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CONTEMPORARY REVIEW

Air Pollution as a Risk Factor for Type 2 Diabetes

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ABSTRACT

Recent studies in both humans and animals suggest that air pollution is an important risk factor for type 2 diabetes mellitus (T2DM). However, the mechanism by which air pollution mediates propensity to diabetes is not fully understood. While a number of epidemiologic studies have shown a positive association between ambient air pollution exposure and risk for T2DM, some studies have not found such a relationship. Experimental studies in susceptible disease models do support this association and suggest the involvement of tissues involved in the pathogenesis of T2DM such as the immune system, adipose, liver, and central nervous system. This review summarizes the epidemiologic and experimental evidence between ambient outdoor air pollution and T2DM.

According to the World Health Organization, 347 million people worldwide have diabetes, with more than 80% of diabetes deaths occurring in low- and middle-income countries (Danaei *et al.*, 2011; Mathers and Loncar, 2006). The vast majority of these cases of diabetes are secondary to type 2 diabetes mellitus (T2DM), formerly known as adult-onset diabetes. The burgeoning number of individuals with T2DM has created multiplicity of challenges that relate not only to the medical care but also related to the enormous fiscal burden posed by this disease on governments and non-profit organizations. The realization that the medical system alone, even with appropriate financial investments, simply cannot satisfactorily address the extraordinary challenge posed by diabetes-related complications, has resulted in a shift in focus on treatment of manifest disease to a prevention paradigm that is dependent on defining modifiable factors that predispose to the development of T2DM which may then be targeted. There is uniform agreement that primary prevention through an understanding of environmental underpinnings of T2DM is perhaps the only sustainable mechanism to reduce T2DM-related morbidity and mortality.

While the literature on the etiology of T2DM suggests a heritable component, as evidenced by clustering of cases and genome-wide association studies, the evidence to support a direct causal association in the preponderant majority of cases is scant (Doria, 2000; Gloyn and McCarthy, 2001; McCarthy and Menzel, 2001; Wheeler and Barroso, 2011). More than 40 genetic susceptibility loci have been reported for T2DM (Villegas *et al.*, 2012). Genetic predisposition while undoubtedly important is not the sole determinant of T2DM development, raising the collective importance of factors including diet and the environment in the genesis of T2DM (Noble *et al.*, 2011; Talmud *et al.*, 2010). It is possible that familial clustering of T2DM may have little to do with genetics, but may simply reflect shared environmental risk factors (eg sedentary lifestyle, pollutant exposures and gut flora to name a few) (Adamo and Tesson, 2008; Ling and Groop, 2009). While a number of factors such as obesity, sedentary lifestyle, stress, unhealthy diet, and smoking have been persuasively demonstrated to contribute to the pathogenesis of T2DM, the role of factors in the physical environment (ie air and water pollution, noise, disruptions in sleep-wake cycle owing to pervasive exposure to light at night-time) has not received much attention. These factors permeate the macro- and microenvironment that we live in, are insidiously present throughout the lifetime of an individual and may pose much more of a threat than single conventional risk factors (Andersen *et al.*, 2012; Coogan *et al.*, 2012; Kramer *et al.*, 2010; Pearson *et al.*, 2010; Reis *et al.*, 2009; Sorensen *et al.*, 2013). In this review, we will focus on the role of ambient air pollution as a risk factor for T2DM, review epidemiologic and investigational studies that have evaluated air pollution as a causal mechanism.

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ASSOCIATION BETWEEN AIR POLLUTION AND T2DM

Epidemiologic Evidence

A number of studies have shown a positive association between long-term ambient air pollution exposures and increased risk of T2DM (Table 1). One of the first studies conducted by Brook *et al.* in Canada investigated the association between diabetes and nitrogen dioxide (NO_2), a traffic-related air pollutant. Nitrogen dioxide, a major component of traffic-related air pollution (Han and Naeher, 2006), was measured using geographic information systems methodology, with individual exposures derived based on a network of samplers in multiple cities to estimate air pollution exposure. Exposure to NO_2 was associated with higher levels of diabetes in women [odds ratio (OR) 1.04; 95% confidence interval (CI): 1.00–1.08], but not in men. Although the authors did not distinguish between type 1 and 2 diabetes, they speculated that the subjects largely had T2DM because the study population had a median age of 60 years (Brook *et al.*, 2008). Dijkema *et al.* (2011) analyzed over 8000 inhabitants aged 50–75 years in a semi-rural area of the Netherlands and observed an odds ratio for T2DM of 1.39 (95% CI: 1.00–1.94) per 10 $\mu g/m^3$ increment in NO_2, suggesting that long-term exposure to traffic-related air pollution may increase the risk for T2DM. A recent cohort study looked at the relationship between exposure to particulate matter <2.5 μm ($PM_{2.5}$) and abnormal glucose tolerance in 2093 pregnant nondiabetic women from the Boston, MA area. Residential traffic density and roadway proximity were used as surrogates for exposure to traffic-related air pollution. Second trimester spatiotemporal exposures ranged from 8.5 to 15.9 $\mu g/m^3$ from $PM_{2.5}$. The prevalence of impaired glucose tolerance was elevated in the highest (vs lowest) quartile of exposure to spatiotemporal $PM_{2.5}$ (OR=2.63; 95% CI 1.15–6.01) (Fleisch *et al.*, 2014). Although these studies used NO_2 as an indicator of traffic-related air pollution, it is possible that the measured associations/effects were due to other components of traffic-related air pollution, such as PM and carbon monoxide (Han and Naeher, 2006).

Few studies have examined the relationship between incident T2DM and ambient air pollution exposure. Krämer *et al.* conducted an investigation of the association of incident T2DM with ambient air pollution using data from the Study on the Influence of Air Pollution on Lung, Inflammation and Aging (SALIA) cohort in Germany. Nondiabetic women who were 54–55 years old at baseline (1985–1995) were followed until 2006. Complement factor 3 cleavage product C_3c was used as a marker for subclinical inflammation. The authors found that T2DM incidence increased by 15% (95% CI 4–27) per interquartile range of traffic-related PM or by 15% (95% CI 4–27) to 42% (95% CI 16–73) per interquartile range of NO_2. Women with high C_3c levels were more susceptible to PM-related risk of diabetes than women with low C_3c levels (95% CI 1.05–1.18 for an increase in C_3c by 10 mg/dL) (Kramer *et al.*, 2010). Andersen *et al.* followed 51,818 participants of the Danish Diet, Cancer, and Health cohort in the Danish National Diabetes Register from baseline (1993–1997) to 2006. Nitrogen dioxide levels were measured at the residential addresses of the cohort participants. After an average of 9.7 years of follow-up, they detected a positive association between air pollution and confirmed cases of diabetes [hazard ratio (HR) 1.04 (95% CI 1.03–1.08)] per interquartile range of 4.9 $\mu g/m^2$ mean NO_2 levels]. The association was stronger in people who were physically active [HR 1.10 (95% CI 1.03–1.16)] or non-smokers [HR 1.12 (95% CI 1.05–1.20)] suggesting that reductions in ambient air pollution exposures may particularly benefit individuals living healthier lifestyles. In one of the few incident studies of T2DM and ambient air pollution exposure among African-Americans, Coogan *et al.* followed 3992 women residing in Los Angeles from 1995 to 2005. The authors reported that those who had higher exposure to air pollutants ($PM_{2.5}$ and NO_2) were more likely to develop T2DM. The incidence rate ratio (IRR) for T2DM for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.63 (95% CI 0.78–3.44), and the IRR for NO_2 (per 12.4 parts per billion) was 1.14 (95% CI 1.07–1.46) (Coogan *et al.*, 2012).

