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NEURODEGENERATIVE DISEASE

C9orf72 RNA foci—a therapeutic target for ALS and FTD?

Hexanucleotide repeat expansions in the *C9orf72* gene have emerged as an important cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. In a new study led by John Ravits and Don Cleveland at the University of California, San Diego, sense and antisense *C9orf72* RNA foci were identified in cells from patients with this repeat expansion, and could represent targets for oligonucleotide-based therapy.

"A key issue was whether the expansion caused RNA-mediated toxicity or loss of gene function," explains Ravits. "A hallmark of RNA-mediated toxicity is RNA foci, and finding these foci, characterizing them and using them as a key read-out for antisense oligonucleotide (ASO) therapy development was an immediate path."

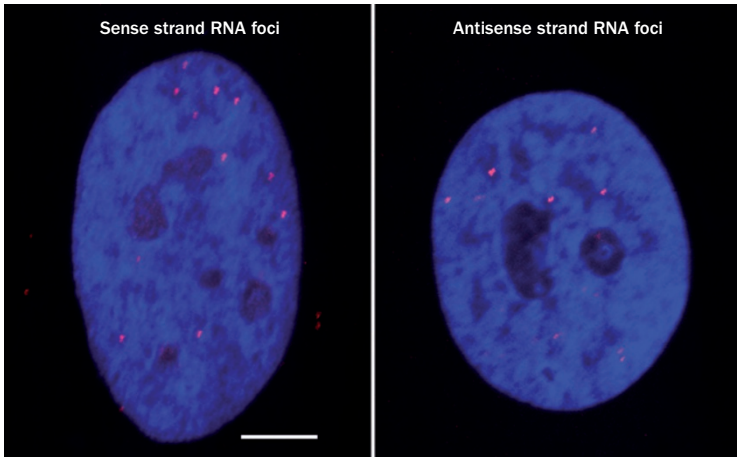
Using fluorescence *in situ* hybridization, Michael Baughn and colleagues discovered GGGGCC-containing RNA foci in a variety of cell types—including fibroblasts, neurons and glia—from patients with the *C9orf72* hexanucleotide expansion. The foci were predominantly localized to the nucleus, although a small proportion were cytoplasmic.

Clotilde Lagier-Tourenne and co-workers assessed the capacity of ASOs to degrade RNA foci in fibroblasts from individuals carrying the *C9orf72* expansion. ASOs that specifically targeted the expansion-containing RNA were found to reduce the number of foci without affecting overall *C9orf72* RNA levels. Expansion-specific ASOs were also effective at depleting RNA foci in an *in vivo* mouse model; again, overall *C9orf72* RNA levels were unchanged, and the intervention was well-tolerated. The team concluded that the expansion confers a toxicity unrelated to loss of *C9orf72* function.

Intriguingly, the researchers found that both the sense and antisense strands of *C9orf72* were transcribed in fibroblasts from patients with the repeat expansion. This finding suggests that ASOs might need to target both sense and antisense RNA foci to be therapeutically effective.

"The selective silencing of a toxic RNA is the Holy Grail of gene silencing approaches, and we showed that we had accomplished it," says Lagier-Tourenne. "ASOs offer a compelling new approach to complex neurodegenerative diseases, and ALS will be a very important testing ground," adds Ravits.

Heather Wood



Cells from individuals with GGGGCC expansions in the *C9orf72* gene show sense and antisense *C9orf72* RNA foci, as visualized by fluorescence *in situ* hybridization. Scale bar, 5μm. Image courtesy of J. Ravits.

Original article Lagier-Tourenne, C. *et al.* Targeted degradation of sense and antisense *C9orf72* RNA foci as therapy for ALS and frontotemporal degeneration. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1318835110

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