Chapter 9
Molecular Mechanisms and Therapeutic Strategies in Spinocerebellar Ataxia Type 7

Alice Karam and Yvon Trottier

Abstract Spinocerebellar Ataxia type 7 (SCA7, OMIM # 164500) is an autosomal dominant neurodegenerative disorder characterized by adult onset of progressive cerebellar ataxia and blindness. SCA7 is part of the large family of autosomal dominant cerebellar ataxias (ADCAs), and was estimated to account for 1–11.7% of ADCAs in diverse populations. The frequency of SCA7 is higher where local founder effects were observed as in Scandinavia, Korea, South Africa and Mexico. SCA7 is pathomechanistically related to the group of CAG/polyglutamine (polyQ) expansion disorders, which includes other SCAs (1–3, 6 and 17), Huntington's disease, spinal bulbar muscular atrophy and dentatorubro pallidoluysian atrophy. Two distinctive characteristics of SCA7 are the strong anticipation by which earlier onset and more severe symptoms are observed in successive generations of affected families, and the loss of visual acuity due to cone-rod dystrophy of the retina. The pathology is caused by an unstable CAG repeat expansion coding for a polyQ stretch in Ataxin-7 (ATXN7). PolyQ expansion in ATXN7 confers toxic properties and leads to selective neuronal degeneration in the cerebellum, the brain stem and the retina. Herein, we summarize the genetic, clinical and pathological features of SCA7 and review our current knowledge of pathomechanisms and preclinical studies.

Keywords Spinocerebellar ataxia 7 · Polyglutamine expansion · Retinopathy Cerebellar degeneration · Aggregation

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9.1 Genetic, Clinical and Pathological Description

The causative mutation of SCA7 was identified in 1995 [1] and the ATXN7 gene was isolated in 1998 [2] and was shown to contain a polymorphic CAG repeat. The wild-type alleles of ATXN7 have between 4 and 36 CAG repeats, while SCA7 alleles have typically beyond 36 CAGs and can even reach >460 repeats [3]. Among CAG/polyQ disorders, SCA7 CAG repeats show the highest tendency to expand upon transmission, explaining the strong anticipation observed in families (mean 19 ± 13 years) [2, 4, 5]. The length of mutant CAG repeats is inversely correlated with the age of onset and the disease duration. The majority of SCA7 alleles ranges between 36 and 55 CAG repeats and are responsible for the classical adult-onset form, which progresses over several decades until death [4]. Repeats >70 CAG typically result in juvenile-onset forms with accelerated disease course. The repeat length also influences the symptoms at onset: large repeat expansions are typically associated with early onset and cause visual loss before cerebellar ataxia, while shorter expansions with later onset cause ataxia symptoms before visual loss [2, 6, 7]. Intriguingly, extremely large CAG expansions (>100 CAG) cause infantile forms with multisystem disorders such as failure to thrive, hypotonia, myoclonic seizures and noncentral nervous systems dysfunctions like congestive heart failure, patent ductus arteriosus, renal failure, and muscle atrophy, and lead to death within few years or months [3, 6, 8–12].

SCA7 progressive cerebellar ataxia is manifested by the inability to coordinate balance, gait, and speech. Additional neurological deficits include slow eye movement, opthalmoplegia, dysphagia, as well as pyramidal signs [2, 6]. Variable levels of cerebellar and pontine atrophy are observed by magnetic resonance imaging [2, 4, 13–16]. Neuropathologically, the neuronal loss is substantial in the Purkinje cell layer, in the dentate nuclei, in the inferior olivary nuclei and in basis pontis, which is associated with the atrophy of spinocerebellar and pyramidal tracts [4, 15, 17, 18]. Atrophy or loss of myelin is observed in the cerebellar white matter and extra cerebellar associated structures [16, 18]. Visual impairment in SCA7 first affects cone photoreceptors and then progresses toward a cone-rod dystrophy and complete blindness [10, 19–21]. Fundoscopy examination shows atrophic macula with granular pigmentation, pale areas with pigmentary atrophy and poor vasculature [4, 20]. Post-mortem retinal sections reveal almost complete loss of photoreceptors and substantial loss of the bipolar and ganglion neurons, associated with a severe thinning of the nuclear and plexiform layers especially in the foveal and parafoveal regions [4, 17, 22]. In addition, damages in the Bruch's membrane, retinal pigmentary epithelium and hypomyelinisation of the optic nerve were also reported [10, 15, 17, 20].

9.2 ATXN7 Protein

The ATXN7 gene encodes two protein isoforms, ATXN7a and ATXN7b, that harbor a polymorphic polyQ stretch in the amino-terminus, three nuclear localization signals (NLS) and one nuclear export signal (NES) (Fig. 9.1a). Besides the NLS and NES, the different C-termini of ATXN7a and ATXN7b are likely to control their subcellular localization, as ATXN7a appears predominantly in the nucleus and ATXN7b in the cytoplasm [23]. However, the extent to which the two isoforms contribute to SCA7 pathogenesis remains unclear, as most studies have been done so far with ATXN7a, which was identified first. ATXN7a and ATXN7b have three conserved domains that are shared with three paralogs, ATXN7L1, L2 and L3: a typical C2H2 zinc-finger (ZnF) motif, an atypical Cys-X9–10–Cys-X5–Cys-X2-His motif, now known as SCA7 domain, and a third domain absent in ATXN7L3 (Fig. 9.1a) [24]. ATXN7 is also regulated by

