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Emerging Concepts of Pathogenesis and Comprehensive Therapeutic Strategies for Spinocerebellar Ataxia Type 3

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Abstract

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph Disease (MJD), is an autosomal dominant neurodegenerative disorder that predominantly involves the cerebellar, pyramidal, extrapyramidal, motor neuron and oculomotor systems. SCA3 presents strong phenotypic heterogeneity and its causative mutation of SCA3 consists of an expansion of a CAG tract in exon 10 of the *ATXN*3 gene, situated at 14q32.1. The *ATXN*3 gene is ubiquitously expressed in neuronal and non-neuronal tissues, and also participates in cellular protein quality control pathways. Mutated *ATXN*3 alleles present about 45 to 87CAG repeats, which result in an expanded polyglutamine tract in ataxin-3. After mutation, the polyQ tract reaches the pathological threshold (about 50 glutamine residues); the protein is considered that it might gain a neurotoxic function through some unclear mechanisms. We reviewed the literature on the pathogenesis and therapeutic strategies of spinocerebellar ataxia type 3 patients. Conversion of the expanded protein is possible by enhancing protein refolding and degradation or preventing proteolytic cleavage and prevents the protein to reach the site of toxicity by altering its ability to translocate between the nucleus and cytoplasm. Proteasomal degradation and enhancing autophagic aggregate clearance are currently proposed remarkable therapy. In spite of extensive research, the molecular mechanisms of cellular toxicity resulting from mutant ataxin-3 remain no preventive treatment is currently available. These therapeutic strategies might be able to improve sign symptoms of SCA3 as well as slow the disease progression.

Keywords

Spinocerebellar Ataxia Type 3, Machado-Joseph Disease, Polyglutamine Disease, Ataxin-3, Therapeutic Strategies

1. Introduction

Spinocerebellar ataxia type 3 (SCA3) or Machado–Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder which is one of the polyglutamine (polyQ) disorders. Usually it is caused by expansion of a CAG triplet in the coding region of a gene. The CAG repeat is translated into an extended glutamine stretch in the mutant protein, resulting gain of toxic function, which induces neuronal loss in various regions of the brain [1]. The main point of all polyQ disorders is the formation of large insoluble protein aggregation, which contains the expanded disease protein [2]. In case of SCA3 patient, the CAG repeat is situated in the penultimate exon of the *ATXN*3 gene on chromosome 14q32.1. The length of mutated *ATXN*3 alleles can vary from 45 to 87 repeats [3]. However, polyQ toxicity has been associated with the expanded proteins that are not only translated from the CAG-expanded genes, but also with the expanded CAG repeat-containing RNA, which causes toxicity by itself [4].

Despite being a monogenetic disease, SCA3 has a complex pathogenesis. Nonetheless, regarding the toxicity resulting from mutant ataxin-3 RNA and protein, and a more understanding of the many cellular processes involved would be great benefit for potential therapeutic strategies. In this review, according to current knowledge of normal and mutant polyQ expanded ataxin-3 functions, as well as the toxic mechanisms of mutant ataxin-3 RNA and protein and potential therapeutic strategies will be discussed, which may improve the sign, symptoms and slow the disease progression of SCA3.

2. Pathological Processes of SCA3

SCA3/MJD is an autosomal dominantly-inherited disorder, which is characterized by the over-repetition of a CAG codon in the *MJD*1 gene. This expansion occurs into a polyglutamine tract that causes a toxic function to the mutant protein-ataxin-3, providing neurodegeneration in some specific brain regions, with particularly severe to cerebellum [5].

