immune checkpoint inhibitors are currently under active investigation.

Oncogenic KRAS regulates asparagine synthase

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Kras is a small GTPase that functions in the transmission of extracellular mitogenic stimuli, and is one of the most frequently mutated genes in non-small cell lung cancer (NSCLC). Previously, Kras has been demonstrated to play a role in tumor metabolism in certain cell types and cancers, but this has yet to be analyzed in the context of NSCLC. We have analyzed how Kras changes metabolic gene expression by expressing a doxycycline-inducible hairpin against Kras in several NSCLC cell lines. One of the most regulated metabolism genes is asparagine synthetase (Asns), which transfers the \( \gamma \)-amino group of glutamine to aspartate, yielding glutamate and asparagine. We find elevated levels of Asns in Kras mutant tumors, and that expression of Asns correlates with poor patient outcome. Knockdown of Asns in the absence of exogenous asparagine in the media results in inhibition of cell growth and induction of apoptosis that is rescued by addition of asparagine. Additionally, under conditions of low glutamine levels, knockdown of Asns sensitizes cells to apoptosis, and overexpression of Asns is protective under these conditions. We also find a role for the glutaminase-activity of Asns in glutamine-mediated anapleurosis of the TCA cycle. These observations suggest Asns may be an interesting and novel therapeutic target for NSCLC tumors with mutations in Kras.

Blood-based biomarkers for lung cancer: Ready for prime time?

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Blood based biomarkers have the potential for improving outcomes in lung cancer, a disease where approximately 40% of patients present with distant metastases at diagnosis. Two important areas of research include the discovery of risk biomarkers (e.g. defining who will develop lung cancer in the future) and the identification of diagnostic biomarkers for use as a screening tool or to assess the likelihood of cancer in patients with a radiographic abnormality such as a lung nodule. Although the pace of biomarker discovery is advancing rapidly across all of these areas, the development of biomarkers to assess the likelihood of cancer in patients with lung nodules has been an intense area of research and several biomarkers are currently being evaluated in prospective trials.

Lung nodules are increasingly identified either incidentally or through the use of screening low dose chest CT. Lung nodules deemed indeterminate lack the features suggestive of benign etiologies and present clinicians with a diagnostic conundrum. Although most lung nodules are benign, patients frequently undergo multiple diagnostic tests, including the use of positron emission tomography (PET), as well as invasive procedures such as transthoracic needle aspiration, bronchoscopy and/or surgery. Therefore, biomarker strategies to distinguish between malignant and benign lung nodules may mitigate the diagnostic burden faced in this setting.

Peripheral blood based detection strategies are an attractive approach for diagnostic markers, given the ease of acquisition and potential for serial testing, and are based on the underlying hypothesis that molecular alterations of tumor cells lead to the synthesis of distinct molecular species that can be detected in the blood. Peripheral blood biomarkers have been identified in both the cellular component (circulating tumor cells, white blood cells) and in the non-cellular fraction (e.g. plasma, serum), and studies have spanned across several different types of molecular species.

The presentation will review the rationale for the use of early detection biomarkers for risk assessment, screening, and diagnosis, and provide a comprehensive overview of blood based biomarkers currently in development, including markers that are available for clinical use. This will include an analysis of existing data from clinical validation and utility studies supporting the use of blood based diagnostic tests as well as a discussion of ongoing prospective trials.

Modeling lung cancer with CRISPR/Cas9

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The CRISPR/Cas9 bacterial system uses short non-coding RNAs as an adaptive defense mechanism against invading DNAs. This system has recently been adapted as a tool to edit mammalian genomes, and requires only the co-expression of the Cas9 endonuclease and a short guide RNA that can direct it to target loci.