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Molecular mechanisms underlying Spinocerebellar Ataxia 17 (SCA17) pathogenesis

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ABSTRACT
Spinocerebellar ataxia 17 (SCA17) belongs to the family of 9 genetically inherited, late-onset neurodegenerative diseases, which are caused by polyglutamine (polyQ) expansion in different proteins. In SCA17, the polyQ expansion occurs in the TATA box binding protein (TBP), which functions as a general transcription factor. Patients with SCA17 suffer from a broad array of motor and non-motor defects, and their life expectancy is normally within 20 y after the initial appearance of symptoms. Currently there is no effective treatment, but remarkable efforts have been devoted to tackle this devastating disorder. In this review, we will summarize our current knowledge about the molecular mechanisms underlying the pathogenesis of SCA17, with a primary focus on transcriptional dysregulations. We believe that impaired transcriptional activities caused by mutant TBP with polyQ expansion is a major form of toxicity contributing to SCA17 pathogenesis, and rectifying the altered level of downstream transcripts represents a promising therapeutic approach for the treatment of SCA17.

SCA17 as a neurodegenerative disease caused by polyQ expansion

The polyQ tract, encoded by a tandem repeat of CAG trinucleotides, is a domain commonly found in many human proteins. The exact number of glutamines within a polyQ tract varies greatly among different proteins and individuals. Once the glutamine number within a polyQ protein reaches above certain thresholds, the polyQ protein becomes misfolded and leads to neurodegeneration in specific brain regions, depending on the protein context.1 Thus far, 9 types of polyQ diseases have been identified, and SCA17 is the latest addition to this disease family. In 1999, Koide et al. were the first to describe a Japanese patient with unique neurologic symptoms that are associated with the expansion of CAG repeat in the TBP gene. This disease was later named SCA17.3 In human TBP, the normal range of polyQ number is between 25 and 42,4 whereas disease onset could occur in patients with as few as 47 repeats.3 SCA17 is late-onset, meaning that the disease symptoms in patients normally start to appear in the middle age. Nonetheless, similar to other polyQ diseases, an inverse correlation between polyQ number and age of onset was found.5 SCA17 patients normally display diffused cortical and brain stem atrophy, as well as subcortical white matter lesions, revealed by brain magnetic resonance imaging (MRI).3,6 However, the most prominent degeneration occurs in the cerebellum, especially the Purkinje neurons within the cerebellum are the most vulnerable.7 The distinct brain pathology explains the wide spectrum of disease symptoms in SCA17 patients, which typically include motor defects, such as ataxia, dystonia and parkinsonism, as well as non-motor defects, including dementia, psychiatric abnormalities and seizures.2,3,8 It is noteworthy that SCA17 is alternatively named Huntington’s disease-like 4, as its clinical features such as rapidly progressive dementia followed by concurrent chorea are also characteristic in Huntington’s disease.9,10 To date, most SCA17 cases were reported...
from China, Japan, Korea, Italy and England. Although the scarcity of reported cases makes it difficult to predict the prevalence of SCA17, it is possible that expanded polyQ repeats can affect the vital function of TBP and early embryonic development such that very few live SCA17 patients were reported.

**Transcriptional dysregulations in SCA17**

Unlike most polyQ proteins, whose biological functions remain elusive, the functions of TBP is well understood. TBP is a general transcription factor that is involved in transcription by all 3 nuclear RNA polymerases. During mRNA transcription, TBP directly binds TATA-box, which is a highly conserved DNA sequence (TATAAA) typically locates about 25 to 30 nucleotide upstream of the transcription start site in metazoa, and 40 to 100 nucleotide upstream of the transcription start site in the yeast *Saccharomyces cerevisiae*. TBP then recruits approximately 13 TBP-associated factors (TAFs) to form TFIID complex, followed by coordinated accretion of TFIIB, TFIIF, non-phosphorylated RNA polymerase II, TFIIE and TFIIH to form the preinitiation complex, which is a large protein complex essential for transcription to occur. Homozygous TBP knockout embryos do not survive beyond the blastocyst stage, highlighting the critical functions mediated by TBP.

The fact that TBP functions as a general transcription factor helped researchers to focus their attention on potential transcriptional dysregulations during SCA17 pathogenesis. Indeed, in vitro electromobility shift assay revealed that mutant TBP with polyQ expansion binds less DNA containing TATA-box, compared with wild type TBP. However, when tested in luciferase assays, mutant TBP with polyQ expansion stimulated, rather than suppressed, TATA-box dependent transcriptional activities. This observation is in agreement with a microarray analysis using brain samples from SCA17 mouse models, as only a few hundred transcripts were down-regulated in the presence of mutant TBP with polyQ expansion. Therefore, mutant TBP with polyQ expansion might not disrupt global gene expression. Considering TBP is involved in the formation of numerous transcriptional complexes, it is likely that mutant TBP affects the functions of some more specialized transcription factors, which leads to impaired transcription in certain restricted pathways.

