

Lung Cancer Pathogenesis After HZE Particle Exposure

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The University of Texas Southwestern Medical Center NSCOR

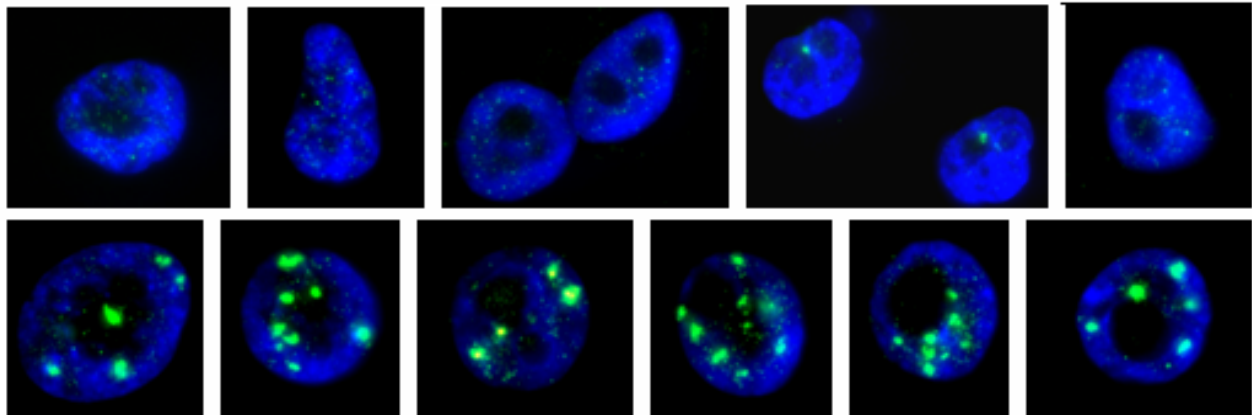
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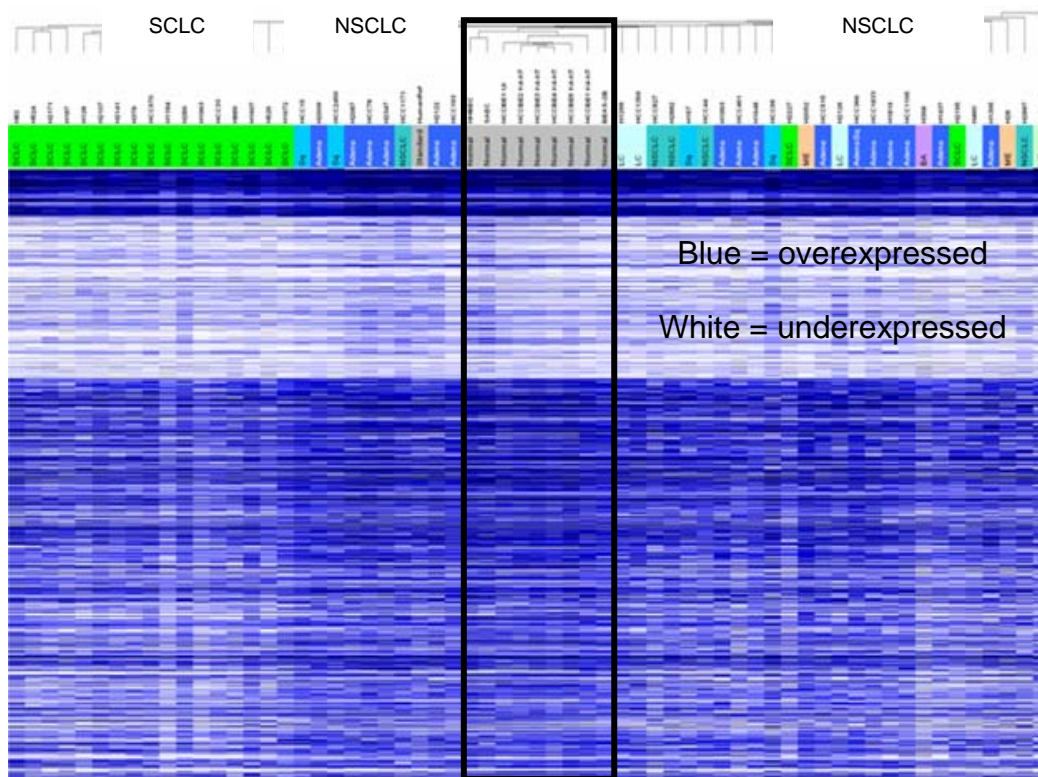
The University of Texas Southwestern Medical Center (UTSW) NSCOR focuses on the development of quantitative dose risk estimates following HZE particle irradiation for the development of key genetic, epigenetic, gene expression, and cellular functional changes in the multistep pathogenesis of lung cancer in both new human bronchial epithelial cell (HBEC) and transgenic mouse models of lung cancer. The risk of developing these changes will also be compared in these models to that of X-irradiation. These dose risk assessments will measure events of both radiation-induced promotion (modification of proliferation kinetics of already-initiated cells) as well as radiation-induced initiation (mutational) events. 3D organotypic culture and animal models will also allow measurement and risk estimation of “bystander” effects. These individual risk estimates can then be combined into a model (such as a two-stage clonal expansion model) for overall risk of developing lung cancer from exposure to galactic cosmic radiation. To achieve these goals, UTSW has assembled a team of scientists who are leaders in the study and translation application of the molecular pathogenesis of lung cancer; in radiobiology and DNA repair; a panel of expert Internal and