The transcription factor Slug induces diverse malignant phenotypes in models of established lung cancer and pulmonary premalignancy

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Inflammation often characterizes the pulmonary tumor microenvironment, as does overexpression of the transcriptional repressors of E-cadherin (e.g., Snail and Slug). While chronic inflammation is now associated with increased lung cancer incidence, Snail and Slug are still best known for their induction of epithelial-mesenchymal transition (EMT) and their contribution to the progression of established lung cancer. Our bioinformatics analysis of lung TCGA data suggests that Slug is among the most impactful of all the transcriptional repressors on patient survival. Therefore, we are now exploring the scope of malignant phenotypes and mechanisms induced by Slug expression in a non-small cell lung cancer (NSCLC) model. We discovered that NSCLC cells exposed to the prototypical inflammatory mediator IL-1B respond with downregulation of epithelial markers (E-cadherin and cytokeratin 18) and upregulation of mesenchymal markers (N-cadherin and vimentin), with the repression of E-cadherin by IL-1B being Slug-dependent. NSCLC cells exposed to IL-1B also demonstrate altered cellular morphology, diminished capacity to form clusters in a 3-dimensional (3D) spheroid model, and increased motility. Using chemical inhibitors of the JNK, MEK/ERK, p38 MAPK, and NF-κB pathways, we determined that JNK and MEK/ERK mediate IL-1B induction of EMT in lung cancer cells. Furthermore, siRNA-mediated knockdown of the Fra-1 component of the AP-1 transcription factor abolished the impact of IL-1B on Slug and E-cadherin in this model, demonstrating a mechanistic link between inflammation and Slug-dependent progression of established lung cancer. Because we have identified a critical role for Snail in lung cancer initiation, we next investigated the contribution of Slug to early lung cancer development. Using human bronchial epithelial cells (HBECS) engineered to express Slug to model pulmonary premalignancy, we observed a diverse array of potentially malignant phenotypes, including EMT, increased production of the pro-angiogenic chemokine CXCL8, enhanced invasion in a 3D air-liquid interface model, and anchorage-independent growth in vitro. Furthermore, we determined that the Slug-driven transformation observed in vitro was not contingent upon an altered proliferation rate, but was more likely related to Slug-driven disruption of stem cell signaling programs. Taken together, our data suggest that Slug may be important in the setting of lung carcinogenesis and that its impact on carcinogenesis extends beyond its repression of E-cadherin. Our data also suggest that Slug may play an important role in the initiation and progression of early stage NSCLC.

Structural analysis identifies an orally active PCNA inhibitor that inhibits the growth of small cell lung cancer cells without causing significant toxicity to nonmalignant cells

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Playing a central role in regulating DNA synthesis and repair, proliferating cell nuclear antigen (PCNA) is indispensable to cancer cell growth and survival. It, therefore, represents a potential molecular target to develop broad-spectrum anti-cancer agents. We discovered a cancer-associated isoform of PCNA (caPCNA), which is ubiquitously and highly expressed in a broad range of cancer cells and tumor tissues. In contrast, this PCNA isoform is not significantly expressed in nonmalignant cells. The secondarily modified region distinguishing caPCNA from normal PCNA expressed in non-malignant cells lies between L126 and Y133 within the interconnector domain of PCNA known to be a major binding site for many of PCNA’s interacting proteins. A cell permeable peptide containing the L126-Y133 sequence blocks PCNA interaction, interferes with DNA replication and homologous combination mediated DNA repair, and induces apoptosis in cancer cells. In contrast, this peptide causes no significant toxicity to normal cell lines.