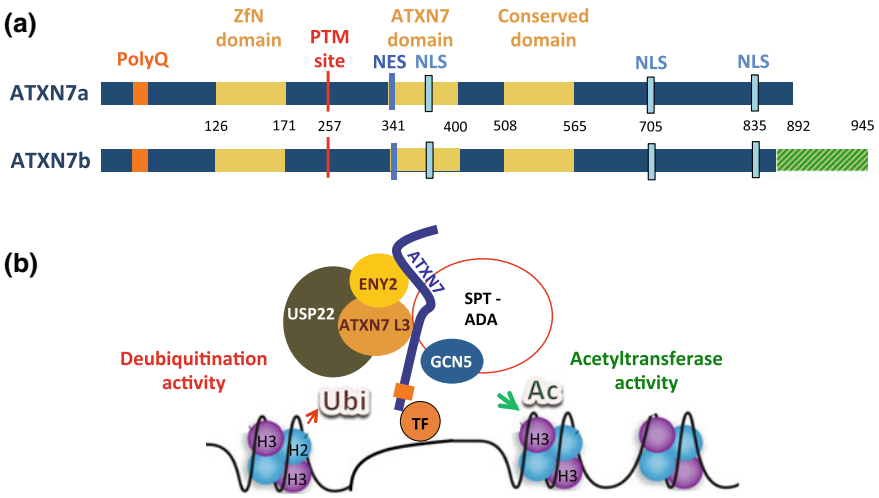

Fig. 9.1 Structural composition of ATXN7 and functional interactions with SAGA components. a Are depicted the sequences of ATXN7a and ATXN7b isoforms with 892 and 945 amino acids, respectively, corresponding to a wild-type allele with 10 CAG-encoding glutamine units. Wild-type alleles contain from 4 to 36 glutamine repeats, whereas mutant pathogenic alleles have beyond 36 glutamines and can even reach >460 residues. The conserved domains are indicated as yellow boxes: a typical C_2H_2 zinc-finger (ZnF) motif, an atypical Cys-X9–10–Cys-X5–Cys-X2-His motif known as ATXN7 domain and a third conserved domain. ATXN7 isoforms have three nuclear localization signals (NLS), one nuclear export signal (NES) and one site (lysine 257) for post-translational modifications including acetylation and SUMOylation, but differ at their carboxy-terminal end. **b** ATXN7 appears to be a molecular scaffold of SAGA. ATXN7 belongs to the deubiquitination module (DUBm), together with the ubiquitin protease USP22, ATXN7L3, and ENY2, and mediates the interaction with GCN5 and the SAGA core complex (SPT-ADA; other subuits are not indicated). ATXN7 can also interact with transcriptional factors such as CRX. SAGA complex harbors both histone acetylation (dependent of GCN5) and deubiquitination (dependent of USP22) activities on histones H3 and H2B, respectively

SUMOylation and acetylation [25, 26]. ATXN7 mRNA and protein are widely expressed in neural and non-neural tissues [27–33]. There is no apparent correlation between cellular or subcellular localization and the vulnerability of neurons to degeneration in SCA7.

ATXN7 and its yeast ortholog sgf73 are core components of SAGA complexes (Spt-Ada-Gcn5 Acetyltransferase) involved in chromatin remodeling (also known in human as the TBP-free TAF-containing complex (TFTC) and the SPT3-TAF9–GCN5 complex (STAGA) [24, 34–36]. SAGA complexes harbor both histone acetylation (dependent of GCN5) and deubiquitination (dependent of USP22) activities, located in distinct functional modules (Fig. 9.1b). ATXN7 belongs to the deubiquitination module (DUBm) together with the human ubiquitin protease USP22, ATXN7L3, and ENY2. Histone acetylation is known to increase decompaction of chromatin and the accessibility of gene promoters to transcription factors, while deubiquitination of monoubiquitinated H2B (H2Bub) is required for optimal transcriptional initiation/elongation [37]. Bonnet et al. [38] recently unveiled a role of SAGA in general RNA polymerase II recruitment and transcription. SAGA is recruited to all active genes to acetylate H3K9 on promoters and to deubiquitinate H2Bub on gene bodies in yeast and human cells. On the contrary to the ATXN7 nuclear function, the role of ATXN7 in the cytoplasm is yet unclear. When overexpressed, ATXN7 associates with and stabilizes microtubules [39]. Yeast two-hybrid screen showed that ATXN7 interacts with several cytoplasmic proteins associated with the vesicular system and centrosomes [40]. In fly and zebrafish, inactivation of ATXN7 causes defect in retina and brain development [41, 42]. In zebrafish, ATXN7 seems to be required for full differentiation of photoreceptors and Purkinje neurons, suggesting that partial loss of function of wild type ATXN7 may account for the selective degeneration in SCA7. The physiological role of ATXN7 in tissue development and homeostasis thus deserves further investigation.

9.3 Pathomechanisms Underlying SCA7 Neurodegeneration

9.3.1 Commonalities and Differences Between PolyQ Disorders

SCA7 and other polyQ disorders share a number of common features. They are adult-onset and progressive neurodegenerative diseases. The dominant inheritance and genetic experimentations indicate that polyQ expansion confers toxic properties to mutant proteins. The toxicity increases with the expanded polyQ length and the age of disease onset and the severity of symptoms are function of the polyQ length. There is an apparent polyQ length threshold above which the disease becomes fully penetrant. Finally, a hallmark of polyQ diseases is the intracellular accumulation of amyloid-like aggregates containing protein fragments bearing the polyQ expansion

[43]. However, polyQ disorders differ on many aspects. While the mutant proteins bear a similar polyQ tract, they do not share any other domain and have different cellular functions. The polyQ proteins are ubiquitously expressed, however, neuronal degeneration affects specific and different brain regions, leading to disease specific symptoms. Therefore, particularities of each disease must come from the protein context into which the polyQ expansion is embedded.

Our current understanding of SCA7 pathogenesis relies on biochemical, molecular and cellular studies and on the characterization of model systems developed in yeast, fly and mouse. Hereafter, we discuss the major characteristics of mutant ATXN7 (mATXN7) toxicity, which might underlie the unique features of SCA7 pathogenesis.

