

The Air Pollution Impact to Maternal Mice and Offspring

Baoming WANG

*A thesis submitted in fulfilment of the requirements for
the degree of Doctor of Philosophy*

School of Life Sciences
Faculty of Science
2021

Certificate of original authorship

I, Baoming WANG declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy (PhD), in the School of Life Sciences at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

This research is supported by This research is supported by an Australian Government Research Training Program, the Sydney Partnership for Health, Education, Research and Enterprise (SPHERE), National Health and Medical Research Council (NH&MRC), and China Scholarship Council (CSC).

Production Note:

Signature: Signature removed prior to publication.

Date: 29/03/2021

Acknowledgment

My gratitude goes first to Prof. Brian Oliver. You gave me an opportunity can continue my research in your lab when I decided to leave the old lab at the first year of my PhD. You taught me a lot during the 3 years, not only on the research, but also on the attitude of life.

To my co-supervisors: Dr. Yik Lung Chan and Prof. Sonia Saad who supported me fully during my entire PhD. Especially Dr. Yik Lung Chan. You treated me like a close friend and taught me all the lab skills without any selfishness.

To my mentor A/Prof. Hui Chen. I feel extremely lucky that you can give me a chance to perform all the experiments in your lab. You always gave 100% help when I need it. I learned a lot from you, especially in writing skills. I feel confident in any scientific questions because I know you and Brian will support me.

To my lab mates: Gerard Li, Varsha Komalla, Karosham Reddy, Senani Rathnayakemudiyanselage, and Behjat Sheikholeslami. Thank you all for your suggestions both in the laboratory and in personal life. You make our group a warm family.

To my lovely wife: Thank you for the unconditional love. Your love made me stronger. I never wanted to give up when I had any difficulties in my life because I know you are always my support. I love you forever.

To my family: dad, mum, and old brother. All of you give me a warm family and taught me how to be an honest and studious person in the world.

Table of Contents

Publications arising from my PhD candidature:	5
Conference Presentations	8
Abstract	10
Chapter 1 General Introduction	12
1.1 Ambient particulate matter in air pollution.....	13
1.1.1 Different sources of PM.....	13
1.1.2 Classification of PM	14
1.2 Intrauterine exposure to particulate matter and cigarette smoke and asthma	16
1.3 Overall hypothesis and aims of this thesis.....	44
Chapter 2 Offspring sex affects the susceptibility to maternal smoking-induced lung inflammation and the effect of maternal antioxidant supplementation in mice	45
Chapter 3 Pulmonary inflammation induced by low-dose particulate matter exposure in mice	72
Chapter 4 Maternal particulate matter exposure impairs transgenerational lung health and is associated with mitochondrial damage	92
Chapter 5 General Discussion and future perspective	129
Take home message	135

Publications arising from my PhD candidature:

Unfortunately I started my PhD in a group which was not able to supervise me correctly, and after one year I changed supervisors and group to Prof Oliver. The data in my thesis is from only the work which I did as part of Prof Oliver's group.

* joint first author

1. **Wang B**, Chen H, Chan YL, Oliver BG. Is there an association between the level of ambient air pollution and COVID-19? *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2020; 319: L416-L421.
2. **Wang B**, Chan YL, Zhou S, Saad S, Chen H, Oliver BG. Offspring sex affects the susceptibility to maternal smoking-induced lung inflammation and the effect of maternal antioxidant supplementation in mice. *Journal of Inflammation* 2020.
3. **Wang B**, Chen H, Chan YL, Wang G, Oliver BG. Why Do Intrauterine Exposure to Air Pollution and Cigarette Smoke Increase the Risk of Asthma? *Frontiers in Cell and Developmental Biology* 2020; 8: 38.
4. Chan YL*, **Wang B***, Chen H, Ho KF, Cao J, Hai G, Jalaludin B, Herbert C, Thomas PS, Saad S. Pulmonary inflammation induced by low-dose particulate matter exposure in mice. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2019; 317: L424-L430.
5. Li G, Chan YL, **Wang B**, Saad S, Oliver BG, Chen H. Replacing smoking with vaping during pregnancy: Impacts on metabolic health in mice. *Reproductive Toxicology* 2020; 96: 293-299.
6. Li G, Chan YL, **Wang B**, Saad S, George J, Oliver BG, Chen H. E-cigarettes damage the liver and alter nutrient metabolism in pregnant mice and their offspring. *Annals of the New York Academy of Sciences* 2020.

7. Chen H, Li G, Allam VSRR, **Wang B**, Chan YL, Scarfo C, Ueland M, Shimmon R, Fu S, Foster P. Evidence from a mouse model on the dangers of thirdhand electronic cigarette exposure during early life. *ERJ Open Research* 2020; 6.
8. Meng X, Zhang B, Yi Y, Cheng H, **Wang B**, Liu Y, Gong T, Yang W, Yao Y, Wang H. Accurate and Real-Time Temperature Monitoring during MR Imaging Guided PTT. *Nano Letters* 2020; 20: 2522-2529.
9. Meng X, Zhang H, Zhang M, **Wang B**, Liu Y, Wang Y, Fang X, Zhang J, Yao Z, Bu W. Negative CT Contrast Agents for the Diagnosis of Malignant Osteosarcoma. *Advanced Science* 2019; 6: 1901214.
10. Chen C, Wang F, Wen S, Su QP, Wu MC, Liu Y, **Wang B**, Li D, Shan X, Kianinia M. Multi-photon near-infrared emission saturation nanoscopy using upconversion nanoparticles. *Nature communications* 2018; 9: 1-6.
11. Jin D, Xi P, **Wang B**, Zhang L, Enderlein J, van Oijen AM. Nanoparticles for super-resolution microscopy and single-molecule tracking. *Nature methods* 2018; 15: 415-423.
12. Wang F, Wen S, He H, **Wang B**, Zhou Z, Shimoni O, Jin D. Microscopic inspection and tracking of single upconversion nanoparticles in living cells. *Light: Science & Applications* 2018; 7: 18007-18007.
13. Sun Y, Zhang W, **Wang B**, Xu X, Chou J, Shimoni O, Ung AT, Jin D. A supramolecular self-assembly strategy for upconversion nanoparticle bioconjugation. *Chemical Communications* 2018; 54: 3851-3854.

