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Cellular and Molecular Pathways Triggering Neurodegeneration in the Spinocerebellar Ataxias

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Abstract The autosomal dominant spinocerebellar ataxias (SCAs) are a group of progressive neurodegenerative diseases characterised by loss of balance and motor coordination due to the primary dysfunction of the cerebellum. To date, more than 30 genes have been identified triggering the well-described clinical and pathological phenotype, but the underlying cellular and molecular events are still poorly understood. Studies of the functions of the proteins implicated in SCAs and the corresponding altered cellular pathways point to major aetiological roles for defects in transcriptional regulation, protein aggregation and clearance, alterations of calcium homeostasis, and activation of pro-apoptotic routes among others, all leading to synaptic neurotransmission deficits, spinocerebellar dysfunction, and, ultimately, neuronal demise. However, more mechanistic and detailed insights are emerging on these molecular routes. The growing understanding of how dysregulation of these pathways trigger the onset of symptoms and mediate disease progression is leading to the identification of conserved molecular targets influencing the critical pathways in pathogenesis that will serve as effective therapeutic strategies in vivo, which may prove beneficial in the treatment of SCAs. Herein, we review the latest evidence for the proposed cellular and molecular processes to the pathogenesis of dominantly inherited spinocerebellar ataxias and the ongoing therapeutic strategies.

Keywords Spinocerebellar ataxias · Cerebellum · Neurodegenerative disorders · Neurodegenerative mechanisms · Therapy

Abbreviations

ADCA	Autosomal dominant spinocerebellar ataxia
Ca^{2+}	Calcium ion
CACNA1A	Calcium channel, voltage-dependent, P/Q type, alpha 1A subunit
CAG	DNA sequence coding for glutamine
CNS	Central nervous system
DRPLA	Dentatorubral-pallidoluysian atrophy
ER	Endoplasmic reticulum
FGF14	Fibroblast growth factor 14
GABA	γ-aminobutyric acid
Glu	Glutamate
HDACs	Histone deacetylases
HSP	Heat shock protein
ITPR1	Inositol 1,4,5-triphosphate receptor type 1
KCNC3	Potassium voltage-gated channel subfamily C member 3
MJD	Machado–Joseph disease
PC	Purkinje cells
PP2	Protein phosphatase 2 (formerly 2A)
PPP2R2B	Serine/threonine protein phosphatase 2 (formerly 2A) 55 kDa regulatory subunit B beta isoform
PRKCG	Protein kinase C gamma
Q	Glutamine

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SCA	Spinocerebellar ataxia
SPTBN2	Beta-III spectrin
TBP	TATA-box-binding protein
UPR	Unfolded protein response
UPS	Ubiquitin-dependent proteasome system

Introduction

Ataxia is a neurological disorder characterised by loss of control of body movements. Patients suffering from ataxia are clumsy and unable to walk steadily, have slurred speech and eventually lose the ability to swallow and breathe smoothly. Ataxia results from variable degeneration of neurons in the cerebellar cortex, brain stem, spinocerebellar tracts and their afferent/efferent connections. Such neurodegeneration can result from multiple sclerosis, brain tumour, alcoholism or an inherited genetic defect. There are over 50 different types of inherited ataxias striking during childhood or adulthood. Autosomal dominant spinocerebellar ataxias (SCAs, also known as ADCAs) comprise a highly heterogeneous group of dominantly inherited ataxias where the age of onset of the clinical symptoms is typically between 30 and 50 years of age, although early onset in childhood and onset in later decades after 60 years have been reported for specific SCA subtypes [1] (Table 1). The prognosis is variable depending on the underlying cause of the spinocerebellar ataxia subtype. Epidemiological data indicate that SCAs might be more common than previously estimated with prevalences over 5–7 in 100,000 in some geographical areas reaching 18.5/100,000 in Japan when including dominant, recessive and sporadic SCAs and familial spastic paraplegia [2]. This is similar to the prevalences reported for other uncommon motor neurodegenerative diseases, such as Huntington or motor neuron diseases.

Clinical Features of the Spinocerebellar Ataxias

During the past 15 years, over 30 dominantly inherited SCA subtypes have been described (Table 1). Although ataxia is the prominent symptom in SCAs, few mutations cause an almost pure cerebellar syndrome and isolated neurodegeneration in the cerebellar cortex. On the contrary, most SCAs are multisystemic disorders presenting clinical variability and even those SCA subtypes regarded as 'pure' cerebellar forms reveal neurodegeneration not only in the cerebellum and spinocerebellar tracts, but also in many other areas of the central and peripheral systems. Table 1 summarises most of the non-ataxia manifestations accompanying various SCA subtypes described so far and the neuropathological findings. With a high phenotypic variability and because of the highest prevalence among all SCA subtypes, SCA3 is the best characterised SCA subtype at the neuropathological level [3, 4]. Four SCA3 subtypes have been proposed which are related to the number of CAG repeats and the age of onset including ataxia and the presence of extrapyramidal affection, essentially dystonia; ataxia with pyramidal syndrome; ataxia with neuropathy and ataxia with parkinsonism and neuropathy as predominant symptoms. A fifth SCA3 subtype would be defined by the presence of ataxia and spastic paraplegia [5, 6]. In addition, there may be involvement, usually subclinically, of lower neurons [7]. This is a subtype presenting essential tremor-like [8] and different combinations of restless legs syndrome [9], REM behaviour disorder [10], disautonomy [11] and peripheral neuropathy, such as neuronopathy or axonopathy [12]. The spared widespread neurodegeneration most likely accounts for other non-ataxic symptoms in SCAs, albeit there has been a debate about the prevalence of the presence of neuropsychiatric symptoms as depression and cognitive impairment [4, 13]. SCA7, with less phenotypic variability than other SCAs, is unique for loss of vision due to retinal pigmentary dystrophy [14]. In the upcoming years, it is likely that the multisystemic nature of SCAs will be more widely recognised. Those cases, as in DRPLA which has been traditionally regarded as almost exclusively present among the Japanese population albeit it reveals now a significant prevalence in other non-Asian populations [15], might lead to the definition of new SCA phenotypes and generalise the idea that ataxia may be a relatively minor neurological symptom in SCA patients.

Cellular and Molecular Pathways Implicated in Neurodegeneration in the Sinocerebellar Ataxias

To date, more than 30 SCA genes or loci have been identified [16] (Table 2). Recognised mechanisms leading to spinocerebellar neurodegeneration include polyglutamine expansions (SCAs 1, 2, 3, 6, 7, 17 and DRPLA); non-coding expansions (SCA10 and SCA12); as well as conventional mutations in genes encoding cytoskeletal proteins (βIII spectrin, SCA5), ion channels (voltage gated potassium channel Kv3.3, SCA13), protein kinases (tau tubulin kinase 2, SCA11; protein kinase C gamma, SCA14), intracellular calcium channels (inositol 1,4,5-triphosphate receptor 1, SCA15), fibroblast growth factors (FGF14, SCA27) and ATPases (AFG3L2, SCA28; Fig. 1).

