

Potential treatment target for KRAS-mutated colon cancer found

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Researchers from the Massachusetts General Hospital (MGH) Cancer Center have identified a new potential strategy for treating colon tumors driven by mutations in the KRAS gene, which usually resist both conventional and targeted treatments. In a paper appearing in the Feb. 17 issue of *Cell*, the team reports that targeting a later step in the pathway leading from KRAS activation to tumor growth may be able to halt the process.

"Not all KRAS-mutant colon cancers are the same," says Daniel Haber, MD, PhD, director of the MGH Cancer Center and co-corresponding author of the *Cell* report. "About half seem to be very dependent on the KRAS mutation for their survival, whereas the other half can continue growing even when KRAS is suppressed. In the KRAS-dependent tumors, we identified how the mutation augments a [pathway](#) well known to be involved in colon cancer and identified a key step toward that pathway which, if suppressed, can induce KRAS-dependent [tumor cells](#) to undergo apoptosis or programmed [cell death](#)."

Mutations that activate KRAS expression are common in several [types of cancer](#) – most frequently colorectal and lung cancers – and are known to indicate treatment resistance. Drugs that directly target KRAS activity have not been successful, and attempts to identify other potential targets have been challenging, since KRAS [mutations](#) may function differently in different cancers. The MGH team first set out to determine the percentage of KRAS-mutant tumors that depend on the presence of the mutation for their growth.

Analysis of a large panel of KRAS-mutant tumor cell lines revealed that about half of them die when KRAS-expression is blocked. More detailed analysis of the KRAS-dependent tumors identified several overexpressed genes, and found that blocking expression of a growth-factor-associated enzyme called TAK1 was the most effective way of inducing tumor cell death. The researchers then showed that treatment with a TAK1 inhibitor led to the death of cultured KRAS-dependent [colon cancer](#) cells and reduced the size of KRAS-dependent tumors implanted under the skin of mice. Further exploration revealed that KRAS activation contributes to tumor development through a pathway involving both TAK1 and the signaling molecule BMP, which serves to augment the Wnt pathway that is known to be involved in both embryonic development and cancer.

"Not all genes that are mutated in cancer can be directly targeted by drugs, but this study shows that if you understand the interrelationships between all the signaling pathways in a particular type of tumor, you may uncover a vulnerability that allows you to bypass the 'undruggable target'," says Haber, who is the Kurt J. Isselbacher/Peter D. Schwartz Professor of Oncology at Harvard Medical School and a Howard Hughes Medical Institute Investigator.

"The TAK1 inhibitor we used in this study is not suitable for human administration, but pharmaceutical companies have small-molecule TAK1 inhibitors which have not yet been developed because their potential application was not clear," Haber adds. "Now we need to establish dosage levels where these or related drugs can work against KRAS-dependent colon cancers without being toxic. Those studies, combined with better understanding of the mechanisms underlying this pathway and the consequences of its suppression, will bring us closer to planning for clinical trials."

Provided by Massachusetts General Hospital

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