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POSTER ABSTRACTS

203.LYMPHOCYTES AND ACQUIRED OR CONGENITAL IMMUNODEFICIENCY DISORDERS

Prenatal Inflammation Promotes Enhanced Allergic Lung Inflammation By Programming Hyperactive ILC2s from Fetal Hematopoietic Progenitors

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Our lab has recently demonstrated that prenatal inflammation, induced by maternal immune activation via viral-mimetic poly(I:C), specifically activates and expands lymphoid-biased developmentally-restricted hematopoietic stem cells (drHSCs) in the fetal liver, resulting in the generation of hyperactivated innate-like B1-B cells in the postnatal period that produce greater levels of IgM, IgG3, and IL-10 on a per-cell basis. We hypothesize that dysregulation and hyperactivation of long-lived fetal-derived innate immune compartments that persist across the lifespan underlies disease susceptibility into adulthood. Here we elucidate a mechanism by which prenatal inflammation imparts persistent changes to lung immunity and function by programming innate lymphoid cell output from fetal hematopoietic progenitors, resulting in adverse responses to allergen challenge into adulthood.

To investigate how prenatal inflammation impacted fetal- and neonatal-derived group-2 innate lymphoid cells (ILC2s), we profiled changes to ILC2 establishment across early postnatal life. In response to prenatal inflammation, ILC2s were significantly expanded at postnatal day (P)9 and remained robustly expanded through adulthood, while also exhibiting a greater proliferation capacity through their peak expansion period postnatally (P14). At P14, prenatal inflammation also robustly increased IL-5 and IL-13 production from ILC2s after *ex-vivo* stimulation, concomitant with higher expression of killer cell lectin-like receptor G1 (KLRG1), indicative of an enhanced activation state.

To determine hematopoietic origins of expanded and hyperactive ILC2s, we profiled changes to an immediate upstream precursor of the ILC lineage within the neonatal bone marrow (BM) and fetal liver after prenatal inflammation. At P14, prenatal inflammation did not alter the establishment of BM common helper-like innate lymphoid progenitors (CHILPs), whereas fetal liver CHILPs were robustly expanded by both cellularity and frequency at embryonic day (E)15.5 and E17.5 compared to saline treated controls. To test if the changes observed in mature ILC2s and their immediate precursors could be programmed at the stem cell level, we transplanted fetal liver drHSCs one day post-poly(I:C) or saline into irradiated adult recipients. One month post-transplantation, donor-derived ILC2s from the prenatal-inflammation condition produced more IL-13 cytokine within the lung microenvironment compared to saline controls, demonstrating that prenatal inflammation programs fetal hematopoietic precursors during development to generate hyperactive ILC2s.

Single-cell RNA sequencing of over 26,000 lung ILC2s at P14 revealed extensive heterogeneity in response to prenatal inflammation. Unsupervised clustering analysis identified clusters unique to prenatal inflammation conditions, with transcriptional profiles significantly overlapping with ILC2 signatures identified in models of allergic airway inflammation (AAI). As prenatal inflammation induced functional and transcriptional shifts in ILC2s that regulate lung immunity, we profiled changes to the developing lung immune landscape in response ILC2 hyperactivation. ILC2 expansion and hyperactivation was concomitant with remodeling of multiple lung immune compartments, including expanded B-cells, T-cells, and eosinophils at P14. We acutely challenged mice intranasally with papain allergen to determine if prenatal inflammation modulated lung innate immune responses. ILC2s and eosinophils expanded in response to papain challenge and exhibited even greater expansion under prenatal inflammation conditions. As eosinophilia is a hallmark feature of AAI, we assessed respiratory mechanics us-

ing the FlexiVent system in adult mice to measure the underlying impact of prenatal inflammation on lung function in the context of acute allergen challenge. Exposure to prenatal inflammation alone caused a decrease in lung compliance and pressure-volume loops, indicative of pulmonary morbidity, that was further exacerbated by papain challenge compared to saline treated controls. Together, our data reveal a mechanism by which prenatal inflammation can program hyperactivity of ILC2s at the fetal HSC-level during embryonic development, resulting in lasting changes to postnatal lung immunity and lung disease susceptibility in offspring.

Disclosures No relevant conflicts of interest to declare.

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