More evidence is available from cross-sectional, hospitalization and mortality studies. Pearson *et al.* conducted a cross-sectional ecological study with diabetes data from the Centers for Disease Control and Prevention (CDC) and $PM_{2.5}$ assessed at the county level for years 2004 and 2005. In models adjusted for known risk factors, they found 10,000 additional cases (1% increase) of prevalent diabetes for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ [2004: $\beta = 0.77$ (95% CI 0.39–1.25), $p < .001$; 2005: $\beta = 0.81$ (0.48–1.07), $p < .001$] (Pearson *et al.*, 2010). In a study of hospitalizations for serious complications of diabetes, in Santiago, Chile between 2001 and 2008, the relative risks of hospitalization for diabetes associated with an interquartile range increase in each criteria air pollutant were the following: 1.15 (1.10, 1.20) for carbon monoxide (IQR = 1.00); 1.07 (0.98, 1.16) for ozone (IQR = 63.50); 1.14 (1.06, 1.22) for sulfur dioxide (IQR = 5.88); 1.12 (1.05, 1.20) for NO_2 (IQR = 27.94); 1.11 (1.07, 1.15) for PM_{10} (IQR = 34.00); and 1.11 (1.06, 1.16) for fine $PM_{2.5}$ (IQR = 18.50) (Dales *et al.*, 2012). A separate 2009 cross-sectional study by Tamayo *et al.* looked at the relationship between residential PM_{10} and HbA_{1c} concentration in 9102 (4356 women; 4746 men) in newly diagnosed T2DM patients in 7 different regions in Germany. Multiple covariates including age, sex, body mass index, diabetes duration, geographic region, year of ascertainment, and social indicators were adjusted for. Adjusted HbA_{1c} was significantly lower in the lowest quartile of PM_{10} exposure compared to quartiles Q2, Q3, and Q4 (Q2 vs Q4: −0.23; 95% CI: −0.44, −0.02/Q3 vs Q4: −0.25; −0.43, −0.06) (Tamayo *et al.*, 2014). Type 2 diabetes mellitus patients in this study thus demonstrated higher HbA_{1c} levels when exposed to higher levels of air pollution.

Besides the association studies linking criteria air pollutants with susceptibility to T2DM, a diagnosis of diabetes may increase susceptibility to air pollution cardiovascular effects. In one of the earliest studies, O'Neill *et al.* demonstrated that 6-day moving averages of all 4 particle metrics [$PM_{2.5}$, particle number, black carbon (BC), and sulfates] were associated with decreased vascular reactivity among patients with diabetes but not those without diabetes. Black carbon increase was associated with decreased flow-mediated vascular reactivity (−12.6%; 95% CI, −21.7 to −2.4), whereas $PM_{2.5}$ was associated with decreased nitroglycerin-mediated reactivity (−7.6%; 95% CI, −12.8 to −2.1). Effects were stronger in T2DM compared with type 1 diabetes (O'Neill *et al.*, 2007). In a study of diabetics in the Boston area, particle exposure in the home and during each trip to the clinic (home/trip exposure) was measured continuously and as a 5-day integrated sample. Baseline brachial artery diameter was negatively associated with particle pollution, including home/trip-integrated BC (−0.02 mm; 95% CI: −0.04, −0.003, for a 0.28 $\mu g/m^3$ increase in BC) as well as $PM_{2.5}$, 5-day average ambient $PM_{2.5}$ (–0.02 mm; 95% CI: –0.05, 0.01) (Zanobetti *et al.*, 2014). In a case crossover analysis of Medicare enrollees during the period 1999–2010 in 121 US communities, short-term exposure to $PM_{2.5}$ was associated with an increase in hospitalization risks

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TABLE 1. Epidemiological Associations among Air Pollutants, Diabetes, and Insulin Resistance