SCAs 1, 2, 3, 6, 7, 17 and DRPLA are all caused by the expansion of a translated CAG repeat sequence leading to an abnormally long polyglutamine (polyQ) tract in the encoded proteins named ataxins 1, 2 and 3, alpha 1A-voltage-dependent calcium channel, ataxin 7, TATA-box-binding protein and atrophin 1, respectively, hence included

Table 1 Clinical and neuropathological heterogeneity in the spinocerebellar ataxias

SCA type	OMIM	Average onset (range in years)	Average duration (range in years)	Signs associated with ataxia	Neuropathology/MRI
SCA1	164400	4th decade (<10 to >60)	15 years (10–28), anticipation	Extrapyramidal (parkinsonism, restless legs), pyramidalism, cognitive, impairment, peripheral neuropathy (neuronopathy), dysautonomy, vocal cord paralysis	Loss of Purkinje cells, neurons of dentate, Bergma's gliosis, variable loss of granule cells, atrophy of middle cerebellar peduncles. Loss of mesencephalic neurons in 3rd and 4th cranial nerves. Intranuclear inclusions
SCA2	183090	3rd–4th decade (>10 to >60)	10 years (1–30), anticipation	Extrapyramidal (parkinsonism, levodopa-responsive parkinsonism), pyramidalism, cognitive impairment, peripheral neuropathy (neuronopathy), dysphagia	Atrophy of cerebellum, pons, frontal lobe, medulla oblongata, cranial nerves, as well as pallor of the midbrain substantia nigra. Cytoplasmic inclusions
SCA3/ MJD	109150	4th decade (10–70)	10 years (1–20), anticipation	Extrapyramidal (parkinsonism, dystonia, restless legs, tremor essentials-like), pyramidalism, (spastic paraplegia), periphecal neuropathy (neuronopathy or axonopathy), lower motor neuron impairment, dysautonomy, REM behavoir disorder, neuropsychiatric symptoms	The cerebellum is relatively spared, spinal cord shows loss of myelinated fibres in the spinocerebellar tracts and posterior funiculi. Loss of neurons and gliosis in the substantia nigra, nuclei pontis (and in the putamen in some cases) as well as nuclei of the vestibular and cranial nerves, column of Clarke and anterior horn. Intranuclear inclusions
SCA4	600223	4th–7th decade (19–72)	Decades	Peripheral neuronopahty (axonophaty), deafness. Absent ankle-jerk reflexes	Cerebellar atrophy
SCA5	600224	3rd–4th decade (10–68)	>25 years slow progression	No non-ataxia symtpoms described	Atrophy of cererebellar vermis and hemispheres
SCA6	183086	5th–6th decade (19–71)	>25 years slow progression	Phenotype overlaps with episodic ataxia type 2, extrapyramidal (parkinsonism), pyramidal, peripheral neuropathy, down-beat nystagmus	Loss of PC and inferior olives neurons
SCA7	164500	3rd–4th decade (0.5–60)	20 years (1–45), anticipation	Retinopathy (cone-rod dystrophy), pyramidal	Olivopontocerebellar atrophy and thinning of the spinal cord. Retinal degeneration. Intranuclear inclusions
SCA8	608768	39 years (18–65)	Normal lifespan	Neuropsychiatric symptoms (executive dysfunction, depression), pyramidal, vibratory sensibility impairment, myoclonus, migraine	Cerebellar and pontine atrophy
SCA9	612876	Adult onset		Pyramidal, extrapyramidal and posterior column symptoms (a case MS-like)	Demyelinating lesions on brain MRI of 3 patients showed cerebellar atrophy
SCA10	603516	36 years	9 years	Epilepsy, cognitive impairment	Cerebellar atrophy
SCA11	604432	30 years (15–70)	Normal lifespan	Pyramidalism	Cerebellar atrophy. Hyperphosphorylated tau
SCA12	604326	33 years (8–55)	Slow progress	Long term isolated tremor as initials presentation cognitive impairment	Cerebral cortical atrophy, enlarged ventricles, PC loss, less prominent cerebellar and pontine atrophies, and INIs
SCA13	605259	Childhood or adulthood (depending on mutation)	Childhood or adulthood (depending on mutation)	Pyramidalism, mental and motor developmental delay	Cerebellar and pons atrophy
SCA14	605361	28 years (12–14)	Decades (1–30)	Facial myokimia myoclonus, decreased vibration sense	Atrophy confined to the cerebellum
SCA15	606658	39 years (20–66)	Decades (verly slow progression)	Described cases of cognitive impairment	Atrophy of the cerebellar vermis with comparative sparing of the tonsils and hemispheres. The brainstem remains unaffected

Table 1 (continued)

SCA type	OMIM	Average onset (range in years)	Average duration (range in years)	Signs associated with ataxia	Neuropathology/MRI
SCA16	Unknown				
SCA17/ HDL4	607136	6–34	>8 years	Isolated parkinsonism, corea, dystonia, dementia, myoclonus, epilepsy	Mild neuronal loss with compaction of the neuropil in the cerebral cortex, mild loss of neurons in the striatum, and moderate loss of PC
SCA18	607458	2nd–3rd decades		Sensorimotor neurophathy with pes cavus	
SCA19/22	607346	34 years (20–45)	Decades	Cognitive impairment, myoclonus	
SCA20	608687	19 to 64 years (mean and median both 46.5 years)	Decades	Pyramidalism, extrapyramidalism	Pancerebellar atrophy with dentate calcification, with olivary pseudohypertrophy in some cases, in the absence of other brainstem or cerebral changes
SCA21	607454	6 to 30 years	Decades	Extrapyramidalism cognitive impairment	Cerebellar atrophy, no lessions of brainstem
SCA22	Unknown				
SCA23	610245	5th–6th decade (43–56 y)	>10 years	Slow saccades, hyperreflexia	Frontotemporal atrophy, atrophy of the cerebellar vermis, pons, and spinal cord. Neuronal loss in the cerebellar vermis, dentate nuclei, and inferior olives, but not in the pons. Thinning of the cerebellopontine tracts and demyelination of the posterior and lateral columns of the spinal cord. Ubiquitin INIs in nigral neurons (Marinesco bodies)
SCA24	607317?				
SCA25	608703	17 months to 39 years although most of those affected had onset in childhood	Unknown	Mild sensory neuropathy, Friedreich's ataxia-like phenotype	Cerebellar atrophy
SCA26	609306	26 to 60 years (42 years)	Unknown		Atrophy of the cerebellum sparing the pons and medulla
SCA27	609307	11 years (7–20)	Decades	Extrapyramidal (dyskinesia), cognitive impairment, pes cavus. Executive deficits	Moderate cerebellar atrophy
SCA28	610246	19.5 years (12–36)	Decades		Cerebellar atrophy
SCA29	117360	Unknown	Unknown	Non-progressive	Hypoplasia or partial aplasia of the cerebellar vermis
SCA30	Unknown	Mid to late life		Pyramidalism	Cerebellar atrophy with preservation of nodulus/uvula and brainstem, lack of prominent nystagmus
DRPLA	125370	0–20 years or 40–60 s	Anticipation	3 classical phenotypes: epilepsy myoclonic progressive, Huntington's disease-like (chorea-dementia), ataxo-choreoathetosis. Combined forms	Atrophy and neuronal loss in the globus pallidus (particularly the lateral segment) and dentate nucleus, brainstem, cerebellar and cerebral white matter. Lipofuscin deposits

16q-ADCA	117210	45–72			Decreases muscle tone, horizontal gaze nystagmus	Cerebellar atrophy, PC degeneration, abnormal dendrites, and somatic sprouts of PC. Intranuclear inclusions
Unassigned	Unknown	3rd–6th decade	decades		Thermoanalgesia, deep sensory loss	Cerebellar, medullar and spinal cord atrophy. Loss of PC and dentate neurons. The inferior olive and lower cranial nerve nuclei also show extensive cell loss. Posterior columns and spinocerebellar tracts are demyelinated. Ubiquitin immunoreactive intranuclear inclusions are absent

in the group regarded as polyglutaminopathies. They all show as common features, the progressive neurodegeneration of neuronal subsets in distinct brain areas and the formation of polyQ-containing protein aggregates forming characteristic nuclear or cytoplasmic inclusions [1]. The age at onset and severity of disease symptoms inversely correlate with the length of the glutamine repeat. SCAs 8, 10 and 12, are caused by repeat expansions located outside of the coding region of the disease genes [17–19]. While SCAs 8 and 10 appear to be caused by toxic RNA gain-of-function mechanisms (albeit SCA8 might be also caused by polyglutamine expansions), SCA12 is caused by dysregulation of the activity of the crucial enzyme protein phosphatase 2 (PP2, formerly named PP2A) in cerebellar Purkinje cells. Different mechanisms are responsible for cerebellar ataxia and neurodegeneration in SCAs 5, 11, 13, 14, 15, 27 and 28 where alterations in amino acid composition in beta-III spectrin (SPTBN2) [20], tau tubulin kinase 2 (TTBK2) [21], potassium channel KCNC3 [22], protein kinase C gamma (PRKCG) [23, 24], the Inositol 1,4,5-triphosphate receptor (ITPR1) [25], fibroblast growth factor 14 (FGF14) [26], and the ATPase family gene 3-like 2 protein (AFG3L2) [27], respectively, elicit disease symptoms in these SCA subtypes. In the rest of SCAs, the genes and, therefore, the mutations remain to be identified and characterised. Understanding the pathogenic mechanisms underlying neurodegeneration in spinocerebellar ataxias is leading to the identification of potential therapeutic targets that will ultimately facilitate drug discovery (Table 3).

