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The Role of Malat1 and Nrf2 in Regulating Diabetogenic Effects of Early Life Air Pollution Exposure

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T3: TEXAS A&M TRIADS FOR TRANSFORMATION
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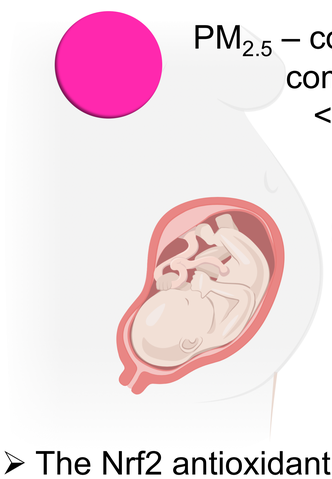
Particulate matter (PM) Air Pollution

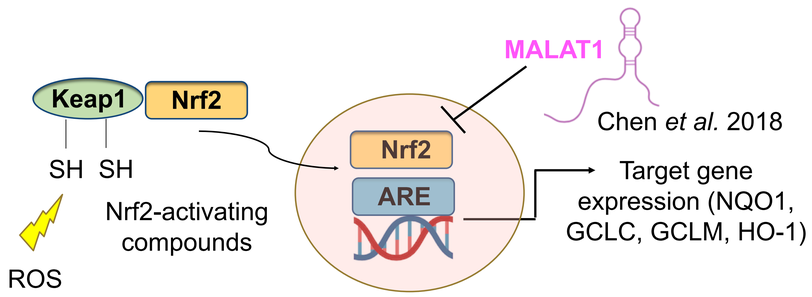
- Early life PM exposure – a critical window of exposure
- Adverse birth outcomes established, with emerging cardiometabolic effects



$PM_{2.5}$ – combustion particles, organic compounds, metals, etc. < 2.5 µm in diameter

$PM_{.1}$ – Ultrafine particles < .1 µm in diameter (100 nm or less)

- The Nrf2 antioxidant response pathway plays an important role in response to PM-induced oxidative stress and insulin resistance in type 2 diabetes (T2D)



ARE: Antioxidant response element

Overall hypothesis: *In utero* PM exposure increases offspring susceptibly to T2D and is modulated by maternal ability to respond to oxidative stress.

Aim 1. Evaluate weight gain and insulin resistance in offspring following *in utero* PM exposure.

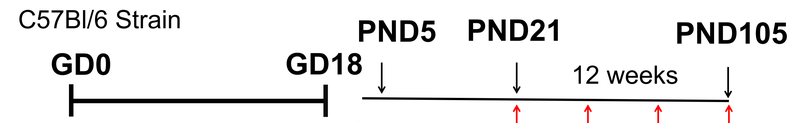
Aim 2. Clarify the role of maternal oxidative stress response in offspring birth outcomes.

References: Chen *et al. Biochem Pharmacol*. 2018 Jun;152:94-103. Rychlik *et al. Proc Natl Acad Sci U S A*. 2019 Feb 26;116(9):3443-3448

Material and Methods

- To mimic real-world conditions, we created an *in utero* inhalation exposure model (Rychilk *et al.* 2019).

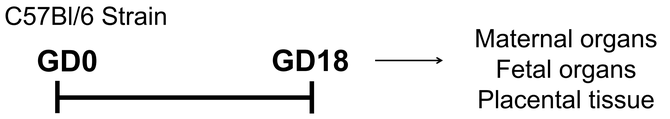
Aim 1. *In utero* PM exposure, offspring diet challenge



Maternal Exposure:
FA, filtered air
HD, high dose (500 µm m^{-3})
n=5 dams per group

- High fat (45%) or low fat (10%) diet
- Weekly weight gain, food consumption, insulin resistance

Aim 2. *In utero* PM exposure in 'knock out' mice

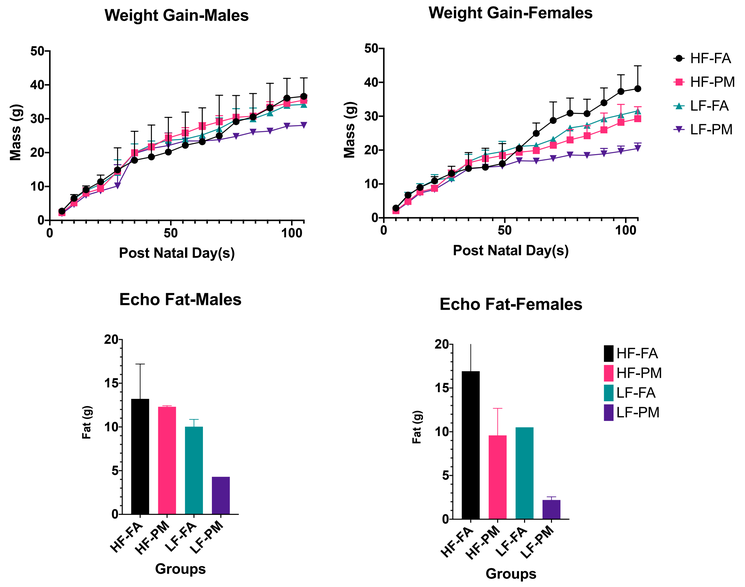


Maternal Exposure:
FA, filtered air
LD, low dose (100 µm m^{-3})
HD, high dose (500 µm m^{-3})
n=6 dams per group

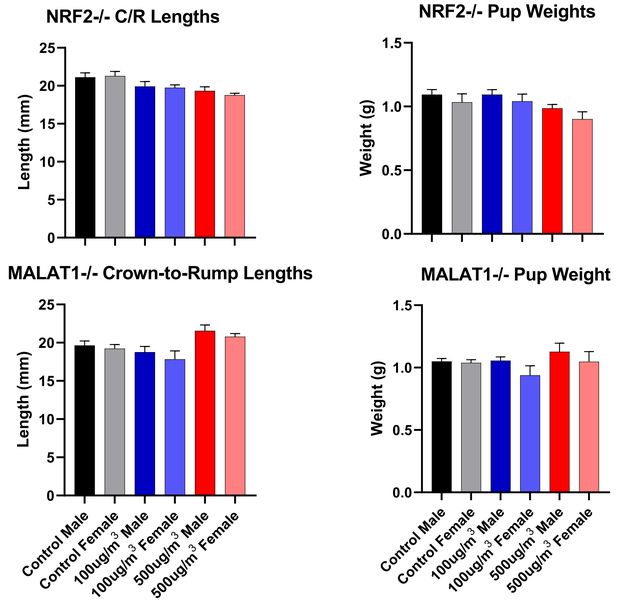
a. WT, wild-type
b. Nrf2, -/- or +/+
c. MALAT1, -/- or +/+

Results and Conclusions

- **Fig 1.** PM-exposed offspring on low fat diet showed decreased weight gain over time with corresponding decreased body fat in both males and females. There was no effect on insulin resistance or glucose levels.



- **Fig 2.** Decreased fetal crown-to-rump lengths and weights in Nrf2 null offspring exposed to high dose. Increased fetal crown-to-rump lengths and weights in MALAT1 null offspring exposed to dose.



- **Conclusions:** While we did not observe an effect of PM on insulin resistance, there was a sustained weight reduction in PM-exposed offspring. This may underlie other health effects related to metabolism and bone health. The mechanisms of action may be driven through the maternal oxidative stress response, which could be mitigated by activation of the Nrf2 pathway via MALAT1 inhibition.

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