Location	Subject number	Main pollutants	Principal findings	Published year
Studies related to diabetes prevalence or incidence				
Ontario, Canada	7634 subjects	NO_2	OR for DM prevalence (1.04; 95% CI 1.00–1.08) increased in women per 1 ppb NO_2. No significant association in men.	2008
Ruhr, Germany	1775 nondiabetic women	NO_2; PM_{10} (mean: 47 $\mu g/m^3$)	Adjusted HR for developing DM over mean 16 years ranged from 1.15 to 1.42 per IQR increase in PM_{10} or in relation to traffic exposures or NO_2.	2010
USA	Unknown, estimated by county level	$PM_{2.5}$	Adjusted DM prevalence associated with $PM_{2.5}$ at county level (1% increase per 10 $\mu g/m^3$) and persistently associated with $PM_{2.5}$ at counties below current annual standards ($PM_{2.5} < 15\ \mu g/m^3$).	2010
West Friesland, the Netherlands	8018 subjects including 619 DM subjects	NO_2	DM prevalence increased with exposure within traffic in a 250 -m buffer when compared to the lowest quartile although non-significant.	2011
USA	NHS: 74 412 subjects HPFS: 15 048 subjects Non-diabetes subjects	$PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$ Mean $PM_{2.5}$: 17.5–18.3 $\mu g/m^3$	Most pollutants not significantly associated with increased HR for developing DM in adjusted model.	2011
Los Angeles, USA	3992 women	NO_2 and $PM_{2.5}$	NO_2 exposure associated with 10-year incidence of DM (adjusted HR 1.25; 95% CI 1.07–1.46). $PM_{2.5}$ not related.	2012
Denmark	51 818 nondiabetic participants	NO_2 level (IQR: 4.9 (μg/m3)	NO2 not related to all new DM cases over mean 9.7 years. Positive associations with confirmed DM (1.04; 95% CI 1.00–1.08) with larger effects in nonsmokers and active people.	2012
Santiago, Chile	Unknown	$PM_{2.5}$, PM_{10}, O_3, CO, NO_2 and SO2	The relative risks (95% CI) of hospitalization for diabetes were: 1.11 (1.07, 1.15) for PM_{10} (IQR = 34.00); and 1.11 (1.06, 1.16) for $PM_{2.5}$ (IQR = 18.50).	2012
Ontario, Canada	62 012 nondiabetic adults	$PM_{2.5}$	The adjusted hazard ratio for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.11 (95% CI: 1.02, 1.21).	2013
Switzerland	6392 subjects	PM_{10} and NO_2	PM_{10} and NO_2 were associated with prevalent diabetes with respective odds ratios of 1.40 (95% CI: 1.17, 1.67) and 1.19 (95% CI: 1.03, 1.38) per 10 $\mu g/m^3$ increase.	2014
Studies related to markers of insulin sensitivity				
Iran	374 children	Mean PM_{10}: 150 $\mu g/m^3$	HOMA-IR increased by 1.1 adjusted for other health parameters in relation to PM_{10} levels.	2009
Taiwan	1023 elderly adults	Mean PM_{10}: 35 $\mu g/m^3$	Significant associations with increases in fasting glucose and HbA_{1c} level with PM_{10}.	2011
Michigan, USA	25 subjects	Mean $PM_{2.5}$: 11.5 $\mu g/m^3$	Increased HOMA-IR (0.7, 95% CI 0.1–1.3) with a 10 $\mu g/m^3$ $PM_{2.5}$ exposure.	2013
German	397 children	Mean PM_{10}: 21.2 $\mu g/m^3$; Mean $PM_{2.5}$: 14 $\mu g/m^3$; Mean NO_2: 21.7 $\mu g/m^3$	HOMA-IR increased 17% in related to NO_2; 18.7% in PM_{10} levels. HOMA-IR also increased in related to $PM_{2.5}$ without statistical significance.	2013
Beijing, China	50 subjects	BC (mean: 7.2 $\mu g/m^3$) and $PM_{2.5}$ (mean: 150.6 $\mu g/m^3$)	Minimum average detectable effect of HOMA-IR is 2.81 with 10 $\mu g/m^3$ PM and 1 $\mu g/m^3$ black carbon.	2013
German	4356 women; 4746 men	Mean PM_{10}: 19.6 $\mu g/m^3$	Adjusted HbA_{1c} was significantly lower in the lowest quartile of PM10 exposure compared to quartiles Q2, Q3, and Q4.	2014
Studies related to diabetes-associated mortality				
Canada	2.1 million adults	Mean $PM_{2.5} \cong 8.7\ \mu g/m^3$	The adjusted HR of diabetes-associated mortality for a 10 $\mu g/m^3$ PM2.5 was 1.49 (95% CI: 1.37, 1.62).	2013
Danish	52 061 subjects	NO_2 (mean 16.9 $\mu g/m^3$)	Mean levels of NO_2 at the residence were significantly associated with mortality from diabetes.	2013
Montreal, Canada	158 350 elderly adults	$PM_{2.5}$ (mean 8.74 $\mu g/m^3$), NO_2 (mean 37.90 $\mu g/m^3$), O_3, CO and SO_2	Positive associations were found between daily non-accidental mortality and all air pollutants but O_3.	2013
USA	121 communities	$PM_{2.5}$	Short-term exposure to $PM_{2.5}$ was associated with an increase in hospitalization risks for diabetes (1.14%, 95% CI: 0.56, 1.73 for a 10 $\mu g/m^3$ increase in 2 days average), along with an increase in all-cause mortality risk (0.64%, 95% CI: 0.42, 0.85).	2014

CI, confidence interval; DM, diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IQR, interquartile range; LUR, land use regression; NHS, Nurses' Health Study; NO_2, nitrogen dioxide; OR, odds ratio; PM_{10}, particulate matter with diameter <10 μm; $PM_{2.5}$, particulate matter with diameter <2.5 μm; $PM_{10\text{-}2.5}$, particulate matter with diameter between 2.5–10 μm.

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for diabetes (1.14% increase, 95% CI: 0.56, 1.73 for a 10 μg/m^3 increase in 2 days average), along with an increase in all-cause mortality risk (0.64%, 95% CI: 0.42, 0.85). While the association between short-term exposure to $PM_{2.5}$ and mortality was higher among Medicare enrollees that had a previous admission for diabetes than among Medicare enrollees that did not had a prior admission for these diseases, this association was not significant (Zanobetti *et al.*, 2014). In a mortality study of 2.1 million deaths during the 1990s Canadian census, Brook *et al.* (2013) found that a statistically significant increased risk for diabetes-related mortality (HR, 1.49; 95% CI 1.37–1.62) with a 10 μg/m^3 elevation in long-term $PM_{2.5}$ exposure. A cross-sectional analysis of 6392 participants in Switzerland examined the association between estimates of average PM_{10} and NO_2 exposure over the 10 years preceding the survey. PM_{10} and NO_2 were associated with prevalent diabetes with respective odds ratios of 1.40 (95% CI 1.17, 1.67) and 1.19 (95% CI 1.03, 1.38) per 10 μg/m^3 increase in the average home outdoor level. Associations with PM_{10} were generally stronger than with NO_2, even in the two-pollutant model. There was some indication that β-blockers mitigated the effect of PM_{10} (Eze *et al.*, 2014). In summary, these studies collectively argued for an important interaction between diabetes and susceptibility to cardiovascular effects including increase in mortality.

In contrast to the studies that have demonstrated an association between ambient air pollution and diabetes, a few others have not found a consistent relationship. Dijkema *et al.*, in a cross-sectional diabetes screening study, evaluated exposure to traffic and T2DM prevalence using distance to the nearest main road, overall traffic flow including in a 250-m circular buffer and land use regression modeled NO_2. Although there was some association with traffic in a 250-m buffer, there was no relationship with other variables. Exposure-response relations seemed somewhat more pronounced for women than for men (non-significant) (Dijkema *et al.*, 2011). The pooled analyses of the Nurses' Health Study and the Health Professionals' Follow-Up did not show a strong association between PM exposure and diabetes incidence. However, a positive association with distance to road (the proxy marker of exposure to traffic-related exposure) was shown among women (Puett *et al.*, 2011). Interestingly, the susceptibility of exposure to women to air pollution has also been seen with regards to cardiovascular events in long-term exposure studies and is even more pronounced in obese women (Miller *et al.*, 2007).

The differences noted between studies that have noted an association and those that have not, may relate to differences in methodology, measurement differences in air pollutant, differences in susceptibility and concomitant risk factors in the study population as well as overall prevalent rates of diabetes. The differences between men and women seen in some of these studies (women > men) may relate to true differences in biologic susceptibility, but on the other hand may also reflect exposure assessment error, particularly in males who tend to be more mobile compared to females.

