Air Pollution Particle Effects on Human Antimycobacterial Immunity

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Background
Twenty-five percent of the global disease burden are related to environmental factors. There is increasing evidence that air pollution increases the rate of respiratory infections worldwide. Indoor air pollution and cigarette smoking have been shown to be major risk factors for the development of tuberculosis (TB). Epidemiological evidence of significantly increased risk of developing TB after exposure to silica, indoor pollution or cigarette smoking suggests that air pollutants are potentially detrimental to antimicrobial effector functions

With a RO1 grant from NIHES we will study the effects of urban air pollution particulate matter (PM2.5) on innate and adaptive human lung immunity against Mycobacterium tuberculosis the bacteria that cause TB in Mexico. PM2.5 will be collected in Mexico City and healthy study subjects from Iztapalapa, a Mexico City known for its high prevalence of TB cases and high air pollution levels, be studied. We will assess antimycobacterial effector functions of bronchoalveolar (lung) cells before and after in vivo PM2.5 exposure (see Aims 1 and 2).

Results from Preliminary Studies using Diesel Exhaust Particles as Model Air Pollution Particles in our Laboratory

Figure 1.

Figure 2.

Figure 3.

Hypothesis
Based on our observations in blood cells, we hypothesize that urban ambient PM2.5:

(1) impair innate and adaptive antimycobacterial immune effector functions of BACs
(2) PM2.5 alters toll-like receptor (TLR)-mediated M.tb-specific cell activation pathways with suppression of several NF-κB and IRF-1-mediated target genes
(3) these alterations lead to altered phagocytosis and decreased M.tb-growth-controlling capacity by the BACs in vitro
(4) the induction of cellular toxicity and immune cell functions are modified by baseline exposure of subjects to PM and by their body burden of oxidative stress.

Specific Aims
Aim 1. To assess PM2.5-induced cellular toxicity and PM2.5 effects on M.tb-specific immunity in human BACs.

We will examine the effects of PM2.5 on:
(a) cellular apoptosis and necrosis
(b) production of pro- and anti-inflammatory cytokines
(c) Th1, Th2 cytokine and TLR gene expression and signaling
(d) M.tb-induced cell activation and Interferon-γ production

Aim 2. To investigate the role of PM2.5 in altering phagocytosis and growth control of M.tb by human BACs.

We will assess the effects of PM2.5 on (a)phagocytosis of M.tb by alveolar macrophages and in stably transfected Chinese Hamster Ovary (CHO) cells expressing scavenger receptor A.
(b) BAC-mediated control of M.tb growth using colony forming unit assays.

Aim 3. To examine personal in vivo PM exposure and its relationship to immune effector functions of BACs.

We will measure and assess
(a) subjects’ urinary concentrations of 1-hydroxypropane, a major metabolite of pyrene as a proxy of combustion-generated pollutants, and 1-aminopropane, a metabolite of the diesel exhaust-specific compound 1-aminopropane, and urinary concentrations of two biomarkers of oxidative stress: 8- hydroxydeoxyguanosine (8-OHdG) marking oxidative DNA damage and malondialdehyde (MDA) marking lipid peroxidation by reactive oxygen species;
(b) personal exposure using time activity questionnaires and geographical indicators of exposure,
(c) quantify the particle load in AMs as a long-term exposure measure; and
(d) statistically examine possible associations between these air pollution exposure measures and the antimycobacterial BAC effector functions and toxicity (Aims 1 & 2).

Study Site
Mexico City is an ideal study site due to its

Novelty of Experimental Approach
Our experimental approach expands on current scientific knowledge in several important ways:

First, we will use PM2.5 collected from an urban megacity environment that individuals inhale and are exposed to under real-life conditions.

Second, we will study primary human lung cells that are exposed to both PM2.5 and M.tb aerogenically. Both PM2.5 and lung cells of study subjects will be obtained from the same study site within the city.

Third, we will assess healthy individuals who are (a) concurrently aerogenically exposed to M.tb in households of individuals with active pulmonary TB (healthy household contacts, HHCs) and (b) healthy control individuals from the same community (CCs, community controls).

Fourth, we will for the first time measure personal PM2.5 exposure profiles (urinary biomarkers, time-activity, geographical location, and PM load in AMs) to determine in vivo ‘baseline’ and lifetime exposure stratification (high – low) for correlation with antimycobacterial primary lung immune cell effector functions.

Fifth, we will assess the effects of PM2.5 on M.tb-specific immune cell effector functions (cytokine production, gene expression) and correlate these effects with a M.tb control assay as a read out of global antimycobacterial immune cell functions.

Significance
PM-induced alterations of innate and adaptive antimycobacterial immune responses may have significant global health implications given the wide geographical scales for both air pollution and M.tb infections.

Next Steps
Develop study protocols and consent forms in Spanish and English for IRB submission in Mexico City and at UMDNJ and obtain IRB approval
Develop standard operating procedures for clinical and laboratory research components.
Train participating clinical and lab personnel in Mexico and the US.

Kick Off: Study in 2012

Collaboration Opportunities
If you are interested of opportunities to work in the context of this grant either in the US (UMDNJ School of Public Health) or in Mexico City (National Institute for Respiratory Diseases / Instituto Nacional de Enfermedades Respiratorias) please contact

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