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Emerging Pathogenic Pathways in the Spinocerebellar Ataxias

Kerri M. Carlson[1], **J. Michael Andresen**[1,2], and **Harry T. Orr**[1,2,3,*]

Kerri M. Carlson: carl2327@umn.edu; J. Michael Andresen: andre387@umn.edu; Harry T. Orr:

[1]Institute of Human Genetics, University of Minnesota, Minneapolis, MN 55455

[2]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455

[3]Department of Biochemistry, Biophysics, and Molecular Biology, University of Minnesota, Minneapolis, MN 55455

I. Summary

The spinocerebellar ataxias (SCAs) are diseases characterized by neurodegeneration of the spinocerebellum. To date, twenty-eight autosomal-dominant SCAs have been described and seventeen causative genes identified. These genes play a role in a broad range of cellular processes. Recent studies focused on the wild type and pathogenic functions of these genes implicate both gene expression and glutamate- and calcium-dependent neuronal signaling as important pathways leading to cerebellar dysfunction. Understanding how these genes cause disease will allow a deeper understanding of the cerebellum in particular as well as neurodegenerative disease in general.

I. Introduction

Ataxia, borrowed from a Greek word meaning "loss of order," is used clinically to describe aberrant regulation of limb movements with poor coordination between limbs. Cerebellar ataxia is the most common form of ataxia and is caused by dysfunction either within the cerebellum or in its afferent and efferent pathways. Spinocerebellar ataxia (SCA) is caused by anomalous function of the spinocerebellum, the part of the cerebellar cortex that receives somatosensory input from the spinal cord.

Although there are sporadic forms of SCA, the term is most often used to refer to the hereditary forms, and in particular the autosomal dominant forms (the focus of this review). The autosomal dominant SCAs are typically late-onset, progressive, and often fatal neurodegenerative disorders. They are characterized by cerebellar ataxia and frequently other symptoms related to dysfunction of additional neural pathways [1,2]. Currently, 28 SCAs are recognized (Table 1). Of the most recent additions, SCA29 describes an early-onset, non-progressive form of SCA that is localized to chromosome 3p26 where it partially overlaps with the SCA15 region [3]. Analysis suggests there is genetic heterogeneity of SCA29 symptoms due to exclusion of the 3p26 region in one putative SCA29 family [4]. In some cases, it is possible that the described SCA loci represent allelic variants of the same disease. For example, SCA16 was shown to be allelic to SCA15 [5]. Likewise, it is possible that both SCA29 and SCA15 as well as SCA19

*Harry T. Orr (Corresponding author): E-mail: orrxx002@umn.edu.
Address for all authors: Institute of Human Genetics, MMC 206 Mayo, 420 Delaware St SE, Minneapolis, MN 55455, Tel: 612-625-3672, FAX: 612-626-7031

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and SCA22 actually represent allelic variants of the same disease. In contrast, SCA30 is a pure cerebellar ataxia without additional symptoms and localizes to a genomic region (chromosome 4) that does not contain any other SCA genes [6].

II. Cellular Pathways to Ataxia

In the SCAs, the pathways leading to neuronal degeneration are complex and depend on both the wild type function of the protein and the cellular context of the mutation. Recent studies of SCA proteins have led to the identification of some common pathways to ataxia consisting of dysfunction in gene expression, synaptic transmission, and other intracellular signaling pathways.

A. Gene Expression: Transcription and RNA Processing

Correct gene expression requires the integration of numerous activities; these include chromatin remodeling and transcriptional regulation as well as RNA processing, export, translation, and degradation. A number of SCA proteins are known to be nuclear and linked to gene expression, including SCA17, SCA7, and SCA1. In addition, transcriptional dysfunction is a recognized hallmark of many SCAs [7].