9.3.2 mATXN7 Misfolding, Accumulation and Toxicity

One major consequence of the polyQ expansion mutation is the intensive intracellular accumulation of mATXN7 in disease tissues. Studies in SCA7 mouse models showed the time-dependent accumulation of mutant, but not wild type ATXN7 in neuronal nuclei [44, 45]. mATXN7 accumulation is faster in neurons targeted by the disease than in spared neurons. Ultimately, protein accumulation leads to the formation of mATXN7 aggregates, observed as nuclear inclusions (NIs) by immunohistochemistry. In post-mortem brains, NIs are widely distributed in degenerated and non-degenerated tissues [18]. However, in SCA7 mice, NIs form faster in vulnerable tissues such as retina and cerebellum, although their detection occurs after the onset of functional defects [44]. The role of NIs in the pathogenesis of polyQ disorders is actively debated. It is now thought that small oligomeric or multimeric forms of the misfolded mutant protein, not visible by immunohistochemistry, are the most toxic species. These species are indeed readily detected at very early stages in SCA7 mice using biochemical approach [44]. PolyQ expansion appears to stabilize mATXN7, which could happen because of a slower turnover, by a propensity to stably oligomerise or both (Fig. 9.2).

One important step in mATXN7 accumulation and toxicity is the proteolysis. Indeed, an amino-terminal fragment of about 55 kDa containing the polyQ expansion is detected in protein samples from SCA7 mice and from SCA7 patients [46], and appears to be the major component of NIs in SCA7 mouse [47]. A similar fragment can be released by caspase-7 cleavage in vitro and in vivo and was shown to be more cytotoxic than the full-length mATXN7 [48]. Interestingly, transgenic mice expressing a mATXN7 form that contain a mutation at the caspase-7 cleavage site show reduced neurodegeneration, improved visual and motor performance and prolonged lifespan [49]. These results suggest that the caspase-7 cleavage is a major step in the pathogenesis. The presumed size of the mATXN7 fragment is short enough for passive diffusion through nuclear pore complexes, but is retained in the nucleus [48]. It harbors the polyQ expansion and the ZnF domain, but not the ATXN7 domain. With this composition, the mATXN7 fragment may alter the

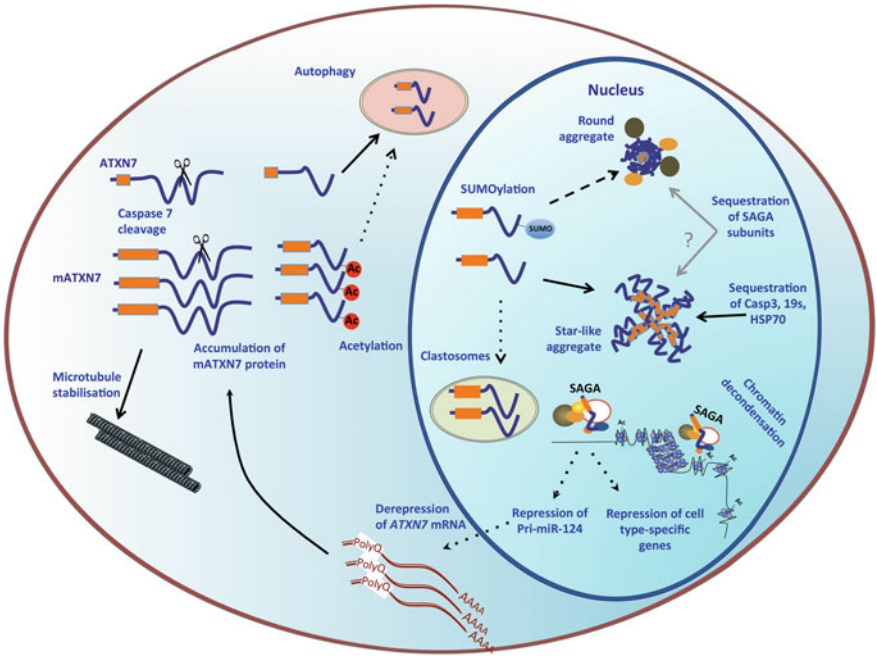

Fig. 9.2 Pathogenic events underlying SCA7 pathogenesis and potential therapeutic targets. Mutant ATXN7 (mATXN7) accumulates and is cleaved by caspase-7 to release amino-terminal fragments (Nter). Acetylation of Nter-mATXN7 at K257 prevents its degradation by autophagy in the cytoplasm. In the nucleus, proteosomal activity of clastosomes, which normally degrades mATXN7, is overwhelmed, leading to mATXN7 accumulation. Aggregation of SUMoylated mATXN7 leads to the formation of «round» aggregates, while the non-SUMOylated mATXN7 forms «star-like» aggregate, which sequestered the activated caspase-3, 19 s proteasome subunit, and HSP70. Components of SAGA (GCN5, ATXN7L3 and USP22) are also sequestered in aggregates. Transcriptional alterations resulting from SAGA dysfunction and perturbation of transcription regulators such as CBP, p53, RORalpha1, lead to down-regulation of cell type-specific genes (such as photoreceptor- and oligodendrocyte-specific genes) and of Pri-miR-124. The low level of miR-124 causes the accumulation of ATXN7 mRNA, which in turn leads to increased level mATXN7. The involvement of non-coding RNA *lnc-SCA7* in the regulation of ATXN7 mRNA level is not depicted here. Therapeutic opportunities include: (i) blocking proteolysis with caspase inhibitors; (ii) preventing acetylation by overexpressing deacetylase; (iii) preventing nuclear accumulation by inducing clastosome formation with interferon beta; (iv) inhibiting the formation of toxic aggregates; (v) upregulating transcription by inhibiting histone deacetylation or ubiquitination or by treatment with neurotrophy factors such as HGF and with the antibiotic Ceftriaxone; (vi) preventing ATXN7 mRNA accumulation or translation using RNA inhibition; (vii) preventing mATXN7 binding to microtubules

function of SAGA complex, either by replacing the full-length protein in the complex or by aggregation and sequestration of SAGA components.