Common Occurring Pathways During Polyglutamine Neurotoxicity: Protein Aggregation, Misfolding, Stability and Clearance

Seven spinocerebellar ataxia subtypes including SCAs 1, 2, 3/Machado–Joseph disease, 6, 7, 17 and DRPLA, are all caused by the expansion of a CAG repeat sequence in specific genes leading to abnormally long polyQ tracts in the encoded proteins [28]. Presumably, a similar pathogenic pathway is involved in these SCAs, since each of the expanded CAG repeats encodes polyglutamine and the pathogenic threshold for disease is roughly the same, at around 40 copies of the repeat in most of the different subtypes. It is assumed that the common toxic gain-of-function mechanisms for the polyglutamine-containing protein are aggregation and deposition of misfolded proteins leading to neuronal dysfunction and eventually cell death. Proteins with expanded stretches of polyglutamine appear to take on an abnormal configuration resulting in the formation and deposition of polyglutamine aggregates in disease

Table 2 Genetic heterogeneity and molecular pathogenesis in the spinocerebellar ataxias

SCA subtype	Genomic location	Gene	Protein	Function	DNA mutation	References
SCA1	6p22.3	ATXN1	Ataxin 1	Transcription regulation	$(CAG)_n$	[52]
SCA2	12q24.12	ATXN2	Ataxin 2	RNA metabolism	$(CAG)_n$	[136]
SCA3/MJD	14q32.12	ATXN3	Ataxin 3	De-ubiquitination, Transcription regulation	$(CAG)_n$	[4]
SCA4	16q24-ter	SCA4	U	U	U	[99]
SCA5	11q13.2	SPTBN2	ß-spectrin, non-erythrocytic 2	Neuronal membrane skeleton	ID, MM	[20]
SCA6	19p13.2	CACNA1A	CACNA1A	Ca^{2+} signalling/homeostasis	$(CAG)_n$	[72]
SCA7	3p14.1	ATXN7	Ataxin 7	Transcription regulation	$(CAG)_n$	[137]
SCA8	13q21	ATXN8OS/ATXN8	Ataxin 8	U	$(CUG/CAG)_n$	[67]
SCA9	U	U	U	U	U	[138]
SCA10	22q13.31	ATXN10	Ataxin 10	Neuritogenesis	Intronic $(ATTCT)_n$	[87]
SCA11	15q15.2	TTBK2	Tau tubulin kinase 2	Tau phosphorylation	FM, MM	[21, 139]
SCA12	5q32	PPP2R2B	PPP2R2B	Regulation of PP2 activity transcription regulation	5′-UTR $(CAG)_n$	[17]
SCA13	19q13.33	KCNC3	KCNC3	K^+ signalling	MM	[91]
SCA14	19q13.42	PRKCG	PRKCG	Phosphorylation	ID, MM	[23]
SCA15[b]	3p26.1	ITPR1	Inositol 1,4,5-triphosphate receptor 1	Inositol 1,4,5-triphosphate calcium signalling	D,MM	[25]
SCA16	8q23–q24.1	U	U	U	U	[140]
SCA17/HDL4	6q27	TBP	TBP	General transcription (TFIID complex)	$(CAG)_n$	[141]
SCA18	7q22–q32[a]	U	U	U	U	[142]
SCA19	1p21–q21[a]	U	U	U	U	[143, 144]
SCA20	11q12.2–11q12.3[a]	U	U	U	Chromosomal duplication	[145]
SCA21	7p21.3–p15.1[a]	U	U	U	U	[146]
SCA22	1p21–q23[a]	U	U	U	U	[144, 147]
SCA23	20p13–p12.2[a]	U	U	U	U	[148]
SCA24	U	U	U	U	U	-
SCA25	2p21–p15[a]	U	U	U	U	[149]
SCA26	19p13.3[a]	U	U	U	U	[150]
SCA27	13q33.1	FGF14	FGF14	Signal transduction, Regulation Na_V channels, Excitability of Purkinje cells	FM, MM, translocation	[26]
SCA28	18p11.21	AFG3L2	ATPase family gene 3-like 2	ATPase	MM	[27, 151]
SCA29[b]	3p26	U	U	U	U	[152]
SCA30	4q34.3–q35.1[a]	U	U	U	U	[153]
DRPLA	12p13.31	ATN1	Atrophin 1	Transcription repression (nuclear receptor corepressor)	$(CAG)_n$	[154]
16q-ADCA	16q22.1	PLEKHG4	Puratrophin 1	Intracellular signalling, cytoskeleton dynamics	5′-UTR SNP	[98]
Unknown	U	U	U	U	U	[155]

Genes noted in genomic location according to Ensembl

D deletion, *FM* frameshift mutation, *ID* in-frame deletion, *MM* misense mutation, *SNP* single nucleotid polymorphism, *UTR* untranslated region, *U* unknown