External Advisors; as well as expert consultants and collaborators. This team has developed a novel immortalized HBEC system that can be genetically manipulated, studied in 2D monolayer and 3D organotypic cultures. Using these HBECs we have preliminary studies with HZE particle irradiation showing that further progression toward lung cancer can be detected and quantified, that specific expression profiles for HZE irradiation exist, and that HBECs genetically manipulated to progress part of the way toward malignancy are even more sensitive to HZE-induced functional changes. In addition, we have developed plans for novel transgenic mouse models to monitor HZE particle induction of lung cancer in the whole animal in real time. The NSCOR has 4 Projects: 1. Genetic and epigenetic changes in human bronchial epithelial cells following exposure to HZE particle irradiation.; 2. Effect of HZE particles on DNA damage-sensing and repair pathways in human lung epithelial and fibroblast cells; 3. Effect of HZE particle irradiation on functional progression of human lung cancer at the cellular and organotypic level; and 4. Effects of HZE particles on the development of lung cancer *in vivo* in novel mouse models. These projects are supported by 4 Cores: Administrative; Cell Culture; Expression Profiling and Proteomics; and Biostatistics and Bioinformatics. The HZE particle irradiation will be done at Brookhaven National Lab, and the biostatistical analysis shows the experiments are powered to help achieve NASA mandated risk estimate confidence levels.

