Vascular endothelium as a target of diesel particulate matter-associated toxicants

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As the layer of cells separating all systemic organs from circulating xenobiotics, the vascular endothelium is gaining increasing attention as a major target of toxicants, even those brought into the body by inhalation. Endothelial cell dysfunction is central to many major cardiovascular outcomes, including atherosclerosis and related outcomes of myocardial infarction and stroke. Injured endothelial cells exhibit reduced dilatory properties, express adhesion molecules critical to inflammation, and fail to release platelet inhibitor molecules nitric oxide and prostacyclin. Exposures to a variety of air pollutants have been shown to negatively impact endothelial function. Vasodilation is impaired by diesel emissions (Knuckles et al. 2008), particulate matter (Nurkiewicz et al. 2006), and ozone (Chuang et al. 2009). Increased vascular inflammation is induced by particulate matter and combustion-source emissions (Yatera et al. 2008; Lund et al. 2011). Clearly oxidative stress is a factor (Cherng et al. 2011), and nitric oxide synthase uncoupling has been reported (Knuckles et al. 2008; Nurkiewicz et al. 2009), but intracellular signaling and transcriptional alterations have not been studied in as much detail.

As a result, much of the intracellular mechanisms underlying endothelial dysfunction remain unknown. In the current issue of Arch Tox, Mattingly and Klinge (2011) have observed that diesel-derived particle components can inhibit normal estrogen signaling in human umbilical vein endothelial cells. Moreover, engine operating conditions alter the chemistry and therefore the potency of the diesel

engine extracts. The highlighted manuscript points to a number of interesting and compelling findings related to potential disruption of nuclear-mitochondrial gene regulation, principally highlighted by the reduced expression of NRF-1, an essential nuclear gene that enhances mitochondrial biogenesis (Klinge 2008). These findings are of additional interest because there is very little known about gender-related susceptibility with regard to the cardiovascular health effects of air pollution. Based on the findings of the present paper, one might speculate that chemical components of diesel particulates would nullify the known cardiovascular health benefits of estrogen signaling.

Part of the difficulty in assessing these mechanisms relates to the fact that inhalation exposures lead to systemic effects that arise from neural alterations, release of inflammatory mediators, and bioavailable components of the PM itself. Direct exposure of endothelial cells to most air pollutants, including diesel particles, is poorly justified as the lung is an exceptional barrier. The compelling findings of disruption of mitochondrial biogenesis in the present study should motivate exploration of cardiometabolic disruption of diesel and related airborne contaminants using more relevant and complementary exposure methods. While the use of extracts is a suitable tool for reductionist research, uptake and distribution kinetics for the numerous chemicals in the extracts (Sumanasekera et al. 2007) has not been well characterized. Gerde et al. (2001) demonstrated systemic delivery of PM-associated benzo[a]pyrene and a number of soluble metal components of PM can readily access the circulation (Wallenborn et al. 2007).

Likely, the same is true of many components of PM, even those not so soluble, as numerous dissolution mechanisms may be at play in macrophages and select regions of the lung environment. Thus, it is rational to consider the vascular endothelial toxicity of extractable components of

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diesel PM, which consist largely of organic compounds, provided consideration is given to the dose and complex chemistry involved. Mattingly and Klinge provide a stellar example of how to approach this problem, by utilizing diesel PM extracts derived from an engine under varied operating conditions. From previously published work, they have a solid understanding of the chemistry of the diesel particulate extract (Sumanasekera et al. 2007). However, the results must be considered in light of the absence of dosimetry information and the immense complexity of the extract mixtures. In our attempt to understand the systemic vascular health effects of environmental contaminants, the questions of dosimetry and kinetics will be as important as ever. Hopefully, resources for conducting such research will be available in coming years, so that the sophisticated cell biological approaches explored by Mattingly and Klinge can be more fully developed for risk assessment and regulatory science purposes.

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