It has been suggested that alternative splicing is an important mechanism for diversity of ataxin-3 regulation, which indicates that there are some mechanisms generating variability, beyond genomic DNA. Ataxin-3 is a family member of cysteine proteases and it is composed of a globular N-terminal Josephin domain (amino acid residues 1 - 182 in the human protein) [6]. With a papain-like fold, it is combined with a more flexible C-terminal tail, which contains 2 or 3 ubiquitin interaction motifs (UIMs) and the polymorphic polyglutamine tract (polyQ tract) [7]. The Josephin domain (JD) contains specific amino acids which are highly conserved, reminiscent of the catalytic residues of a deubiquitinating cysteine protease. The catalytic pocket contains glutamine (Q9) and a cysteine (C14) residue located in the N-terminal part of JD, and a histidine (H119) and an asparagine (N134) in the JD C-terminal part. The catalytic triad characteristic of cysteine proteases consists of cysteine, histidine, and asparagine [8]. However, the physiologic role of ataxin-3 is still unknown, but it is thought that the

wild-type form is responsible for a deubiquitinating enzyme (DUB) in the ubiquitin-proteasome pathway [9] [10]. Recently, it has been well established that ataxin-3 can be directly activated by ubiquitination and it also has a deneddylase activity [11] [12]. Further, it has been proposed that ataxin-3 is also involved in transcriptional regulation. Moreover, a study has shown that ataxin-3 interacts with the major histone acetyltransferases cAMP-response-element binding protein (CREB)-binding protein, p300, and p300/CREB-binding protein-associated factor and inhibits transcription by these coactivators. This inhibited transcription suggests that transcriptional repression may be a potential mechanism for pathology of this disease [9] [13].

"Toxic fragment hypothesis" is one of the polyQ disorder pathogenesis, which concerns the proteolytic cleavage of polyQ expanded protein. For mutant ataxin-3, this proteolytic cleavage is thought to responsible for the generation of cytotoxic and aggregation prone shorter soluble fragments containing the expanded polyQ toxic entity [14] [15] [16] [17]. A recent study in a mouse model, ataxin-3 derived cleavage fragments were shown to contain expanded polyQ-containing protein fragments C-terminal of amino acid 221. Interestingly, the ataxin-3 C-terminal fragments were enriched in disease-relevant brain structures, such as the cerebellum and substantianigra in the two SCA3 brains, compared to healthy regions of brain [18]. Several proteolytic enzymes such as caspase and calpain were identified that could be responsible for the generation of potentially toxic ataxin-3 fragments. These mutant ataxin-3 fragments are more susceptible to aggregation and capable inducing toxicity to a larger extent than full-length mutant ataxin-3 [19] [20] [21]. However, ataxin-3 participates in the regulation of aggresome formation by colocalizing with aggresomes and preaggresome particles of the misfolded cystic fibrosis transmembrane regulator (CFTR) mutant CFTRDeltaF508 and associates with histone deacetylase 6 and dynein, proteins required for aggresome formation and transport of misfolded protein.Ataxin-3 is also responsible for degradation of proteins sent from the endoplasmic reticulum [21]. Combining with its enzymatic properties, these facts propose that ataxin-3 normally participates in protein quality control pathways in the cell [11] [23]. Furthermore, it has been proposed that this protein may be important not only for a correct cytoskeleton organization, but also for muscle differentiation through the regulation of the integrin signaling transduction pathway [24] [25]. After mutation, the polyQ tract reaches the pathological threshold (about 50 glutamine residues); the protein is thought that it may gain a neurotoxic function. As a consequence, it leads to selective neuronal cell death, but the process is still unclear [26] [27].

Ataxin-3 is responsible for the formation of intranuclear inclusions in many brain regions [28]. These neuronal inclusions are also found in other polyglutamine disorders, which are heavily ubiquitinated and contain some heat shock molecular chaperones and proteasomal subunits, which are suggested that they are repositories for aberrantly folded and aggregated proteins [29]. Role of ubiquitinated neuronal intranuclear inclusions (NIIs) has been regarded as a neu-

ropathology hallmark of polyglutamine disorders. Moreover, the significance of NIIs in the pathogenesis still remains a matter of controversy [30]. Recently some neuropathology studies have suggested that inclusions have no direct role as pathogenic structures and may be remaining byproduct of neuronal efforts to wall of abnormal proteins as a nontoxic manner [31] [32].

