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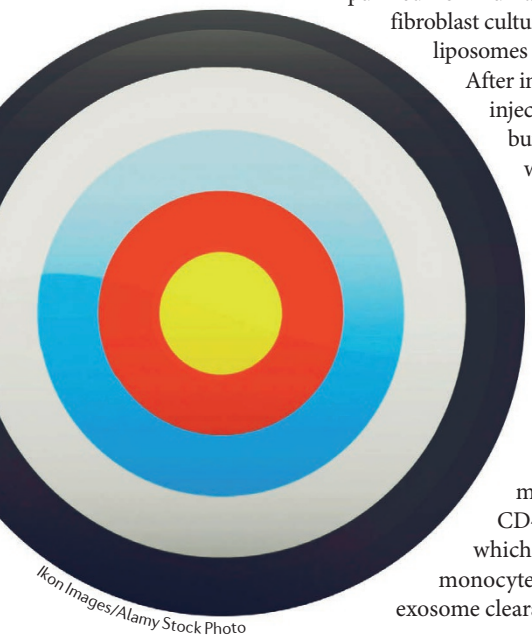
CANCER

RNA-based approaches target KRAS

Activating mutations in the *KRAS* oncogene commonly occur in human tumours and are associated with cancer initiation, metastasis and poor prognosis. Despite significant effort, direct and specific therapeutic targeting of *KRAS* has so far proved elusive. Two new papers now report the use of RNA-based approaches to reduce *KRAS* expression in mouse models of pancreatic and lung cancer, resulting in tumour regression and increased survival.

Previous studies have demonstrated the potential for RNA-based approaches to target *KRAS* in cancer models; however, achieving efficient delivery has been a major challenge so far. Kalluri and colleagues therefore explored whether exosomes — secreted vesicles that enable intercellular communication — can function as efficient carriers of short interfering RNA (siRNA) to tumours.

First, the authors electroporated siRNA into exosomes (iExosomes) purified from human foreskin fibroblast cultures, as well as into liposomes (iLiposomes). After intraperitoneal injection, iExosomes, but not iLiposomes, were detected in the circulation of mice. This enhanced retention of exosomes in the circulation was likely due to the presence of integrin-associated transmembrane protein CD47 on exosomes, which suppressed monocyte-mediated exosome clearance.



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Importantly, iExosomes containing siRNA targeting *KRAS*^{G12D} (a common mutation found in human pancreatic cancer), significantly reduced *KRAS*^{G12D} mRNA, resulting in suppression of RAS activity, impaired cell proliferation and enhanced apoptosis in a human pancreas ductal adenocarcinoma cell (PDAC) line.

Next, the authors investigated the therapeutic utility of iExosomes in mouse models of pancreatic cancer. In mice with *Kras*^{G12D}-expressing orthotopic tumours, intraperitoneal injections of iExosomes suppressed tumour *Kras*^{G12D} expression and downstream KRAS signalling, reducing tumours to nearly undetectable levels after 30 days of treatment. iLiposomes also blunted tumour growth but to a much lesser extent than iExosomes, whereas control mice exhibited extensive tumour burden.

Similarly, iExosome treatment of genetically engineered pancreatic cancer mouse models (KTC and KPC mice) exhibited antitumour efficacy with increased survival, without signs of cytotoxicity. iExosomes also suppressed PDAC progression in the advanced, highly metastatic KPC689 orthotopic tumour setting, increasing survival and limiting metastasis.

Meanwhile, Macleod and colleagues used an antisense oligonucleotide (ASO)-based approach to target *KRAS* in lung cancer. They developed AZD4785, a *KRAS*-targeting ASO with a novel chemistry: 2′-4′-constrained ethyl (cEt) modifications that enhance potency and eliminate the need for any complex delivery formulation.

The authors first demonstrated that AZD4785 potently and selectively downregulates wild-type and mutant *KRAS* mRNA and protein levels in a panel of carcinoma cell lines, while selectively inhibiting the proliferation of tumour cells expressing mutant *KRAS*, demonstrating their *KRAS* dependency.

In vivo, in the NCI-H358 *KRAS*^{G12C}-mutant and NCI-H1944 *KRAS*^{G13D}-mutant lung cancer xenograft mouse models, systemic delivery of AZD4785 downregulated *KRAS* mRNA in tumour tissue, reduced downstream effector pathway activity and achieved a tumour growth inhibition (TGI) of 72% and 80%, respectively, compared with vehicle-treated mice. In both mouse models, treatment with AZD4785 delayed the time to reach the surrogate survival end point of an increase in tumour size of fourfold compared with the control groups.

Furthermore, in the LXFA 983 lung cancer patient-derived xenograft model that carries a *KRAS*^{G12C} mutation, systemic delivery of AZD4785 reduced *KRAS* expression, achieved a 95% TGI and delayed the time to reach the surrogate survival end point compared with control mice.

Notably, despite substantial knockdown of *KRAS* mRNA and protein levels in many tissues, studies in both mice and monkeys revealed that *KRAS*-specific cEt ASOs were not associated with any adverse effects. AZD4785 is currently in a phase I trial in patients with *KRAS*-mutant solid tumours.

Together, these studies demonstrate the potential of RNA-based approaches to effectively target *KRAS* in cancer.

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ORIGINAL ARTICLES Kamerkar, S. *et al.* Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* **546**, 498–503 (2017) | Ross, S. J. *et al.* Targeting KRAS-dependent tumors with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS. *Sci. Transl Med.* **9**, eaal5253 (2017)