The *BigH3* Tumor Suppressor Gene in Radiation-Induced Malignant Transformation of Human Bronchial Epithelial Cells

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Carcinogenesis is a multi-stage process with sequences of genetic events governing the phenotypic expression of a series of transformation steps leading to the development of metastatic cancer. Previous studies from this laboratory have identified a 7 fold down- regulation of the novel tumor suppressor *Big-h3* among radiation induced tumorigenic BEP2D cells. Furthermore, ectopic re-expression of this gene suppresses tumorigenic phenotype and promotes the sensitivity of these tumor cells to etoposide-induced apoptosis. To extend these studies using a genomically more stable bronchial cell line, we ectopically expresses the catalytic subunit of telomerase (hTERT) in primary human small airway epithelial (SAE) cells and generated several clonal cell lines that have been continuously in culture for more than 250 population doublings and are considered immortal. Comparably-treated control SAE cells infected with only the viral vector senesced after less than 10 population doublings. The immortalized clones demonstrated anchorage dependent growth and are non-tumorigenic in nude mice. These cells show no alteration in the p53 gene but a decrease in p16 expression. Exponentially growing SAEh cells were exposed to graded doses of 1 GeV/nucleon of ^{56}Fe ions accelerated at the Brookhaven National Laboratory. Irradiated cells underwent gradual phenotypic alterations after extensive in vitro cultivation. Transformed cells developed through a series of successive steps before becoming anchorage independent in semisolid medium. These findings indicate that hTERT-immortalized cells, being diploid and chromosomally stable, should be a useful model in assessing mechanism of radiation carcinogenesis.