SCA17 is caused by polyglutamine expansion in the basal transcription factor TATA binding protein (TBP). Despite the broad role TBP plays in eukaryotic gene transcription, only a small subset of genes are misregulated in SCA17 transgenic mice [8]. *In vitro*, an expanded polyglutamine tract reduces the ability of TBP to dimerize (a regulation mechanism) and increases its binding to the general transcription factor TFIIB. *In vivo*, these altered interactions lead to a depletion of TFIIB at specific gene promoters such as *Hspb1*, a neuroprotective factor important for axonal and neurite integrity [8]. Mutant TBP also has decreased affinity for DNA, which may be relevant to disease pathogenesis [9]. Mice overexpressing expanded TBP with a deletion that prevents DNA binding have a more severe phenotype than mice overexpressing full-length mutant protein. Fragments of TBP lacking the DNA binding domain have been observed in SCA17 transgenic mice suggesting that proteolytic processing of TBP may occur naturally in the cell and be important in SCA17 pathogenesis [9]. Together these studies suggest that mutant TBP leads to transcriptional alterations that impair neuronal function.

In SCA7, a polyglutamine expansion in ataxin-7 (ATXN7) causes disease. ATXN7 is a member of the transcriptional coactivator complexes TFTC (the TATA-binding protein free TAF-containing complex) and STAGA (the SPT3/TAF9 GCN5 complex) that activate transcription in part through histone acetyltransferase (HAT) activity. Because retinal degeneration is a unique feature of SCA7, many studies have focused on the retinal photoreceptors as a means of gaining insight into ATXN7 function. In three different SCA7 mouse models, it is clear that mutant ATXN7 results in the down-regulation of multiple photoreceptor specific genes but the means of this down-regulation differs (Reviewed in [7]). In both yeast and human cell lines, incorporation of mutant ATXN7 into TFTC/STAGA complexes decreases TFTC/STAGA-mediated HAT activity [10,11]. Likewise, a decrease in histone acetylation is observed in mice overexpressing mutant ATXN7 throughout the central nervous system, which is consistent with a decrease in HAT function observed in cell models [11]. In contrast, in both a retinal specific SCA17 transgenic model and in SCA7 knockin mice, the chromatin structure of the rod photoreceptors was decondensed, suggesting histone hyperacetylation [12]. A closer look at the SCA17 transgenic mice demonstrated increased recruitment of the TFTC/STAGA complexes to the promoters of down-regulated genes accompanied by increased acetylation, suggesting that chromatin remodeling affects gene transcription in this model [12]. Although the affect of mutant ATXN7 on TFTC/STAGA function appears to differ in each model studied, it is clear that *in vivo* mutant ATXN7 affects chromatin remodeling and leads to transcriptional down-regulation. In addition to a role in chromatin remodeling, the yeast ATXN7 homolog

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plays a role in RNA metabolism by recruiting the TREX-2 mRNA export complex to the SAGA transcription complex and is perhaps involved in targeting a gene to the nuclear pore complex [13]. Perturbations in this pathway may contribute to SCA7 pathogenesis.

The cellular function of ataxin-1 (ATXN1), the protein mutated in SCA1, remains unclear; however, research implicates ATXN1 in both transcriptional regulation and, more recently, RNA splicing. In mouse cerebellar lysate, ATXN1 is stably associated into two different, large protein complexes: one containing the transcriptional repressor capicua (CIC) [14] and one containing the mRNA splicing factor RBM17 [15]. *In vivo*, more wild type ATXN1 is associated with CIC than with RBM17. In contrast, mutant ATXN1 preferentially associates with RBM17. In an SCA1 knockin model, the presence of mutant ATXN1 leads to both an increase in the large RMB17/ATXN1 complexes and a decrease in the CIC/ATXN1 complexes suggesting that SCA1 pathogenesis is due in part to both a gain and loss of ATXN1 function. First, an increase in RBM17/mutant ATXN1 complexes may lead to aberrant splicing of important genes affecting neuronal function and survival. Second, a decrease in ATXN1/CIC complexes may subsequently lead to reduced function of these transcriptional complexes within the cell [15].

