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Authors

Bartelt, Luke C
Switonski, Pawel M
Adamek, Grażyna
et al.

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ATAXIA

Dysregulation of zebrin-II cell subtypes in the cerebellum is a shared feature across polyglutamine ataxia mouse models and patients

Luke C. Bartelt[1,2,3], Pawel M. Switonski[4], Grażyna Adamek[4], Fabiana Longo[2], Juliana Carvalho[3], Lisa A. Duvick[5], Sabrina I. Jarrah[6], Hayley S. McLoughlin[6], Daniel R. Scoles[7], Stefan M. Pulst[7], Harry T. Orr[5], Court Hull[8], Craig B. Lowe[3]*, Albert R. La Spada[2,9,10]*

Spinocerebellar ataxia type 7 (SCA7) is a genetic neurodegenerative disorder caused by a CAG-polyglutamine repeat expansion. Purkinje cells (PCs) are central to the pathology of ataxias, but their low abundance in the cerebellum underrepresents their transcriptomes in sequencing assays. To address this issue, we developed a PC enrichment protocol and sequenced individual nuclei from mice and patients with SCA7. Single-nucleus RNA sequencing in SCA7-266Q mice revealed dysregulation of cell identity genes affecting glia and PCs. Specifically, genes marking zebrin-II PC subtypes accounted for the highest proportion of DEGs in symptomatic SCA7-266Q mice. These transcriptomic changes in SCA7-266Q mice were associated with increased numbers of inhibitory synapses as quantified by immunohistochemistry and reduced spiking of PCs in acute brain slices. Dysregulation of zebrin-II cell subtypes was the predominant signal in PCs of SCA7-266Q mice and was associated with the loss of zebrin-II striping in the cerebellum at motor symptom onset. We furthermore demonstrated zebrin-II stripe degradation in additional mouse models of polyglutamine ataxia and observed decreased zebrin-II expression in the cerebella of patients with SCA7. Our results suggest that a breakdown of zebrin subtype regulation is a shared pathological feature of polyglutamine ataxias.

INTRODUCTION

CAG-polyglutamine (polyQ) repeat diseases are a group of nine genetic neurodegenerative disorders caused by the expansion of a CAG trinucleotide repeat in a coding exon of different genes (*1*). The CAG-polyQ repeat diseases share many common features of protein aggregation and selective neuronal vulnerability but differ in their clinical manifestations and affected brain regions (*2*). The molecular mechanisms of CAG-polyQ neurodegeneration are poorly understood; however, there are highly representative mouse models (*3*–*7*). A mouse model for spinocerebellar ataxia type 7 (SCA7) was generated through knock-in of 266 CAG repeats in the endogenous mouse ataxin-7 locus, and these SCA7-266Q mice develop early onset, rapidly progressive cerebellar and retinal degeneration (*3*), akin to juvenile-onset SCA7 in human patients (*8*–*10*).

One emergent theme gleaned from experiments in polyQ mouse models is the shared impact on transcription regulation, such that these disorders are categorized as "transcriptionopathies" (*11*). This impact on transcription is mediated by the nuclear accumulation of toxic polyQ proteins (*5*), which interferes with transcription regulatory proteins, such as TATA-binding protein and CREB-binding protein (*12*, *13*). Transcriptional mechanisms are particularly relevant in SCA7, given that the ataxin-7 protein performs its primary role in the nucleus as a core component of the STAGA transcription coactivator complex (*14*, *15*), which facilitates genome-wide RNA polymerase II–mediated transcription (*16*). The STAGA complex has several functional domains, including a histone acetyltransferase module that catalyzes deposition of the activating H3K9ac mark and a deubiquitinase (DUB) module that removes H2BK120ub modifications, tuning both the structural and transcriptional properties of target genes (*17*–*19*). Ataxin-7 sits in the DUB module, and polyQ repeat expansion leads to structural impairments of the STAGA complex and alters global distribution of H3K9ac and H2BK120ub modifications, resulting in widespread transcription dysregulation (*20*–*22*). The transcriptional signatures associated with SCA7 cerebellar degeneration correlate with SCA1 and SCA2, implying common transcriptional impacts by different polyQ-expanded ataxin proteins, despite no overlap in their currently known functions (*23*–*25*). The mechanisms linking these highly shared patterns of gene expression in polyQ cerebellar degeneration remain unknown.

The cerebellum is a highly organized and complex region of the central nervous system (CNS) with more than 15 distinct cell types coordinating together to maintain proper cerebellar function (*26*). The action of these cells is organized around the Purkinje cell (PC), which is among the largest and most metabolically active neurons in the CNS (*27*, *28*) and serves as the sole output neuron of the cerebellar cortex (*29*). PC dysfunction and neurodegeneration are central to the development of ataxic phenotypes in SCA7 mice and human patients (*30*). However, numerous studies have also demonstrated the critical involvement of Bergmann glia and cerebellar astrocytes in SCA7 PC degeneration, indicating a non–cell-autonomous contribution

[1]University Program in Genetics & Genomics, Duke University Medical Center, Durham, NC 27710, USA. [2]Departments of Pathology & Laboratory Medicine, Neurology, Biological Chemistry, and Neurobiology & Behavior, University of California, Irvine, Irvine, CA 92697, USA. [3]Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC 27710, USA. [4]Department of Neuronal Cell Biology, Institute of Bioorganic Chemistry, Polish Academy of Sciences, 61-704 Poznan, Poland. [5]Institute for Translational Neuroscience, and Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA. [6]Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA. [7]Department of Neurology, University of Utah, Salt Lake City, UT 84132, USA. [8]Department of Neurobiology, Duke University School of Medicine, Durham, NC 27710, USA. [9]Department of Neurology, Duke University School of Medicine, Durham, NC 27710, USA. [10]UCI Center for Neurotherapeutics, University of California, Irvine, Irvine, CA 92697, USA.
*Corresponding author. Email: alaspada@uci.edu; (A.R.L.S.); craig.lowe@duke.edu (C.B.L.)