ANTICANCER DRUGS

Turning cancer off

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Eukaryotic translation initiation factor 4E (EIF4E), an essential component in the protein translation machinery, is involved in a wide range of cancers, making it an attractive anticancer target. However, the development of small-molecule inhibitors that directly interfere with the binding of EIF4E to mRNA has proved challenging. Now, Graff and colleagues, reporting in the *Journal of Clinical Investigation*, provide the first *in vivo* evidence of the feasibility of EIF4E-targeted therapy for cancer by using an alternative strategy: the development of EIF4E-specific antisense oligonucleotides (ASOs).

In tumours, elevated EIF4E function results from the overexpression of *EIF4E* itself or increased phosphatidylinositol 3-kinase (PI3K), AKT or mammalian target of rapamycin (mTOR) signalling. The increased EIF4E function leads to the preferential enhancement of potent regulatory growth proteins such as cyclin D1, and increases ribosome loading of mRNAs that are involved in malignancy, such as MYC and vascular endothelial growth factor (VEGF).

To specifically target EIF4E the authors used ASOs, which work by recognizing and hybridizing to target mRNA to trigger ribonuclease H-mediated RNA destruction. Five 2-methoxyethyl-modified bases were attached to the ASOs to increase their potency, nuclease resistance and tissue half-life, which have been limitations of earlier generations of ASOs.

In vitro, ASOs targeting *EIF4E* reduced malignancy-related proteins and induced apoptosis in a range of cancer cells. They also decreased the formation of vessel-like structures in human umbilical vascular endothelial cells, which suggests that lowering of EIF4E levels might also reduce the response of cells to angiogenic stimuli.

Next, the authors investigated the effects of ASOs *in vivo*. Injection into nude mice bearing a human breast cancer or prostate cancer xenograft resulted in 65% reduction in *EIF4E* expression in the breast xenograft and 56% reduction in the prostate xenograft, manifesting in the dramatic suppression of growth of these tumours.

Importantly, further studies of the ASOs indicated that they were well-tolerated. When ASOs that target both human and mouse EIF4E were injected into non-tumour bearing mice, there was no appreciable change in body mass, liver mass, spleen mass or liver transaminase levels compared with mice treated with saline or a non-silencing ASO. This was in spite of a reduction of up to 80% in *EIF4E* RNA expression in these mice.

Overall, these data indicate that tumour tissues may be more susceptible to reductions in EIF4E levels than normal tissues. This promising demonstration of the feasibility of specifically targeting EIF4E for the treatment of human malignancies has led to the advancement of EIF4E-specific ASOs to clinical trials.

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ORIGINAL RESEARCH PAPER Graff, J. R. *et al.* Therapeutic suppression of translation initiation factor eIF4E expression reduces tumor growth without toxicity. *J. Clin. Invest.* **117**, 2638–2648 (2007)
FURTHER READING Hennessy, B. T. *et al.* Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nature Rev. Drug Disc.* **4**, 988–1004 (2005)