In addition to its interaction with CIC and RBM17, ATXN1 transiently interacts with a number of transcription factors *in vivo*. ATXN1 and RORα have been found together in a complex with the transcriptional regulator Tip60, with which ATXN1 interacts directly [16]. RORα is crucial for Purkinje cell development, and germline mutation of RORα leads to ataxia due to defects in Purkinje cell maturation [17]. In an SCA1 transgenic model, expression of mutant ATXN1 leads to a decrease in both RORα levels and the transcription of a number of RORα regulated genes [16]. Secondly, ATXN1 and RORα are coexpressed in Purkinje cells during a critical time in development, suggesting that developmental defects in Purkinje cell maturation may make Purkinje cells more susceptible to the effects of mutant ATXN1 later in life [16].

Alterations in gene expression are implicated in other SCAs. Ataxin-2 (ATXN2), the mutant protein in SCA2, interacts with poly(A)-binding protein 1 (PABPC1) and can assemble into polyribosomes, suggesting a role for ATXN2 in RNA metabolism [18,19]. In SCA3, nuclear localization of mutant ataxin-3 (ATXN3) in transgenic mice enhanced disease pathogenesis [20]. Likewise, microarray analysis in a different SCA3 model demonstrated transcriptional dysregulation further supporting a role for nuclear dysfunction in SCA3 [21]. ATXN3 is a deubiquitinating enzyme that can bind and edit mixed linkage ubiquitin chains [22]. ATXN3 knockout mice show an increase in ubiquitinated proteins supporting an *in vivo* role for ATXN3 in the ubiquitin/proteasome pathway [23]. In nuclear receptor mediated transcription, a role for the ubiquitin/proteasome pathway in both chromatin remodeling via histone modification and transcriptional regulation has been established (Reviewed in [24] and [25]). Interestingly, ATXN3 has been shown to act as a transcriptional repressor via its interaction with histone deacetylase 3 and the nuclear receptor corepressor (NCoR) [26]. This repressor activity is dependent on its ubiquitin interaction motifs [26], suggesting a link between ATXN3's function in the ubiquitin/proteasome pathway and its role in transcriptional regulation.

B. Synaptic Transmission: Glutamate and Calcium Signaling

Afferent input of Purkinje cells is mediated by glutamate stimulation of ionotropic AMPA-type glutamate receptors (Purkinje cells do not express NMDA-type receptors) as well as metabotropic glutamate receptors. The AMPA receptors cause local depolarization of dendritic spines that leads to activation of voltage-gated calcium channels. Disruptions in these dendritic calcium spikes and downstream action potentials are involved in a number of SCAs, including SCA5, SCA6, SCA13, SCA15, SCA20, and SCA27.

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The voltage-gated calcium channel expressed in Purkinje cells is the type P/Q $Ca_v2.1$, a heterotetramer that includes the CACNA1A subunit. A CAG expansion in *CACNA1A* causes SCA6. Two reports of SCA6 mouse models that knockin the CAG mutation suggest that contrary to previous cell culture experiments, the polyglutamine expansion does not greatly disrupt key aspects of calcium conductance. These data support the hypothesis that SCA6 is caused more by a gain of function rather than a partial loss of function [27,28]. Part of the gain of function may be due to the accumulation of mutant calcium channels leading to an increase in calcium signaling [29]. Alternatively, this toxic gain of function may also be the result of proteolytic cleavage and translocation of the CACNA1A C-terminus (containing the polyglutamine stretch) to the nucleus where it is toxic to the cells [30].

Calcium release is further propagated by release from intracellular stores, particularly the endoplasmic reticulum, which contains the inositol triphosphate (IP3) receptor (ITPR1) calcium channel. Null or missense mutations in *ITPR1* cause SCA15 through a haploinsufficiency mechanism [31]. Loss of ITPR1 function would be expected to dampen propagation of calcium signals.

