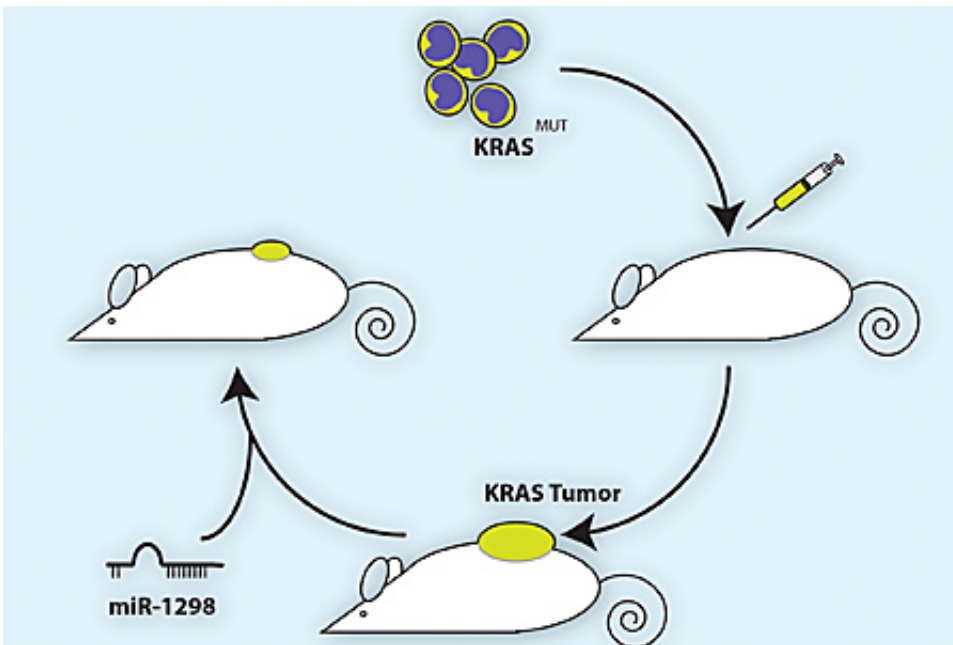


MicroRNA specifically kills cancer cells with common mutation

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Using a mouse model, Tariq Rana, PhD, and colleagues discovered that microRNA miR-1298 specifically kills cancer cells with a common mutation in the *KRAS* gene. Credit: UC San Diego Health

Approximately 20 percent of all human cancers have mutations in a gene called *KRAS*. *KRAS*-mutant cancers are among the most difficult to treat, with poor survival and resistance to chemotherapy. Researchers at University of California San Diego School of Medicine and Moores Cancer Center used microRNAs—small pieces of genetic material—to systematically inhibit thousands of other genes to find combinations that

are specifically lethal to cancer cells driven by a *KRAS* mutation.

The study, published October 3 in *Cancer Research*, provides new information about *KRAS*-driven cancers and offers a potential therapeutic target for their eradication.

"For decades researchers have tried to directly inhibit *KRAS* activity, but there are no well-defined binding pockets in the protein that we can target with small-molecule drugs," said senior author Tariq Rana, PhD, professor of pediatrics at UC San Diego School of Medicine and Moores Cancer Center. "Instead of trying to deter *KRAS* itself, we took the approach of looking for other molecules that, when inhibited, are lethal to cells only when *KRAS* is also mutated."

To do this, Rana and team used microRNAs, small pieces of genetic material similar to DNA. MicroRNAs don't encode proteins. Instead, microRNAs bind messenger RNAs that do encode proteins, inhibiting their translation or hastening their degradation. Normal cells use microRNAs to help control which genes are turned on or off at different times. MicroRNAs tend to be less active in [cancer cells](#).

In this study, the researchers created a library of more than a thousand human microRNA mimics, each with a different sequence and capable of binding different messenger RNA targets. First, they tested each microRNA on colorectal cells grown in the lab. Half the cells had a *KRAS* mutation that made the protein more active, as is the case in many cancers. The other half had normal *KRAS*. The microRNA sequences that killed only the *KRAS*-mutant cells were then tested again in a panel of lung cancer cell lines with and without *KKRAS* mutations.

From this screen, one microRNA in particular stood out for its ability to suppress *KRAS*-dependent cell growth in both colorectal and [lung cancer cells](#): miR-1298. MicroRNA-1298 inhibits two proteins in cancer cells,

FAK and LAMB3. When the researchers silenced either of these proteins, they saw the same effect as adding miR-1298—*KRAS*-driven cancer cells stopped growing.

In human lung cancer tissue samples, Rana and team discovered that elevated LAMB3 levels were associated with poorer survival for patients with *KRAS* mutations. The researchers looked at data from a group of 259 [lung cancer](#) patients for whom *KRAS* status and survival outcome were known. Of those, 143 were *KRAS*-positive and 116 were *KRAS*-negative. After about 10 years, survival probability for *KRAS*-positive patients with high LAMB3 levels was approximately 20 percent, compared to approximately 60 percent for *KRAS*-positive patients with low LAMB3.

"This clinical finding suggests LAMB3 could be used as a prognostic biomarker, and underscores LAMB3's potential as a therapeutic target for *KRAS*-driven cancers," Rana said. "What's more, it highlights miRNAs as important tools for probing complex biological processes, identifying new therapeutic targets and developing potential new RNA-based therapeutics."

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More information: Y. Zhou et al. miR-1298 Inhibits Mutant *KRAS*-Driven Tumor Growth by Repressing FAK and LAMB3, *Cancer Research* (2016). [DOI: 10.1158/0008-5472.CAN-15-2936](https://doi.org/10.1158/0008-5472.CAN-15-2936)

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