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THERAPY

Implementing interference

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URLs
Birc5
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=332

RNA interference has become an invaluable tool in biological research, and could also become a powerful therapeutic modality. Challenges in developing small interfering RNA (siRNA)-based therapies include the efficient delivery of the siRNA to the target tissue and the non-invasive assessment of this delivery. Anna Moore and colleagues have developed a dual-purpose probe that enables both tumour delivery and imaging of siRNA.

The probe consists of magnetic nanoparticles (MN), which allow visualization by magnetic resonance imaging (MRI), labelled with Cy5.5 dye, to also enable near-infrared *in vivo* optical imaging (NIRF). These imaging moieties are conjugated to an siRNA duplex targeting the gene of interest, and also to myristoylated polyarginine peptides (MPAPs) that increase translocation across the cell membrane.

The authors first tested a probe targeting green fluorescent protein (GFP) (MN–NIRF–siGFP) in 9L glioma cells that expressed either GFP (9L-GFP cells) or, as a control, red fluorescent protein (9L-RFP cells). *In vitro*, the MPAPs increased the cellular uptake of MN-NIRF-siGFP, as visualized by increased Cy5.5 fluorescence. A concentration-dependent decrease in green fluorescence in the 9L-GFP cells was observed, but no change in red fluorescence in the 9L-RFP cells occurred.

Is MN-NIRF-siGFP effectively delivered and active *in vivo*? MRI and NIRF imaging of mice bilaterally implanted with 9L-GFP and 9L-RFP tumours indicated that injected MN-NIRF-siGFP accumulated in tumour tissue. Efficient silencing of GFP after 48 hours was confirmed by the loss of green fluorescence in 9L-GFP tumours, but no change in red fluorescence in 9L-RFP tumours. This was further confirmed by the quantitative reverse transcription PCR of *Gfp* mRNA levels. In addition, no toxicity to the mice was observed, and the effects on GFP fluorescence did not appear to be a result of MN-NIRF-siGFP cytotoxicity.

The authors also developed a potentially therapeutic siRNA probe targeting the anti-apoptotic gene *Birc5*, which encodes survivin (MN-NIRF-siSurvivin). They administered MN-NIRF-siSurvivin twice a week for two weeks to nude mice bearing subcutaneous human colorectal carcinoma tumours derived from LS174T cells. As with MN-NIRF-siGFP, MN-NIRF-siSurvivin efficiently accumulated in tumours and silenced survivin, resulting in an increase in apoptosis compared with the nanoparticle alone (without an siRNA) or a mismatch control.

These probes accumulated in tumours without a tumour-targeting moiety, probably owing to the increased permeability of tumour blood vessels. However, heterogeneous accumulation was observed, which is consistent with local differences in factors such as permeability within a tumour. Therefore, tumour-specific targeting might further increase efficacy.

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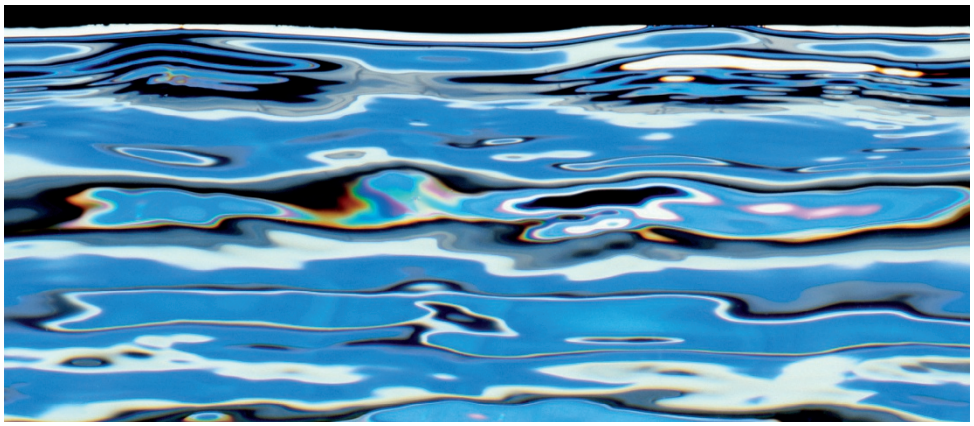

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