国立研究開発法人
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National Cancer Center Japan

Discovery of splicing vulnerability and novel therapy in RAS Q61 cancers ~Nature~
Collaborative Team of Dana-Farber Cancer Institute and National Cancer Center Japan

March 3, 2022
National Cancer Center Japan

Highlights

- An essential role of silent mutations in splicing and production of a functional KRAS Q61K oncogenic protein was uncovered.
- Splicing vulnerabilities that can be exploited therapeutically were identified in *KRAS*, *NRAS* and *HRAS* Q61X mutant cancers.
- A proof of concept was demonstrated that the induction of aberrant splicing in a mutant selective manner using an antisense oligonucleotide approach leads to tumor cell growth inhibition *in vitro* and *in vivo*.

Summary

RAS family members are the most frequently mutated oncogenes in human cancers. Although KRAS G12C-specific inhibitors show clinical activity in patients with cancer, there are no direct inhibitors of NRAS, HRAS or non-G12C KRAS variants. New research by the collaborative team of Dr. Pasi A. Jänne from Department of Medical Oncology, Dana-Farber Cancer Institute (Boston, USA) and Dr. Yoshihisa Kobayashi from Division of Molecular Pathology, National Cancer Center Japan (Tokyo, Japan) uncovered the requirement of a silent mutation in KRAS G60G for a functional KRAS Q61K oncogenic protein. The team further reveal that the region around RAS Q61 has splicing vulnerabilities. The induction of aberrant splicing by mutant-selective antisense oligos demonstrated therapeutic effects *in vitro* and *in vivo*. By studying a mutant-specific vulnerability in splicing, a novel mutant selective RAS Q61 cancer treatment strategy was uncovered, which could potentially be therapeutically exploited in other genetic contexts.

Publication

Journal name: Nature

Title: Silent mutations reveal therapeutic vulnerability in RAS Q61 cancers

Authors: Yoshihisa Kobayashi*, Chhayheng Chhoeu, Jiaqi Li, Kristin S. Price, Lesli A. Kiedrowski, Jamie L. Hutchins, Aaron I. Hardin, Zihan Wei, Fangxin Hong, Magda Bahcall, Prafulla C. Gokhale, Pasi A. Jänne*

*Co-Correspondence

DOI: 10.1038/s41586-022-04451-4

URL: https://www.nature.com/articles/s41586-022-04451-4

Publication date: March 2, 2022 (London time)

Enquiries

- On Research

Yoshihisa Kobayashi

Division of Molecular Pathology

National Cancer Center Japan

E-mail: yoshikob@ncc.go.jp

- From the press and media

Office of Public Relations National Cancer Center Japan

Office of Public Relations, Strategic Planning Bureau

E-mail：ncc-admin@ncc.go.jp