[a] Genes not noted according to HUGO Gene Nomenclature Committee

[b] SCA29 maps to the same genomic location than SCA15

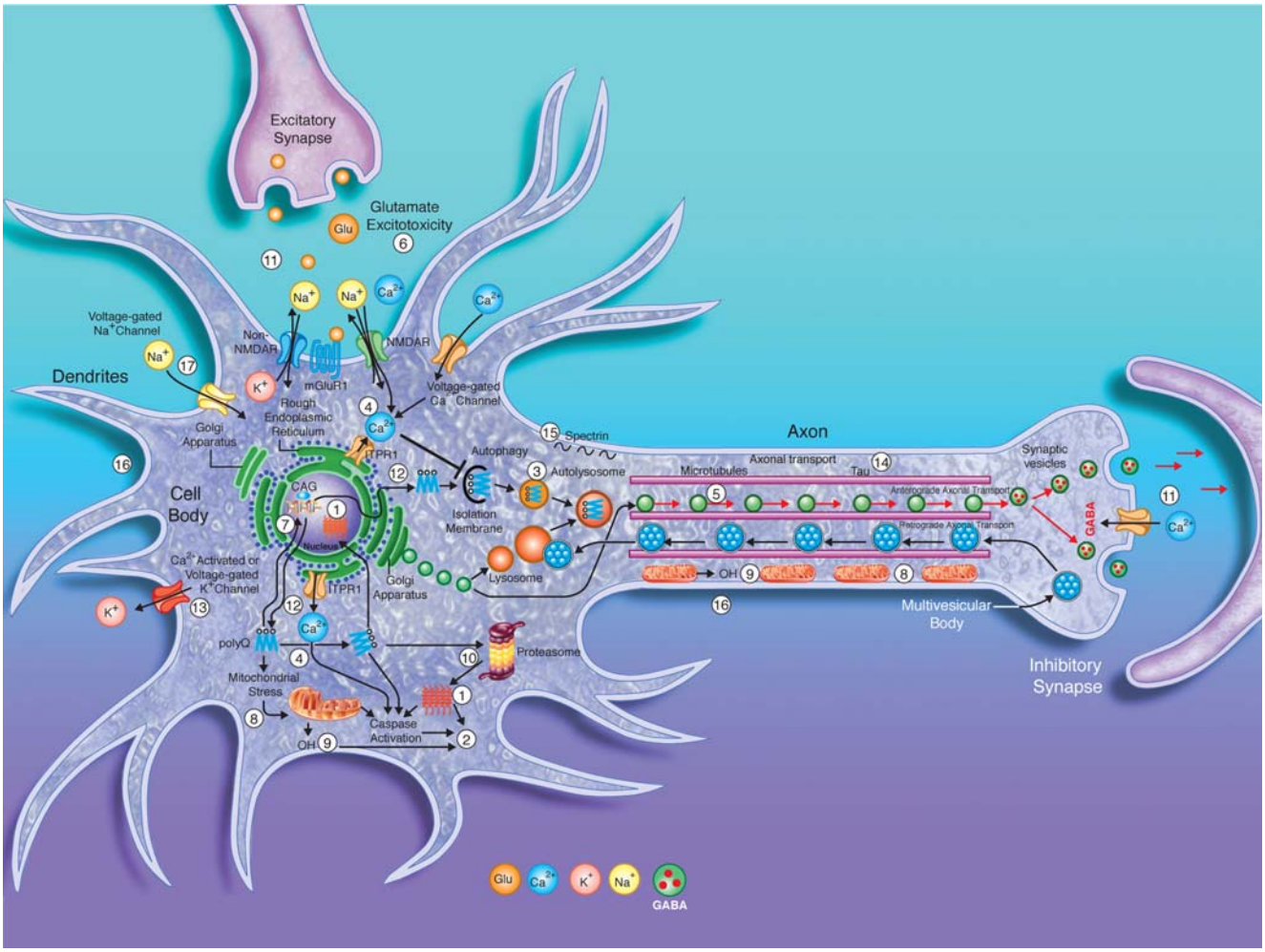

Fig. 1. Molecular mechanism of neurodegeneration in the spinocerebellar ataxias. *1* aggregation, *2* apoptosis, *3* autophagy, *4* Ca^{2+} homeostasis/signalling alterations, *5* disruption of axonal transport and vesicle trafficking, *6* excitotoxicity, *7* interference with gene transcription, *8* mitochondrial impairment, *9* oxidative stress, *10* alterations of proteasome degradation, *11* synaptic neurotransmission deficits, *12* unfolded protein response (*UPR*), *13* potassium channel dysfunction, *14* tau phosphorylation, *15* neuronal membrane skeleton, *16* neuritogenesis, *17* voltage-gated Na^{+} channels. Ca^{2+} calcium ions, *ER* endoplasmic reticulum, *GABA* γ-aminobutyric acid, *Glu* glutamate, *ITPR1* inositol 1,4,5-triphosphate receptor type 1, K^{+} potassium ions, *mGluR1* metabotropic glutamate receptor type 1, Na^{+} sodium ions, *Q* glutamine

neurons forming characteristic nuclear or cytoplasmic inclusions, which are neuropathological hallmarks in these diseases [29]. These inclusions contain cellular components such as ubiquitin, the proteasome, HSP70, and transcription factors among others [30–32]. Whether the toxicity is a direct result of the aggregate or results from intermediary structures formed during the process of aggregation has been object of controversy, but blocking aggregation is still one approach attempted to minimising toxicity. A possible mechanism for aggregate formation by the mutant protein would be by loss of native state stability by the expanded polyglutamine and, thus, leading to the formation and accumulation of a partially unfolded, aggregation-prone species, resulting in fibrillisation. This phenomenon probably accounts for the earlier age of onset and higher severity of disease symptoms observed when mutant ataxins contain longer numbers of glutamines.

Ataxin 3, an ubiquitin-specific cysteine protease that associates with the proteasome, deubiquitinates proteins by binding polyubiquitin chains through several ubiquitin interaction motifs (UIMs) within the Josephin domain, which is located near the polyQ tract [33]. Elucidation of the molecular structure of the Josephin domain within ataxin 3 has led to propose a model for recognition of interactions and formation of stable complexes with HHR23B located in the same surface involved in the interaction with UBA domains, the S5a polyUb-binding site and the proteasome. These observations have provided a link between ataxin 3 and the UPS that is of particular relevance to other neurodegenerative diseases such as in

Table 3 Cellular and molecular pathways implicated in the spinocerebellar ataxias

SCA subtype	Identified cellular and molecular pathways	Numbers on Fig.1
SCA1	Aggregation, apoptosis/caspases, autophagy, calcium and dopaminergic signalling, dysruption of vesicular transport, ER, gene transcription, HSR, mitochondrial dysfunction, PI3K/Akt, PP2, PRKC, SUMOylation, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–12, 14, 16)
SCA2	Aggregation, apoptosis/caspases, autophagy, calcium and dopaminergic signalling, ER, gene transcription, HSP, mitochondrial dysfunction, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–4, 7–12, 17)
SCA3	Aggregation, apoptosis/caspases, autophagy, dopaminergic signalling, ER, gene transcription, HSR, mitochondrial dysfunction, SUMOylation, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–3, 7–12)
SCA5	Neuronal membrane skeleton, synaptic neurotransmission deficits (glutamate, GABA)	(6, 11, 15)
SCA6	Aggregation, apoptosis/caspases, autophagy, dopaminergic signalling, ER, gene transcription, HSR, mitochondrial dysfunction, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–4, 7–12)
SCA7	Aggregation, apoptosis/caspases, autophagy, ER, gene transcription, HSR, mitochondrial dysfunction, SUMOylation, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–3, 6–12)
SCA8	Aggregation, apoptosis/caspases, gene transcription, mitochondrial dysfunction, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1, 2, 6–9, 11, 12, 15)
SCA10	Neuritogenesis.	(16)
SCA11	Dysruption of vesicular transport, tau phosporylation	(5, 14)
SCA12	Apoptosis/caspases, dysruption of vesicular transport, gene transcription, PP2, tau phosphorylation	(2, 5, 7, 14)
SCA13	Potassium channel signalling	(13)
SCA14	Calcium, neuritogenesis, synaptic neurotransmission deficits (glutamate, GABA)	(4, 11, 16)
SCA15	Calcium	(2, 4, 16)
SCA17/ HDL4	Aggregation, apoptosis/caspases, autophagy, dopaminergic signalling, ER, gene transcription, HSR, mitochondrial dysfunction, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–3, 7–12)
SCA27	Dopaminergic signalling, signal transduction, sodium voltage channel	(11, 17)
SCA28	Mitochondrial dysfunction	(2, 9)
DRPLA	Aggregation, apoptosis/caspases, autophagy, ER, gene transcription, HSR, mitochondrial dysfunction, synaptic neurotransmission deficits (glutamate, GABA), UPR, UPS	(1–3, 7–12)
19q-ADCA	Actin dynamics, intracel.lular signalling, synaptic neurotransmission deficits	(7, 11)

SCA1 [34]. It seems that the expanded polyglutamine within ataxin 3 alters its normal function and produces functional disruptions of the UPS pathway [35]. Alternatively, reduction of proteasome activity may result from caspase-dependent cleavage of proteasome subunits owing to aggregated protein-induced apoptosis [36]. Since the UPS plays a prominent role in the detoxification and targeting of damaged proteins for degradation, derangements of this system might lead to an abnormal accumulation of a variety of toxic proteins, including those containing the polyglutamines that would otherwise have been degraded, ultimately leading to neuronal dysfunction and death. Molecular chaperones, proteins that can repair or facilitate proteasome degradation of abnormally folded proteins, play a role in SCAs as aggregates in human post-mortem tissue often immunostain for chaperones [29]. This evidence indicates that the mechanisms of cell survival mediated by the endoplasmic reticulum (ER) chaperones and the unfolded protein response (UPR) are activated during neurodegeneration in spinocerebellar ataxias. The presence of unfolded proteins in the ER can cause ER stress or an imbalance between the load of unfolded proteins and the capacity of the ER protein-folding machinery. In order to restore ER homeostasis, neurons activate the ER stress response or UPR, eventually leading to transcriptional activation of genes encoding for chaperons. Consistently, experimental overexpression of molecular chaperones modulates the formation of protein aggregates in cultured cells, transgenic mice and fruit flies, diminishing the toxicity of glutamine expansions [30, 37, 38]. Chaperones seem to stabilise the misfolded monomeric conformation by preventing the intramolecular transition that gives rise to spherical and annular oligomers and, simultaneously, stabilising a conformation that promotes inclusion body formation [39]. Alternatively, by interacting with the disease proteins, chaperones prevent abnormal interactions with other proteins in the cell that are causal in toxicity.

