Modeling Cell-Intrinsic Effects of Low vs High LET Ionizing Radiation on Lung Epithelial Progenitor Cells

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RATIONALE

Abundant populations of epithelial progenitor cells maintain the epithelium along the proximal-to-distal axis of the airway. Disruption of this epithelial barrier leads to tissue remodeling and increases risk of cancer progression. Exposure of lung tissue to ionizing radiation (IR) results in dose-dependent tissue remodeling and predisposition to cancer. The impact of IR on lung epithelial progenitor cell populations is unknown. We hypothesized that IR depletes the available epithelial progenitor cell pool in a dose- and energy-dependent manner.

METHODS

In order to investigate the effects of radiation on the epithelial lining of airways, we cultured primary airway epithelial cells from irradiated mice in a unique 3D epithelial-fibroblast co-culture system. Epithelial progenitor cells were prepared from dissociated lungs of mice exposed to varying doses of low- and high-linear energy transfer (LET) radiation and were harvested 18 hours post irradiation. Since the type of progenitor cells vary along the proximal-to-distal airway axis, lung epithelium was fractionated into proximal and distal subsets based upon surface Sca1 staining. These epithelial cell fractionations were mixed with a defined population of cultured lung fibroblasts, enrobed in Matrigel, and cultured on TransWell inserts. Colony-forming efficiency (CFE) was assessed at culture day 14.

RESULTS

Dose-dependent decreases in colony formation were observed in lung epithelial progenitor cells from mice exposed to low-LET radiation. Whole-body exposure to 2 Gy low-LET radiation resulted in a 49.1% decrease in CFE of the total input epithelial cell population. Doses exceeding 4 Gy resulted >90% loss of CFE. Similar dose-dependent decreases in CFE were observed among both the Sca-1 positive proximal airway and Sca-1 negative distal airway subfractionations, indicating that progenitors from both the proximal and distal regions of the lung show similar susceptibility to radiation-induced decreases in clonogenic potential. Dose-dependent effects on 3D colony growth were also observed when epithelial progenitor cells were cultured from mice exposed to high-LET IR.

CONCLUSIONS

Both low- and high-LET radiation resulted in the acute loss of epithelial colony growth in 3D culture assays. This decrease was apparent in both the total lung epithelial progenitor population and sub-fractions representing proximal and distal regional airway progenitors. Ongoing studies will investigate mechanisms of epithelial recovery following acute progenitor cell depletion and how the behavior of airway epithelial progenitor cells is influenced by energy and dose rate.