Gamma H2AX staining - control human bronchial epithelial cells: typical of all cells

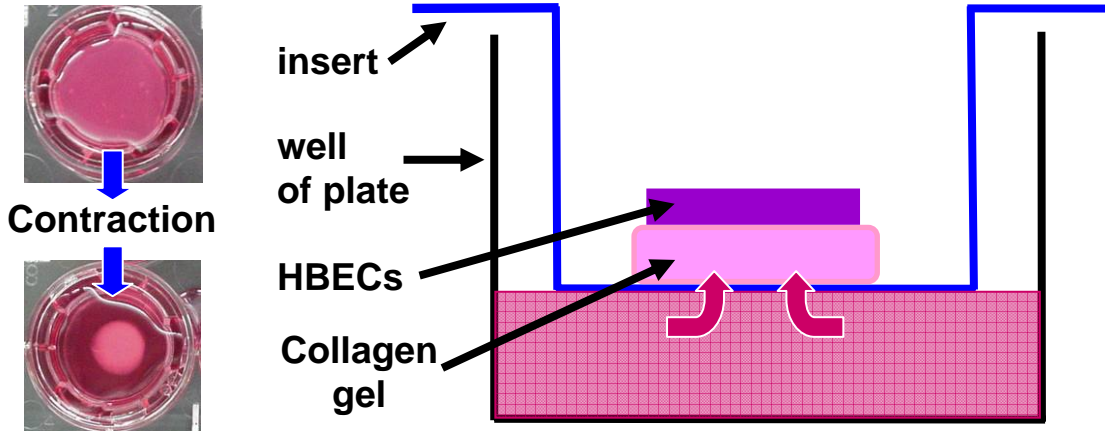


Gamma H2AX staining – HBEC + 1 GeV HZE + 3 days: typical of ~6% of cells

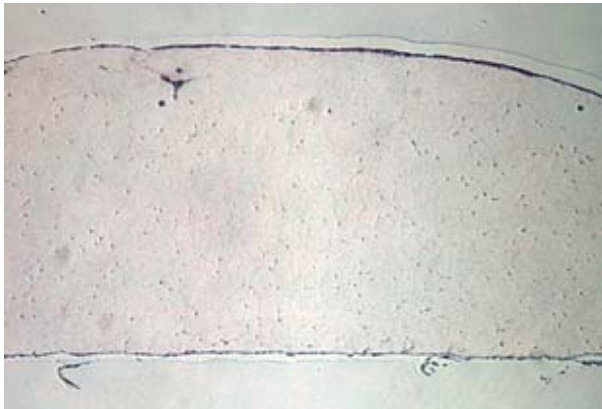
Normal Human Bronchial Epithelial Cells



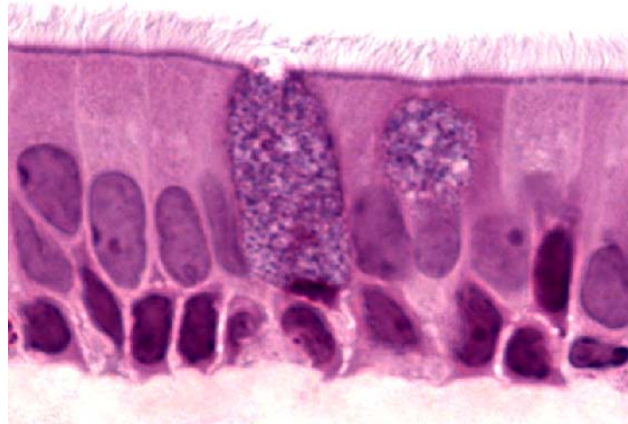
A subset of human bronchial epithelial cells (HBECs) show persistent double-strand DNA damage after 1GeV HZE (top image). When immortalized HBECs are compared to each other and small (SCLC) and non small cell lung carcinoma (NSCLC) cell lines, the immortalized “normal” cells cluster together (bottom image).



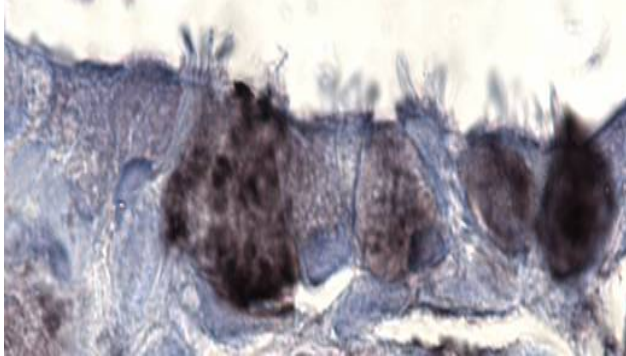
Development of human lung organotypic cultures. Lung fibroblasts are combined with type I collagen, allowed to contract over a period of 4 to 7 days. Human bronchial epithelial cells (HBECs) are then seeded onto the top of the collagen gels for 4 days to create the organotypic (3D) culture. Cultures are then placed into a transwell insert (6-well dish) which is fed from beneath by culture medium placed into the well below the insert, thereby leaving the upper surface of the tissue emerged from the media. After several weeks, the epithelial cells differentiate into ciliated and mucous-producing cells.



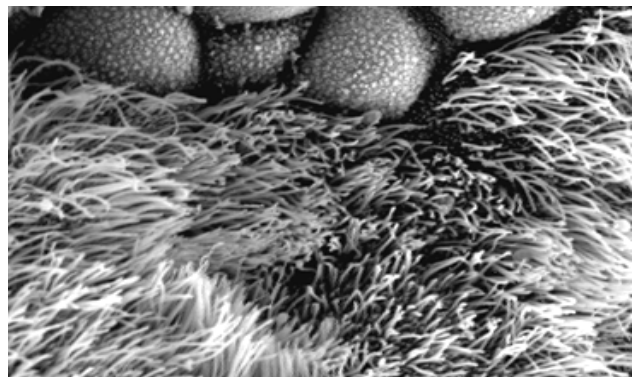
Low power H&E image of 3D cultures



H&E of normal human bronchial tissue



Clones of HBECs can differentiate in 3D cultures into both ciliated and mucous cells



Scanning electronic microscopic image of ciliated cells in 3D culture