Evidence from Animal Studies Linking Air Pollution Exposure and Insulin Resistance

A number of animal studies have now suggested that air pollution and components of air pollution may induce abnormalities in insulin resistance (IR) *in vivo* (Figure 1). Unless otherwise specified, references to $PM_{2.5}$ in this section specifically refer to

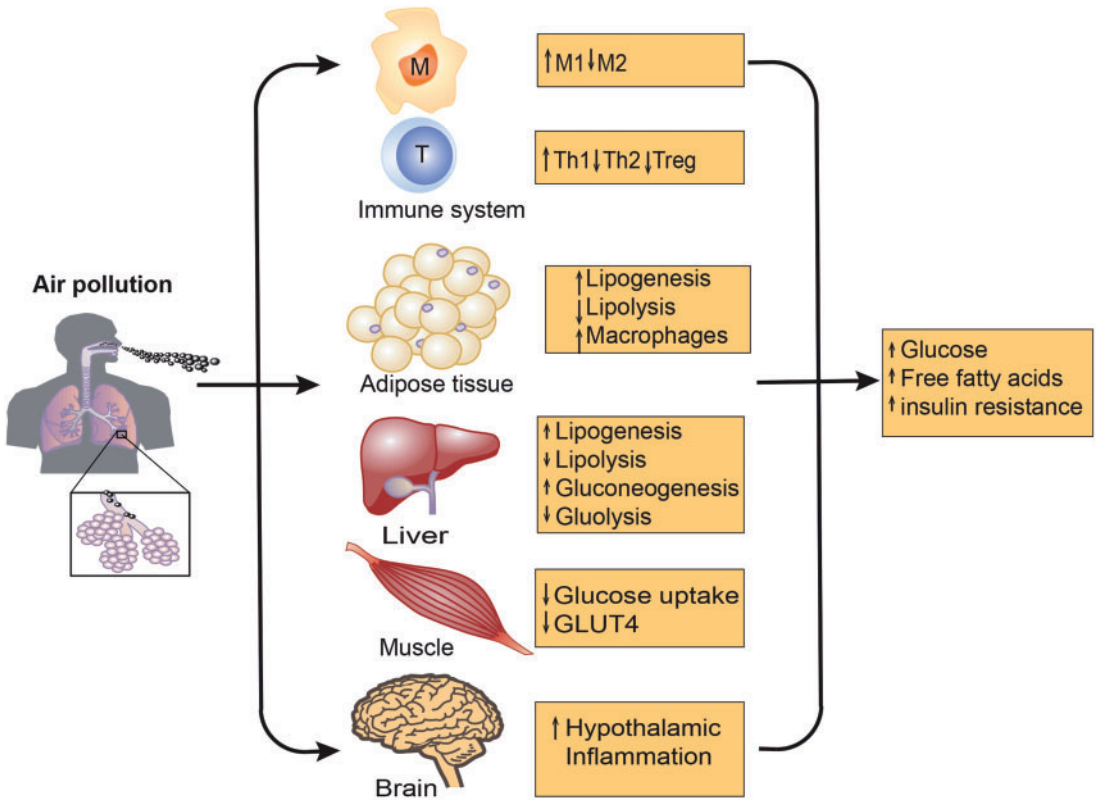

FIG. 1. Effect of air pollution on immune system, adipose tissue, muscle, liver, and brain. M1, classically activated macrophages; M2, alternatively activated macrophages; Th1, T helper type 1; Th2, T helper type 2; GLUT4, glucose transporter type 4.

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concentrated ambient particles (CAP) exposure. In one of the first studies to demonstrate a link, Sun *et al.* observed increased visceral adiposity, systemic inflammation and enhanced IR in C57BL/6 mice after 24 weeks of concentrated ambient $PM_{2.5}$ exposure (mean = 72.7 μg/m^3) in a whole-body exposure system. Circulating TNF-α, IL-6, E-selectin, intracellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1, and resistin were significantly increased in the mice exposed to $PM_{2.5}$ compared with filtered air (Sun *et al.*, 2009). Impaired insulin signaling in the aorta was evidenced by decreased PI3K/Akt/endothelial nitric oxide synthase (eNOS) phosphorylation (Sun *et al.*, 2009). In subsequent experiments by the same group, Xu *et al.* evaluated the effect of $PM_{2.5}$ (mean concentration = 111.0 μg/m^3) exposure in young C57BL/6 mice (3 weeks old) fed concomitant normal or high-fat diet. After only 10 weeks of exposure to $PM_{2.5}$, mice on normal chow exhibited an increase in homeostasis model assessment of insulin resistance (HOMA-IR) and postprandial glucose that approached that seen with high-fat diet-fed mice exposed to filtered air (Xu *et al.*, 2010). These results appear to suggest enhanced susceptibility to exposure early on in life as evidenced by a reduced time frame of development of IR. Liu *et al.* further evaluated the time course of development of changes in HOMA-IR and postprandial glucose in C57BL/6 mice aged 18 weeks that were fed high-fat diet and simultaneously exposed to $PM_{2.5}$. Mean $PM_{2.5}$ level in the chamber was 116.9 ± 34.2 μg/m^3. Although there were no significant differences in body weight and insulin sensitivity at 8 weeks, the $PM_{2.5}$-exposed group at 17 weeks had elevated fasting glucose, HOMA-IR, abnormal glucose tolerance, and attenuation of whole-body insulin sensitivity. $PM_{2.5}$-exposed mice also demonstrated a decrease in aortic relaxation in response to both acetylcholine and insulin and reduced Akt phosphorylation in insulin responsive tissues (aorta, liver, skeletal muscle and white adipose tissue) at the end of 17 weeks of exposure, indicating development of IR (Liu *et al.*, 2014a). Zheng *et al.* (2013) found evidence of increase in insulin receptor substrate 1 (IRS-1) serine phosphorylation at 1101 and 636 in the liver after 10 weeks of $PM_{2.5}$ exposure, suggesting impaired hepatic insulin signaling. Liu *et al.* (2014a) also observed similar results. Defective IRS-1 signaling will lead to reduced PI3K-Akt signaling and suppression of insulin-induced glucose transporter translocation resulting in peripheral IR. In another study, the effect of CAP exposure over a substantive duration of a rodent's lifespan was evaluated (to simulate lifetime exposure in humans, mean concentration of $PM_{2.5}$ was 72.7 μg/m^3). At the end of the exposure, $PM_{2.5}$-exposed mice demonstrated IR and decreased glucose tolerance compared with the FA-exposed group. $PM_{2.5}$ exposure decreased phosphorylation of Akt in the liver, skeletal muscle, white adipose tissue, and brown adipose tissue (Xu *et al.*, 2011a). In a recent study, Liu *et al.* extended the effects of $PM_{2.5}$ to a genetically susceptible diabetic mouse model (KKAy) exposed to $PM_{2.5}$ (mean = 102.9 ± 19.16 μg/m^3). Although there were no differences at baseline, the mice showed significant elevation in glucose levels in response to intra-peritoneal glucose challenge after 5 weeks of $PM_{2.5}$ exposure, with these differences not seen at 8 weeks of exposure between the groups. In the same study, $PM_{2.5}$ inhalation for 5 weeks but not 8 weeks significantly decreased O_2 consumption, respiratory exchange ratio, CO_2, and heat production compared to respective FA group (Liu *et al.*, 2014b). One explanation may relate to the fact that KKAy mice develop severe abnormalities in peripheral glycemic control and insulin over 10 weeks with the effects of the intrinsic disease mitigating any overall effect of $PM_{2.5}$.