It has been suggested that increasing oxidative stress and an inability to protect against free radicals with age is observed in polyQ disorders, which could lead to mitochondrial dysfunction and cell damage [33] [34] [35] [36]. In a cell model of overexpressing mutant ataxin-3 with 78 CAGs showed significantly reduced antioxidant enzyme levels, increased mitochondrial DNA damage, and reduced energy supply, which indicates mitochondrial dysfunction. Moreover, mitochondrial DNA damage was also observed in SCA3 transgenic mice expressing full-length ataxin-3 with 98 to 104 glutamines. There were less mitochondrial DNA copies were seen both in the disease-affected pontine nuclei of these transgenic SCA3 mice compared to the unaffected hippocampus in the mutant cells and SCA3 patient samples implying mitochondrial DNA damage due to oxidative stress [37] [38]. Other side, mitochondrial dysfunction was tested by the finding that the mitochondrial respiratory chain complex II activity was somewhat compromised in SCA3 [39]. Usually, damaged mitochondria are unable to scavenge free radicals and prevent cell energy impairment. Therefore, this process may further increase oxidative stress in the cell. Oxidative stress is then hamper vital cellular functions, potentially resulting in activation of apoptotic cascades, which are responsible for neuronal death [40]. Therefore, mitochondrial dysfunction causes defects in the cellular defense mechanism against oxidative stress could play a role in the pathogenesis of SCA3.

Several studies have observed that bidirectional transcription is also involved in the triplet repeat disorders [41]. An alternative promoter for an antisense noncoding RNA was found in SCA7, which is caused by a CAG repeat expansion in the *ATXN7* gene [42]. However, ataxin-3 was found to have one of the highest relative amounts of antisense transcriptional tags [43]. Because of the involvement of antisense transcripts in triplet repeat disorders, additional research is required to explore the potential involvement of bidirectional transcription in SCA3.

More recently, it was observed that short CAG repeat-containing RNAs of around 21 nucleotides, originating from mutant CAG repeat-containing RNAs was found to induce cell death [44]. However, the toxicity was CAG repeat dependent and it was blocked by antisense oligonucleotides against the CAG repeat sequence. The mutant short CAG repeat-containing dicer-dependent small RNAs were involved in RNA interference (RNAi)-induced gene silencing of CUG repeat enclosing transcripts. Inhibition of microRNA processing strongly enhanced ataxin-3-induced neurodegeneration was found in a transgenic SCA3 animal [45]. Above these findings suggest that both short RNAs and microRNAs contribute to the pathology seen in SCA3 and other polyQ disorders.

Other side, repeat-associated non-ATG translation was recently observed as a novel class of protein toxicity, in which coding RNA transcripts with mutant CAG repeats is translated in the absence of an ATG start codon. In all three possible CAG repeat reading frames, this repeat-associated non-ATG translation was found, which result in the translation of proteins with polyQ, polyA, and-polyserine (polyS) repeats [46]. Repeat-associated non-ATG translation together with bidirectional transcription are responsible for seven potential reading frames translation such as ATG translated polyQ proteins, non-ATG translated polyQ, polyA and polyS proteins and bidirectional non-ATG translated polyleucine (polyL), polycysteine (polyC) and polyA proteins [47]. Sense CAG and antisense CTG transcription are together, this means a total of nine possible toxic entities are involved in the pathogenesis of SCA3 and other polyQ disorders.

