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Title: Clara cells serve as the progenitors to regenerate alveolar epithelium in response to severe lung injury

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Body: Bleomycin treatment or influenza virus infection can induce severe damage in distal lung with the loss of large amounts of alveolar type II (AT2) and type I (AT1) cells. During the repair process, new AT2s and AT1s have to be produced to regenerate the damaged alveoli. A recent study showed that the newly generated AT2s were not derived from pre-existing AT2s after bleomycin treatment, indicating the existence of other progenitor cells for alveolar regeneration [1]. We have used a genetic lineage tracing system to follow Clara cells in mice. We show that large numbers of the newly generated AT2s and AT1s are derived from Clara cells after alveoli damage by bleomycin treatment or influenza virus infection. The intermediates between Clara cells and AT2s are SPC-expressing bronchiolar cells (or SBECs). SBECs are only observed in damaged area and initially positive for Clara cell marker Clara Cell Secretory Protein (CCSP) and gradually become CCSP negative. Anatomical analysis shows that SBECs at the tips of bronchioles appear to dilate to regenerate alveolar epithelium in a process similar to that seen during the development of embryonic alveolar epithelium. These findings show that Clara cells are the progenitors to regenerate alveolar epithelium in response to severe lung damage. [1] Chapman, H. A. et al. Integrin alpha6beta4 identifies an adult distal lung epithelial population with regenerative potential in mice. J Clin Invest 121, 2855-2862 (2011).