receptor_alpha			insulin_réceptor_substrate_2
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RNA_binding_motif_RNP1_RRM_protein_3			nuclear_casein_kinase_and_cyclin-dependent_kinase_substrate_1
RINA_pinding_motif_RNP1_RRM_protein_3			Invroid_normone_receptor_aipna
			ritesbandrial carrier bornolog 2 C. clogene
thiorodovin 2			thioredovin_2
P450 ovidoreductase			P450 ovidoreductase
P450 cvtochrome oxidoreductase			P450 cvtochrome oxidoreductase

#### Figure 2D





Functional gene lists were generated by NetAffx queries at the Affymetrix website (<u>www.affymetrix.com</u>) and identified from differentially expressed genes (DEGs) list based on the query term, "apoptosis". Genes were then median centered with average linkage, hierarchically clustered using Cluster 3.0 and displayed through Java Treeview. Heat map of DEGs with significant O<sub>3</sub> effect were identified separately at each time point. Red indicates genes that have high expression values across both groups, green indicates genes that have low expression values across both groups, and black indicates median expression.

**SI Figure 3:** Heatmap of liver gene expression showing differentially expressed genes (air versus  $O_3$ ) for Steroid, insulin and fatty acid receptor signaling network in rats exposed to  $O_3$  for 6hr/day for 1-day (immediately after exposure).



Functional gene lists were generated by NetAffx queries at the Affymetrix website (<u>www.affymetrix.com</u>) and identified from differentially expressed genes (DEGs) list based on the query term, "steroid, insulin and fatty acid signaling". Genes were then median centered with average linkage, the normalized expression values for those probesets present on both lists were converted to z values and hierarchically clustered using Cluster 3.0 with average linkage and displayed with Treeview. Red indicates genes that have high expression values across both groups, green indicates genes that have low expression values across both groups, and black indicates median expression.

**SI Figure 4.** Ingenuity pathway analysis showing ozone exposure-induced changes in liver steroid receptor (A), insulin receptor (B) and fatty acid signaling (C).





Figure 4B







Three functional probeset lists based on queries of "steroid receptor", "insulin receptor" or "fatty acid" were obtained from NetAffx. Each of these lists was compared to the list of differentially expressed genes (DEGs) for the one day zero hour time point to identify DEGs in each of the three functional categories. Each functional list was processed separately by Ingenuity Pathway Analysis (IPA) to produce a direct relationship graph. The graph constructed from the Ingenuity knowledgebase depicts some of the biological relationships among the probesets on the list. The shape of a gene-labeled object indicates its molecular function and its color indicates whether it is upregulated (red) or downregulated (green). The features of the connecting lines convey the nature of the molecular interaction. For a detailed legend of these IPA graphs see the ingenuity.com website.

**SI Table 1:** Effect of acute ozone exposure on the expression of probe sets belonging to different biological processes in the liver.

	Number of probes on array	Number of DEGS from Master List	Per Cent Master List DEGs on
Process			Functional List
Amino acid	4650	507	11
biosynthesis			
Apoptosis	2345	259	11
Diabetes	743	117	16
Gluconeogenesis	80	21	26
Glycolysis	114	20	18
Mitochondria	671	111	17
Steroid Metabolism	416	77	19
Tricarboxylic	29	10	34
Unfolded protein	154	26	17

Significantly different probes for specific biological processes were identified from a master differentially expressed genes list (DEGs) for air versus O<sub>3</sub> exposure which included genes for all three time points (Immediately after 1-day 6-hr, immediately after 2-day, 6-hr and 18 hours after 2-day, 6-hr).