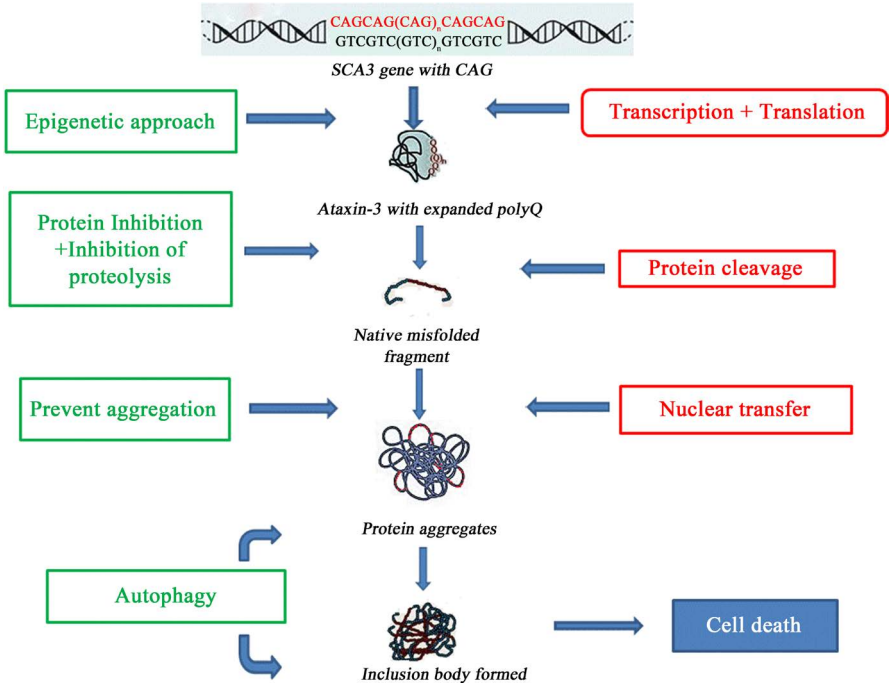
3. Treatment Strategies

Still, it is hard to find an effective treatment for SCA3 or any other polyQ-expansion disorders. According to anecdotal evidence, a number of small scale clinical trials have been attempted for SCA3 (**Table 1**). These trials did not yield any promising results yet. A number of pathogenic mechanisms have been described to explain neuronal degeneration and dysfunction of SCA3. However, there are limited targets for therapeutic intervention available for SCA3 treatment [48]. Now, it is demand for a SCA3 therapy directed at slowing the progression and preventing the neurodegeneration. That's why a further identification of the key molecular players in the cascade requires for neuronal dysfunction and cell death in SCA3 is paramount for the development of effective therapeutic therapies [41]. Most of them act on reversal of cellular defect and targeting the expression, processing or conformation of the pathogenic protein [49]. Recent potential therapeutic strategies target various known processes of SCA3 pathogenesis, are discussed (**Figure 1**).

Table 1. Clinical therapeutic trials of SCA3.

Method	Pharmacological drugs	Outcome of trials	References
Double-blind crossover study	Sulfamethoxazole-trimethoprim	Improved spasticity or rigidity, rather than ataxia	Ogawa M Cerebellum. 2004; 3(2):107-11.
Double-blind randomized study	Buspirone, a 5-HT1A agonist	The effect is partial on ataxia, not major	Ogawa M Cerebellum. 2004; 3(2):107-11.
Double-blind placebo-controlled randomized study	5 - hydroxytryptophan	Improving neurological symptoms	Trujillo-Martín MM, Serrano-Aguilar P, Monton-Alvarez F, Carrillo-Fumero R MovDisord. 2009 Jun 15; 24(8):1111-24.
Double-blind, placebo-controlled crossover trial	Tetrahydobiopterin	Short-term effect	Sakai T, Antoku Y, Matsuishi T, Iwashita H J Neurol Sci. 1996 Mar; 136(1-2):71-2.
Double-blind randomized study	Taltireline hydrate, fluoxetin, tandospirone and lamotrigine	Some Positive results were reported	Shirasaki H, Ishida C, Nakajima T, Kamei H, Koide T, Fukuhara N RinshoShinkeigaku. 2003 Apr; 43(4):143-8.

Legends: In this table, a number of small scale clinical trials have been attempted for SCA3. Most of the trials outcomes were remain unsuccessful.



Legends: Right sided red boxes indicate pathogenesis of SCA3. This disease initially is appeared by proteolytic cleavage to generate a toxic fragment. The expanded polyglutamine tract allows transition which may cause toxicity in many ways. The peptide has ability to produce toxicity as a monomer or it may form toxic oligomers by itself. The oligomers can configure into larger aggregated species and finally are deposited in macromolecular intracellular inclusions. Alterations in transcription, metabolism or impairment of the proteasome or stress response pathways are the principal toxic effects and ultimately it causes cell death. Left sided green boxes indicate different therapeutic strategies. Therapeutic strategies based on targeting the specific polyglutamine protein and counteract cellular defects induced by the toxic species. Transcriptional misregulation can take part to the pathogenesis of SCA3. Therefore, epigenetic approach might be good therapeutic option for SCA3. By inhibiting polyglutamine protein expression, the protease inhibitors block the generation of a toxic fragment, normal cellular interactions, peptides or small molecules. These could be helped to stabilize the polyglutamine protein in a non-toxic form. Increase degradation is done by activation of proteasome or autophagy pathways which could reduce protein levels. Inhibition of self-association could stop the formation of toxic aggregates and prevent cellular defect.