Proteins that remain misfolded are degraded primarily by the ubiquitin–proteasome system, but also by the autophagic phagosome–lysosome system, which contributes to the routine turnover of cytoplasmic components [40]. Autophagy has revealed to play an essential role in the cellular clearance of toxic aggregated proteins in a cell culture model of polyglutamine-expanded ataxin 1-

mediated neurodegeneration [41]. The precise mechanism by which aggregated mutant ataxin 1 is captured by autophagosomes is unclear, but it appears that inhibition of mTOR, a negative regulator of autophagic clearance, induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of neurodegeneration [42]. This study has established that autophagy efficiently degrades cytoplasmic insoluble aggregates and points to a possible therapeutic strategy by modulating the autophagic process to promote clearance of aggregated disease proteins. It is important to note that autophagy may also induce cell death in neurons that accumulate protein aggregates in a way that results in a pathological condition, although the underlying mechanisms remain unknown.

Dysregulation of Transcription and Gene Expression

Compelling evidence implicates those ataxins containing long stretches of polyglutamines in the regulation of gene transcription. Nuclear expression of polyglutamine-expanded proteins is an essential step in polyglutamine pathogenesis, and the resulting transcriptional dysregulation caused by ataxins containing expanded polyglutamines results in neuronal dysfunction and death in a few SCAs [43]. Interference with gene expression occurs by the effects of the mutation exerted on the interaction of ataxins with transcriptional regulatory proteins and DNA or on chromatin remodelling. For instance, in SCA1, ataxin 1 interacts with several transcription factors regulating transcription including the transcriptional co-repressors/activators Lanp/Anp32a [44], PQBP-1 [45], silencing mediator of retinoid and thyroid hormone receptors [46], HDAC3 [46] (Matilla, unpublished observations), Boat [47], Gfi-1/senseless [48], Capicua [49], Tip60 [50] and SP1 [51]. The mutant forms of ataxin 1 exert alterations in the expression levels of genes regulated by those transcriptional regulators leading to alterations of Wnt-receptor signalling, retinoid acid/Thyroid hormone signalling, and nucleic acid binding [52]. Similarly, ataxins 2, 3 and 7, and the *SCA17* and *DRPLA* gene products, the basal transcription factor TATA-binding protein and atrophin 1, respectively, are directly involved in transcription as components of transcriptional regulatory complexes [53–56], and the genes and pathways regulated by these factors are just being identified. Interference with transcriptional regulations of specific subset of genes by polyglutamine expansions lead to neuronal dysfunction such as axonal and neurite integrity [57] and accounts for the cell-type specificity degeneration observed in spinocerebellar ataxias, through the sequestration of factors by the long glutamine stretches within the mutant proteins, whose expression are confined to cells that degenerate in these conditions [44]. Therefore, they would then become unavailable to perform their normal cellular duties with potentially lethal consequences. Remarkably, Anp32a/Lanp is a potent specific regulator of protein phosphatase 2 (PP2) activity, and its expression is predominantly confined to cerebellar Purkinje cells [44, 58]. Therefore, dysregulation of PP2 activity is a scenario underlying cerebellar neurodegeneration in SCA1. Accordingly, in both SCA1 and SCA12, cell death might be provoked by similar pathogenic mechanisms. Similarly, inactivation of the tissue-specific transcription factor CRX in SCA7 by the polyglutamine-based association with mutant ataxin 7 could contribute to the cone-rod dystrophy observed in SCA7 mice and patients [59].

One group of nuclear proteins that bind to and whose activity are altered by mutant ataxins is histone acetyltransferases (HATs). HATs are responsible for the acetylation of histones and several other important proteins, and this modification results in altered function of the target protein [60]. HATs also regulate cellular processes at levels as different as modifying transcriptional competence of chromosomes, temporal regulation of promoter activity and protein activation/inactivation. The altered balance between protein acetylation and deacetylation may be a crucial process contributing to pathogenesis induced by mutant proteins containing expanded polyglutamines [61]. Importantly, restoration of this balance is possible by genetic or pharmacological reduction of the opposing enzyme group, i.e. the histone deacetylases (HDACs). This is leading to new therapeutic strategies with HDAC inhibitors to treat neurodegeneration [61–63].

Alterations in Synaptic Neurotransmission

Alterations in glutamate synaptic neurotransmission underlie some mechanism mediating neurodegeneration in SCAs. In SCA1 transgenic mice, motor dysfunction precedes neuronal death, demonstrating that mutant ataxin 1 produces disruption of motor functions in SCA1 not by killing cells, but by affecting some Purkinje cellular functions including alterations in synaptic plasticity [64]. Elevated intracellular calcium levels mediated by calcium-permeable glutamate receptors have been proposed as a possible mechanism [65]. The importance of maintaining proper glutamate transmission in the Purkinje cell/parallel fibre synapse for proper motor function is supported from studies with ataxia mouse mutants. For instance, mice lacking mGluR1 display significant motor deficits and, importantly, introduction of mGlur1 expression into Purkinje cells of $mGluR1^{-/-}$ mice restores normal motor function [66].

RNA-mediated neurotoxicity has been implicated in SCA8 pathogenesis [19]. Recent studies have revealed that the SCA8 expansion is expressed in both directions (CUG

and CAG) and that a novel gene expressed in the CAG direction encodes a pure polyglutamine expansion protein (ataxin 8; ATXN8) [67]. Moreover, the expression of non-coding (CUG)(n) expansion transcripts (ataxin 8 opposite strand, ATXN8OS) and the discovery of intranuclear polyglutamine inclusions suggests that SCA8 pathogenesis may involve toxic gain-of-function mechanisms at both the protein and RNA levels. The SCA8 mice have revealed a loss of cerebellar GABAergic inhibition and, similar to human patients, intranuclear inclusions containing expanded polyQ in Purkinje cells and other neurons. This recent data could provide a convincing explanation for the lack of penetrance observed in SCA8 patients [68, 69].

Alterations in Calcium Homeostasis

Evidence points to derangements of neuronal calcium signalling in neurodegeneration of spinocerebellar ataxias. Cerebellar Purkinje cells seem to be particularly sensitive to fluxes in intracellular calcium levels, which could result from different sources, such as the reduction of chaperone activity and ER stress. Several neuronal genes abundantly expressed in Purkinje cells that are involved in calcium signalling or homeostasis are down-regulated in the cerebellum of SCA1 mutant mice before the occurrence of detectable motor impairment or pathology [65, 70]. This suggests a major role of disruption of calcium homeostasis in cerebellar Purkinje cells that could be importantly involved in the pathogenic process and/or the survival of these cells in SCA1.

In SCA2, mutant ataxin 2, but not wild-type, specifically associates with the cytosolic C-terminal region of type 1 ITPR1, an intracellular calcium release channel [71]. Association of Atxn2[58Q] with the receptor increases the sensitivity of ITPR1 to activation by inositol-tri-phosphate in planar lipid bilayer reconstitution experiments. This evidence indicates that disturbed neuronal Ca^{2+}-signalling may play an important role in SCA2 neuropathology.

SCA6 is caused by polyglutamine expansion in the *CACNA1A* gene, which encodes an alpha (2.1) subunit, formerly named [alpha]1A, the major pore-forming subunit of the $Ca_V2.1$ voltage-dependent P/Q-type calcium channel [72, 73]. Voltage-dependent calcium channels are made up of beta and gamma-s accessory subunits. Alpha subunits are membrane glycoproteins of approximately 2,400 amino acids in length in which primary structure predicts the presence of four homologous domains, each consisting of six transmembrane domains and a pore-forming P loop. P/Q-type calcium channels are high-voltage-activated calcium channels found primarily in neurons and expressed at high levels in granule cells and Purkinje cells of the cerebellar cortex. Their principal role is believed to be in synaptic transmission. Patch-clamp recordings of Purkinje cells in SCA6 mice have revealed a non-inactivating current that is highly sensitive to a spider toxin omega-agatoxin, indicating that the human $Ca_v2.1$ expressed in PC exhibits typical P-type properties [74]. Furthermore, the voltage dependence of activation and inactivation and current density are not different between SCA6 mice and control, suggesting that alterations of the channel properties do not underlie the pathogenic mechanism of SCA6. This supports for gain-of-function mutation mechanisms in SCA6.

