Proliferative and Clonogenic Potential of Lung Progenitor Cells Exposed to Ionizing Radiation

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RATIONALE
The mammalian airway is lined by an epithelium that is maintained by abundant region-specific progenitor cells. In the distal mouse conducting airway, normal epithelial maintenance and repair following injury is accomplished by CCSP-expressing cells. Chronic exposure of the epithelium to external toxicants and ionizing radiation (IR) can result in DNA damage and changes in the viability and/or function of cells leading to tissue remodeling and initiation of cancer. However, significant gaps exist in our understanding of the effects of IR on pulmonary progenitor cells that have been shown to serve as targets for neoplastic progression. We hypothesized that the lung epithelium is a sensitive target for radiation effects and that defects in epithelial progenitor cell activity following radiation exposure contribute to local tissue remodeling.

METHODS
Mice were exposed to varying doses of either low linear energy transfer or high linear energy transfer (LET) IR and airways assessed for changes in the proliferative and clonogenic behavior of epithelial progenitor cells. The effects of IR on the proliferative kinetics of epithelial cells were determined using DNA precursor labeling (IdU incorporation) coupled with dual immunofluorescence of IdU with cell type-specific markers. The impact of IR on the in vivo clonal expansion of epithelial progenitor cells was determined by lineage tracing. Tamoxifen exposure of CCSP-CreER/Confetti mice was used to randomly introduce one of four genetic tags into the CCSP-expressing epithelial progenitors. Immunodetection of each of the four tags was used to quantify clonal expansion of epithelial progenitor cells as a function of IR exposure.

RESULTS
Dose- and time dependent increases in lung epithelial progenitor cell activity were observed in mice exposed to whole body IR. Six Gy whole body low-LET resulted in a mild proliferative response in the airway epithelium 7 and 30 days post IR, as evident by nuclear IdU incorporation. However, 8 Gy exposures resulted in a significant increase in the proliferative kinetics of epithelial progenitor cells at both 7 and 30 days post IR. The epithelium in airways of mice exposed to either low or high-LET IR showed an increase in the frequency of contiguous clonal patches 60 days after IR exposure.

CONCLUSIONS
Our data demonstrate that both low- and high-LET IR exposure results in altered airway epithelial progenitor cell activity in the lung, evident by increased proliferation and clonal expansion. These data are guiding our ongoing studies to define mechanisms that contribute to radiation-induced tissue remodeling of the airway epithelium, the relative in vivo responses to high vs. low LET IR, and the risk of IR-induced lung cancer development.