Further analysis indicated that the accumulation of the mATXN7 fragment is associated with an increased acetylation at lysine-257 (K257) located close to the caspase-7 cleavage site [50]. In the absence of lysine acetylation, the fragment is

degraded by autophagy. These results suggest that aberrant K257 acetylation prevents the clearance of the fragment by autophagy, and thereby slows down its turnover. Interestingly, the same K257 residue was shown to be a specific site for SUMOylation [26]. SUMO modification not only decreases the propensity of mATXN7 to aggregate, but also influences the shape and the protein composition of aggregates. With SUMO, aggregates are homogenous, round and strongly stained with SUMO antibodies, while in the absence of SUMO, aggregates are heterogeneous, have a star-like shape and are immunostained for chaperones, proteasomes and activated caspase-3, suggesting that this type of aggregates are associated with cells that undergo cytotoxic. In conclusion, proteolysis and post-translational modifications are involved in the accumulation of ATXN7. Whether acetylation and SUMOylation are in competition to modify K257 in order to trigger specific mATXN7 fate or whether they act successively on K257 through rounds of deacetylation/deSUMOylation remain to be determined.

In the brain of SCA7 patients, mATXN7 aggregates often colocalize with nuclear bodies formed by the promyelocytic leukemia (PML) protein [51, 52]. A subset of PML bodies formed by PML IV isoform and known as clastosomes, contain components of ubiquitin-proteasome system and chaperones and were suggested to be a site for protein degradation in the nucleus. Interestingly, PML IV-positive clastosomes actively recruit soluble mATXN7, but not the wild type form, for degradation through the proteasome [53]. Moreover, interferon beta, which induces PML IV expression and clastosome formation, enhances the clearance of the mATXN7 and increases the survival of rat primary Purkinje neurons [53, 54]. In patients, endogenous clastosomes might prevent the accumulation of mATXN7 for several decades before onset of aggregation. Over time, the degradative activity of clastosomes might be overwhelmed by the aggregation process.

9.3.3 Transcriptional Alterations

Studies performed on cellular and mouse models of SCA7 have identified transcriptional alterations as an early pathogenic event associated with neuronal dysfunction [44, 55–58]. Transcriptome analysis of SCA7 mouse retina revealed an early and progressive down-regulation of most photoreceptor-specific genes [55], while expression profile of SCA7 mouse cerebellum showed down-regulation of genes involved in the maintenance and function of neuronal dendrites and CNS myelin sheath [56].

The possibility that transcriptional alterations in SCA7 could result from dysfunction of SAGA acetylation and deubiquitination has been explored in several studies, specially because mATXN7 had been shown to properly incorporate in SAGA [24, 34, 59]. The outcome of these studies differs given the model system investigated. In yeast and HEK2937 kidney cells, mATXN7-containing SAGA lacks critical subunits and leads to the reduction of GCN5 acetylation activity and gene transcription [34, 59]. In agreement with GCN5 dysfunction, promoters of

photoreceptor-specific genes were shown to have histone H3 hypoacetylation, which would explain their decreased expression in SCA7 mouse retina [34]. However, at variance with the above studies, mATXN7-containing SAGA purified from SCA7 mouse retina was correctly assembled and had normal acetylation activities [57]. In this study, promoters of photoreceptor-specific genes were found hyperacetylated, but the presence of RNA Pol II on promoters was strongly reduced, which would explain the low level of photoreceptor-specific mRNA transcripts [57]. The discrepancy between these studies is yet unclear and might dependent on the use of two different SCA7 mouse models [Prp SCA7-c92Q and R7E (see Table 9.1)] or on the analysis of different stages of retinal degeneration.

Table 9.1 Mouse models of SCA7 retinal degeneration

Models	Design[a]	Retina pathology[b]	References
R7E (R7N)	Human rhodopsin (rods) ATXN7a cDNA 90Q (10Q)	(i) Reduction of rod then cone ERG activity (ii) Thinning of retina layer, loss of photoreceptor OS and polarity, enlargement of nucleus, dark degeneretion, apoptosis, proliferation, gliosis (iii) Expression profiles showed repression of photoreceptor-specific genes and re-activation of developmental gene; chromatin decondensation and H3 hyperacetylation; activation of cellular stress response signaling (iv) Onset at 3–5 weeks	[24, 47, 55, 57, 68, 72, 73]
Prp SCA7-c92Q (Prp SCA7-c24Q)	Murine prion (brain except for PC) ATXN7a cDNA 92Q (24Q)	(i) Reduction of cone then rod ERG activity (ii) Thinning of retina layer, apoptosis, gliosis (iii) Repression of photoreceptor-specific genes; H3 hypocetylation (iv) Onset at 11 weeks	[34, 58]
$SCA7^{266Q/5Q}$ (WT mice)	Mouse ATXN7 mouse ATXN7 266Q(5Q)	(i) Reduction of cone then rod ERG activity (ii) Thinning of retina layer, loss of photoreceptor OS, enlargement of nucleus, apoptosis, gliosis (iii) Repression of photoreceptor-specific genes; chromatin decondensation (iv) Onset at 5 weeks	[44, 57]
$SCA7^{100Q/100Q}$ (WT mice)	Mouse ATXN7 mouse ATXN7 100Q(5Q)	(i) Reduction of rod ERG activity (ii) Thinning of retina layer, loss of photoreceptor OS, dark degeneration (iii) Reduced expression of photoreceptor-specific genes (iv) Onset at 6 weeks(transcription anomalies)	[61][c]

BAC bacterial artificial chromosome; *PC* Purkinje cells; *OS* outer segments
[a]promoter/targeted cells/cDNA or gene/repeat length
[b](i) dysfunction; (ii) neuropathology; (iii) molecular altertions; (iv) onset
[c]YT personal observations

