ABSTRACT

Transcriptional dysregulation in SCA3

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Ataxin-3 (ATXN3) the disease protein in spinocerebellar ataxia type 3 (SCA3) can act as a transcriptional repressor through inhibition of histone acetyltransferases (HATs) and blocking access of HATs to histone acetylation sites suggesting that transcriptional dysregulation contributes to SCA3 pathogenesis. Indeed, cell models of SCA3 showed differential expression of several genes encoding transcription factors, inflammatory cytokines and cell surface proteins prior to cell death. Also, in cerebella of transgenic SCA3 mice, altered expression of genes involved in glutamatergic and calcium signalling, GABA receptor subunits, transcription factors and heat shock proteins regulating neuronal survival and differentiation occurs before the onset of neurological symptoms. On the one hand, transcriptional dysregulation in SCA3 may be caused by depletion of transcriptional components into nuclear inclusions formed by mutant ATXN3. On the other hand, polyQ expansion in ATXN3 may alter its normal function in transcriptional regulation.

Previously, we found that ATXN3 binds to target genes and represses transcription by interaction with transcriptional corepressors and histone deacetylation whereas mutant ATXN3 has a reduced ability to form deacetylating repressor complexes at target genes. Moreover, ATXN3 interacts with specific transcription factors and synergistically enhance transcription of target genes in response to oxidative stress compared to a reduced capability of mutant ATXN3 to activate transcription at target genes. These findings suggest that ATXN3 apart from its role in protein quality control is a component of transcriptional complexes regulating the activity of specific genes in response to different stimuli. To identify target genes of ATXN3, we undertook chromatin immunoprecipitation sequencing of genomic fragments bound by ATXN3 using induced pluripotent stem cell-derived neurons from control and SCA3 patients. Currently, we are analyzing identified ATXN3-bound genomic regions to distinguish genes and pathways modulated by normal and mutant ATXN3.