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RNA-mediated Disease Mechanism of Spinocerebellar Ataxia Type 10

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The pathogenic mechanisms of myotonic dystrophy types 1 and 2 (DM1 and DM2) have primarily been attributed to microsatellite repeat-expansion RNA mediating trans-dominant gain of function. Similar gain-of-function mechanisms by repeat-expansion RNA have been implicated in a growing number of dominant non-coding expansion disorders, including fragile X tremor ataxia syndrome (FXTAS), spinocerebellar ataxia type 8 (SCA8), spinocerebellar ataxia type 12 (SCA12), spinocerebellar ataxia type 31 (SCA31) and Huntington's disease like 2 (HDL2), in which expanded repeats are located within non-coding regions.

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant neurodegenerative disorder caused by unstable expansion of ATTCT repeats in intron 9 of *ATXN10* gene on chromosome 22 q13.31. The mechanism by which the ATTCT expansion causes the SCA10 phenotype is still unknown. We have shown that the expansion mutation does not alter *ATXN10* expression at the mRNA or protein level, indicating that neither a gain nor a loss of function of ataxin-10 protein is likely the pathogenic mechanism of SCA10. Here we present data suggesting that, in SCA10, expanded AUUCU RNA triggers neuronal dysfunctions. We detected intranuclear AUUCU inclusions in SCA10 cells by RNA-FISH, similar to other non-coding repeat expansion disorders. Furthermore, we characterized their intranuclear localization and nucleic acid contents, demonstrating that the inclusions are located at perinucleolar compartments and enriched for the AUUCU expansion, but not intronic flanking sequences. We identified several RNA-binding proteins interacting with expanded AUUCU repeats and studied their co-localization with the inclusions. Interestingly, one of these proteins, which is a splicing factor, misregulated the expression of its neurally enriched paralog at the level of alternative splicing.

Although SCA10 differs in the key protein and downstream mechanisms that lead to neurodegenration, its pathogenic mechanism resembles DM1 and DM2 in that non-coding expanded repeat RNA accumulates in cells and sequesters key protein(s).

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