This hypothesis has been confirmed by a plethora of studies. In a cellular model of SCA17, expression of mutant TBP with 105Q led to decreased cell viability and defective neurite outgrowth. Moreover, mutant TBP showed enhanced interaction with transcription factor Sp1, which caused reduced occupancy of Sp1 on TrkA promoter and decreased TrkA expression. In a drosophila model of SCA17 expressing mutant human TBP with 80Q, the function of Suppressor of Hairless (Su(H)), a transcription factor that participates in Notch signaling, was impaired, which contributes to SCA17 like phenotypes including progressive neurodegeneration, late-onset locomotor impairment and early death. Interestingly, the number of glutamines within TBP varies greatly among different species: yeast TBP does not contain a polyQ region; drosophila TBP has less than 10 glutamines within the polyQ region; whereas rodent TBP has nearly 15 glutamines in the polyQ region. This phenomenon indicates that rodent models should be preferable in faithfully recapitulating SCA17 disease conditions. To date, several SCA17 rodent models have been established, including transgenic mouse and rat models, as well as conditional knock-in mouse models. These models displayed SCA17 like phenotypes, such as motor deficits and shortened life span. Moreover, pronounced cerebellum degeneration, especially Purkinje cell death, was found in all these models. Close examination of these models revealed a handful of transcription factors whose functions were affected by mutant TBP with polyQ expansion. For example, the function of transcription factor IIB (TFIIB), another general transcription factor, was impaired by mutant TBP, which resulted in a reduced level of the small heat shock protein HSPB1 in a transgenic mouse model expressing TBP105Q. Mutant TBP also sequestered and impaired nuclear factor-Y (NFY), a master regulator of the chaperone system, and reduced the expression of several chaperones including Hsp70, Hsp25 and HspA5 in a neuron-specific knock-in mouse model. The toxicity of mutant TBP is commonly assumed to be caused by certain gain of function mechanisms, which means mutant TBP shows enhanced interaction with certain proteins and damages their endogenous functions. However, recent studies indicate that some loss of function mechanisms could also contribute to the pathogenesis of SCA17. X-box binding protein 1 (XBP1), a transcription factor involved in ER stress response, and MyoD1, a muscle-specific transcription factor, were found to bind less mutant TBP than wild type.
The decreased interactions suggest that mutant TBP may not be as efficient as wild type TBP in facilitating transcriptional activities mediated by these transcription factors (Fig. 1). Moreover, these findings suggest that a gain of toxic function or a loss of function of mutant TBP is also dependent on the length of the expanded polyQ repeat.

It should be noted that mutant TBP does not have to bind to the DNA sequence to impact gene transcription. Some genes without TATA-box in their promoter sequences can also be affected by mutant TBP. Moreover, a truncated form of mutant TBP without the DNA binding domain sequestered TFIIB and inhibited TATA-box dependent transcriptional activity in cultured cells. When the same construct was used to generate a transgenic mouse model, the mice showed even more severe pathological phenotypes and died at the age of 3-8 weeks.

**Concluding remarks and future directions**

SCA17 is a devastating neurodegenerative disease without effective treatments. Nonetheless, our deep understanding about TBP and the availability of several good animal models make SCA17 an ideal polyQ disease model to study how polyQ expansion impairs endogenous protein functions and induces neurodegeneration. Although the effects of mutant TBP on gene transcription have been well documented, it remains unclear how SCA17 also shows selective pathology in specific types of tissues or cells, a phenomenon that is well known for other polyQ diseases. It is likely that polyQ expansion confers toxicity in a cell-type dependent manner, depending on the cell-type related expression and posttranslational modulation polyQ proteins and their partners. To address this issue, we have generated floxed TBP105Q knock-in mouse model. By crossing these mice with different lines of Cre transgenic mice, we are able to control mutant TBP expression at endogenous level in specific types of cells. Some of the discoveries discussed above were done using this approach. We are in the process of incorporating more Cre lines to get a more comprehensive picture. On the other hand, Purkinje cell specific transcriptome analysis, achieved by laser capture microdissection or Purkinje cell specific promoter, has been successfully performed in SCA1, another polyQ disease. These techniques could be readily transferred to SCA17 research, and bring us much needed information about Purkinje cell specific degeneration in SCA17. Given the well-characterized functions of TBP and its associated proteins, SCA17 would offer an ideal system to investigate the mechanisms underlying the selective pathology in polyQ diseases.

**Figure 1.** Transcriptional dysregulations in SCA17 A brief summary of our current understanding about the transcription factors and their mediated cellular processes impaired by mutant TBP. Mutant TBP affects the activities of these transcription factors through 2 distinct mechanisms. One is gain of function, which means mutant TBP showed enhanced interactions with the transcription factors, thereby sequestering them from their functional locations. The other one is loss of function, which means while wild type TBP is an essential component of the transcriptional complexes, mutant TBP fails to carry out the same functions as wild type TBP.
Despite impressive advances in understanding the molecular mechanisms underlying SCA17 pathogenesis, how to translate our current knowledge into therapeutic strategies remains one of the greatest challenges. Gene silencing techniques (such as antisense oligonucleotide, microRNA and shRNA) are being actively pursued as an option to treat polyQ diseases. Considering the essential functions of TBP, it is highly desirable that mutant allele-specific silencing is used when testing the efficacy for SCA17 treatment. Alternatively, normalizing the expression of transcripts disrupted in SCA17 could also be tested for therapy. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is one of such proteins whose expression was reduced by mutant TBP. Increasing MANF level by genetic approaches in a SCA17 knock-in mouse model had robust improvements in both behavioral performances and neuropathology. MANF is also neuroprotective in several other neurologic disorders, including Parkinson disease and ischemic stroke. Therefore, developing the MANF-based therapeutic approach has the potential to alleviate or treat multiple diseases. More efforts are needed to expand our reservoir of potential therapeutic targets, and to validate these targets for SCA17 treatment.

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