2024_55_Materials_AP: Imaging a potential mechanistic link between air pollution exposure and Alzheimer's disease

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The World Health Organisation estimates that exposure to ambient air pollution results in 4.2 million deaths/year. Air pollution particulate matter (PM) is a cocktail of soot aggregate, secondary organic aerosols, nitrates, sulphates, dust, bioaerosols and different redox active trace transition metals. PM from vehicle emissions and abrasive wear contain oxidising, neurotoxic metals such as Fe, Cu and other toxic metals that can lead to increased production of damaging reactive oxygen species (ROS), as well as genotoxicity. There is mounting evidence for a causal link between air pollution exposure and neurodegenerative diseases. PM including Magnetite (Fe_3O_4) nanoparticles have been found in brains retrieved from adult and child human subjects that lived in extremely polluted cities [10.1177/0192623307313011; 10.1073/pnas.1605941113], together with features of early-stage neurodegenerative Alzheimer's Disease (AD) including Tau cortical tangles, amyloid-β (Aβ) plaques and abnormal neurovascular units. Furthermore, mice that are exposed to polluted air showed an increased level of Aβ plaques and brain inflammation. Although a causal link between metal-rich pollution PM and neurodegeneration in AD has been made, there is no direct experimental evidence for a link between AD and air pollution exposure.

The goal of this project is to directly image the effect of air pollution exposure on cultured cells, in the presence and absence of Aβ. Some redox-active transition metals that are present in PM, notably Fe and Cu, are also prevalent endogenously in the brains of patients with AD, can generate ROS and cause aggregation of Aβ that was shown to play a central role in the pathogenesis of AD. The student will directly correlate the presence of PM (via electron microscopy) with Aβ and degree of its aggregation (confocal microscopy and antibody-based structural characterisation) and subcellular damage (electron microscopy and machine learning) and test whether PM and Aβ together enhance neurotoxicity. We will characterise how the PM changes its physical and chemical form in the environment (e.g. via hetroaggregation, or interaction with other species) and how this changes its toxicity.

Impact: The project will identify which, if any, components of PM in air pollution are neurotoxic; if we know which components are most toxic we can generate guidance about how to reduce health impacts and suggest strategies to design our cities to reduce exposure to these toxins. We will also develop a new underpinning multiscale (nm – 10s of µm) chemical imaging tools to image pollution and its interaction with cells and microorganisms, that could in future be applied to study a range of other environmentally relevant problems.