SCA14 is caused by mutations in protein kinase C gamma (PKC gamma). Interestingly, 18 of 22 mutations are concentrated in the C1 domain, which binds diacylglycerol and is necessary for translocation and regulation of PKC gamma kinase activity. Wild-type PKC gamma, but not C1 domain mutants, inhibits Ca^{2+} influx in response to muscarinic receptor stimulation [75]. The sustained Ca^{2+} influx induced by muscarinic receptor ligation causes prolonged membrane localization of mutant PKC gamma. In vitro kinase assays revealed that most C1 domain mutants are constitutively active, albeit they are unable to phosphorylate transient receptor potential (TRP) channels in vivo. Therefore, mutant PKC gammas fail to phosphorylate TRP channels resulting in sustained Ca^{2+} entry. Such an alteration in Ca^{2+} homeostasis and Ca^{2+}-mediated signalling in Purkinje cells contribute to the neurodegeneration characteristic of SCA14.

SCA15 is caused by deletions and missense mutations in the ITPR1. The ITPR1 couples to intracellular Ca^{2+} channels to facilitate Ca^{2+} release from the endoplasmic reticulum after activation by the intracellular second messenger inositol 1,4,5-triphospate. SCA15 results then from impaired inositol 1,4,5-triphospate-mediated intracellular second-messenger signalling and disturbed calcium release altering intracellular calcium homeostasis.

Mitochondrial Stress and Apoptosis

Multiple lines of evidence suggest that neuronal death in spinocerebellar ataxias result from the direct activation of apoptotic pathways [76]. In addition to the role of mitochondria in intracellular calcium homeostasis as discussed earlier, polyglutamine-expanded cellular death of cerebellar neurons by polyglutamine-expanded containing proteins, is preceded by recruitment of caspases into polyQ aggregates [77]. This is followed by activation of caspases 3 and 9, and of mitochondrial apoptotic pathways mediated by members of the Bcl-2 family, such as Bax and Bcl-x(L) [78, 79]. Both factors are known key components of neuronal apoptosis by regulating mitochondrial release of cytochrome-*c* and Smac/DIABLO. Consistently with these observations, mutant ataxin 7 in SCA7 induces translocation of cytochrome-*c* and Smac/DIABLO to the cytosol preceded by activation of caspases 9 and 3. This suggests that mutant ataxin 7 causes

apoptotic death of cerebellar neurons by promoting mitochondrial release of cytochrome-*c* and Smac/DIABLO. Alternatively, pro-apoptotic pathways could be activated by displacement of harmful factors sequestered by expanded polyglutamines, or through non-canonical mechanisms of caspase activation. In any case, the toxic proteins promote mitochondrial dysfunction and increased free radical production associated with oxidative damage, and abnormal energy metabolite concentration and utilisation.

Further evidence of mitochondrial dysfunction resulting or contributing to ataxia is exemplified by AFG3L2, an ubiquitous nuclear-encoded mitochondrial m-AAA protease that forms hetero-oligomeric paraplegin-AFG3L2 and homo-oligomeric AFG3L2 complexes in the inner mitochondrial membrane. These complexes ensure protein quality control in the inner membrane, jointly with a chaperone-like activity on the respiratory chain complexes. Very recently, mutations in AFG3L2 have been identified in SCA28 (F.Taroni and S. Di Donato, personal communication). In this SCA subtype, respiratory chain dysfunction and increased reactive oxygen species production caused by AFG3L2 haploinsufficiency seem to lead to dark degeneration of Purkinje cells and cerebellar dysfunction [27]. This data implicates impaired mitochondrial proteolysis as a novel pathway in cerebellar neurodegeneration.

Emerging Pathways

Most of the crucial pathways leading to toxicity by the disease proteins in spinocerebellar ataxias remain to be discovered. Emerging lines of evidence are pointing to the biological functions of the disease proteins as responsible for the detrimental effects of the mutations associated with neuronal toxicity in spinocerebellar ataxias. In support of this evidence, in SCA1 the polyQ expansion is not sufficient to cause disease. It appears that phosphorylation of a specific serine residue in ataxin 1 by the protein kinases A and B/Akt play a crucial role in modulating the ability of the mutant form of ataxin 1 to induce neurodegeneration by influencing its biological interactions with other proteins and the formation of nuclear inclusions [80]. Therefore, the protein context and the cellular proteins with which ataxin 1 normally interacts are important in the disease process, indicating that for instance blocking the phosphorylation events could be a viable treatment. In support of this, the protein context remarkably appears to be a modifying factor of the age of onset in spinocerebellar degeneration [81]. In SCA2, ataxin 2 contains an RNA-binding Lsm domain characterised by a conserved sequence motif consisting of two short segments known as Sm1 and Sm2, which are separated by a variable linker [82]. Lsm domain proteins are involved in a variety of essential RNA processing events including RNA modification, pre-mRNA splicing, mRNA decapping and degradation, and some of them are also important components of spliceosomal small nuclear ribonucleoprotein (snRNPs) complexes [83]. Interestingly, ataxin 2 interacts with A2BP1 (ataxin 2-binding protein 1) [84], whose RNA-binding *Caenorhabditis elegans* homologue, fox-1, regulates tissue-specific alternative splicing [85]. Deciphering the mechanisms by which ataxin 2 regulates alternative splicing should provide insights into the pathways dysregulated during disease progression leading to the identification of potential therapeutic targets.

More recently, the genetic defects have been identified in three spinocerebellar ataxias. In-frame deletions in the beta-III spectrin gene SPTBN2 co-segregate with SCA5 in American and French families [20]. It appears that these spectrin mutations alter the levels, distribution, and stability of the beta-III spectrin-associating protein and Purkinje cell specific glutamate transporter EAAT4. In a German family, missense mutations within the *SCA5* gene co-segregating with the disease in affected individuals may disrupt the ability of spectrin to bind to the actin cytoskeleton. These observations suggest that disruption of glutamate signalling and vesicle trafficking may play a role in the pathogenic mechanisms in SCA5, which are pathways previously implicated in neurodegeneration in SCA1, Alzheimer's and Huntington's diseases and amyotrophic lateral sclerosis.

SCA10 is uniquely caused by an intronic pentanucleotide ATTCT repeat within the *E46L* gene, now designated *ATXN10* [86]. The E46L protein is widely expressed throughout the brain, contains two armadillo (arm) repeat domains, and interacts with the heterotrimeric GTP-binding protein (G-protein) [87]. It has been proposed that E46L enhances heterotrimeric G-protein signalling to mediate neurite formation. E46L belongs to the armadillo repeat family of proteins where the arm repeats mediate protein–protein interactions to modulate a myriad of cellular processes, including intracellular signalling, cytoskeletal regulation, nuclear transport, and regulation of gene expression both during development and throughout adult life [88]. Therefore, E46L might be regulating important cellular processes through the mediation of G-protein intracellular signalling.

The microtubule-associated protein tau (encoded by MAPT) and several tau kinases have been implicated in neurodegeneration, but only MAPT has a proven role in disease. Mutations in the gene encoding tau tubulin kinase 2 cause spinocerebellar ataxia type 11 [21]. Affected brain tissue shows substantial cerebellar degeneration and tau deposition.

