Air Pollution-induced Diabetes is Mediated via Macrophages in the Gut

PD Dr. Claudia Cavelti-Weder
23rd ETH-Conference on Combustion Generated Nanoparticles
Increased diabetes prevalence with air pollution

Eze, Environment International. 2014

IUP Heidelberg, NO2 levels over Europe
Increased diabetes prevalence with air pollution

Ecological study

- County-level prevalence of diabetes
- PM$_{2.5}$

*Worldwide phenomenon* (USA, CA, DE, SE, DK, NL, IT, China).

A similar association exists for **smoking** and **increased diabetes risk**.

Air pollution is also associated with an **increased cardiovascular risk**.
Increased diabetes prevalence with air pollution

Ecological study

- County-level prevalence of diabetes
- \( \text{PM}_{2.5} \)

Correlation or causation?
Physical inactivity, unhealthy food, poor socioeconomic status, genetic disposition

Pearson et al., Diabetes Care. 2010
Mouse studies confirm increased diabetes risk with air pollution

Inhalation chambers in mice

Concentrated ambient air during 6 hours/day

• Mouse studies support that air pollution leads to diabetes.
• The mechanism how air pollution causes diabetes is unknown.

Sun, Circulation. 2009
Hypothesis and Research Question

Current dogma:
- Lung = primary target organ of air pollution

Rationale to look at the gut:
- Particles reach the gut
- Increased gut permeability
- Altered gut microbiota
- More GIT-diseases with air pollution

Is air pollution-induced diabetes mediated via gut or lung exposure?
Hypothesis and Research Question

Question 1: Is air pollution-induced diabetes mediated via the lung?

Question 2: Is air pollution-induced diabetes mediated via the gut?

Question 3: Is diabetes due to insulin secretion defect or insulin resistance?

Question 4: Is innate immunity involved in air pollution-induced diabetes?

Question 5: Is adaptive immunity involved in air pollution-induced diabetes?
Methods

Solid form of air pollution

- **PM**: Particulate matter ("Feinstaub")
  - PM$_{2.5}$ (particles <2.5 µm)
  - PM$_{10}$ (particles <10 µm)
- **DEP**: Diesel exhaust particles

![Diagram of particulate matter exposure]

Particulate matter
Diesel exhaust particles

Lung exposure
- 2 x 30 (=60) µg/week

Gut exposure
- 5 x 12 (=60) µg/week

*United States Environmental Protection Agency*
Question 1:
Is air pollution-induced diabetes mediated via the lung?

Lung exposure
Intratracheal instillation

Control (PBS) | Diesel exhaust particles

Control (PBS) | Particulate matter
Question 1:
Is air pollution-induced diabetes mediated via the lung?

⇒ Lung exposure causes lung inflammation
**Question 1:**
Is air pollution-induced diabetes mediated via the lung?

Glucose tolerance tests

1 month

2 months

3 months

4 months

5 months

- **Diesel exhaust particles**
- **PBS (Controls)**

⇒ **Lung exposure causes lung inflammation, but not diabetes**
**Question 2:**
Is air pollution-induced diabetes mediated via the gut?

Glucose tolerance tests
- **1 month**
- **2 months**
- **3 months**

**Systemic inflammation**
- **Diesel exhaust particles**
- **PBS (Controls)**

⇒ Gut exposure causes diabetes, but not via systemic inflammation
Question 3:
Is diabetes due to **insulin secretion defect** or **insulin resistance**?

$$\Rightarrow$$ Insulin secretion defect, no “metabolic disease” phenotype
Question 3:
Is diabetes due to insulin secretion defect or insulin resistance?

⇒ Insulin secretion defect, no “metabolic disease” phenotype
Question 3: Is diabetes due to insulin secretion defect or insulin resistance?

Beta-cell mass

Islet gene expression

⇒ Insulin secretion defect not due to less beta-cells, but functional insulin secretion defect
Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?

Flow cytometry

Air pollution ➔ Isolation of lamina propria cells ➔ Staining for flow cytometry
Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?

Gut gene expression

Flow cytometry: loss of anti-inflammatory macrophages
Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?

**CCR2-/- mice**
- Lack inflammatory macrophages

**CSF1R inhibitor**
- Depletes both subgroups

⇒ Loss of anti-inflammatory macrophages upon air pollution; mouse models with low macrophage numbers are protected.
Question 5: What about the role of adaptive immunity in the gut?

Flow cytometry

Air pollution

Isolation of lamina propria cells

Staining for flow cytometry

=> No changes in adaptive immune cell populations upon air pollution

Rag2-/- mice lack adaptive immunity

Gut adaptive immunity is not altered upon air pollution; Adaptive immunity is not required for air pollution-induced diabetes
Answers to Research Questions

Question 1: Is air pollution-induced diabetes mediated via the lung? ✗

Question 2: Is air pollution-induced diabetes mediated via the gut? ✔

Question 3: Is diabetes due to insulin secretion defect or insulin resistance? ✗

Question 4: Is innate immunity involved in air pollution-induced diabetes? ✔

Question 5: Is adaptive immunity involved in air pollution-induced diabetes? ✗
Summary

Impact: 16% of global mortality is due to pollution

Cohen, Lancet. 2017
Thank you for your attention

Laboratory Translational Diabetes

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Translational Diabetes
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