Air pollution mediates the development of type 2 diabetes via oral exposure by disrupting innate mucosal immunity

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Background/Introduction:

It is estimated that the number of people affected by diabetes mellitus would pass a monumental landmark of over half a billion worldwide over the next decade. Besides the classical risk factors, air pollution emerged as an additional risk factor in recent years. Previously, we demonstrated that long-term exposure to air pollution via the gut instigated a diabetic phenotype and a shift towards pro-inflammatory colonic macrophages. The aim of the current study was to assess the transcriptional response of colonic macrophages upon oral diesel exposure to elucidate the mechanism of air pollution-induced diabetes.

Research Design and Method:

Male C57BL/6N mice were treated with 60 µg/week DEP (NIST 1650b) or PBS alone via oral gavage. The metabolic phenotype of the mice was monitored by monthly glucose tolerance tests. The transcriptional response was assessed by single cell RNA sequencing of colon macrophages isolated from mice exposed to DEP or PBS. Peritoneal macrophages were treated with DEP or PBS *in vitro* to measure the secretion of pro-inflammatory cytokines in the supernatant. For rescue experiments, mice were treated with IL-1beta antibody after they had developed air pollution-induced diabetes. The glucose tolerance and immune cells of the mice were characterized thereafter.

Results:

Single-cell transcriptomic analyses confirmed an increase in Ccr2+ inflammatory macrophage relative to Ccr2- anti-inflammatory macrophages upon exposure to DEP. The transcriptomic profiles showed an up-regulation of inflammatory and interferon-responses in mice exposed to DEP. Diesel exposure led to an increase in IL-1beta secretion as shown by *in vitro* experiments on peritoneal macrophages. This effect was reversed by the addition of the NLRP3-specific blocking agent, MCC950. *In vivo*, pharmacological blocking of IL-1beta after DEP-induced impaired glucose tolerance reversed the diabetic phenotype and the shift towards the M1-like pro-inflammatory colonic macrophage subpopulation.

Conclusion:

DEP exposure leads to a predominance of inflammatory colon macrophages inside the lamina propria of the gut, which triggers the development of type 2 diabetes from air pollution exposure. Our results point towards the NLRP3/IL-1beta pathway as a potential target for treatment or prevention strategies of air pollution-induced type 2 diabetes mellitus.