Figure 1. Pathogenesis and different therapeutic strategies of SCA3.

1) Role of Antioxidants:

Now-a-days, it has proposed that some evidence could play a role in neuronal dysfunction and neurodegeneration in SCA3 where defect occur in the cellular defence mechanism against oxidative stress. However, the extent of oxidative stress involvement is still unknown, but antioxidants might have some role to provide some neuroprotective effects. Free radical scavengers have ability to attenuate some accumulation of reactive oxygen species, and it can be divided into enzymatic and non-enzymatic antioxidants. The whole range of these antioxidants has been established that they provide enough opportunity for therapeutic targeting. Recently, antioxidant-based therapies for SCA3 have been researched, but some lessons can be helpful to learn from the HD research field [50]. Creatine is a supplementation of the naturally occurring antioxidant, was shown to slow ongoing cortical atrophy in a 16-week randomized double-blind phase II

clinical trial with HD patients [51]. However, a study was done in United States applying coenzyme Q10 (CoQ10), a lipid-soluble benzoquinone, measuring clinical severity by the Scale for Assessment and Rating of Ataxia (SARA), the Unified Huntington's Disease Rating Scale part IV (UHDRS-IV) (**Table 2**). The study was done in 2009-2012 in United States applying coenzymes Q10, Statin and Vitamin-E in 319 participants (SCA1, SCA3, SCA6) at 12 medical centers. The result has shown that exposure to CoQ10 was associated with lower SARA and higher UHDRS-IV scores in SCA1 and 3 [52]. Therefore, CoQ10 is really associated with a better clinical outcome in SCA1 as well as SCA3.

2) Epigenetic approach:

There is a deregulation of transcription which results from mutant ataxin-3, has been well established in a SCA3 mouse model. Here mRNA expressions of proteins are involved in calcium mobilization, signal transduction and neuronal differentiation were found, which are down regulated [53]. According to the function of the affected proteins, this transcriptional misregulation can take part in the pathogenesis of SCA3 [54]. It has been conceived as a problem of transcriptional regulation, where mutant proteins disrupt act as a key factor. Many of them have acetyltransferase activity. Interestingly, there are some HDAC inhibitors such as suberoylanilidehydroxamic acid, sodium butyrate, and phenylbutyrateare supposed to increase gene expression, have shown well efficacy in various neurodegenerative diseases [55]-[60]. Recently, sodium butyrate was examined for efficacy in SCA3 transgenic mice, and was shown to reverse the mutant ataxin-3-induced histone hypoacetylation and transcriptional downregulation in the cerebellum. It also improved the ataxic symptoms of these mice. Thus, it significantly showed good therapeutic potential for the treatment of SCA3 [54]. Earlier, mouse studies have been shown that sodium butyrate has good capacity in reaching the brain [55]. Another study was done using valproic acid (VPA), a pan-HDAC inhibitor to evaluate the clinical safety and efficacy of VPA treatment for SCA3/MJD patients. The result showed that a significantly improved SARA measures of locomotors function in SCA3 patients with Multi-dose VPA treatment. Therefore, VPA has a significant role to improve clinical symptoms of SCA3 patients [61].

Moreover, the neuroprotective effects of HDAC inhibitors are well responsive, and they might have ability to correct the transcriptional defects. Also, they

Table 2. Study in United States applying coenzyme Q10, Statin and Vit-E.