An expanded CAG trinucleotide repeat located within the promoter region of the gene encoding a brain-specific regulatory subunit of the protein phosphatase 2 (formerly 2A; PPP2R2B) has been associated with SCA12 [17]. Neurodegeneration in SCA12 is confined to the cerebellum. The serine/threonine protein phosphatase 2 regulates a wide

array of cellular processes including cell growth and differentiation, DNA replication, cellular morphogenesis, long-term depression, and apoptosis [89]. It has been proposed that the *SCA12* repeat expansion alters the levels of expression of one splice variant (termed B beta1) of PPP2R2B by influencing the efficiency of the promoter driving expression, with potentially lethal consequences. It remains possible that the *SCA12* expansion could also have an effect on *PPP2R2B* splicing, or alter gene expression in some other fashion. Thus far, there is little evidence to suggest that the repeat is translated into polyglutamine. Protein phosphatase 2 dephosphorylates a diversity of kinases, including PKB/Akt and PKCs, which appear to mediate in neurodegenerative processes in SCAs 1 and 14, respectively [23, 80]. Interestingly, dysregulation of PP2 promotes tau hyperphosphorylation, microtubule destabilisation, modification of synapse structure, and neurodegeneration in Alzheimer's disease (AD) [90]. And significantly, the levels of PP2 activity are decreased in AD for unknown mechanisms. Therefore, disruption of normal brain/cerebellar PP2 functions could be a common player in the pathogenic mechanisms of neurodegenerative conditions.

In SCA13, missense mutations in exon 2 of the potassium channel *KCNC3* gene have been found associated with neurodevelopmental and neurodegenerative phenotypes [91]. KCNC3 (also known as Kv3.3) is a fast-rectifying voltage-gated Shaw subtype potassium channel abundantly expressed in the cerebellum, and the mutations appear to impair channel activity being consistent with a dominant negative effect of the mutant allele. It appears that the channel mutations shift the activation curve in the negative direction and slowed channel closing and, therefore, might change the output characteristics of fast-spiking cerebellar neurons, in which KCNC channels confer capacity for high frequency firing.

The disease symptoms in SCAs 14 and 27 are elicited by alterations in amino acid composition within the gamma subunit of protein kinase C (PRKCG) [23, 24] and the FGF14 [26], respectively. These alterations appear to dysregulate protein function and specific cellular pathways. Calcium-phospholipid-dependent protein kinase C comprises a family of enzymes that transduce the plethora of signals promoting lipid hydrolysis, thus regulating a variety of cellular processes, such as membrane-receptor signal transduction, control of gene expression, and synaptic plasticity [92]. PRKCG is highly expressed in brain and spinal cord, with particularly high expression in Purkinje cells of the cerebellar cortex during dendritic development, where it seems to act as a negative regulator of dendritic growth and branching [93]. Mutant *PRKCG* gene products are less stable than the normal protein leading to abnormal activation patterns, altered membrane targeting, and enhanced activity. It is speculated that the SCA14 phenotype results from gain-of-function mechanisms rather than haploinsufficiency, because no chain-terminating mutations have been found and heterozygous PKC-null animals are neurologically normal [94]. Most mutations causing SCA14 are located in the PKC gamma C1B regulatory subdomain, and SCA14 mutant PKC gamma proteins showed enhanced phorbol-ester-induced kinetics when compared with wild-type PKC gamma [95]. SCA14 mutant PKC gamma shows reduced kinase activity of downstream components of the MAPK signalling pathway. These results show that SCA14 mutations located in the C1B subdomain "open" PKC gamma protein conformation leading to increased C1 domain accessibility, but inefficient activation of downstream signalling pathways.

Alterations in protein stability of FGF14 underlie neurodegeneration of the cerebellum and basal ganglia in SCA27 [26]. FGF14 is a member of a subclass of fibroblast growth factors that is expressed in the developing and adult central nervous system, and has been implicated in neuronal signalling, axonal trafficking, and synaptosomal function [96]. Neuropharmacological studies in mice showed that Fgf14-deficient mice have reduced responses to dopamine agonists indicating that FGF14 is required for striatopallidal mediated dopaminergic-signalling. Therefore, dysfunction of this pathway could account for the cortical hyperexcitabillity and the parkinsonism-associated symptoms in SCA27. Current clamp recordings from PC in cerebellar slices has revealed attenuated spontaneous firing in Fgf14-deficient neurons [97]. Unlike in the wild-type animals, more than 80% of $Fgf14^{-/-}$ PC are quiescent and failed to fire repetitively in response to depolarizing current injections. Immunohistochemical examination revealed reduced expression of Nav1.6 protein in $Fgf14^{-/-}$ PC. Together, these observations suggest that FGF14 is required for normal Nav1.6 expression in Purkinje neurons, and that loss of FGF14 impairs spontaneous and repetitive firing in Purkinje neurons by altering the expression of Nav1.6 [97].

A single nucleotide substitution in the 5′ untranslated region of the gene encoding the Purkinje cell atrophy associated protein puratrophin 1, also known as pleckstrin homology domain containing family G (with RhoGef domain) protein 4 (PLEKHG4), a protein implicated in intracellular signalling and actin dynamics at the Golgi apparatus, is associated with a spinocerebellar ataxia subtype characterised by pure cerebellar atrophy and sensorineural hearing impairment [98]. Interestingly, the puratrophin 1 gene is located to the same chromosomal region where the *SCA4* gene localises [99]. Although the heterozygous C/T single-nucleotide substitution within the puratrophin 1 gene detected in the chromosome 16q22.1-linked ADCA Japanese families has not been detected in SCA4 families with ataxia and peripheral neuropathy, the puratrophin 1 gene cannot be excluded of being associated with disease symptoms in SCA4 yet.

Therapeutic Strategies

There are currently no known effective treatments to modify disease progression in any of the SCAs or related neurodegenerative disorders, although some benefits on ataxic symptoms have been reported in a few therapeutic trials (reviewed in [1, 100, 101]). Some benefits regarding ataxic symptoms have been reported with gabapentin, 5-hydroxytryptophan, buspirone or tansodpirone, sulfamethoxazole/trimethoprim or lamotrigine in SCA3, acetazolamide in SCA6, NMDA modulators or antagonists and deep brain stimulation in SCA2 with tremor. Dopaminergic and anticholinergics drugs have been used to alleviate tremor, bradykinesia or dystonia in SCA2 and SCA3. Restless legs and periodic leg movements in sleep usually respond to dopaminergic treatment. Spasticity in SCAs is effectively treated with baclofen, tizanadine or mimentine. In selected cases where other treatments have failed, botulinum toxin has been successfully used to treat dystonia and spasticity. Intention tremor has been ameliorated with benzodiazepines, β-blockers, or chronic thalamic stimulation. Muscle cramps, which are often present at the onset of the condition in SCAs 2, 3, 7 and DRPLA, are alleviated with magnesium, chinine or mexiletine.

The efficacy of lithium treatment has been examined in a knock-in mouse model of SCA1 ($Sca1^{154Q/2Q}$) that replicates many features of the human disease [102]. The effects of lithium on a marker altered early in the course of SCA1 pathogenesis, coupled with its positive effect on multiple behavioural measures and hippocampal neuropathology, make it an excellent candidate treatment for human SCA1 patients. Lithium has been reported to be beneficial in animal models of brain injury, stroke, Alzheimer's, Huntington's, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and spinal cord injury. Clinical trials assessing the effects of lithium in SCA1 and other neurodegenerative diseases are under way, and a recent clinical trial suggests that lithium halts the progression of ALS. Albeit there are clinical benefits of lithium treatment, common side effects include muscle tremors, twitching, ataxia and hypothyroidism. Long term use of lithium has been linked to hyperparathyroidism, hypercalcemia (bone loss), hypertension, kidney damage, nephrogenic diabetes insipidus (polyuria and polydipsia), seizures and weight gain. Albeit lithium is a promising drug that can be potentially beneficial to ataxia patients, clinical and biological responses to dose with time should be carefully evaluated and monitored in any clinical trial.

