A6

Tri-complex Inhibitors of the Oncogenic, GTP-Bound Form of KRASG12C Overcome RTK-Mediated Escape Mechanisms and Drive Tumor Regressions in Preclinical Models of NSCLC


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RAS proteins are small GTPases that drive cell proliferation and survival when bound to GTP. Mutant RAS proteins are found in approximately one third of NSCLC, and exist predominantly in the GTP-bound state, leading to aberrant downstream signaling via interaction with effectors such as RAF. Recently, multiple potent, covalent inhibitors of the oncogenic mutant KRASG12C have entered development and are driving high lung cancer response rates in early clinical trials. These inhibitors target the inactive, GDP-bound form of KRASG12C, KRASG12C(ON), and thus rely on the residual intrinsic hydrolysis of GTP to cycle KRASG12C proteins through the GDP-bound state. This mechanism is vulnerable to adaptive responses in cancer cells that increase upstream signaling to further elevate the relative abundance of the active, GTP-bound state, KRASG12C(ON). An inhibitor that directly targets KRASG12C(ON) would overcome this limitation. We have developed tri-complex inhibitors of KRASG12C(ON) that promote a ternary complex between KRASG12C and the immunophilin cyclophilin A (CypA). KRASG12C(ON) inhibitors attenuate both RAS-MAPK signaling and cell viability in cancer cell lines bearing KRASG12C mutations. In vivo administration of a KRASG12C(ON) inhibitor drives dose-dependent tumor regressions in the NCI-H358 KRASG12C NSCLC xenograft mouse model and is well tolerated. Consistent with targeting the KRAS(ON) and inhibitory activity in vitro is unaffected by RTK activation, whereas the activity of first-generation KRASG12C(OFF) inhibitors is significantly attenuated. In addition, proliferation of NCI-H358 cells in vitro is suppressed for a significantly longer duration with KRASG12C(ON) inhibitor treatment compared to KRASG12C(OFF) inhibitors. The ability to target the GTP-bound form of mutant KRAS permits a broad array of combination opportunities. Combination of
KRASG12C(ON) inhibitors with agents targeting pathway nodes both up- and downstream of RAS, as well as other parallel pathways, can drive combination benefit in distinct cancer histotypes. Tri-complex inhibitors that target the active, GTP-bound form of KRAS thus represent a second generation of KRASG12C inhibitor. Chemical modulation of the noncovalent and covalent interactions of our tri-complex inhibitors provides an exciting opportunity to step beyond KRASG12C to target the GTP-bound state of additional RAS variants, and we demonstrate in vitro covalent inhibition of KRASG13C.

A07

The Genomic Landscape of SMARCA4 Alterations and Association with Patient Outcomes in Lung Cancer


Vulnerability in Lung Cancer

Background: Genomic abnormalities in the subunits of the SWI/SNF (Switch/Suicte NonFermentable) chromatin remodeling complex occur in approximately 20% of solid tumors. The tumor suppressor SMARCA4 is the most commonly altered gene within the SWI/SNF chromatin remodeling complex in lung cancer, but its relationship to other genomic abnormalities and clinical impact is unknown. Methods: We evaluated all non-small cell lung cancer patients with SMARCA4 alterations detected by MSK-IMPACT next-generation sequencing (NGS) and who were treated at Memorial Sloan Kettering Cancer Center (MSK). A cohort of patients with metastatic non-small cell lung cancer who had MSK-IMPACT without SMARCA4 alterations and were treated during the same time period was used as a compare group. Clinical and molecular features were compared to examine how SMARCA4 alterations relate to molecular phenotype, and in patients treated with immune checkpoint inhibitors (ICIs), we assessed how these interactions impacted efficacy. Results: We identified 404 of 4,813 NSCLC patients (8% of NSCLCs) with SMARCA4-mutant lung cancer. We found that the presence of SMARCA4 abnormalities is enriched in patients with KRAS, STK11, and KEAP1 mutations, but independently and additively shortens overall survival with these co-occurring alterations. Based on SMARCA4 protein expression and site of SMARCA4 mutations, we describe two distinct classes of SMARCA4 alterations associated. We also found that treatment with ICIs is associated with improved outcomes in patients with SMARCA4-mutant tumors and the class of mutations associated with protein loss correlates with increased response to ICIs. Conclusion: SMARCA4 alterations are associated with KEAP1, STK11, and KRAS mutations in patient with NSCLC, but individually represent a novel negative prognostic biomarker. Despite association with poor outcomes, SMARCA4-mutant lung cancers may also be uniquely sensitive to immunotherapy.

