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Editorial

Pathological and Historical Journey of PolyQ Diseases

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The polyglutamine (Poly Q) diseases are an assembly of inborn neurodegenerative diseases categorized with the genomic abnormalities of more than 40 repeats of cytosine-adenine-guanine (CAG) triplet in coding regions of specific genes related to disease. The CAG triplet codon codes for glutamine (one-letter code, Q) and its expansion has a strong positive correlation with the onset of disease. The expansion of CAG in the disease-causative genes results in the formation of amyloid proteins with a peculiar pathogenic extension of polyQ tract. The extended polyglutamine protein is toxic to neurons and the severity of disease is dependent on length of polyQ. There are so far, 9 disorders mentioned that make a group of PolyQ type of diseases, which include Huntington's ailment (HD), spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7 and 17 and dentatorubral pallidoluysian atrophy (DRPLA). A common characteristic of the polyQ ailments is deterioration of neurons in the specific regions of the brain, which cause impairment in the basic functioning like motor disturbance that depend on the part of the brain that is affected.

Fischbeck and coworkers in 1991 for the first time observed the extension of CAG repeats in exon 1 of the androgen receptor gene of spinal and bulbar muscular atrophy (SBMA) in affected patients [1], after which it has been discovered in other different inherited neurodegenerative problems [2]. Several population and animal studies indicate that in different polyQ diseases, there is formation of intranuclear inclusions. In 1997 formation of intranuclear inclusions were for the first time observed in mouse model of Huntington disease and in patients suffering from HD [3]. The intranuclear inclusions were also reported in other diseases like in SCA 3 and SCA 1, cytoplasmic aggregates in SCA 6, SCA and SCA 17. Initially it was reported that there was no intranuclear formation in SCA 2 but later it was observed that they were present in this disease [4]. The formation of large fibrillar inclusions was observed as an end stage of aggregation and nucleation. In the starting phase, there is formation of polyQ monomers, which transits into polyQ oligomers which then convert into protofibrils and fibrils. All the intermediates are directly or indirectly related to the inclusion formation observed in patients. In HD, to understand the aggregation process and the mechanism involved behind nucleation, studies were done which showed a transition from monomers to oligomers as there was involvement of N-terminal Htt in the oligomer core [5]. In the aggregation process fibrils get elongated and in the later step oligomers itself act as a seed for elongation of monomers. Oligomers can act in both process of fibril formation and act as a seed for the monomer formation, both in 'on' and 'off' pathway.

Expansion of polyQ stretches share structural similarities with different distinct conformations of amyloid proteins and subsequent cellular toxicity caused by them, which is blocked by common antibodies [6].

As the patients present themselves only after the onset of diseases, various model system are required for the study of progression of the diseases and for development of diagnostics for early diagnosis of the disease. Therefore, it is important to elucidate the molecular mechanism of these amyloids it is beneficial to create different model systems that provide an operative path towards the elimination of

these amyloids. Various model system of polyQ diseases have been established in the past. Some model system like SCA3 model in *Drosophila*, Full length Htt model in *C. elegans*, transgenic huntingtin, CA1 and SBMA in mice and HD exon 1 model in primates are well established [7]. The cytopathology and the molecular mechanisms can be easily studied in invertebrate organism. Different model organisms offers great insight to understand this intricate cellular signaling mechanisms in a reproducible way to measure phenotypic outcomes arising due to polyQ.

Conflict of Interest

There is no conflict of interest.

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