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A CRISPR-Cas13a system for efficient and specific therapeutic targeting of mutant KRAS for pancreatic cancer treatment

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Abstract

Mutant KRAS is a known driver oncogene in pancreatic cancer. However, this protein remains an “undruggable” therapeutic target. Inhibiting mutated KRAS expression at the mRNA level is a potentially effective strategy. Recently, a novel CRISPR-Cas effector, Cas13a has been reported to specifically knock down mRNA expression under the guidance of a single CRISPR-RNA in mammalian cells. Here we demonstrate that the CRISPR-Cas13a system can be engineered for targeted therapy of mutant KRAS in pancreatic cancer. In initial screening, we show that the bacterial Cas13a protein and crRNA significantly knock down mutant KRAS mRNA expression, identifying a CRISPR-Cas13a system that can induce up to a 94% knockdown efficiency. Introducing a single mismatch into the crRNA-target duplex enabled the CRISPR-Cas13a system to specifically recognize KRAS-G12D mRNA with no detectable effects on wild-type KRAS mRNA. More importantly, CRISPR-Cas13a-mediated KRAS-G12D mRNA knockdown potently induced apoptosis *in vitro* and elicited marked tumor shrinkage in mice. Our work describes an optimization strategy for the development of a CRISPR-Cas13a system to affect efficient and specific knockdown of the oncogenic mRNA, establishing the CRISPR-Cas13a system as a flexible, targeted therapeutic tool.

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