Interestingly, histone hyperacetylation in R7E mouse retina correlates massive chromatin decondensation of photoreceptor nuclei, which are enlarged compared to wild type [57]. It is thus possible that the overall perturbation of chromatin organization accounts for major changes in the expression of photoreceptor-specific genes. Besides hyperacetylation, chromatin decondensation in R7E retina might also result from an abnormal low expression of histone H1, which is involved in chromatin compaction [60]. The importance of GCN5 in SCA7 pathogenesis was recently addressed using a mouse genetic approach [61]. One allele inactivation of GCN5 accelerates retina degeneration in SCA7 mice, but does not worsen the transcriptional repression of photoreceptor-specific genes, suggesting that GCN5 might have non-transcriptional function in the retina. Furthermore, total loss of GCN5 in Purkinje cells leads to milder ataxia than SCA7 mouse ataxia. This suggests that GCN5 could participate to some degree to SCA7 cerebellar ataxia. Potential dysfunction of DUBm activity of SAGA has also been investigated in SCA7 cellular and mouse models. Monoubiquitination of H2B is globally increased in cultured cells expressing mATXN7 and in the cerebellum of SCA7 mice, but in the latter correlation with transcriptional alterations has not been established [62–64]. Two components of DUBm, ATXN7L3 and USP22, are sequestered in mATXN7 aggregates, which might lead to DUBm dysfunction and hence an increased H2Bub [63, 64]. Although the current data would support that SAGA dysfunction accounts for SCA7 transcriptional dysregulations, it remains to determine how the dysfunction of a general co-activator complex like SAGA, which is involved in the expression of all RNA Pol II-regulated genes, would only affect specific subsets of genes in SCA7 affected tissues.

Interestingly, a recent study suggests that the increased expression of mATXN7 would be an indirect consequence of mATXN7-containing SAGA dysfunction [65]. In fact, SAGA regulates the microRNA miR-124, which in turn controls the abundance of ATXN7 transcripts and of a non-coding RNA lnc-SCA7. The level of lnc-SCA7 also seems to control the level of ATXN7 transcripts by a mechanism yet unclear. Dysfunction of SAGA in SCA7 leads to post-transcriptional derepression of ATXN7 transcripts, due to the reduced level of miR-124 and the increased level of lnc-SCA7. Given that miR-124 is highly expressed in the cerebellum and retina and that the levels of lnc-SCA7 and ATXN7 are tightly correlated, the cross-talk between these two noncoding RNAs in the post-transcriptional regulation of ATXN7 transcripts is thought to account for the tissue specificity of SCA7.

Besides SAGA dysfunction, other mechanisms are proposed to contribute to chromatin modifications and transcriptional alterations in SCA7. mATXN7 aggregates sequester CBP [45], a histone acetyltransferase, and impair CBP-mediated and RORalpha1-mediated transcription in cultured neurons [66]. Most interesting, a study in PC12 cells made a link between metabolic defect in SCA7 and transcriptional alterations [67]. Abnormal mitochondria were observed in SCA7 mouse retina, [68] and reduced electron transport chain activity and metabolic acidosis were reported in muscle biopsy of patients [69]. In PC12 cells expressing mATXN7, p53 is sequestered in aggregates and its transcriptional activity is reduced, leading to dysregulation of metabolic proteins, such as TIGAR, AIF and

NOX1 [67]. These alterations result in a reduced respiratory capacity, associated with an increased reliance on glycolysis for energy production and a subsequent reduction of ATP in SCA7 cells. Investigation of these transcriptional and metabolic pathways in SCA7 mice is thus warranted, in particular because loss of AIF in mice results in primarily neurodegeneration of cerebellar and retinal neurons.

9.4 Insights from Pathophysiological Studies of SCA7 Mouse Models

Different transgenic and knock-in mouse models have been generated during the past years and have provided important insights into the nature of SCA7 neurodegeneration (Tables 9.1 and 9.2).

9.4.1 Retinopathy

In SCA7 models, the retina develops normally before showing a progressive reduction of electroretinograph activity, thinning of the retina and repression of photoreceptor-specific genes [44, 47, 58]. Early on, these transcriptional alterations were attributed to the dysfunction of CRX (cone-rod homeobox protein), a key transcription factor of photoreceptor genes. This is because CRX was previously shown to require interaction with ATXN7 and SAGA for its transactivation activity on photoreceptor gene promoters, and because mATXN7 was shown to suppress the transactivation activity in SCA7 retina [58, 70]. Later on, analysis of SCA7$^{266Q/5Q}$ KI and R7E mouse retina showed that transcriptional alterations were not restricted to CRX target genes [44, 55]. In particular, the expression profile of R7E retina unveiled the dysregulation of transcriptional programs controlling the maintenance of mature photoreceptors, thus showing on the one hand the down-regulation of the photoreceptors specific transcription factors CRX, NRL (neural retina leucine zipper protein), and Nr2E3 (Nuclear Receptor Subfamily 2, Group E, Member 3) as well as most of their target genes, and on the other hand the re-activation of OPTX2, STAT3 and HES5 that normally inhibit the differentiation of precursor neurons into mature photoreceptors during development [55]. And indeed, SCA7 photoreceptors progressively lose their outer segments and cell polarity, and relapse to round cell shape [68]. Thus, SCA7 retinopathy primarily results from the progressive regression of mature photoreceptor to an ill-defined state, which occurs long before cell demise (Fig. 9.3a). This atypical scheme of slow degeneration contrasts with most photoreceptor degenerative processes reported in mice, where alterations of outer segment integrity rapidly leads to cell death [71]. Yet the initial trigger leading to SCA7 photoreceptor degeneration remains to be determined.