Two SCA mutations impinge on glutamate signaling just upstream of calcium release. SCA5 is caused by mutations in β-III spectrin (SPTBN2), which stabilizes the EAAT4 (SLC1A6) glutamate transporter at the cell surface [32]. Deleterious mutation in *SPTBN2* would then lead to a decrease in reuptake of glutamate from the synapse and a strengthening of glutamatergic signaling. SCA20 is caused by a chromosomal duplication of 260 kb on chromosome 11q12 [33]. A prominent candidate gene in this genomic region is *DAGLA*, which is highly expressed in Purkinje cell dendritic spines and serves to weaken glutamatergic signaling [33]. Further experiments are necessary to determine whether duplication of *DAGLA* itself is primarily responsible for symptoms or if other genes in the critical region are more important.

Additional SCA mutations alter propagation of action potentials through voltage-gated sodium and potassium channels. SCA13 is caused by mutations in the KCNC3 voltage-gated potassium channel. This channel plays an important role in depolarizing both the dendritic calcium spikes and the somatic sodium spikes in Purkinje cells, as well as being present in granule cells and deep cerebellar neurons [34]. Different mutations in *KCNC3* that cause an increase or a decrease in channel activity are both capable of causing SCA13 [34]. SCA27 is caused by inactivating mutations in *FGF14. Fgf14* null mice mimic the ataxia, suggesting that the (dominant) disease might be due to haploinsufficiency [35]. Studies have demonstrated that *Fgf14* null mice have electrophysiological abnormalities and a loss of expression of the Purkinje cell $Na_v1.6$ voltage-gated sodium channels consistent with a role for FGF14 in stabilizing $Na_v1.6$ [35]. It is interesting to note that loss of function alleles of the SCN8A subunit of $Na_v1.6$ channels also cause an autosomal recessive syndrome that includes cerebellar ataxia [36].

Finally, although the mutant protein in SCA1 acts primarily in the nucleus, downstream glutamate signaling is indirectly dysregulated. This includes downregulation of the SCA genes *ITPR1* and *SPTBN2* as well as additional glutamate or calcium signaling pathway genes: the mGluR1 metabotropic glutamate receptor subunit (*GRM1*), EAAT4 glutamate transporter (*SLC1A6*), the SERCA2 and SERCA3 calcium pumps (*ATP2A2, ATP2A3*), and the CARP regulator of IPTR1 (*CA8*) [16,37].

Although all of the SCA proteins in this group impinge on Purkinje cell dendritic calcium spikes, some mutations are predicted to facilitate calcium spikes and some are predicted to inhibit them. The SCA5 and SCA6 mutations may act by increasing calcium release, while those for SCA15, SCA20 (via DAGLA) and SCA27 would be expected to decrease calcium levels. Finally, different point mutations that cause SCA13 are predicted to have opposing

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effects on calcium. Together these data suggest that misregulation of Purkinje cell firing in either direction (facilitation or inhibition) will have untoward consequences and lead to dysregulated movement.

C. Additional Pathways to Ataxia

While many of the genes mutated in the SCAs play a clear role in gene expression and dendritic signaling, the existence of additional pathways to ataxia indicate the complexity of this phenotype. Three SCA genes are involved in phosphorylation-dependent intracellular signaling. SCA11 is caused by nonsense mutations in tau tubulin kinase (*TTBK2*), which is expressed abundantly in the brain and phosphorylates the microtubule associated protein tau [32]. Pathogenic mutations in *TTBK2* lead to a reduction in *TTBK2* transcript levels suggesting that loss of *TTBK2* function may have important consequences for tau regulation and neuronal integrity [38].

Similarly, a CAG repeat expansion in the 5′UTR *of PPP2R2B* causes SCA12. *PP2R2B* encodes BB1 and BB2, regulatory subunits of protein phosphates A (PP2A) involved in determining subcellular localization and substrate specificity of the enzyme. The pathogenic consequences of the SCA12 mutation remain unknown, though PP2R2B may play a role in recruiting PP2A to the outer mitochondrial membrane, where it helps to regulate mitochondrial morphology and promote apoptosis [39].

