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MATERNAL IMMUNE ACTIVATION (MIA) ALTERS NEONATAL LUNG IMMUNITY

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INTRODUCTION: Asthma affects over 300 million people worldwide, making it the most prevalent chronic respiratory disease [1]. Asthma is characterized by airway inflammation, and susceptibility to asthma is associated with prenatal immune perturbation including parasitic infections and environmental pollutant exposure [2–5]. As the lungs are not fully developed until weeks after birth [6], neonatal lung immune development may critically influence developing lung function and asthma susceptibility. Recent studies have shown that dysregulation of type 2 innate lymphoid cells (ILC2s) may play a role in the development and progression of asthma [4], [7], [8]. Lung ILC2s are among the first immune cells to seed the lung during the perinatal period and expand maximally during neonatal development [9]. ILC2s are activated by cytokines produced by lung epithelial cells [3], [10], [11]. Once activated, ILC2s produce increased levels of type 2 cytokines that recruit inflammatory cells in the lung and have been implicated in asthma development [12]. An example of a type 2 cytokine is IL-5, which regulates eosinophil recruitment and activation in asthma [12]. Our recent work has shown that exposure to prenatal inflammation can alter the production and function of immune cells developing postnatally by perturbing the establishment of upstream hematopoietic progenitors in the fetal period. We hypothesize that prenatal inflammation drives susceptibility to asthma by affecting ILC2 functions and causing dysregulation of immune cell establishment in the developing lung [4], [5], [9], [13]. To test this, we used a model of prenatal inflammation involving maternal immune activation (MIA), in which the TLR agonist polyinosinic:polycytidylic acid (pIC) is injected to mimic a mild viral infection during pregnancy [14]. Models of MIA have been used to test how prenatal immune perturbations impact the central nervous system and result in neurological disorders and behavioral changes [15]. However, the effects of MIA or prenatal inflammation on lung immune cell establishment have not been previously investigated. Therefore, we aimed to investigate how MIA impacts ILC2 and immune cell establishment and cytokine production in the neonatal lung, and how this influences asthma susceptibility in a mouse model.

METHODS: To investigate the impacts of MIA on lung immune establishment, we injected pIC or saline (as a control) into pregnant mice at mid-gestation on embryonic day (E)14.5. We then profiled neonatal lung immune cellularity of ILC2s and multiple immune cell lineages (B-, T-, NK-cells, dendritic cells, monocytes, alveolar macrophages, eosinophils, neutrophils) in offspring on postnatal day (P)3, P6, and P9. Additionally, to assess changes to the lung microenvironment in response to MIA, we measured the expression of 25 different inflammatory cytokines across P3, P6, and P9 in MIA or saline-treated mice.

RESULTS AND CONCLUSIONS: Cellularity of all profiled immune cells steadily increased throughout neonatal lung development. There were no statistically significant changes in immune cell number in response to MIA across postnatal days 3-6, but surprisingly, ILC2s were significantly expanded at P9 compared to the saline-treated controls. Further, we observed increased levels of IL-5 at P9 in pIC-treated mice. Coincident with the observed increase in ILC2s, this IL-5 trend suggests that MIA impacts neonatal ILC2 establishment and contributes to increased levels of type 2 cytokines at P9 in the lung. These data align with our recent findings demonstrating ILC2 expansion and type 2 cytokine hyperproduction at P14 in response to MIA. Altogether, the effects of early immune perturbation due to MIA on lung ILC2 establishment may increase asthma susceptibility. Future work will seek to elucidate the molecular underpinnings of ILC2 expansion in response to prenatal inflammation as a driver of asthma, thereby helping to reduce asthma prevalence and severity worldwide.

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