Name of study	Pharmacological agents	ARA and UHDRS-IV scores	Effect on Diseases
Double blind cross section	Coenzyme Q10 (CoQ10)	Improved	SCA1 & SCA3
Double blind cross section	Statin	Not Improved	-
Double blind cross section	Vitamin E	Not Improved	-

Legends: In this table, a study from 2009-2012 in United States applying coenzymes Q10, Statin and Vitamin-E in 319 participants (SCA1, SCA3, SCA6) at 12 medical centers were performed. Here, coenzymes Q10 made a promising outcome on SCA1 and SCA3 patients.

increase the acetylation of other non-histone proteins such as tubulin, Hsp90 and upregulated levels of heat shock proteins such as Hsp70 [62] [63] [64] [65]. Furthermore, effects of specific acetyltransferase target compounds are still unknown; it might be very difficult to optimize them to reduce toxicity. More studies of development of selective HDAC inhibitors and their molecular mechanisms can provide better therapeutic strategies [49].

3) Targeting Mutant Ataxin-3:

The most advantage of monogenic disorders such as Machado-Joseph disease is that silencing of the responsible gene, which gives result alleviation of mutant protein toxicity. For gene-silencing treatment of SCA3, the transcriptions of non-allele specific downregulation of all ataxin-3 are tested in both wild-type and SCA3 rats [66]. This allele-nonspecific silencing of ataxin-3 in the striatum showed locally reduced neuropathology in SCA3 rats and without adverse effects in both wild-type and SCA3 rats. However, an allele-specific downregulation targeting mutant allele is a more impressive and favorable approach for therapeutic application in SCA3. It has been also observed for all neurodegenerative diseases [67] [68]. There are two mechanisms have been proposed for allele-specific downregulation of mutant ataxin-3.

One approach is allele-specific silencing, which was got from the RNAi pathway using shRNAs directed against single nucleotide polymorphisms (SNP) unique to the mutant ataxin-3 transcript [69]. This SNP at the 3' end of the *ATXN*3 gene was found in over 70% of SCA3 patients [70]. However, the SNP-specific shRNA have a specific role in silencing mutant ataxin-3 and it also found as neuroprotective in SCA3 mouse and rat models [5] [68].

Another most straightforward approach is to selectively reduce expression of the expanded allele. The small interfering RNAs have a significant role to selectively knockdown gene expression and now it has been validated in mouse models of polyglutamine disease [71] [72]. RNAi-based approaches with some abasic substitutions and single-stranded silencing RNAs (ssRNAs) have been shown a significant role of allele, which selectively inhibiting ataxin-3 expression [73] [74]. There are also some small molecules, such as antisense oligonucleotides (AONs) or peptide nucleic acids (PNAs), can be achieved allele-specific silencing of mutant ataxin-3 by binding to the expanded CAG repeat in vitro. That's probably result in translational blockage of mutant ataxin-3 [1] [74].

Alternative oligonucleotide therapy has well proposed, where the polyQ repeat is removed from the ataxin-3 protein by exon skipping [75]. With the help of exon skipping, AONs are used as target-specific splicing signals and mask an exon in the pre-mRNA from the splicing machinery. Thus it has been shown by the exclusion of the target exon from the mRNA [76] [77]. Very recently exon skipping of the polyQ encoding region of ataxin-3 has been well observed, and shown that formation of a shorter ataxin-3 protein lacking the polyQ repeat. The short form of ataxin-3 protein remained in the main functional domains and ubiquitin binding capacity, and didn't have toxicity in cells [75]. Later, approach

of the same exon skipping was confirmed as a secondary effect of the previously described ssRNAs directed against the CAG repeat [74].

4) Inhibition of proteolysis:

There are many studies have been implicated in caspase activation in the pathogenesis of polyglutamine diseases for induction of apoptosis and their cleavage of the polyglutamine proteins [78] [79] [80]. Recently, prevention of the formation of the cleavage-induced, highly toxic, mutant ataxin-3 fragments has been proposed for comprehensive treatment of SCA3. There are some specific caspase inhibitors have been applied in a mouse model of HD, and were shown that they have capability of slowing the disease process [81]. The function of caspase in the brain is quite complicated and may be important for function of the normal brain by influencing synaptic plasticity, apoptosis, dendritic development, and formation of memory [82] [83]. Using caspase inhibitors in the brain might interfere with these processes and would be potential treatment for SCA3. Inhibition of calpains has shown an effective role in reducing mutant ataxin-3 toxicity in various kinds of cell and animal models [16] [19] [84]. Recently a study was done, where inhibited calpain activity in mouse models of MJD by overexpressing the endogenous calpain-inhibitor calpastatin. Calpain blockage has the ability to reduce the size and number of mutant ataxin 3 inclusions, neuronal dysfunction and neurodegeneration. By reducing fragmentation of ataxin 3, calpastatin overexpression can modify the subcellular localization of mutant ataxin 3 restraining the protein in the cytoplasm, reducing aggregation and nuclear toxicity. Overcoming calpastatin depletion has also observed upon mutant ataxin 3 expression. Therefore, mutant ataxin 3 proteolysis is done by calpains mediates in its translocation to the nucleus, aggregation and toxicity and that inhibition of calpains may provide an effective therapy for SCA3 [85].

5) Prevention of protein aggregation:

The aggregation of ataxin-3 protein is a specific point of SCA3, and the process which is responsible for toxicity of mutant ataxin-3 also leads to the formation of aggregates. Recently, increased levels of some molecular chaperones, just like HSP40 and HSP70, have been observed to reduce both toxicity and aggregation of expanded polyQ tracts in several cells and mouse models, which improved phenotypes [86] [87]. This pharmacological induction of molecular chaperone Hsp70 has been proposed for aid in protein refolding and degradation (e.g. geldanamycin and geranylgeranylacetone) in polyglutamine diseases like HD [88] [89] [90]. Another indication of molecular chaperones that they have ability to increase the solubility of expanded polyQ [91] [92], which might be also responsible for increased degradation of the protein by the proteasome [93] [94]. Other chemical chaperones such as trimethylamine N-oxide, glycerol and dimethyl sulfoxide have some role to influence protein folding and stable proteins in their native conformation. These chaperones have been observed for their efficacy in cells overexpressing a truncated form of mutant ataxin-3. The outcome of the test has been shown that both aggregate formation and

cytotoxicity were reduced [95]. Although there are many approaches targeting the mutant ataxin-3 aggregation, still no promise for clinical application has been identified.

6) Protein clearance and activation of autophagy:

Targeting misfolded disease proteins may be beneficial during stimulating cellular degradation pathways. Recently, it has been shown that autophagy acts as a protective mechanism in polyglutamine disease (reviewed in [96]). Previously it has been viewed that silencing of mutant ataxin-3 after disease rescues, the neuropathology of a SCA3 mouse model and during the expression of the mutant transgene is stopped, it can be contended that cells are able to clear the toxic products [5] [97]. Rapamycin, the mTOR inhibitor, stimulates autophagy, has been effective in cell of Drosophila as well as mouse disease models [98] [99] [100] and may be a beneficial drug candidate. It has been shown that the upregulation of autophagy was done by rapamycins, which resulted in a reduction of aggregates and the level of soluble mutant ataxin-3 despite the level of wild-type protein appeared unaffected [101]. Another compound lithium chloride was also shown to have therapeutic potential in a *D. melanogaster* SCA3 model. The ultimate mechanism is thought that they have ability to rely on upregulation of autophagy, though anti-apoptotic effects have also been concerned in [102]. Recently, lithium carbonate was carried out a phase II clinical trial with for SCA3 and showed significant role for reducing the progression of gait ataxia severity [103]. Another study has been shown that lithium administration improved only in the reduction of tremors during the disease process. This result does not support lithium chronic treatment as a promising strategy for the treatment of Machado-Joseph disease (MJD) [104]. Another side, Trehalose, a chemical chaperone and mTOR-independent autophagy enhancer, has shown promise in cell models of SCA3 by targeting autophagy to reduce PolyQ aggregation. A study was done using two trehalase analogs, lactulose and melibiose, was examined for their potentials in spinocerebellar ataxia treatment. It has shown that the *ATXN*3 aggregation is significantly restricted by lactulose and melibiose because of their abilities to up-regulate autophagy in a cell model. These findings strongly suggest the therapeutic applications of novel trehalosein polyglutamine aggregation-associated neurodegenerative diseases like SCA3 [105].

