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**Diesel soot exposure modulates functional differentiation and maturation of bone marrow-derived dendritic cells**

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Exposure to environmental pollutants has been associated with dysfunctional immune responses, like allergy and asthma. One of the goals of the ongoing EU 5FP project MAAPHRI (Multidisciplinary Approaches to Airborne Pollutant Health-Related Issues) is to evaluate the immunomodulatory potential of diesel soot and of total exhaust, by analyzing effects of diesel particle exposure on primary cells which are key regulators of the immune system.

Immune responses are tightly orchestrated by dendritic cells (DC), which are the first immune cells to encounter invading germs. DC are present at exposed locations such as respiratory organs, where they take up foreign matter like bacteria and viruses, but also pollutant particles. DC present in skin or mucosal surfaces are immature DC (iDC), and develop into mature, immunostimulating DC only upon encountering hostile germs. We have investigated whether diesel soot interferes with this process.

Diesel soot was generated using a regular on-road European diesel car engine, with Euro3-compliant fuel and regular semi-synthetic oil (generous gift of Jean-Paul Morin and Frederic Dionnet, INSERM E9920 and CERTAM, Rouen, France). Particles were collected with a silicone carbide monolith particle trap and counterblown with clean compressed air. Mouse iDC were generated by culturing BALB/c mice-derived bone marrow cells with the growth factor GM-CSF for 9 days in absence or presence of diesel soot and other particles. Subsequently, iDC were matured with lipopolysaccharide (LPS), which indicates for the cells presence of bacteria and leads to activation and maturation. Functional maturation was evaluated by flow cytometry using monoclonal antibodies for the cell surface markers CD11c, CD80, CD86, and an oxidative response assay (NO<sub>2</sub>).

In absence of diesel soot, bone marrow-precursor cells efficiently differentiated into CD11c<sup>+</sup> iDC, whereas differentiation was suppressed when diesel soot was added. Similar inhibitory effects on differentiation were observed for other carbonaceous particles such as graphite 1-2 μm, but could not be detected for PRINTEX XE2-soot and carbon black grade VULCAN M. Upon LPS treatment, soot-exposed iDC were unable to upregulate maturation-associated cell surface markers, CD80 and CD86. Interestingly, exposition of DC cultures to other carbonaceous particles resulted in the development of two subpopulations after addition of LPS. One population contained cells which were positive for CD80 and CD86, whereas the other population consisted of cells which were CD80 and CD86 negative. Functional responses were characterized in more detail for soot-exposed DC which revealed that these DC were severely impaired in LPS-induced responses such as cytokine secretion (IL-10, IL-6, TNFα) and oxidative burst (NO production). Taken together, these data show that diesel soot and some, but not all, other fine particles impair differentiation and functional maturation in response to biological stimuli. Exposure to particles may in this way have severe consequences for proper induction and regulation of immune responses. Immunomodulatory effects of other pollutants will be evaluated in the ongoing 6FP project NOMIRACLE (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe) project

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