

## Impairment of Cellular Transcriptional Machinery in Poly(Q) Disorders

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Rec date: Sep 23, 2014; Acc date: Sep 25, 2014; Pub date: Oct 01, 2014

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**Keywords:** Poly(Q) diseases; Inclusion bodies; Transcription; CBP; Histones acetylation

### Introduction

Polyglutamine or poly(Q) diseases represent a group of fatal human disorders which exhibit some common neurodegenerative symptoms and share somewhat similar mechanism of pathogenesis. Some of the common clinical symptoms of poly(Q) diseases include progressive loss of body coordination, memory, difficulty in speech and intellectual disabilities [1]. Most forms of the poly(Q) disorders are dominantly inherited, exhibit age dependent phenotypic manifestations, progressive in nature and result in degeneration of specific group of neurons in the brain as per the characteristics of each disease type [2,3]. Some of the commonly known poly(Q) disorders include Spinal and Bulbar Muscular Atrophy (SBMA), Huntington's Disease (HD), six of the Spinocerebellar ataxias (SCA1, 2, 3, 6, 7 and 17) and Dentato Rubral Pallidoluysian Atrophy (DRPLA) [2,4].

### Poly(Q) mediated impairment of transcriptional machinery

Pathogenesis of most of the poly(Q) diseases are initiated by the expansion of CAG nucleotide repeat within the coding sequence of target gene. Expansion of CAG repeat produces extended tract of glutamine and alters the intrinsic conformation of target protein. The abnormally folded protein interacts with other proteins having inherent CAG repeats and interrupts the molecular function of associated proteins [5]. Such protein aggregates are known as Inclusion Bodies (IB) which grow in size with age and translocate into the nucleus. Nuclear transportation of inclusion bodies result in sequestration of many more of glutamine rich transcription factors such as cAMP response element binding protein (CBP), TBP (TATA binding protein), TAFII130 and Specificity protein 1(sp1) [6-9]. Sequestration of above noted transcription factors impair the rate of cellular transcription. Poly(Q) mediated impairment of transcription machinery has been proposed to be a major cause of cellular toxicity and neurodegeneration.

One of the factors which have caught foremost attention in contemporary poly(Q) research is CBP [6,8]. CBP (CREB binding protein) is a vital transcription factors which interacts with numerous other factors to regulate the rate of transcription of several crucial genes [10,11]. CBP harbours inherent property of Histone acetyltransferase (HAT) activity which facilitates acetylation of core histones and subsequent opening of chromatin DNA to make them readily accessible for RNA polymerase and other transcription factors [12,13]. Occurrence of 18 glutamine repeats at the C-terminal of CBP facilitate its interaction with expanded poly(Q) repeats of the mutant proteins [6,8]. In Huntington's disease, mutant Htt protein interacts with CBP and sequesters them into the inclusion bodies [6-8]. Consequently, age dependent progressive reduction in the cellular level

of CBP could be seen in affected tissues. Interestingly, CBP proteins have been demonstrated to localise in the inclusion bodies of poly(Q) affected post-mortem tissues, cell cultures and disease models [6-9,13]. Sequestration of CBP in inclusion bodies leads to hypoacetylation of core histones and undermines the transcription activities. Subsequently, impaired transcription leads to deprivation of cellular survival factors and ultimately, affected cells are marked for apoptosis. Sequestration of CBP into poly(Q) aggregate intensify the degeneration rate of selective neurons as CBP is a cofactor of cAMP response element binding protein and sequestration of CBP results in repression of cAMP response element genes. Moreover, CREB dependent transcription protects the neuronal cells during stress condition by promoting expression of survival factor such as Brain Derived Neurotrophic Factor (BDNF) [14]. Interestingly, level of BDNF is also regulated by Htt protein, and therefore, extended length of poly(Q) tract in Htt protein results in a lower level of BDNF in HD [14]. In addition, lower level of CBP in HD mice compromises the long term potentiation of hippocampal region [15,16]. Subsequently, age dependent progressive deterioration of synaptic plasticity in CA1 cells of brain hippocampus result into loss of cognition as manifested in most of poly(Q) disorders [16].

Sequestration of CBP in inclusion bodies also compromises the function of CBP dependent additional transcription factors. On the other hand, sequestration of transcriptional coactivators of CBP such as TAFII130 also confines the functional diversity of CBP. TAFII130 is a coactivator of CBP which sequesters itself in inclusion bodies by interacting with expanded poly(Q) stretches during disease pathogenesis [17]. Interestingly, enhanced expression of TAFII130 has been demonstrated to rescue the functional status of CBP in poly(Q) disease condition [17]. In addition to the above noted transcription factors, transcriptional efficiency of several other neuronal genes which are involved in signal transduction and calcium homeostasis have also been reported to be impaired in poly(Q) disease models [18]. Down regulation of these neuronal genes are evident in Purkinje cells much before the manifestation of detectable phenotype of SCA1 [18]. Intriguingly, in case of SCA3, several inflammatory response genes exhibit up-regulation whereas expressions of some cell-surface receptor genes are repressed [19].

### Concluding Remarks

As discussed earlier, it is increasingly clear now that poly(Q) mediated sequestration of essential transcription factors and subsequent impairment of cellular transcription machinery is one of the major aspects of cellular toxicity and neurodegeneration. In this context it is important to note that tissue specific up-regulation of several transcription factors and co-factors have been demonstrated to alleviate poly(Q) induced neurotoxicity in disease models [20,21]. Therefore, enriching the global cellular transcriptional efficiency could

suppress the toxic effects of inclusion bodies and poly(Q) mediated neurodegeneration.

## Acknowledgement

Research programmes in laboratory is supported by grants from the Department of Biotechnology (DBT), Government of India, New Delhi; Department of Science and Technology (DST), Government of India, New Delhi and Delhi University R & D fund to SS.

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