ANTISENSE THERAPEUTICS

Systemic reawakening of a silent gene to improve survival in SMA

Spinal muscular atrophy (SMA), a degenerative neuromuscular disease that is caused by a genetic defect in the survival of motor neuron 1 (*SMN1*) gene, is a leading cause of infant mortality. There is no effective treatment at present. Reporting in *Nature*, Krainer and colleagues now show that subcutaneous (s.c.) administration of an antisense oligonucleotide can increase median survival in a mouse model of severe SMA by up to 25-fold.

Current drug development approaches for SMA focus on molecular targets in the lower spinal cord, as an impairment of motor neuron function in the central nervous system (CNS) is the most pronounced pathology in SMA. One of these approaches is the use of antisense oligonucleotides to 'reawaken' a human *SMN1* paralogue, *SMN2*, which is normally silent due to exon skipping.

Intracerebroventricular (i.c.v.) administration of one such antisense oligonucleotide, ASO-10-27, had previously been shown to modestly increase survival in a mouse model of severe SMA. However, it has become apparent that non-CNS pathologies, including cardiovascular defects, can also have a role in this disease. The authors combined systemic s.c. and i.c.v. administration of ASO-10-27 to newborn *Smn1*-deficient pups that were transgenic for *SMN2*, and found that median survival increased from 10 days (control) and 16 days (i.c.v. delivery only) to 108 days (s.c. delivery) and 173 days (combination of i.c.v. and s.c. delivery). Using s.c. administration at higher doses, median survival was increased to 248 days, with 2 out of 18 mice that were treated with the highest doses still alive and active after more than 500 days.

An analysis of *SMN2* splicing changes induced by ASO-10-27 showed that systemic treatment led to functional restoration of the SMN protein in many tissues. There were also moderate splicing changes in the CNS after s.c. administration, which could be due to the incomplete closure of the blood–brain barrier in neonates and/or retrograde transport of the oligonucleotide in neurons. The authors speculate that this contributes to the extended survival, similarly to combined s.c. and i.c.v. treatment.

The fact that all mice with SMA are small prompted the authors to examine the growth hormone–insulin-like growth factor 1 (IGF1) axis. They found that *Smn1*-deficient mice, compared to heterozygous littermates, had undetectable levels of IGF1 and that s.c. administration of ASO-10-27 restored IGF1 levels. Although the absence of SMN did not affect IGF1 directly, it led to a reduction in IGF-binding protein acid labile subunit (IGFALS), a protein that extends the half-life of IGF1 in circulation. As IGF1 is involved in cardiac development and function, and is neurotrophic, it is possible that a deficiency in IGF1 contributes to the pathogenesis of severe SMA.

The authors point out that it will be crucial to determine the extent to which SMA mouse models accurately mimic human SMA, but this study implies that drug delivery approaches that target both sides of the blood–brain barrier may be significantly more effective, and that ASO-10-27 is a promising drug candidate.

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ORIGINAL RESEARCH PAPER Hua, Y. *et al.* Peripheral SMN restoration is essential for long-term rescue of a severe spinal muscular atrophy mouse model. *Nature* **478**, 123–126 (2011)