A08

MYC-Driven SCLC Has Unique Metabolic Vulnerabilities

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Vulnerabilities in Lung Cancer

Small-cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung tumor that has been treated clinically as a homogeneous disease. Recent discoveries suggest that SCLC is heterogeneous with distinct molecular subtypes. Whether metabolic differences exist among SCLC subtypes is largely unexplored. We have aimed to determine whether metabolic vulnerabilities exist between SCLC subtypes that can be therapeutically exploited. Toward this end, we performed steady-state metabolomics on tumors isolated from distinct genetically engineered mouse models (GEMMs) representing the MYC and MYCL-driven subtypes of SCLC. We discovered that SCLC subtypes driven by different MYC family members have distinct metabolic profiles. Purine nucleotide biosynthesis and arginine/urea cycle pathways were enriched specifically in MYC-driven SCLC (Huang et al., Cell Metab 2108; Chalishazar et al., Clin Can Res 2019). MYC-driven SCLC preferentially depends on arginine-regulated pathways for polyamine biosynthesis and mTOR pathway activation. Chemoresistant SCLC cells exhibited increased MYC expression and similar metabolic liabilities as chemoresistant MYC-driven cells. Arginine depletion with pegylated arginine deiminase (ADI-PEG20) dramatically suppressed tumor growth and promoted survival of mice specifically with MYC-driven tumors, including in GEMMs, human cell line xenografts, and in new patient-derived xenograft (PDX) models. ADI-PEG20 was significantly more effective than the standard-of-care chemotherapy in GEMMs; however, tumors eventually relapse and acquire resistance to ADI-PEG20. Our current efforts are focused on identifying mechanisms of ADI-PEG20 resistance. We find that expression of the argininosynthetic enzyme ASS1 is frequently induced in ADI-PEG20 relapsed tumors in mouse and PDX models. Metabolite profiling of ADI-PEG20-resistant tumors suggests that ASS1 induction is associated with metabolic rewiring, which we predict will be associated with new metabolic vulnerabilities. Pathway analyses of metabolite data are consistent with the notion that ASS1 induction causes increased consumption of aspartate to generate arginine, and thereby ameliorate the demand for exogenous arginine. We predict that the diversion of aspartate away from nucleotide biosynthesis will lead to increased demand on other metabolic pathways for nucleotide biosynthesis. Preliminary data have identified pathways whose inhibition may cooperate with ADI-PEG20 to further extend the survival of mice with MYC-driven SCLC.

A09

Transcriptional Subtypes Resolve Tumor Heterogeneity and Identify Therapeutic Vulnerabilities in Lung Cancer


Non-small cell lung cancer (NSCLC) is the leading cause of cancer death. Adenocarcinomas are the most prominent type of NSCLC, characterized by intense diversity both with respect to genetics and therapeutic response. More than 75% of adenocarcinomas are devoid of druggable driver events. Herein, we deconvolute tumor heterogeneity in order to discover therapeutically tractable dependencies in this patient subset. By relying on transcriptome and genetic data from >800 patient tumors from the early and advanced setting, we identify three stable and reproducible tumor subtypes. In patients, the subtypes are not strongly associated with genetic events and multiregional biopsies demonstrated subtype stability, despite genetic diversity. We also identified context-dependent prognostic relevance for the transcriptional subtypes. Further interrogation revealed that genetically engineered murine models (GEMM) recapitulate human lung adenocarcinoma subtypes and can therefore be used to discover subtype-specific dependencies. We identified significant differences in subtype-selective sensitivity to MEK inhibitors using an unbiased chemical screen, which reproduced across model systems and validated in a clinical trial. Our results shed new light on MAPK dependence and provide proof of concept for the therapeutic relevance of the transcriptional subtypes, the fidelity of various in vitro and in vivo model systems, and demonstrate that these preclinical