Multiple mutations in the brain-specific serine/threonine kinase PKCγ can cause SCA14 [40]. Both cell culture experiments and an SCA14 transgenic mouse model demonstrate that these mutations in PKCγ alter the downstream signaling ability of PKCγ [41,42].

In addition to a role in RNA metabolism, recent studies have begun to shed light on additional functions of ATXN2 in the cytoplasm. ATXN2 is predominantly cytoplasmic and associates with endophilin A1/A3 at the endoplasmic reticulum and plasma membrane and may be involved in endocytosis [43].

Finally, SCA8 is caused by a CTG expansion at the *ATXN8OS* locus [44]. The repeat at this locus is bidirectionally transcribed resulting in both a noncoding CUG transcript and short CAG transcript encoding a pure polyglutamine protein that forms inclusions in mice and in humans [44]. How and the extent to which the two transcripts combine to cause pathology in SCA8 remains to be elucidated.

III: Conclusions

In this review we highlighted some of the emerging pathways that play an important role in SCA cerebellar dysfunction. Whether these pathways function independently of each other or are all interconnected remains to be determined, though the fact that 18 of 23 proteins that cause hereditary ataxia in humans connect to each other either directly or indirectly via protein-protein interactions suggests a high degree of convergence [45]. As a group, the SCAs show many of the hallmarks of other neurological diseases including age-related neurodegeneration present in sporadic and hereditary forms along with pathology of specific cellular populations despite ubiquitous expression of the disease protein. Given these features, the SCAs provide a rich resource for studying key aspects of neuronal biology, such as regulation of calcium levels and gene expression. Therefore, insights gained from studies of the SCAs are likely to have broader implications for neurodegenerative disease in general.

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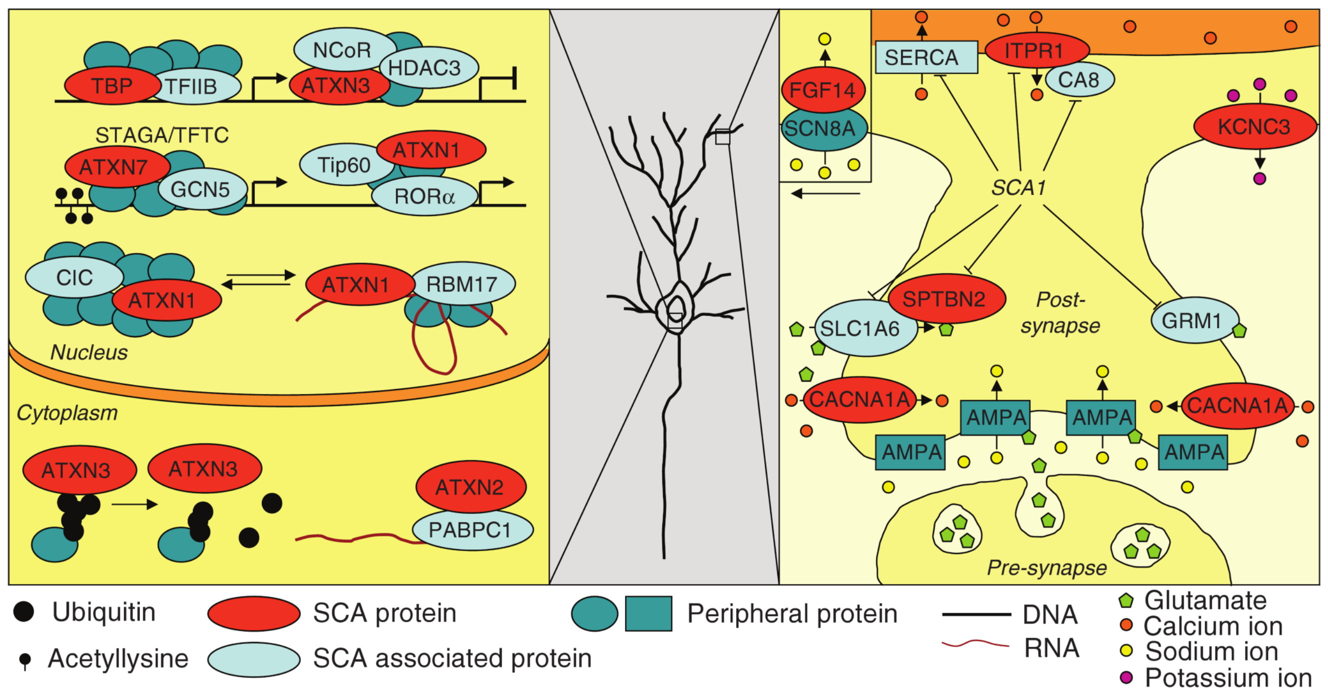