Table 9.2 Mouse models of SCA7 cerebellar degeneration

Models	Design[a]	Cerebellar pathology[b]	References
P7E (P7N)	Pcp-2 (Purkinje) hATXN7a cDNA 90Q (10Q)	(i) Reduction of rotarod function (ii) Purkinje reduced dentritic (iii) Sequestration of chaperones and proteasome subunits in aggregates (iv) Onset at 11 months	[45, 47]
B7E2 (B7N)	PDGF-ß (ubiquitous) ATXN7a cDNA 128Q (10Q)	(i) Ataxic phenotypes (ii) Purkinje reduced dentritic arborization (iii) Sequestration of transcription factors and co-regulators in aggregates (iv) Onset at 3–5 months	[45]
Prp SCA7-c92Q (Prp SCA7-c24Q)	Murine prion (brain except PC) ATXN7a cDNA 92Q (24Q)	(i) Reduction of rotarod function (ii) Purkinje neuron shrinkage, reduced dentritic arborization and dark degeneration (no cell loss); thickened Bergmann glia radial processes, reduced glutamate uptake (iii) Reduced GLAST expression and -dependent glutamate uptake (iv) Onset at 13–15 weeks	[46, 74]
Gfa2-SCA7-92Q (Gfa2-SCA7-10Q)	Human Gfa2 (Bergmann glia) ATXN7a cDNA 92Q (10Q)	(i) Reduction of rotarod function (ii) Purkinje neuron shrinkage, reduced dentritic arborization and dark degeneration; thickened Bergmann glia radial processes, reduced glutamate uptake (iii) Reduced GLAST expression and GLAST-dependent glutamate uptake (normal GLT1 expression) (iv) Onset at 9–12 months	[74]
PrP-floxed-SCA7-92Q BAC	BAC murin prion (whole brain) floxed ATXN7a cDNA 92Q	(i) Reduction of rotarod function; reduced stride length on footprint (ii) Purkinje reduced dentritic arborization; reduced molecular layer thickness; late thickened Bergmann glia radial processes (iii) Reduced EAAT4 glutamate transporter expression (normal GLAST expression) (iv) Onset at 21 weeks	[76, 84, 85]
Ataxin-7-Q52 (WT mice)	PDGF-ß ATXN7 cDNA 52Q	(i) Reduction of rotarod function; decreased locomoter activity; ataxic wobbling gait (ii) Purkinje neuron shrinkage and reduced dentritic arborization (no cell loss); loss of inferior olive neurons	[56]

(continued)

Table 9.2 (continued)

Models	Design[a]	Cerebellar pathology[b]	References
		(iii) Expression profiles showed reduced expression of oligodendrocyte myelin specific genes and deregulation of many other pathways; p53 activation of Bax and Puma (iv) Onset at 9 months	
$SCA7^{266Q/5Q}$ (WT mice)	Mouse ATXN7 mouse ATXN7 266Q (5Q)	(i) Reduction of performance on rotarod, beam walking test balance and fine paw coordinatio)n and locotronic test (motor coordination); reduced survival (ii) Purkinje neuron shrinkage (no reduced dentritic arborization and no cell loss); gliosis (iii) Reduced GLAST and GLT1 expression; increased Interferon beta (iv) Onset at 5 weeks	[44, 54, 75]
$SCA7^{100Q/100Q}$ (WT mice)	Mouse ATXN7 mouse ATXN7 100Q (5Q)	(i) Reduction of performance on rotarod, footprint anomalies, reduced survival (11 months) (ii) Purkinje neuron shrinkage (no cell loss); gliosis	[61]

BAC bacterial artificial chromosome; *PC* Purkinje cells; *OS* outer segments
[a]promoter/targeted cells/cDNA or gene/repeat length
[b](i) dysfunction; (ii) neuropathology; (iii) molecular alterations; (iv) onset

Degenerating photoreceptors in SCA7 retina ultimately die through a mechanism reminiscent of dark neuronal cell death [68]. Dark degeneration also occurs in SCA7 mouse cerebellum and was reported in several mouse models of polyQ disorders. Interestingly, apoptosis was also observed in R7E mouse retina, but only occurs for a short time window during early disease stages. Concomitant with the apoptotic wave, stealthy cells expressing proliferation markers were observed, which afterwards express photoreceptor specific genes, suggesting that new photoreceptors might be produced to replace the dead ones at early disease stages. From these observations, it appears that R7E photoreceptors go through different cell fates as a response to mATXN7 toxicity (e.g. apoptosis, cell reshaping, dark degeneration, proliferation, etc.) [68]. Different cellular responses may be triggered by different mATXN7 toxic species, since the relative amount of full-length mATXN7, proteolytic fragments, soluble and insoluble aggregates varies considerably from early to late disease stages and might influence the way individual photoreceptors respond to these different proteotoxic products [68]. The overall proteotoxic stress in R7E retina induces a stress response involving the Jnk/c-Jun signaling pathway, which in turn accounts for Nrl repression [72, 73]. It was shown that inhibition of c-Jun activation delays retinal degeneration in R7E mice.

