Insult during infancy: early life antibiotics disrupt lung repair following influenza-A infection and injury

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BACKGROUND

- Infants with early life exposures to antibiotics have greater susceptibility to respiratory infections.
- Many infants are exposed to antibiotics during the birthing process.
- Consequences of fetal dysbiosis from antibiotics are not yet understood.
- Infant mice exposed to perinatal antibiotics experience non-resolving lung inflammation and impaired repair of the alveolar-capillary barrier after viral infection.
- Alveolar type 2 (AT2) cells are critical players in lung homeostasis and enable regeneration after injury by proliferating and differentiating into new alveolar type 1 (AT1) cells .

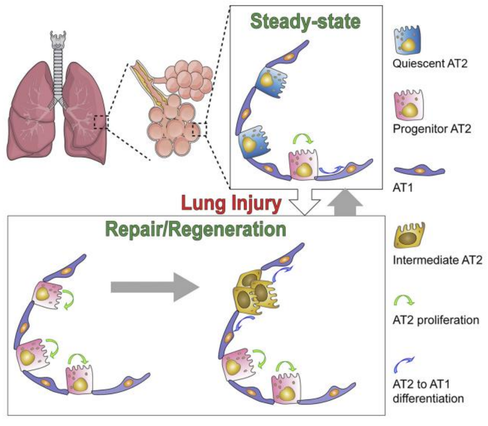
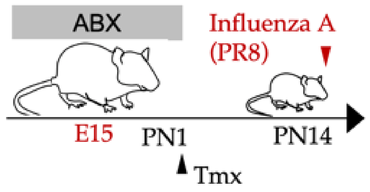


Figure reproduced from, Chen et al. *2020.* Heterogeneous groups of alveolar type II cells in lung homeostasis and repair. *Am J Physiol Cell Physiol.* 319: C991-C996.

APPROACH

Newborn mice exposed to perinatal antibiotics experience impaired recovery from viral pneumonia.

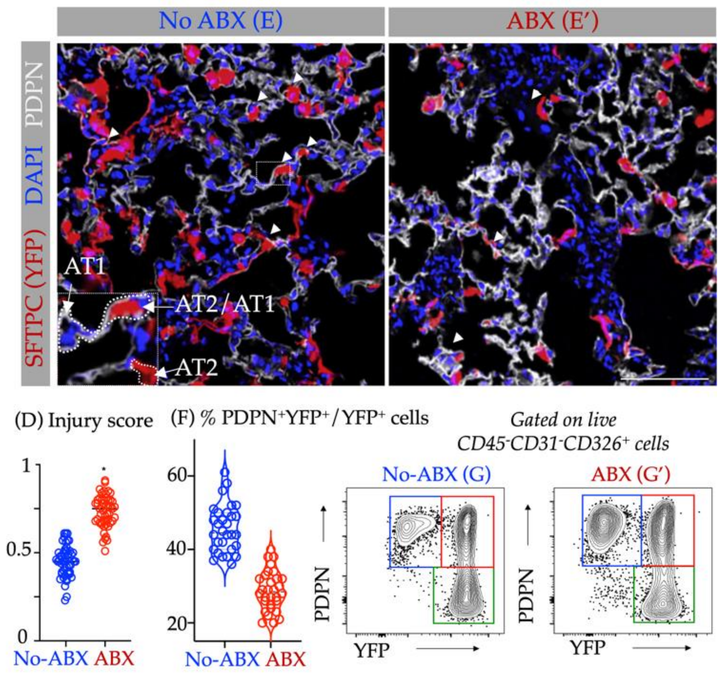
- *Sftpc*^{CreERT2}*R26*^{YFP} mice were used. These knock-in mice express a tamoxifen-inducible Cre recombinase in the locus for surfactant protein C, so when induced, type II alveolar cells can be identified.
- To model early life antibiotic exposure, pregnant mice were treated with ampicillin, or control (no antibiotic) 5 days before delivery.
- Infant mice (post-natal day 14) were challenged with a sublethal dose of murine-adapted influenza A H1N1 strain PR8.



- The frequency of AT2 cells (YFP^{+}) and AT2 cell-derived AT1 cells (YFP^{+} Podoplanin [PDPN]$^{+}$ cells) were determined at 7 days post infection and quantified by immunohistochemistry and flow cytometry.

RESULTS AND ONGOING ANALYSIS

- The frequency of AT2-derived AT1 cells was decreased in antibiotic-exposed infant mice as quantified by immunohistochemistry and flow cytometry. Statistical analysis and experimental replicates are on-going.



- Initial findings suggest that less differentiation of AT2 to AT1 cells impairs lung recovery following influenza in infant mice that were perinatally exposed to antibiotics.
- Future work will characterize subpopulations or intermediate cell stages in the differentiation program from AT2 to AT1. We hypothesize that the cell transition between AT2 and AT1 may stall in a damage-associated transient progenitor (DATP) cell type that drives aberrant proliferation and loss of lung identity.

HYPOTHESIS

We hypothesize that early life antibiotics disrupt repair of the alveolar-capillary barrier after viral insult via delay in transition between alveolar type 2 (AT2) to alveolar type 1 (AT1) cells.

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