Figure 1.

Gene expression and dendritic signaling pathways affected in SCA pathogenesis. A general neuron is shown because Purkinje cell involvement in SCA3 pathogenesis is minimal; however, the synaptic events specifically associated with Purkinje cell signaling are depicted. Note that the FGF14/SCN8A interaction takes place in the proximal dendrite and cell body. SCA proteins are represented in red while the proteins they interact with based on experimental data are depicted in light blue. Hypothetical proteins in the complex are shown in dark blue. Standard HUGO gene names are used except for TFIIB (GTF2B), NCoR (NCOR1/NCOR2), RORα (RORA), Tip60 (KAT5), AMPA (AMPA-type glutamate receptor), SERCA (sarco/endoplasmic reticulum calcium-ATPase). In addition to key protein interactions, the genes downregulated in a SCA1 transgenic mouse model are also noted in the dendrite. ATXN1, 2, 3, and 7 are the proteins involved in SCA1, 2, 3, and 7 respectively (also see Table 1).

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Table 1

Summary of Autosomal-Dominant Spinocerebellar Ataxias

Disease	Location	Gene	Mutation Type	Recent References
SCA1	6p23	*ATXN1*	CAG expansion	[15,16]
SCA2	12q24	*ATXN2*	CAG expansion	[43]
SCA3	14q32	*ATXN3*	CAG expansion	[20-23]
SCA4	16q22.1	Unknown		
SCA5	11p13	*SPTBN2*	In-frame deletion	[32]
SCA6	19p13	*CACNA1A*	CAG expansion	[27,28,30]
SCA7	3p14	*ATXN7*	CAG expansion	[10-13]
SCA8	13q21	*ATXN8*	CTG and/or CAG expansion	[44]
SCA10	22q13	*ATXN10*	Noncoding repeat expansion	[46]
SCA11	15q15.2	*TTBK2*	1bp insertion	[38]
SCA12	5q32	*PPP2R2B*	Noncoding repeat expansion	[39]
SCA13	19q13	*KCNC3*	Missense mutation	[34]
SCA14	19q13	*PRKCG*	Missense mutation	
SCA15	3p26	*ITPR1*	Deletion or missense mutation	[5]
SCA17	6q27	*TBP*	CAG expansion	[8,9]
SCA18	7q31-q32	Unknown		
SCA19	1p21-q21	Unknown		
SCA20	11q12.2-q12.3		Chromosomal duplication	[33]
SCA21	7p21.3-p15.1	Unknown		
SCA22	1p21-q23	Unknown		
SCA23	20p13-p12.2	Unknown		
SCA25	2p21-p15	Unknown		
SCA26	19p13.3	Unknown		
SCA27	13q34	*FGF14*	Missense mutation or 1bp deletion	[35]
SCA28	18p11.22 -q11.2	Unknown		
SCA29	3p26	Unknown		
SCA30	4q34.3-q35.1	Unknown		[6]
SCA-16q linked	16q22	*PLEKHG4*	Noncoding SNP	[47]