Under review

14. **Wang B**, Chen H, Li G, Chan YL, Wang G, Oliver BG. Maternal particulate matter exposure impairs transgenerational lung health and is associated with mitochondrial damage. *Journal of Hazardous Materials*.

15. **Wang B**, Chen H, Denaki D, Cowie C, Oliver BG. Differential inflammatory and toxic effects in-vitro of wood smoke and traffic related particulate matter from Sydney, Australia. *Science of The Total Environment*.
16. Chen H, **Wang B**, Li G, Steele J; Stayte S; Vissel B; Chan YL; Yi C; Saad S; Machaalani R; Oliver BG. Brain health is independently impaired by E-vaping and high-fat diet. *Brain Behavior and Immunity*.
17. Woldhuis R, Bozier J, **Wang B**, Timens W, Heijink I, Berge M, Brandsma C, Oliver B. E-cigarette vapor induces cellular senescence in lung fibroblasts and may contribute to lung pathology. *Thorax*.

Conference Presentations

1. Thoracic Society of Australia and New Zealand meeting (2018): Poster presentation

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Maternal L-Carnitine Supplement Relieves Lung Damage in Offspring from Cigarette Smoke Exposed Mothers

2. Centre for Air pollution, energy and health Research (2019): Poster presentation

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Chronic low dosage of maternal particulate matter exposure can affect dam's and offspring's lung health

3. New Horizon 2019: Poster presentation

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver L-Carnitine mitigates impact of maternal smoking on lung health in mice offspring

4. Thoracic Society of Australia and New Zealand branch meeting (2019): Oral presentation

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Maternal exposure to low dose particulate matter induced transgenerational hyperresponsiveness in mice

5. 19th NSW Asthmatic Meeting (2019): Poster presentation

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Maternal exposure to low dose particulate matter induced transgenerational hyperresponsiveness in mice

6. European Respiratory Society Meeting (2019) :

Poster presentation:

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Impact of chronic maternal particulate matter exposure during pregnancy on offspring's lung health

Poster discussion:

Baoming WANG, Yik Lung Chan, Sonia Saad, Hui Chen, and Brian Oliver. Impact of chronic maternal particulate matter exposure during pregnancy on offspring's lung health

Awards and Prizes

2016: 4 years PhD scholarship from China Scholarship Council

2019: Best presentation from Thoracic Society of Australia and New Zealand branch meeting

2019: Best poster from 19th NSW Asthmatic Meeting

Abstract

Epidemiological studies have shown that maternal exposure to cigarette smoke and air pollution are two predominant *in utero* environmental toxicants which can increase the risk of developing multiple respiratory diseases in the offspring. The proposed mechanisms include reducing mitochondrial function and mitochondrial renewal mechanisms (mitophagy) and activating inflammasome and other inflammatory pathways. However, whether maternal smoking could induce the sex-dependent susceptibility in respiratory disorders and whether chronic low dose particulate matter (PM) exposure which is within the international standard could induce any transgenerational pulmonary disease has not been widely studied.

Firstly, Female Balb/c mice (8 weeks) were exposed to cigarette smoke (SE) for 6 weeks prior to mating, during gestation and lactation. Half of the SE dams (mothers) were given L-Carnitine supplementation (1.5mM in drinking water, SE+LC) during gestation and lactation. Then, another Male Balb/c Mice (6 weeks, Animal Resources Centre, WA, Australia) batch was intranasally exposed to saline or traffic-related PM₁₀ (1 µg or 5 µg/day) for 3 weeks. Furthermore, the female BALB/c mice (6 weeks) were exposed to PM_{2.5} (PM_{2.5}, 5 µg/day) or saline (SHAM) 6 weeks before pregnancy and during pregnancy and lactation; or for only 6 weeks before pregnancy (Cessation, 5 µg/day). Lung tissues from models were analysed.

Results: Compared to female offspring, maternal SE significantly increased levels of inflammatory markers (phosphorylated(p)-extracellular signal-regulated kinase (ERK1,2), p-p38 Mitogen-activated protein kinase (P38) MAPK, p-Mitogen-activated protein kinase (NF-kB). Three weeks of PM exposure (5 µg/day) significantly increased total macrophages and lymphocytes number in the bronchoalveolar lavage fluid (BALF) accompanied by increased levels of NLRP3 and Interlukin-1 (IL1-β). Chronic exposure to low dose PM significantly increased tissue elastance and damping during lung function tests, followed by increased leukocytes in the BALF, mitochondrial dysfunction, and airway remodelling, including alveolar membrane damage and increased collagen deposition. Maternal exposure to low dose

PM also significantly increased tissue elastance and damping during lung function test followed by increased leukocytes in the BALF and mitochondrial dysfunction without airway remodelling. The mouse model of asthma induced by ovalbumin (OVA) showed that maternal exposure to the low dose PM could significantly increase tissue elastance during lung function test in the offspring, suggesting the worse asthmatic symptoms.

In conclusion, male offspring are more susceptible to the adverse effects of maternal smoking. Chronic exposure to the low dose PM could induce chronic obstructive pulmonary disease (COPD)-likes pathology in the dams and worsen asthmatic symptoms in the female offspring.