The role of constituents in air pollution and their concomitant effects (co-exposure) with $PM_{2.5}$ has not been well studied. Because transition metals, such as nickel, represent an important component of exposure in certain environments, Ying *et al.* evaluated the effects of Nickel exposure alone and in combination with $PM_{2.5}$ using ApoE knockout mice. Nickel exposure decreased aortic relaxation responses concomitant with a decrease in eNOS dimers, an effect that was potentiated by co-exposure to $PM_{2.5}$ (mean = 66.5 μg/m^3) for 3 months (Ying *et al.*, 2013). Using the same exposure protocol, Xu *et al.* (2012) found that Nickel + $PM_{2.5}$ significantly increased fasting glucose and worsened IR measured by HOMA-IR without significant changes in peripheral cytokines such as TNF-α, IL-6, IL-12 and IFN-γ. Decreased phosphorylation of AMP-activated protein kinase-α was noted in the co-exposure group compared with exposure to $PM_{2.5}$ alone. $PM_{2.5}$ + Nickel significantly induced microcirculatory dysfunction and increased monocytic cell infiltration into lung and adipose. In a study to evaluate the effects of ozone, Bass *et al.* evaluated the effects of 0.25 or 1.0 ppm, 6 h/day for 2 days (acute) or 2 days/week for 13 weeks (subchronic) in Brown Norway rats of different ages. Acute ozone exposure to 1.0 ppm O_3 but not 0.25 ppm caused glucose intolerance in rats of all ages without elevation of fasting blood glucose when compared to FA. Time-course analysis indicated rapid glucose intolerance with acute exposure with recovery 18-h post ozone.

Taken together, these studies suggest that exposure to $PM_{2.5}$ may induce IR as measured by HOMA and post-glucose load studies, typically over a period of 8–10 weeks in C57 BL/6 mice, with appearance of effects in a more constrained time frame in the young as well as genetically susceptible mice. Abnormalities in insulin signaling, including decreased Akt/eNOS and IRS phosphorylation in insulin-responsive tissues, further strengthen the evidence linking air pollution and IR and diabetes. While these studies offer important proof of principle, the relative importance of various insulin responsive tissues (skeletal, muscle, vs. liver) as well the effects of air pollution on IR and β-cell function may need additional investigation, ideally with gold standard measures such as hyperinsulinemic-euglycemic (peripheral glucose uptake) and hyperglycemic clamp measurements (to assess the impact on β-cell function). The addition of high-fat diet while exaggerating effects of $PM_{2.5}$ in some studies is not always seen and may related to effects of diet overwhelming the weaker effects of $PM_{2.5}$.

MECHANISTIC INSIGHTS INTO AIR POLLUTION AND DIABETES

Immune Activation

Inflammation is widely believed to play a key pathogenic role in the development of obesity-induced IR and T2DM (Despres and Lemieux, 2006; Horng and Hotamisligil, 2011; Hotamisligil, 2006). Adipose tissue macrophages (ATMs) have a classically activated (M1) phenotype in obese individuals and an alternatively activated (M2) phenotype in lean individuals (Lumeng *et al.*, 2007). M2 macrophages in lean subjects secrete suppressive cytokines such as IL-10 which may potentiate insulin signaling in adipocytes. In contrast, M1 macrophages in obese subjects produce pro-inflammatory mediators and induce IR through IKK-β- and JNK-mediated serine phosphorylation of IRS-1 and -2 (Cai *et al.*, 2005; Hirosumi *et al.*, 2002; Yuan *et al.*, 2001). Interruption of inflammatory monocyte/macrophage trafficking by ablation of C-C chemokine receptor type 2 (CCR2) or depletion of M1 macrophages by CD11c knockout reduces obesity-induced

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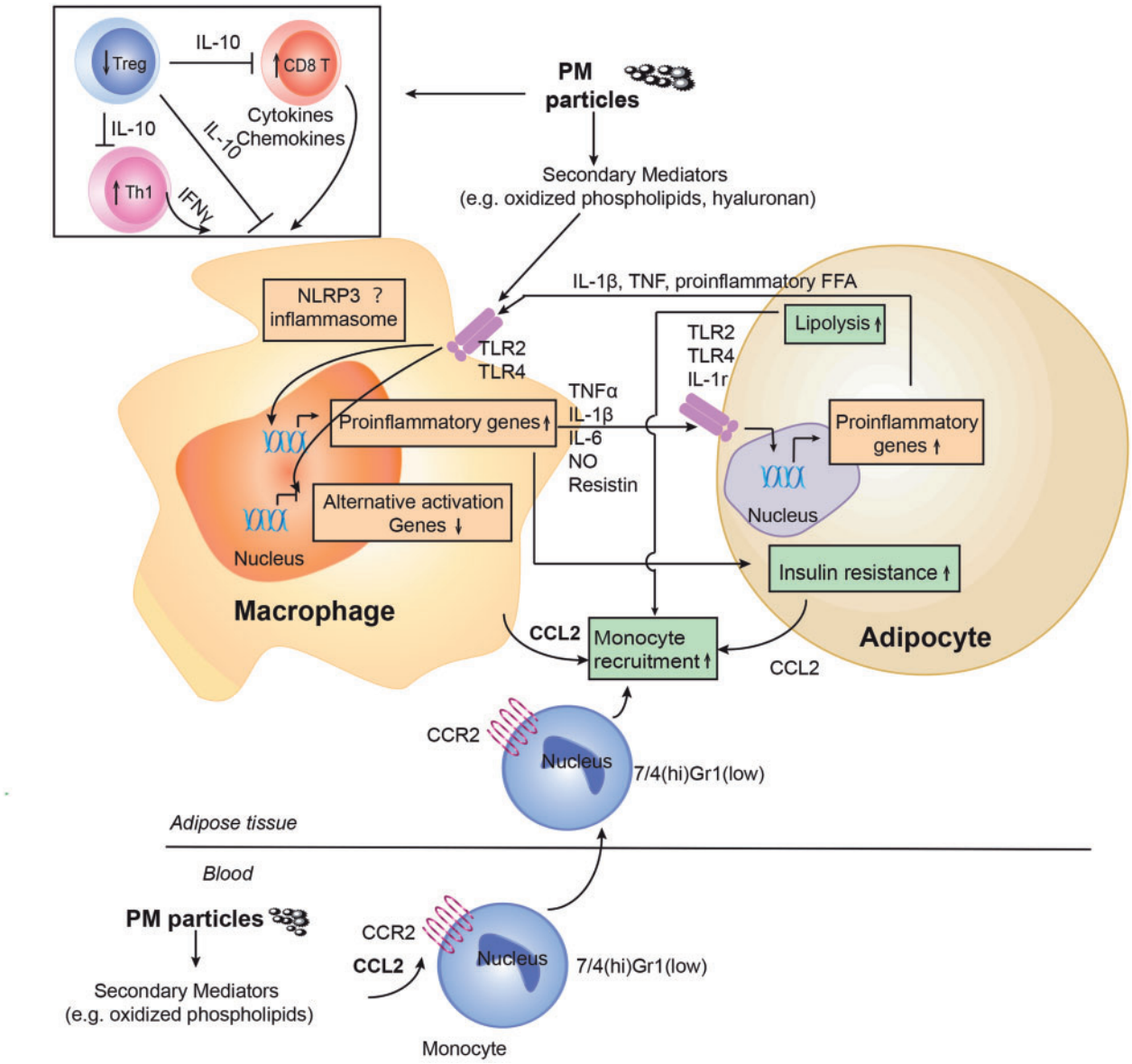

