|  |
| --- |
| **Altering excess glucose responses directly and via female sex hormone manipulation protects against key features of obese experimental asthma.** |
| **Alexandra C. Brown1\***, Olivia R. Carroll1\*, Jemma R. Mayall1, Henry M. Gomez1, Samantha L.E. Vinzenz1, Richard Y. Kim1,2, Chantal Donovan1,2, Evan J. Williams1,Katherine J. Baines1, Bronwyn S. Berthon1, James W. Pinkerton3, Philip M. Hansbro4, Peter A.B. Wark1,5,6,7, Paul S. Foster1,Katie Wynne1, Hayley A. Scott1, Lisa G. Wood1, Jay C. Horvat1 |
| **1**University of Newcastle and Immune Health Program, Hunter Medical Research Institute Newcastle, New South Wales, Australia, 2School of Life Sciences, Faculty of Science, University of Technology Sydney, Sydney, New South Wales, Australia, 3Respiratory Pharmacology & Toxicology Group, National Heart & Lung Institute, Imperial College London, London, United Kingdom, **4**Centre for Inflammation, Centenary Institute, and Faculty of Science, University of Technology Sydney, Sydney, New South Wales, Australia, 5Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, New South Wales, Australia, 6School of Medicine, Monash University, Melbourne, Victoria, Australia, 7AIRMED Alfred Health, Melbourne, Victoria, Australia. |
| **Introduction:** Obesity is linked with severe lung disease, especially in females. Indeed, obese, female asthma is a recognised distinct subtype of severe asthma with poor therapeutic options. The mechanisms underpinning this association between obesity and severe lung disease, and why the effects of obesity on asthma occur mainly in females, remains unknown. We have previously shown that obesity-associated increases in macronutrients are associated with altered airway inflammation in asthmatics and that the oral contraceptive pill (OCP) protects against airway inflammation and disease symptoms in both lean and obese female asthmatics. Here, we aimed to investigate how excess glucose levels and the OCP affect the pathogenesis of disease in experimental models of obese and non-obese asthma.  **Methods:** We assessed the effects of the glucose lowering drug, AZD1656, or oral ethinylestradiol/levonorgestrel (representing the combined OCP) on blood glucose levels (BGL), glucose metabolism related gene expression, lung function and immune cell populations in bronchoalveolar fluid in obese and non-obese mice with and without experimental asthma.  **Results:** We show that obesity is associated with increased BGL and promotes severe, steroid-insensitive asthma in mice. Obesity in experimental asthma also has significant effects on eosinophils in the airways, increasing the proportion expressing the glucose transporter, GLUT1. AZD1656 reduces BGL, airway eosinophils, and protects against disease in both obese and non-obese female experimental asthma. Importantly, the OCP differentially alters dysregulated metabolic gene expression, in association with protecting against disease in both obese and non-obese female experimental asthma.  **Conclusion:** Together these findings demonstrate how excess glucose levels in obesity affect the immunopathogenesis of asthma. They also highlight the important and interacting role that female sex hormones and metabolism play in determining the pathogenesis and severity of disease. Most importantly, these data highlight the potential for modulating glucose metabolism for the treatment of obesity-associated severe asthma.  **Grant Support:** PRC Healthy Lungs |