Innovative approaches, such as RNA interference (RNAi) with the aim of inhibiting polyglutamine-induced neurodegeneration, prevention of protein misfolding and aggregation by overexpression of chaperones and regulation of gene expression by application of histone deacetylase inhibitors, are proving effective in pre-clinical trials. In SCA1, intracerebellar injection of vectors expressing short hairpin RNAs profoundly improves motor coordination, restores cerebellar morphology, and resolves characteristic ataxin 1 inclusions in Purkinje cells of transgenic mice [103]. While these results prove that RNAi therapy improves cellular and behavioural characteristics in pre-clinical trials, its application in patients to protect or even reverse disease phenotypes shall be delayed until proper toxicity tests are assessed. Pointing to a different target, molecular chaperones provide a first line of defence against misfolded, aggregation-prone proteins. Many studies have analysed the effects that chaperone overexpression has on inclusion body formation and toxicity of pathogenic polyQ fragments in cell culture, and it is clear that overexpression of molecular chaperones might prove beneficial for the treatment of neurodegenerative diseases [104]. They prevent inappropriate interactions within and between non-native polypeptides, enhance the efficiency of de novo protein folding and promote the refolding of proteins that have become misfolded as a result of the mutations and cellular stress [105]. Chemical and molecular chaperones might also prevent toxicity by blocking inappropriate protein interactions, by facilitating disease protein degradation or sequestration, or by blocking downstream signalling events leading to neuronal dysfunction and apoptosis. Congo Red, thioflavine S, chrysamine G and Direct Fast have proved effective in suppressing aggregation in vitro and in vivo [106, 107], albeit their efficacy in vivo is limited by their abilities to cross the blood–brain barrier. Several low molecular mass chemical chaperones, such as the organic solvent dimethylsulfoxide and the cellular osmolytes glycerol, trimethylamine n-oxide and trehalose, have proved effective in preventing cell death triggered by mutant ataxin 3 by increasing its stability in their native conformation [108]. Trehalose was identified in an in vitro screen for inhibitors of polyQ aggregation, and its administration reduces brain atrophy, improves motor dysfunction, and extends the lifespan of mice resembling the polyglutamine disorder Huntington's disease [109]. In vitro experiments suggest that the beneficial effects of trehalose result from its ability to bind and stabilise polyglutamine-containing proteins. More recently, a new generation of small chemical compounds that directly target polyQ aggregation without significant cytotoxicity have been identified in high-throughput screens using cell-free assays or by targeting cellular pathways [110, 111]. These compounds inhibit polyQ aggregation in cultured cells and intact neurons and can rescue polyQ-mediated neurodegeneration in vivo. By a different mechanism, a small molecule that acts as a co-inducer of the heat shock response by prolonging the activity of heat-shock transcription factor HSF1, arimoclomol, significantly improves behavioural phenotypes, prevents neuronal loss, extends survival rates and delays disease progression in a mouse model of neurodegeneration [112]. Similarly, activation of heat-shock responses with geldana-

mycin inhibits aggregation and prevents cell death [113]. This suggests that pharmacological activation of the heat shock response may therefore be an effective therapeutic approach to treating neurodegenerative diseases. However, excessive up-regulation of chaperones might lead to undesirable side effects, such as alterations in cell cycle regulation and cancer [114]. Therefore, a delicate balance of chaperones is likely to be required for a beneficial neuroprotective effect. For instance, chemical or molecular chaperones, used in combination with a pharmacological agent that up-regulates the synthesis of molecular chaperones, might be a valid therapeutic approach for treating spinocerebellar ataxias caused by polyglutamine expansions. Aggregate formation has also been successfully targeted with inhibitors of transglutaminase, such as cystamine, which reduces apoptotic cell death and alleviates disease symptoms by the expanded polyglutamine [115, 116].

Compounds targeting mitochondrial function such as coenzyme Q10 [117], creatine [118] and taurousodeoxycholic acid (TUDCA) [119]; or autophagy, such as the mTor inhibitor rapamycin and various analogous [42], have proved effective at reducing cellular toxicity in animal models, and are currently being tested in clinical trials. Caspase activation, which usually precedes neuronal cell death, can be targeted with caspase inhibitors such as zVAD-fmk, CrmA, cystamine, FADD DN, and minocycline [77]. These have proved efficient to decrease microglia activation, prevent disease progression, delay onset of symptoms and extend survival rates in several mouse models of neurodegeneration [120–122]. Other agents promoting the clearance of mutant proteins in the CNS or Ca^{2+} signalling blockers and stabilisers, such as specific inhibitors of the NR2B-subunit of *N*-methyl-D-aspartate glutamate receptors, blockers/antagonists of metabotropic glutamate receptor mGluR5 and inositol 1,4,5-trisphosphate receptor InsP3R1, such as remacemide; intracellular Ca^{2+} stabilisers such as dantrolene; dopamine stabilisers, such as mermaid-ACR-16; dopamine depleters; and agents inducing anti-excitotoxic effects, such as riluzole, or alleviating cognitive components, such as horizon-dimebon; they all may be partially beneficial for the treatment of some neurological symptoms in spinocerebellar ataxias [71, 123, 124]. Neuroprotective drugs like olesoxime have proved to increase microtubule dynamics, re-establish neuritic outgrowth, improve myelination and prevent apoptotic factor release and oxidative stress [125]. Inhibition of potassium channels with 3,4-diaminopyridine has proved efficient in normalising motor behaviours in young SCA1 mice; and in restoring normal PC volume and dendrite spines density and the molecular layer thickness in older SCA1 mice. Aminopyridines, such as fampridine, increase PC excitability and are also efficient for treating down-beat nystagmus [126].

The role that some ataxins play in transcription and, more importantly, the suppression of cytotoxic effects mediated by some of their co-transcriptional regulators are being used to modulate the pathological effects of mutant ataxins, opening the path for new therapeutic strategies for treating some of the SCAs. Recent progress in HDAC research has made possible the development of inhibitors of specific HDAC family proteins and these compounds could prove effective candidates for treatment of spinocerebellar ataxias [127, 128]. Neuroprotective and neurorestoration strategies addressed to specific bioenergetic defects might hold particular promise in the treatment of spinocerebellar conditions. Drugs, such as rasagiline, have proved efficient in protecting neuronal cells against apoptosis through induction of pro-survival Bcl-2 and neurotrophic factors [129]. Recent alterations of the insulin growth factor (IGF-1) pathway have been reported to be implicated in both SCA1 and SCA7 [130], suggesting that in vivo neuroprotection exerted by IGF-1 through the PP2-regulated PI3K/Akt signalling pathway, could potentially be used to halt cerebellar neurodegeneration [131, 132].

Gene therapy and stem cell and grafting approaches are being considered for treating spinocerebellar neurodegenerations. Delivery of proteins or compounds by viral vectors represents one such gene therapeutic approach. Neural cell replacement therapies are based on the idea that neurological function lost during neurodegeneration could be improved by introducing new cells that can form appropriate connections and replace the function of lost neurons. This strategy although potentially effective is still in early experimental stages. Since neurogenesis does occur in the adult nervous system, another approach is based on the stimulation of endogenous stem cells in the brain or spinal cord to generate new neurons. Studies to understand the molecular determinants and cues to stimulate endogenous stem cells are under way [133]. Although promising, we are only starting to learn the potential and challenges of these emerging therapies, especially for their use in treating human neurodegeneration.

Conclusions

Herein, we review common themes occurring in spinocerebellar neurodegenerative conditions. Progressive neurodegeneration in spinocerebellar ataxias is mediated by mutant proteins capable of inducing neuronal damage and synaptic neurotransmission deficits by interfering with several conserved cellular and molecular pathways including protein aggregation and clearance, dysregulation of transcription and gene expression, the ubiquitin–proteasome system, alterations of calcium homeostasis, and activation of pro-apoptotic routes among others. These pathways interact and enhance

each other leading to the accumulation of cellular damage that eventually leads to dysfunction and, ultimately, the demise of neurons through a series of multiple events. This evidence indicates that targeting simultaneously several pathways is necessary to therapeutically prevent neurodegeneration, preserve neuronal function and alleviate the neurological symptoms. The growing understanding of how dysregulation of these pathways trigger the onset of symptoms and mediate disease progression is leading to the identification of conserved molecular targets influencing the critical pathways in pathogenesis that will serve as effective therapeutic strategies in vivo, which may prove beneficial in the treatment of spinocerebellar ataxias. Improved ataxia rating scales and SCA functional indexes recently developed [134, 135] to validate neurological assessment methods and therapeutic interventions will be very useful to measure the severity of the ataxia symptoms in future clinical trials in SCA patients.

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