4 REGENERATIVE ASYNCHRONY IS A DRIVER IN CHRONIC INFLAMMATION IN AGING

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Purpose of Study Age-associated chronic diseases are associated with a pro-inflammatory state. It has been challenging to determine cause and effect – do age-associated pathologies increase inflammation or does inflammation induce age-associated pathologies or both? We previously showed that disease-related regenerative asynchrony in repairing lung is the cause of chronic inflammation and fibrosis. Thus, we hypothesized that the aged lung is itself asynchronously regenerating leading to a pro-inflammatory pulmonary milieu.

Methods Used Tracheas and intra-cardiac blood were harvested from C57BL6 mice in two age groups of both genders. Young mice were between 8 and 20 weeks of age. Aged mice were between 23 and 33 months of age. Tracheal epithelial progenitor cells were isolated and cultured for 6 days with continuous exposure to BrdU. Cellular regeneration was analyzed by flow cytometry for 7-AAD DNA staining in BrdU⁺ cells. Concentrations of an initial screening set of cytokines in plasma and cell culture supernatants from days 2 and 6 of culture were measured using magnetic bead-based assays.

Summary of Results Fewer airway epithelial progenitors underwent mitosis from the aged than the young mice ($16.9 \pm 10.4\%$ vs. $62.2 \pm 9.4\%$ of the cultured cells at 6 days). The tracheal epithelial progenitors from aged mice were asynchronously distributed along the cell cycle (G₁, S, G₂/M: 44, 25, and 31%) compared to those from young mice (62, 14, and 24%). Plasma concentrations of IL-1 β , IL-6, TNF α and TGF β were not significantly different between age groups. Concentrations of TGF β were significantly different between age groups in supernatant from day 2 (aged = 112.43 ± 16.31 pg/mL, young = 171.23 ± 13.70 pg/mL; $p < 0.05$) but not from day 6 of culture (aged = 159.60 ± 29.83 pg/mL, young = 214.15 ± 9.94 pg/mL; $p = \text{NS}$). Concentrations of IL-1 β were not significantly different between age groups in supernatant from day 2 of culture (aged = 2.01 ± 0.23 pg/mL, young = 2.10 ± 0.24 pg/mL; $p = \text{NS}$) but remained higher in aged compared to young progenitors on day 6 (aged: 2.17 ± 0.31 pg/mL, young: 1.26 ± 0.10 pg/mL; $p < 0.05$).

Conclusions Our data support the concept that aging induces progenitor cell mitotic asynchrony. It is possible that this epithelial mitotic asynchrony contributes to the pro-inflammatory state associated with aging, as seen in other chronic inflammatory states.