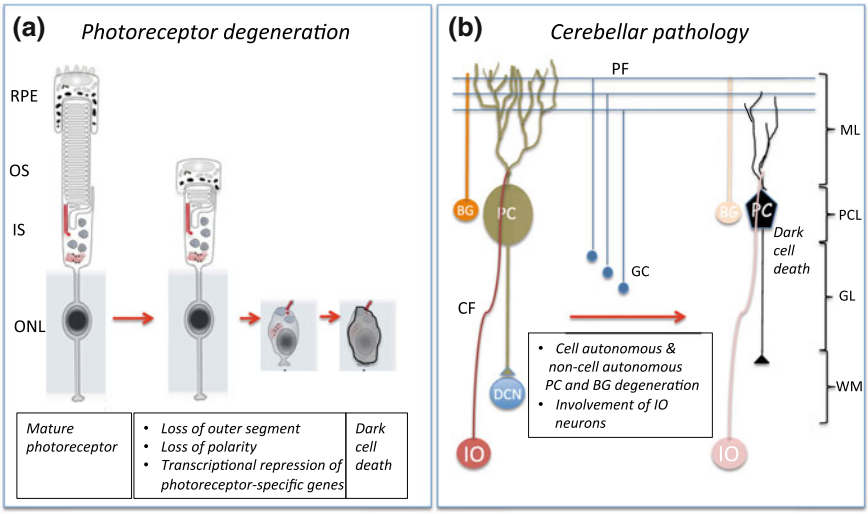

Fig. 9.3 Schematic of the major degenerative pathways of photoreceptors (a) and Purkinje neurons (b) in SCA7 mice. ONL, outer nuclear layer; IS, inner segment; OS, outer segment; RPE, retinal pigmented epithelium; PC, Purkinje cell; BG, Bergmann glia; IO, inferior olive; GC, granular cell; DCN, deep cerebellar nuclei; CF, climbing fiber; PF, parallel fiber; GL, granular layer; ML, molecular layer; PCL, Purkinje cell layer; WM, white matter. Other cerebellar cell types are not depicted

9.4.2 Cerebellar Pathology

Analyses of the PrP-SCA7-c92Q mouse model have highlighted the importance of cell–cell interactions in the cerebellar pathology [46]. These mice develop motor defects and show dark degenerating Purkinje neurons. Interestingly, Purkinje cell pathology occurs despite the fact the MoPrP promoter drives the expression of mATXN7 in all cerebellar neurons, except for Purkinje cells, suggesting that they are affected via a non cell-autonomous mechanism. In this model, Bergmann glia cells, which also express mATXN7, display pathological signs as well [74]. Given that Bergmann glia are regulators of glutamate levels in the surrounding environment of Purkinje cells and that dark degeneration often results from excitotoxicity, new transgenic mice were generated to express mATXN7 only in Bergmann glia cells to assess whether the pathology would affect Purkinje cells as well. Indeed, Gfa2-SCA7-92Q mice also show Purkinje cell degeneration and motor dysfunctions. Moreover, in this model, like in PrP-SCA7-c92Q mice, Bergmann glia cells express low levels of the glia-specific glutamate transporter GLAST, and hence have a decreased glutamate uptake function, supporting the hypothesis that glutamate accumulation leads to excitotoxicity and Purkinje dark degeneration [74]. However, compared to PrP-SCA7-c92Q mice, Gfa2-SCA7-92Q mice develop a late onset and milder ataxia, suggesting that other dysfunctional neurons may account for PC degeneration in PrP-SCA7-c92Q mice. Several pathological features of PrP-SCA7-c92Q were replicated in SCA7$^{266Q/5Q}$ KI mice, including decreased

motor functions, shrunken Purkinje cells and reduced expression of GLAST as well as GLT-1 (also named EAAT2 or SLC1A2), another glia-specific glutamate transporter [75].

The contribution of different cell types and their interaction to the cerebellar pathology was further addressed using a new set of engineered mice in which mATXN7 cDNA was flanked by loxP sites at the start site of translation in the murine PrP gene in a bacterial artificial chromosome (PrP-floxed-SCA7-92Q BAC) [76]. When crossed with mice expressing Cre recombinase under Bergmann glia promoter (Gfa2) or under promoter specific to Purkinje and inferior olive neurons (Pcp2), mATXN7 was deleted specifically in these cell types. Deletion of mATXN7 from Bergmann glia has mild beneficial effects and does not prevent Bergmann glia pathology. In contrast, deletion of mATXN7 from Purkinje and inferior olive neurons improves motor performance and histopathology as well as prevents Bergmann glia pathology. Finally, deletion of mATXN7 in the three cell types is more effective to prevent the pathology. These observations led to two conclusions. First, Bergmann glia pathology is in large part non-cell autonomous in SCA7. Second, it is likely that the dysfunction of inferior olive neurons accounts for the SCA7 motor dysfunction. This is because it was observed that the cerebellar pathology in P7E mice, which express mATXN7 only in Purkinje cells, is less severe than in PrP-SCA7-c92Q mice, which express mATXN7 in all cerebellar neurons, except for Purkinje cells. Together, these results further highlight a complex cell–cell interaction between Bergmann glia, Purkinje and inferior olive neurons in the development of SCA7 cerebellar dysfunction (Fig. 9.3b).

The expression profile of the cerebellum of Ataxin-7-Q52 transgenic mice, which also display motor dysfunction and Purkinje cell pathology, revealed gene deregulations affecting different pathways including synaptic transmission, axonal transport, glial functions and neuronal differentiation [56]. Perhaps the most interesting finding is the down regulation of a set of myelin-associated proteins (CNP, MAG, MBP, MOG, MOBP and PLP1) and of their regulators, the transcription factor Olig1 and transferrin [56]. This is consistent with the loose and poorly compacted myelin sheaths observed in the cerebellar white matter of these mice, and with the myelin pallor and loss of myelinated fibers reported in the cerebellar white matter of SCA7 patients [18]. Defect in white matter in SCA7 might also result from excitotoxic mechanisms, as relation between excitotoxicity and structural and functional damage to the white matter was observed in injury models [77]. Reminiscent to the loss of photoreceptor maturation in SCA7 mouse retina, mATXN7 toxicity might compromise genetic programs controlling oligodendrocyte maturation and myelin sheath integrity and function.