FIG. 2. Mechanisms underlying air pollution-mediated immune activation. PM, particulate matter; TLR, Toll-like receptor; Treg, regulatory T cells; CCL2, C-C motif ligand 2; CCR2, C-C chemokine receptor type 2; NLRP3, NOD-like receptor family, pyrin domain containing 3; NO, nitric oxide; TNF-α, tumor necrosis factor-α.

adipose inflammation and IR (Patsouris *et al.*, 2008; Weisberg *et al.*, 2006). Genetic disruption of IKK-β or JNK in myeloid cells has also been shown to prevent obesity-induced IR in mice (Arkan *et al.*, 2005; Solinas *et al.*, 2007). Recent studies suggest that activation of $CD8^+$ T cells and $CD4^+$ T cells plays an essential and early role in adipose tissue inflammation and IR. Nishimura *et al.* (2009) reported that depletion of $CD8^+$ T cell protected mice from obesity-induced inflammation and IR, which could be reversed by adoptive transfer of $CD8^+$ T cells. In another study, Winer *et al.* demonstrated $CD4^+$ T cells, especially IFN-γ-producing Th1 cells, found to be significantly increased in obesity and contributed to classical activation of ATMs. In contrast to Th1-polarized T cells, Th2 cells are protective for obesity-induced IR. Adoptive transfer of $CD4^+$ T cells (but not $CD8^+$ T cells) into T-cell-deficient $Rag1^{-/-}$ mice reduced obesity-induced IR, predominantly through Th2 mechanisms (Winer *et al.*, 2009).

The mechanisms underlying initiation of systemic inflammation in response to air pollution may involve multiple pathways (Figure 2) but is widely thought to originate in the lung (Hiraiwa and van Eeden, 2013). Hypothesized mechanisms include: (1) activation of innate immune cells in the lung by $PM_{2.5}$ resulting in the release of inflammatory cytokines and chemokines, leading to the systemic activation of immune system (Goto *et al.*, 2004; Kampfrath *et al.*, 2011). This may occur directly through the uptake of $PM_{2.5}$ or more likely may involve generation of secondary reactive intermediates through oxidative pathways in the lung; (2) uptake of particles or secondary antigens generated in response to oxidation by antigen-presenting cells that may then present antigens to the T cells in the draining lymph node and activate adaptive immunity (Deiuliis *et al.*, 2011); (3) leachable components such as reactive oxygen species/transition metals and organic secondary intermediates such as oxidized phospholipids, quinines, semiquinones, and

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aldehydes generated in the lung that may overflow into the circulation leading to an inflammatory response (Dominici *et al.*, 2007; Kampfrath *et al.*, 2011; Liberda *et al.*, 2010); (4) pulmonary inflammation may then activate central nervous system (CNS) pathways that may facilitate systemic inflammation (Liu *et al.*, 2013; Rajagopalan and Brook, 2012; Simon and Liedtke, 2008).

It is widely believed that inhaled particles may result in exuberant activation of defense mechanisms by interacting with various receptors or through the release of secondary mediators. Toll-like receptors (TLRs) and NOD-like receptors (NLR), a class of receptors that play a key role in innate immune recognition, have been identified as key mediators of inflammatory response to a variety of environmental and occupational exposures including air pollutants(Bauer *et al.*, 2012; Dostert *et al.*, 2008). Biological components of $PM_{2.5}$ such as endotoxin, bacterial, virus, and fungal spores may activate TLRs directly or indirectly through secondary mediators such as reactive oxygen species (Becker *et al.*, 2002; Inoue *et al.*, 2006; Shoenfelt *et al.*, 2009). Shoenfelt *et al.* found that different components of particulate air pollution may induce inflammation through distinct TLR receptors, using Chinese hamster ovary cells expressing TLR2 or TLR4. PM (which has high levels of redox active metals and low levels of endotoxin) induces cytokine secretion in a TLR2-dependent mechanism, whereas $PM_{2.5\text{-}10}$ which has high levels of endotoxin, induces cytokine secretion in a TLR4-dependent mechanism (Shoenfelt *et al.*, 2009).

The importance of innate immune responses with air pollution exposure was investigated in additional studies. Sun *et al.* (2009) confirmed that intratracheally delivered $PM_{2.5}$ enhanced myeloid cell migration, adhesion to the mesenteric microcirculation and accumulation in visceral fat. In subsequent experiments, Xu *et al.* (2010), while investigating the effects of $PM_{2.5}$ exposure, detected increased macrophage infiltration in visceral adipose tissue and vascular dysfunction. Deficiency of p47phox improved abnormalities in IR, vascular function, and visceral inflammation in response to $PM_{2.5}$, suggesting an involvement of oxidative stress during this process (Xu *et al.*, 2010). To further delineate the nature of the innate immune response and the pathways responsible for innate immune activation with air pollution, Kampfrath *et al.* exposed C57BL/6, $Nox2^{-/-}$ (C57BL/6 background), Balb/c ($TLR4^{wt}$), mice deficient in TLR4 [Tlr4Lps-d ($TLR4^{d}$)], background strain BALB/cAnPt for a duration of 20–26 weeks. Mean concentration of $PM_{2.5}$ in the chamber was $92.4 \pm 2.1\,\mu g/m^3$. $PM_{2.5}$ increased inflammatory monocytes ($CD11b^{+}Ly6C^{hi}$) in the periphery in $TLR4^{wt}$ mice, which was markedly diminished in $TLR4^{d}$ mice. $PM_{2.5}$ exposure was associated with increased NAPDH oxidase derived from superoxide and increased macrophage infiltration, which was reversed in $TLR4^{d}$ mice as well as $Nox2^{-/-}$ mice (Kampfrath *et al.*, 2011). In these experiments, $PM_{2.5}$-exposed mice had significantly higher oxidized derivatives of 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (PAPC) in the BAL fluid. Both palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC) and palmitoyl-2-glutaryl phosphatidylcholine (PGPC) increased with $PM_{2.5}$ exposure. Incubation of $PM_{2.5}$ by itself with BAL had no effect on oxidized phospholipids, arguing against a direct effect of particles in oxidation and suggesting an endogenous mechanism of oxidation of PAPC. Interestingly, incubation of bone marrow-derived macrophages to oxidized PAPC recapitulated a stereotypical inflammatory response reminiscent of the *in vivo* effects in the lung with $PM_{2.5}$ exposure including phosphorylation of a cytosolic sub-unit of NADPH oxidase p47, an effect abolished by TLR deficiency and inhibition of interleukin-1 receptor-associated kinase (IRAK), suggesting that TLR4-IRAK signaling occurred upstream of NADPH oxidase activation.

