Drug Targets for Overcoming Resistance to KRAS G12C Inhibitors (G12Cis) in Cancer

Innovative therapies to overcome resistance to KRAS G12C inhibitors (G12Cis) in KRAS-mutant cancers.

Technology

The investigators have identified a collection of new genes that could be targeted with small-molecule inhibitors or degraders in combination with existing G12Cis (e.g., Amgen's Sotorasib or Mirati's Adagrasib) for improved treatment of KRAS-mutant tumors resistant to G12Cis. Using an in-house, genome-wide CRISPR/Cas9 screen on genetically-defined KRAS mutant non-small cell lung cancer (NSCLC) cell lines co-mutated with resistance drivers (*STK11* and/or *KEAP1*), the researchers have identified several synthetic lethal (SL) genes that sensitize G12Ci-resistant tumors to treatment with Sotorasib or Adagrasib. As described in *Mukhopadhay et al. Cancer Res. 2023 in press*, these SL genes belong to several distinct biological pathways, including cell signaling, translation initiation, DNA damage, glycolysis, and glycoprotein metabolism. A subset of interesting SL targets was further validated in cell viability assays using genetic (siRNA) knockdown across multiple NSCLC cell lines. Of particular interest are two serine/threonine kinases, VRK1 and RIOK2, which have not previously been linked to G12Ci resistance pathways nor NSCLC. As shown in proof-of-concept studies, genetic knock-down of VRK1 or RIOK2 in combination with Adagrasib (MRTX-849) caused a significant improvement in cell-killing efficacy relative to siRNA or MRTX-849 treatment alone. The synergic effects of G12Ci + VRK1 or RIOK2 genetic targeting (using siRNAs) were confirmed using doxycycline-inducible shRNAs. Overexpression of VRK1 or RIOK2 in certain NSCLC cell lines stimulated G12Ci resistance, underscoring the protective role of VRK1 and RIOK2 against G12Cis. VRK1 was also validated pharmacologically by using a commercially available VRK1 inhibitor, which suggests its tractability to modulation by small molecule inhibitors. These data establish that inhibiting or degrading VRK1 and/or RIOK2 could be an innovative and tractable strategy for combating resistance to G12Cis.

Background

In 2023, the global market for NSCLC therapeutics was estimated to be around $10B and is projected to grow at a CAGR of 7.2% (2023-2033). NSCLC is the most common subtype of lung cancer and the leading cause of cancer-related deaths globally. Approximately 30% of NSCLC cases harbor KRAS mutations, half of which are KRAS-G12C. KRAS is the most frequently altered gene in the RAS/ERK signaling pathway, with mutations occurring in 25-30% of NSCLCs. The development of KRAS G12Cis represents a significant advance in chemical biology and drug discovery. However, in the clinic, these drugs have shown limited long-term benefits due to the emergence of multiple resistance mechanisms. Moreover, certain NSCLC subtypes, including those with specific co-mutations (such as *STK11* and *KEAP1*), exhibit intrinsic resistance to G12Cis. This necessitates the development of innovative combination strategies to overcome/prevent G12Ci resistance or enhance sensitivity to G12Cis.

Applications

Category

Life Sciences/Therapeutics/Oncology

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- Development of new combination therapies for the treatment of KRAS-mutant cancers, including lung cancer (NSCLC), colorectal cancer, and pancreatic cancer
- Identification of additional potential drug targets (using the investigator's unique CRISPR/Cas9 screen) for enhancing the sensitivity of G12Cis or other cancer therapies (existing or under development)
- Development of personalized treatment strategies leveraging the investigator's unique CRISPR/Cas9 screening methodology

Advantages

- **Innovative therapeutic strategy:** Targeting the identified SL genes in combination therapy is expected to overcome G12Ci resistance
- **Unique screening platform:** Provides a comprehensive landscape of new targets for possible combination therapies
- **Personalized approach:** Combination therapies could be developed and/or administered based on a patient's tumor resistance genotype
- **Novel targets in NSCLC resistance:** VRK1 and RIOK2 have not been previously linked to G12Ci resistance mechanisms nor NSCLC
- **Pharmacologically tractable targets:** VRK1 is an intracellular kinase likely amendable to inhibition by small-molecule compounds as demonstrated by existing tool compounds. Structures are available for VRK1 and RIOK2 to facilitate drug discovery efforts

Development Status

The team has identified several SL genes and validated a subset through genetic cell viability experiments, and in the case of VRK1, pharmacological validation studies using an existing tool compound. The next step is to carry out high-throughput primary screening for inhibitors of VRK1 and RIOK2 using a commercially available DNA-encoded library (DEL) at a CRO. Additional target validation work will also be done on other SL gene targets (such as *ELP3* and *ELP5*).

Intellectual Property

NYU has filed a U.S. provisional patent application covering the method of inhibiting or degrading SL protein targets in combination with G12Cis or SHP2 inhibitors in the context of KRAS-mutant cancer to overcome or prevent resistance to G12Cis or SHP2 inhibitor treatments or enhance sensitivity to such treatments.

References

1. Wong KK, Neel BG, et al. , https://pubmed.ncbi.nlm.nih.gov/37729426/