Identification and Characterization of Non Small Cell Lung Cancer Stem Cells

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The discovery of rare tumor cells with stem cell features first in myeloproliferative disease and later in solid tumors has emerged as an important area in cancer research. Through these studies the cancer stem cell model has emerged, which postulates that many tumors are initiated and progressed by a population of self-renewing malignant stem cells, referred to as cancer stem cells. This new tumor growth paradigm suggests that tumor metastasis and recurrence may be driven by a residual population of highly aggressive cancer stem cells. Furthermore this model argues that complete cancer remission may only be achieved by eradicating the malignant stem cell population charged as the source of tumor cell renewal.

Lung cancer is the most commonly lethal form of cancer in the world with about 90% of the nearly one million new cases succumbing to the disease. While progress is being made in understanding lung cancer pathogenesis and improving therapy, prognosis remains poor. One approach to improving outcome in lung cancer has been to therapeutically target a unique, phenotypically defined lung cancer stem cell population. However despite the relatively rapid pace of cancer stem cell research in solid tumors such as breast, brain and colon cancers, similar progress in lung cancer remains hampered in part due to an incomplete understanding of lung stem cell hierarchy and the complex heterogeneity of the disease.

To address this challenge, putative lung cancer stem cells were prospectively isolated from patient lung tumors and lung tumor cell lines using methods that have been reported to enrich for other stem cell populations in other cancers. As a result, a subpopulation of cells with elevated aldehyde dehydrogenase (ALDH) activity within many NSCLCs was identified with properties indicative of a cancer stem cell population including enhanced tumorigenicity in xenograft models, clonogenicity in culture and the capacity for self-renewal. In support of this, analysis of 282 clinically annotated non small cell lung cancer samples found elevated ALDH1A1 expression, the protein that drives ALDH in lung cancer, was associated with poor patient prognosis. Finally, molecular characterization of isolated ALDH+ lung cancer cells revealed elevated expression of stem cell transcripts including Notch signaling transcripts, suggesting enhanced pathway activity. Suppression of Notch signaling through chemical inhibition or knockdown of the proto-oncogene *NOTCH3* resulted in a significant reduction in clonogenic ALDH+ cells indicating the importance of Notch signaling in lung cancer stem cell homeostasis and as a potential target for lung cancer stem cell directed therapy.