Airway regeneration is delayed by prior depletion of bone marrow Clara cell secretory protein-expressing cells

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Rationale: The contribution of bone marrow (BM) to repair of lung injury is controversial, in part due to the robust restorative capacity of endogenous lung progenitor cells. We have previously shown that a subpopulation of bone marrow cells express Clara cell secretory protein (CCSP); a marker of airway progenitor cells. To study how endogenous bone marrow CCSP-expressing cells affect local progenitor regeneration, we used the CCtk transgenic mouse model in which the Herpes simplex thymidine kinase suicide gene is expressed under the control of the CCSP promoter. Ganciclovir treatment results in elimination of CCSP-expressing cells.

Methods: Wild type female mice were lethally irradiated and transplanted with male BM cells from either CCtk or wild type mice. After two months to establish bone marrow engraftment, animals were treated with ganciclovir 7 mg/day for 20 days to eliminate bone marrow CCSP-expressing cells in the CCtk BM group with no effects in lung. Mice were treated with naphthalene 200 mg/kg to injure airway epithelium and were sacrificed after 2, 5 and 10 days of naphthalene treatment. Airway recovery was assessed using CCSP immunofluorescence staining. Inflammatory cells were estimated by total and differential cell counts of bronchoalveolar lavage (BAL) cells. Quantitative real-time PCR analysis was done to compare expression of epithelial and secretory cell markers. Arterial blood gases (PaO2/FIO2 ratio) were analyzed for each time point.

Results: Mice showed significant differences between groups only at day 5. The CCtk BM group showed less CCSP+ cells lining the airway epithelium (score of 2.75±0.17 vs. 4±0; p<0.001), more inflammatory cells in BAL (6.09 ± 1.10 x 10⁵ vs. 3.03 ± 1.93 x 10⁵; p=0.023), lower PaO2/FIO2 ratio (497.6 ± 43.03 vs. 666.6 ± 96.7; p=0.0315) and down regulation of secretory cell markers CCSP, Cyp2f2, Pon1, Aox3 and Fmo3 genes (p ≤ 0.01), compared to animals with wild-type bone marrow.

Conclusion: Bone marrow CCSP-expressing cells play a beneficial role in airway regeneration after naphthalene injury.