9.5 Opportunities for Therapeutic Development

Cellular and mouse models have provided several directions for therapeutical strategies (Fig. 9.2). Given the vulnerability of Purkinje cells to excitotoxicity-mediated dark degeneration and the reduced expression of GLAST and GLT-1, any

strategy to diminish glutamate levels in the cerebellum deserves consideration for preclinical assays with SCA7 mice. One of them is the β-lactamic antibiotic ceftriaxone, which induces GLT-1 expression via NF-kappaB and hence promotes glutamate clearance [78]. Interestingly, administration of ceftriaxone in the SCA28 murine model ($Afg3l2^{+/-}$) protects Purkinje cells from excitotoxicity-mediated dark degeneration [79]. The ceftriaxone-induced GLT-1 expression was long lasting and effective enough to prevent the onset of ataxia in pre-symptomatic and to stop the progression in post-symptomatic mice. In addition to its protective effect on Purkinje cells, the reduction of glutamate levels in the cerebellum might as well be beneficial for the function and maintenance of oligodendrocytes [77]. Ceftriaxone is a promising compound for SCA7 as well as for other SCAs showing excitotoxic-mediated Purkinje cell degeneration.

Another potential therapeutic strategy would be to provide factors with neurotrophic effects in the cerebellum and retina. In particular, the genetic programs of mature photoreceptors and oligodendrocytes are altered and represent specific targets for therapeutic intervention. Although a variety of strategies exist to enhance the protection of these cells [80, 81], the identification of initial triggers that compromise the genetic maturation programs deserves further attention to orientate the therapeutic development. Interestingly, hepatocyte growth factor (HGF) plays a neurotrophic role in the cerebellum during development and in adults [82]. Overexpression of HGF was shown to provide beneficial effect in ALS mice by maintaining GLT-1 levels [83]. Overexpression of HGF in $SCA7^{266Q/5Q}$ KI mice restores GLT-1 and GLAST levels, protects Purkinje cells from shrinkage and reduces motor dysfunction [75]. HGF is currently under consideration for therapeutic development of a number of human pathologies including brain injury, which will contribute to evaluate its efficacy and safety.

One of the most significant therapeutic target is the intracellular accumulation of mATXN7, which strongly correlates with the initiation and progression of SCA7. This has encouraged the implementation of several strategies to prevent mATXN7 accumulation and aggregation, to increase clearance or to interfere with protein synthesis. For instance, the strategy consisting in caspase-7 cleavage inhibition through pharmacological approach or genetic intervention is promising, as proteolysis is an early step in protein accumulation [49]. Interferon beta, which fosters the clearance of mATXN7 over the wild type form through the induction of PML-clastosomes, protects cultured rat primary Purkinje neurons [53, 54]. Interferon beta has been investigated in preclinical assay in $SCA7^{266Q/5Q}$ KI mice and treatment of asymptomatic mice significantly decreases mATXN7 aggregation and improves motor functions [54]. The treatment was not efficient enough to protect against weight loss and premature death, likely because this mouse model has a very severe disease course. Nevertheless, since interferon beta has been used for many years in the treatment of multiple sclerosis, it may hold promise as a potential treatment to delay motor symptoms in SCA7 patients.

One emerging strategy to prevent the expression of toxic polyQ proteins makes use of RNA interference (RNAi), a natural process of gene silencing mediated by small RNAs. RNAi is widely used for biological applications and is now being

harnessed to silence mRNAs encoding pathogenic proteins for therapy. As with any therapeutics, the clinical usefulness of RNAi will depend on its efficacy and safety. To this end, several issues were addressed in preclinical assays using mouse models. Furrer et al. [84] asked to which level mATXN7 must be suppressed in PrP-floxed-SCA7-92Q BAC mice to rescue the phenotype. The results indicate that a reduction of 50% even after the onset of motor phenotype, can prevent disease progression and achieve important amelioration of motor function, cerebellar neuropathology and mATXN7 aggregation. Another important issue concerns potential deleterious effects that could result from concomitant wild-type mRNA suppression. Lessons from zebrafish and fly indicated that partial inhibition of wild-type ATXN7 could affect the differentiation of photoreceptor and Purkinje neurons [41, 42]. Ramachandran et al. [85] utilized adeno-associated viral vectors to introduce miRNA in the deep cerebellar nucleus of Prp SCA7-92Q BAC mice and to test non allele specific silencing where both wild type mouse and mutated human ATXN7 were reduced by about 35–50%. The authors found a significant improvement of motor functions and cerebellar neuropathology, and reexpression of genes abnormally reduced in untreated mice. The non allele specific silencing appeared well tolerated and can be added to the list of similar strategies successfully developed in other polyQ disease models. Nevertheless, selective inhibition of the mutant transcript that would leave the wild-type one intact would be safer and is in theory feasible by exploiting differences between transcripts down to a single base pair; the RNAi sequence would have a complete homology to the mutant transcript and a single nucleotide mismatch with the wild type. In populations with strong founder effect such as South African, a common SNP linked to the SCA7 mutation was identified in 50% of SCA7 patients [86]. Using short-hairpin RNA targeting this polymorphism, allele-specific mATXN7 suppression was achieved in patients' cells [87]. Together, these studies provide the first proofs of efficacy of RNAi strategy to prevent mATXN7 expression. However, those are the initial stages of development and other challenges such as the clinical relevance of off-targets and inflammatory responses, the longevity of RNAi effect in the treatment of chronic neurodegenerative pathology, the brain or retina delivery approach, etc., need to be met. The substantial progress in using gene silencing for treating skin and retinal diseases, for instance, holds promise to bring RNAi technologies in clinic for SCA7 and other polyQ disorders.

9.6 Final Remarks

While biochemical approaches and the characterization of cellular and animal models of SCA7 have greatly advanced our understanding of disease pathogenesis in SCA7, much more needs to be learned before we get a solid comprehension of the pathogenic mechanisms underlying neuronal specific dysfunction and neuronal cell loss. While some of the therapeutic strategies against SCA7 are promising, as they can take first steps into clinical trials, further fundamental investigations are

required to propose new molecular targets for SCA7. Since SCA7 shares many common pathological features with other degenerative disorders affecting the cerebellum and the retina, identification of therapeutics in SCA7 or in one of these diseases is likely to be cross-beneficial.

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