Recently, it is observed that H1152 has ability to capable of ameliorating neuronal death and the neurological phenotype of SCA3 mice model. H1152 specifically reduced the mutant ataxin-3 protein levels after intraperitoneal injection during non-expanded ataxin-3 levels remained unchanged. The reduction of mutant ataxin-3 was occurred by augmentation of the proteasome activity. That's why it promotes protein degradation [106]. Otherside, temsirolimus is also extensively used to increase autophagy in mouse models, and already is used for treatment of renal cell carcinoma. It is suitable for use in patients and might therefore be a candidate for clearance modulation based treatment of SCA3 [101].

7) Preventing alteration of Calcium Homeostasis:

Alteration of cellular calcium homeostasis is responsible for SCA3 pathogene-

sis. Recently, Dantrolene is used in transgenic SCA3 mice improved motor performance and prevented neuronal cell loss, because it inhibits excessive calcium release [107]. Dantrolene acts as an inhibitor of calcium release from the ER in neuronal cells [108]. There are many clinical trials have been done for other diseases using Dantrolene, showed no adverse effects [109] [110]. Caffeine, another compound acts through adenosine A2A receptor antagonism and has ability to decrease neuropathology in a SCA3 mouse model [111] [112]. However, the mechanism of this of caffeine has not been well established [113]. Indeed consumption of caffeine is safe and easily implementable prophylactic strategy to delay onset of SCA3 [112].

8) Transplantation of stem cell:

Transplantation of stem cell might be a new strategy for SCA3 treatment, including embryonic stem cells, mesenchymal stem cells (MSCs), neuronal stem cells, and induced pluripotent stem cells. This therapy can act through several mechanisms, just like cell replacement, trophic support, neuroprotection, and immunomodulation [114]. Some studies have showed that transplanting murine mesenchymal stem cells to a mouse cerebellum in an animal model of cerebellar ataxia significantly improved motor functions and saved the degenerated Purkinje cells [115]. However, the selection of suitable cellular grafts, factors for controlling stem cell differentiation, survival, and maturation are also u4.nclear, and still there are no current studies for stem cell application in SCA3.

4. Conclusion & Perspective

There is no clear model that has been established that how polyQ expanded ataxin-3 leads to the specific symptoms of SCA3. In this review, we try to describe these pathogenesis and possible points of therapeutic strategies. There are so many therapeutics agents could be promising to better clinical outcome for SCA3 patients. It is possible to target the stability and conversion of the expanded protein by enhancing protein refolding and degradation or preventing proteolytic cleavage, which inhibits the formation of the toxic fragments. Another option is to prevent the protein to reach the site of toxicity by altering its ability to translocate between the nucleus and cytoplasm. Proteasomal degradation and enhancing autophagic aggregate clearance are current prospects for therapy. Other side, alternating the pathways of aggregation remains a pivotal therapeutic approach as facilitating mitochondrial health and function. Described therapeutic strategies really beneficial to improve sign symptoms and slow the disease progress of SCA3. It requires further research to open new approaches for therapeutic strategies in SCA3 and these would be ideal candidates to benefit for promising new molecular therapies.

Statement of Human and Animal Rights

For this type of study formal consent is not required.

Informed Consent

No patient is used for this study.

Authors' Contributions

All authors contributed to a draft of the manuscript and were subsequently involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

SCA—Spinocerebellar ataxia
MJD—Machano-joseph disease
PolyQ—Polyglutamine
CAG—Trinucleotide
JD—Josephin domain
DUB—Deubiquitinating
CREB—cAMP-response-element binding protein
NIIs—Neuronal Intranuclear Inclusions
HDAC—Histone deacetylase
SARA—Scale for Assessment and Rating of Ataxia
UHDRS-IV—Unified Huntington's Disease Rating Scale part IV
VPA—Valproic acid
AONs—Antisense oligonucleotides
HD—Huntington's disease
MSC—Mesenchymal stem cells