c-Kit lung cells ameliorate the course of experimental asthma

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Rationale: Asthma is a triad of intermittent airway obstruction, bronchial hyperreactivity and chronic inflammation with structural changes in the airways. The ideal therapy should relieve symptoms, attenuate inflammation and prevent or reverse remodeling (1). The need for new therapeutic options has boosted the search for resident or non-resident stem/progenitor cells for lung repair (2). Although it is well known that several stem/progenitor populations are involved in maintenance and repair of lung, they may have uncertain therapeutic prospective because no one of them can replenish all cell types lost due to various injuries. In this regard, extrapulmonary cells including marrow-, adipose tissue- and umbilical cord blood-derived stromal cells, embryonic stem cells and induced pluripotent stem cells were tested (3,4). Emerging evidence points to the involvement of c-kit-positive cells in lung homeostasis, but their therapeutic potential is unknown (5). The importance of c-kit in lung biology is supported by the observations that c-kit mutant mice have abnormal lung architecture and that the expansion of epithelial progenitors depends on c-kit activation (6). Additionally, c-kit-positive cells were detected in transplanted human lungs (7), in a subset of non-small-cell lung carcinomas (8) and among CD133-positive epithelial progenitors (9). Interestingly, a fraction of c-kit-positive cells activated during the repair of experimental emphysema was found to be of non-bone marrow origin (10).
Objectives: To identify and isolate c-kit cells from mouse lungs and to test whether they can interfere with the pathophysiological features of asthma in an animal model. To compare in vivo effects of c-kit cells and marrow-derived mesenchymal stem cells.
Methods: Mouse lung c-kit cells and bone marrow-derived mesenchymal stem cells were intratracheally delivered in the ovalbumin mouse model of allergic asthma.
Results: Functional improvement observed with both cell types was more prominent with c-kit cells that engrafted, proliferated, differentiated into epithelial cells and positively affected airway remodeling. Reduction of cell number, decrease of interleukin-4, interleukin-5, interleukin-13 and increase of interleukin-10 in bronchoalveolar lavage were observed with both cell types. Exposed to pro-inflammatory cytokines, c-kit cells upregulated indoleamine 2,3-dioxygenase and TGF-β. Moreover, in vivo upregulation of calcitonin gene-related peptide and vasoactive intestinal peptide indicates that these neuropeptides may represent important mediators of the beneficial effects. Although c-kit cells share with mesenchymal stem cells anti-inflammatory effects, the stronger impact of lung-derived cells on airway hyperresponsiveness may be attributed to their higher retention in the tissue combined with evident epithelial repair and upregulation of aforementioned neuropeptides.
Conclusion: Intratracheally administered lung c-kit cells repair epithelium, positively modulate airway remodeling, reduce inflammation and improve function demonstrating their ability to re-establish tissue homeostasis in the course of experimental allergic asthma.

References:

1. Pascual RM, Peters SP, J Allergy Clin Immunol 2005;116:477-486.
2. Kotton DN, Morrisey EE, Nat Med 2014;20:822-832.
3. Weiss DJ et al, Proc Am Thorac Soc 2011;8:223-272.
4. Lau AN et al, Mol Ther 2012;20:1116-1130.
5. Kajstura J et al, N Engl J Med 2011;364:1795-1806.
6. Lindsey JY et al, Am J Respir Crit Care Med 2011;183:1644-1652.
7. Da Silva CA et al, Respir Res 2006;7:90.
8. Donnenberg AD et al, PLoS One 2012;7:e52885.
9. Germano D et al, Am J Respir Crit Care Med 2009;179:939-949.
10. Hegab AE et al, Mol Ther 2008;16:1417-1426.