The C-C chemokine receptor type 2 has been shown to be critically involved in obesity-induced inflammatory monocyte/macrophage recruitment into adipose tissue (Weisberg *et al.*, 2006). To investigate the involvement of CCR2 in air pollution-mediated inflammation, Liu *et al.* (2014a) demonstrated that $PM_{2.5}$ exposure ($116.9 \pm 34.2\,\mu g/m^3$, approximately 17 weeks)-induced visceral macrophage infiltration into adipose tissue was abolished by genetic ablation of CCR2. Furthermore, SREBP1c-mediated transcriptional programming, fatty acid uptake, and p38 MAPK activity were also reduced in mice deficient in CCR2 (Liu *et al.*, 2014a).

To further characterize the relationship of innate and adaptive immune responses in the lung, WT C57BL/6, Foxp3-green fluorescent protein (GFP) reporter, and chemokine (C-X-C motif) receptor 3 knockout ($CXCR3^{-/-}$) mice were exposed to $PM_{2.5}$ ($115.5 \pm 9.25\,\mu g/m^3$) or FA for 24–28 weeks in a whole-body exposure system. $PM_{2.5}$ exposure resulted in increased CD11b+CD11c+ macrophages and CXCR3+ T cells in the lung, in the mediastinal lymph nodes, and spleen. The number of activated CD44+CD62L−CD4+ T cells in the lung was also increased in $PM_{2.5}$-exposed WT mice. CXCR3 deficiency completely prevented the movement of CXCR3+CD4+ and CXCR3+CD8+ T cells into the lung, an effect that was associated with an increased retention of these populations in the spleen in the $CXCR3^{-/-}$ mice exposed to $PM_{2.5}$, suggesting impairment of homing to the lung. Central memory cell population as determined by CCR7 expression on CD44+CD62L+ cells was significantly increased with $PM_{2.5}$ in both WT and $CXCR3^{-/-}$ mice compared with FA groups, suggesting that CXCR3 is not involved in the trafficking of this subset of cells. GFP+ regulatory T cells increased with $PM_{2.5}$ exposure in the spleen and blood of Foxp3-GFP mice, but were present at very low levels in the lung irrespective of $PM_{2.5}$ exposure (Deiuliis *et al.*, 2011). Consistent with the prior study by Kampfrath, $PM_{2.5}$-exposed mice had significantly higher ratios of oxidized derivatives of PAPC (POVPC and PGPC) in the BAL fluid, with the ratio of PGPC/POVPC to PAPC nearly doubling with exposure to $PM_{2.5}$. These findings suggest robust innate and adaptive immune activation in response to the air pollution with recruitment via CXCR3 mechanisms.

In summary, air pollutants activate the innate immune system by either direct recognition by pattern recognition receptor TLRs (via interacting with biological components such as endotoxin, bacterial, virus, and fungal spores) or by indirect secondary mediators such as oxidized lipids (POVPC and PGPC), cytokines, and reactive oxygen species. Persistent innate immune system activation then results in adaptive immune system activation by recruiting effector T cells through chemokine receptors such as CCR2 and CXCR3 into the lung, with additional effects of regulatory T cell pathways circulation/spleen. The overall effects of chronic exposure to $PM_{2.5}$ in animal models appear to be consistent with systemic type 1 immunity (Th1)-dominant immune responses, with a skew from M2 toward M1 and from Th2 toward Th1 in tissue depots.

Adipose Mechanisms

In addition to enhanced macrophage infiltration and phenotypic switch toward M1- and Th1-dominated responses, recent studies have suggested that unfolded protein response (UPR)/endoplasmic reticulum (ER) stress is involved in $PM_{2.5}$ exposure-induced adverse effects (Mendez *et al.*, 2013; Rajagopalan and Brook, 2012). The unfolded protein response/endoplasmic reticulum stress is an evolutionarily conserved response designed to

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alleviate protein misfolding (Walter and Ron, 2011). There are 3 major pathways involved in this process: IRE1α, PERK, and ATF6 (Zhong *et al.*, 2012). UPR-associated proteins, ATF-4, GRP94, Hsp70, Hsp90, and BiP, significantly increased in human bronchial epithelial cells exposed to *in vitro* $PM_{2.5}$ (Liu *et al.*, 2013; Watterson *et al.*, 2009). After incubation with PM particles ($PM_{10,}$ 12.5 μg/m^3 $PM_{2.5,}$ 25 μg/m^3) for 24 h, Watterson *et al.* (2009) noticed that exposure led to a significant increase of ATF6 cleavage in cultured human bronchial epithelial (BEAS-2B) cells. In addition, the other 2 UPR pathways, PERK and IRE1α, are also involved in the pathogenesis of particulate exposure. Laing *et al.* (2010) reported that ROS produced in $PM_{2.5}$ exposure (74.6 μg/m^3, 10 weeks) activated PERK-mediated UPR pathway which is critical for $PM_{2.5}$-induced apoptosis. Phosphorylation of eIF2α was also increased in the liver along with induction of CHOP/GADD153, a C/EBP homologous transcription factor which is associated with apoptosis in the lung and liver (Laing *et al.*, 2010). This study also demonstrated a critical role for NADPH oxidase-dependent oxidant stress in the activation of $PM_{2.5}$-induced ER stress (Laing *et al.*, 2010). Mendez *et al.* (2013) also reported that $PM_{2.5}$ (94.4 μg/m^3, 10 months) induces UPR/ER Stress, lipid deposition, and adipocyte differentiation changes in adipose tissue. There was an increase of expression of ER stress-associated genes (such as BiP/GRP78, Xbp-1, and Edem1) in adipose tissue of $PM_{2.5}$-exposed mice, along with an increased size of adipocytes. ER stress is an important regulator of adipocyte lipid metabolism and adipose tissue inflammation (Deng *et al.*, 2012; Kawasaki *et al.*, 2012). Consistent with this, expression of the genes involved in lipogenesis (Acaca), lipid transport (CD36), TG synthesis (dgat2), and adipocyte differentiation/lipid droplet formation (Smaf1, Ceacam1, Fsp27, Plin1, Fit2) in WAT was reported to be affected by exposure to $PM_{2.5}$ (Mendez *et al.*, 2013). Xu *et al.* (2011b) observed that in response to $PM_{2.5}$ exposure, ApoE-/- mice (96.89 μg/m^3, 2 months) reduced the expression of brown adipocyte-specific genes, whereas white adipocyte-specific genes were differentially upregulated in brown adipose tissue. Thus, exposure to air pollutants may adversely affect adipose tissue lipid metabolism and brown to white adipose transition. In additional careful experiments performed in metabolic cages, $PM_{2.5}$ exposure resulted in reduced VO_2, VCO_2 levels, consistent with a reduction in metabolism. These effects were associated with a reduction in uncoupled protein-1 (UCP-1) expression in BAT consistent with an impact of CAP on thermogenesis (Liu *et al.*, 2014b).

