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

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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.

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