synthesized using an independent method, and sequenced by Sanger. The results confirmed the presence of an RNA transcript spanning exon 19 of MPRIP and exon 12 of RET. Furthermore, FISH was performed with the RET (10q11.2) break-apart probe, and confirmed the rearrangement involving the RET region of chromosome 10.

Conclusions: These results show the Archer™ Fusion-Plex™ Lung Thyroid Panel can accurately detect gene fusions with both known and unknown partner and driver genes. Further investigation is needed to better understand the clinical significance and prevalence of the novel MPRIP and RET fusion.

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
Translational application of microRNA profiling for early detection of lung cancer: A comparison of sputum and blood

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Background: Lung cancer has the highest mortality rates of all the cancers in Canada with a 5 year survival rate of less than 15%. Asymptomatic in its early stages, methods to screen high risk individuals are in dire need to allow earlier diagnosis and curative intent treatment. MicroRNAs (miRNAs) are small, non-coding strands of RNA that are shown to lead to carcinogenesis when dysregulated. They are promising candidates for biomarkers as they are stable, detectable in small quantities and are expressed in a tissue specific manner. Through the use of a miRNA panel developed by our group that demonstrated good sensitivity and specificity using sputum as a medium to measure miRNA, we aimed to compare the efficacy of measuring miRNA in sputum and blood to develop a miRNA profile for non-small cell lung cancer (NSCLC).

Objective: To examine miRNA profiles of NSCLC cases versus healthy controls to compare the efficacy of sputum and blood for potential screening purposes using microarray analysis.

Methods: A case control study of stage I/II cancers, matched with controls having similar smoking history, age, and gender, was performed. Participants were recruited at the Royal Alexandra Hospital in Edmonton, Alberta, Canada. Both sputum and blood are collected and analyzed via Qiagen miRNA kits. 10 cases and 10 controls miRNA samples were submitted for microarray analysis. miRNAs were labelled, hybridized, and quantified using single-color experimental design. Specific miRNAs from past literature were then compared in cases and controls using Mann Whitney U test.

Results: Sputum does not have consistent levels of miRNA present when compared to blood, and principle component analysis (PCA) plots show more random patterns in sputum when compared to blood. By using heat maps and hierarchical clustering, no apparent clusters are seen when compared cases and controls in both sputum and blood. A type II error could be responsible for this finding due to the small sample size.

Conclusions: Microarray analysis shows that sputum is less consistent when measuring miRNAs compared to blood overall. These findings have already been applied to the next phase of our research which will examine miRNA levels in high risk individuals as a means of establishing it as a robust screening test for lung cancer.