Hepatic Mechanisms

Sun *et al.* (2009) have shown that exposure to $PM_{2.5}$ (72.7 μg/m^3, 128 days) was associated with decreased insulin signaling in the liver, providing evidence for impairing effects of air pollution on hepatic IR. Defective insulin signaling resulted in impaired activation of PI3K/Akt signaling and suppression of insulin-induced GLUT4 translocation. Exposure to $PM_{2.5}$ also induced hepatic lipid deposition and reduced gluconeogenesis (Liu *et al.*, 2014a; Zheng *et al.*, 2013). Tan *et al.* (2009) reported that 6 weeks of exposure to concentrated PM (85 μg/m^3) did not enhance the amount of hepatic fat but significantly increased steatohepatitis grade (inflammation) compared to FA exposure in C57BL/6 mice fed a high-fat diet. They have suggested that ambient PM may induce cytokine secretion by Kupffer cells. Circulating fine PM may then accumulate in hepatic Kupffer cells and trigger inflammation and hepatic stellate cell collagen synthesis (Tan *et al.*, 2009). Zheng *et al.* (2013) demonstrated that 10 weeks of $PM_{2.5}$ exposure (74.6 μg/m^3) caused a nonalcoholic steatohepatitis-like phenotype and reduced hepatic glycogen storage in mice. $PM_{2.5}$ exposure led to c-Jun N-terminal kinase (JNK), NF-κB, and TLR4-mediated inflammatory pathways activation. $PM_{2.5}$ exposure also suppressed IRS-1-mediated signaling and PPARα/PPARγ2 expression in the liver. These changes were associated with abnormalities in IR and glucose homeostasis (Zheng *et al.*, 2013). Collectively, liver as one of the major organs regulating insulin sensitivity is heavily involved in $PM_{2.5}$-induced IR by many mechanisms including glucose transportation, lipolysis/lipogenesis balance, insulin signaling, and hepatic inflammation.

CNS Mechanisms

There is little debate that the CNS plays a critical role in appetite/satiety mechanisms and overall metabolic control. In particular, small groups of neurons located in the hypothalamus regulate a variety of processes through complex neuronal connections with the rest of the brain. These include regulation of glucose, blood pressure, and peripheral inflammation, with perturbations in these circuits resulting in dysregulation of homeostatic control loops setting the stage for IR and T2DM at least in animal models (Purkayastha and Cai, 2013). Many groups have observed hypothalamic inflammation in diet-induced obesity and IR models. Upregulation of IL-6 and NF-κB was noted very early (within days) in mice on high-fat diet, prior to substantial weight gain. Furthermore, neuronal injury in the hypothalamic arcuate nucleus occurs within the first week of high-fat feeding, suggesting an early involvement of the CNS in diet-induced obesity and IR (Thaler *et al.*, 2012). Purkayastha *et al.* (2011) also demonstrated an essential role of hypothalamic endoplasmic reticulum stress in obesity-induced peripheral inflammation and peripheral dysglycemia with these abnormalities being partially reversed by interruption of central ER stress with tauroursodeoxycholic acid. The mechanisms by which central inflammation occurs with caloric excess are unclear but may involve complex afferent pathways that feed to these centers or perhaps even circulating entities that access "permissive" areas in the circumventricular areas of the brain. Recent studies have suggested that toxicants from cigarette smoke and polluted air may activate transient receptor potential cation channel, subfamily A, member 1 (TRPA1) receptors in airway sensory neurons and result in neurogenic inflammation (Simon and Liedtke, 2008). Oxidants such as hydrogen peroxide, ozone, aldehydes, and other reactive oxygen species are major components of automobile exhaust, tobacco smoke, and smoke from fires (Pryor and Stone, 1993; Uysal and Schapira, 2003). Andrè *et al.* (2008) demonstrated that unsaturated aldehydes in cigarette smoke aqueous extract induced neurogenic inflammation by stimulating TRPA1 channels. An extracellular Ca^{2+}-dependent release of neuropeptides from capsaicin-sensitive airway sensory nerve terminals was induced by cigarette smoke aqueous extract and unsaturated aldehydes. Furthermore, bronchial contraction induced by cigarette smoke aqueous extract could be inhibited by HC-030031, a TRPA1-specific antagonist (Andre *et al.*, 2008). PM particles have also been shown to permeate the CNS via translocation along the olfactory nerve into the olfactory bulb and exert direct effects on CNS inflammation (Block *et al.*, 2012; Nakane, 2012). Recent findings by Fonken *et al.* (2011) suggest that chronic $PM_{2.5}$ exposure (94.38 μg/m^3, over 10 months) results in increased hippocampal inflammatory cytokine expression and impairments in spatial learning memory and behavior. Follow-up studies to this initial proof of concept investigation suggest that a few weeks of $PM_{2.5}$ exposure is

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sufficient to induce reactive gliosis and expression of TNF-α and IL-6 in the medial basal hypothalamus in KKay, a genetically susceptible mouse model of T2DM. Central nervous system inflammation then leads to the metabolic dysfunction and inflammation in peripheral tissues (unpublished data). Suppression of IKK-β in hypothalamus reversed $PM_{2.5}$-induced metabolic dysfunction (unpublished data) and peripheral inflammation as evidenced by reduction in circulating inflammatory monocytes. These results suggest that dysregulation of central circuits involved in metabolic control may provide a unifying mechanism for air pollution-mediated metabolic effects.

CONCLUSIONS

Growing evidence suggest that air pollution is an important determinant of chronic metabolic disease. Although the current epidemiologic data suggest that air pollution may play a minor role in human health compared to other more dominant factors such as lifestyle choices and genetic factors, the pervasive, persistent, and lifelong exposure to air pollutants may arguably make this an important determinant of cardiometabolic health, especially in areas that have high levels of air pollution. Animal studies have generally shown stronger effects because most of the studies have used concentrated particles to mimic high level of air pollution. In animal studies, similar HOMA-IR and postprandial glucose were found between normal diet-fed mice exposed to concentrated $PM_{2.5}$ for 10 weeks and high-fat diet-fed mice exposed to filtered air, suggesting that high levels of air pollution may be equivalent to high-fat diet in terms of its effects. Emerging data from both epidemiologic and experimental studies are beginning to provide insights into possible mechanisms. Immune activation (toward type 1), ER stress, oxidative stress, and CNS inflammation have all been invoked in air pollution-related diabetes. Activation of TLRs (TLR2, TLR4) via generation of secondary mediators such as oxidized lipids (POVPC and PGPC), cytokines, and reactive oxygen species may represent an important mechanism that may help explain the effects of inhalational stimuli on distant target organ tissues. These are attractive pathways to be examined in future epidemiologic studies to help identify air pollution effects and to stratify risk. In the ultimate analysis, careful consideration of air pollution mitigation strategies must be part of a larger societal response to reduce the burden of cardiometabolic disease.

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