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PHOTODISC

ANTISENSE THERAPEUTICS

Nuclear RNA more susceptible to knockdown

The therapeutic potential and efficacy of antisense oligonucleotides (ASOs) has been hampered by their limited intracellular uptake. Now, Wheeler *et al.* show that mutant RNA that is retained in the nucleus — which occurs in the hereditary genetic disease myotonic dystrophy, for example — is particularly sensitive to ASO-mediated knockdown. Indeed, in a transgenic mouse model of myotonic dystrophy type 1 (DM1), ASO-mediated knockdown of the mutant RNA produced sustained improvements in various characteristics of the disease that lasted up to 1 year after stopping treatment.

ASOs exert their effects by inducing RNase H-mediated degradation of the mutant RNA to which they are targeted. Previous studies have indicated that this process is likely to occur mainly in the nucleus, and so the authors of this study proposed that by targeting transcripts that are confined in the nucleus the efficacy of ASOs could be enhanced.

They used the *HSA*^{LR} mouse model of DM1 to test this hypothesis, in which the mice express an expanded CUG repeat in the 3′ untranslated region (UTR) of human skeletal actin (*ACTA1*). In humans, the CUG repeat in DM1 occurs in the 3′ UTR of dystrophia myotonica protein kinase (*DMPK*). The ASOs used in this study were modified to enhance biostability and RNase H activity (termed MOE gapmer ASOs).

Subcutaneous injection of candidate ASOs twice a week for 4 weeks into *HSA*^{LR} mice reduced the level of mutant RNA in hindlimb muscles in a dose-dependent manner, resulting in improvements in muscle electrical control and in the muscle transcriptome (which is perturbed in DM1 because of the toxic effects of the mutant RNA in the nucleus). Further experiments confirmed that these effects were due to the enhanced sensitivity of expanded CUG repeats to ASO-mediated knockdown and not to a general increase in muscle-specific uptake of ASOs, as ASO accumulation in muscle in *HSA*^{LR} mice was similar to that in wild-type mice.

They then tested the concept with another type of RNA that is retained in the nucleus: metastasis-associated lung adenocarcinoma transcript 1 (*Malat1*). A greater than 80% knockdown of *Malat1* in muscle was seen in wild-type and *HSA*^{LR} mice when they were injected with *Malat1*-specific ASOs. Finally, the therapeutic application of this strategy was also demonstrated, as ASOs targeted to *DMPK* in transgenic mice expressing this mutant RNA (800 CUG repeats) produced significant *DMPK* knockdown.

Together, the results of this study suggest that ASOs are particularly efficacious in treating genetic disorders in which mutant nuclear-retained RNA causes toxic effects.

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ORIGINAL RESEARCH PAPER Wheeler, T. M. *et al.* Targeting nuclear RNA for *in vivo* correction of myotonic dystrophy. *Nature* **488**, 111–115 (2012)
FURTHER READING Muntoni, F. & Wood, M. J. A. Targeting RNA to treat neuromuscular disease. *Nature Rev. Drug Discov.* **10**, 621–637 (2011)