

A Mini Review on The Roles of Beta-Amyloid and Tau Proteins in Huntington's Disease

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Huntington's disease (HD) is a neurodegenerative disorder that can progress and cause behavioural difficulties, cognitive decline, and movement disorders. The aetiology of this disease is mostly caused by an abnormal CAG repeat sequence in the huntingtin gene, which is present in all humans. HD can be diagnosed through several methods, such as physical examination, reviewing family history, brain imaging, genetic testing, as well as neurological and psychiatric examinations. To date, treatment for HD only manages the symptoms, for example, tetrabenazine is used for treating involuntary movements, and risperidone is an antipsychotic drug. Hence, a better understanding of HD is needed for a more specific treatment option. Beta-amyloid (A β) and tau proteins are well known to be the key contributors towards the progression of Alzheimer's disease, which is also a neurodegenerative disease. This review focuses on the roles of these two proteins in HD.

Keywords: Huntington's disease; beta-amyloid; tau protein

I. INTRODUCTION

In 1872, George Huntington described Huntington's disease (HD) among residents of Long Island, USA. HD is a progressive neurodegenerative disease that has several characteristics, which include behavioural difficulties, cognitive decline, and movement disorder. Although this disorder can manifest at any age between infancy and elderliness, onset of symptoms often happens in middle age. In 1993, a group of investigators discovered the gene that causes this disease – the huntingtin. Huntingtin gene contains a CAG repeat sequence, and it can be found in every human. However, the exact function of this gene has not been fully elucidated, yet. In HD, there is an abnormal CAG repeat expansion inside the huntingtin gene. Mutation of the gene occurs on chromosome 4, in which the gene contains an abnormally high number of CAG repeat. The higher the number of triplets repeats, the earlier in life HD may develop. In the process of passing the gene from a father to the child, this gene can further lengthen leading to HD onset in younger

age. This phenomenon is known as anticipation (Gatto *et al.*, 2020).

In general, HD can be diagnosed via physical examination, reviewing family history, as well as neurological and psychiatric examinations. If patients have shown the symptoms of HD, doctors will suggest a genetic test that can confirm the diagnosis. When patients do not show any symptoms but have family history of HD, doctors can order predictive genetic test. During neurological examination, neurologists will perform some tests for motor, sensory and psychiatric symptoms. Neurologists may also test for memory, mental ability, and language skills of patients. In psychiatric examination, several factors, such as emotional state, ability of judgment and behaviour of patients will be evaluated. Diagnosis of HD is also possible with magnetic resonance imaging, which can detect small changes in the brain that can be a sign of neurodegeneration. Hence, cognitive symptoms may develop at the initial stage or before the disease can be diagnosed. Symptoms such as chorea

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(involuntary body movements) usually developed at the early stages of HD. Symptoms that usually developed in later stages include motor incoordination and muscle inflexibility. Furthermore, patients may experience personality changes, emotional problems, and hallucinations. Nowadays, it is possible to detect HD with tissue or blood samples using genetic test (Sontheimer, 2015).

The symptoms of HD can be controlled by some drugs that moderate neurotransmitters. For example, tetrabenazine is used for the treatment of involuntary movements associated with HD. Risperidone, which is an antipsychotic drug can help to control chorea and delusions. However, these symptomatic treatments are insufficient in managing HD. For instance, only chorea and some of the psychiatric symptoms responded to the drug therapy, but other motor problems, as well as dementia, are not solved. In addition, almost all drugs that are used to treat the symptoms of HD have several side effects, which include fatigue, agitation, and sedation. Therefore, they are recommended to be used in HD patients that are suffering from severe symptoms (Wyant *et al.*, 2017). The variability of symptoms of HD and difficulty to target the cause of the disease (i.e. the huntingtin gene mutation) have made the combinational therapy, which attenuates several dysfunctional pathways and proteins to be the most ideal approach in handling the perplexing portrait of HD (Masnata *et al.*, 2020).

A better understanding on HD is necessary in order to find a more effective treatment to the disease. The current understanding on the disease pathogenesis has been focused on huntingtin gene mutation, while the studies on other gene or proteins are very limited, especially those that are involved in other neurodegenerative diseases. Beta-amyloid (A β) and tau are two proteins that have been widely reported in the pathogenesis of Alzheimer's disease (AD). However, their role in other neurodegenerative diseases is less discussed. Hence, this review article explores on the potential role of A β and tau proteins in the pathogenesis of HD.

II. THE ROLE OF BETA-AMYLOID PROTEIN IN HUNTINGTON'S DISEASE

A β represents peptides of 36–43 amino acids, which are the main constituent of the amyloid plaques that are usually found in the brains of those with AD. These peptides are

derived from the amyloid precursor protein and cut by gamma-secretase and beta-secretase to form A β . A β molecules can create flexible soluble oligomers by aggregation. Some misfolded oligomers, which are known as the 'seed' may induce other A β molecules to create the misfolded oligomeric form, causing a chain reaction similar to a prion infection. These oligomers are toxic to nerve cells. Although the normal physiological role of A β is not well understood, some studies discovered that A β might be involved in activities such as cholesterol transport regulation, acts as a transcription factor, activation of kinase enzymes, as well as antimicrobial activities (Weller & Budson, 2018). In addition, inhibition of A β construction by blocking beta-secretase in neural cultures can cause cell death (Plant *et al.*, 2003). The cell death could be restored by the addition of A β at physiological doses (Pearson & Peers, 2006) through the regulation of potassium channel and prevention of neuronal apoptosis (Brothers *et al.*, 2018; Soucek *et al.*, 2003; Yu *et al.*, 2006). The other physiological effects of A β include increased recovery after posttraumatic brain injury, blockage of blood-brain barrier leakage and inhibition of oncogenic viruses, therefore suppressing cancer. On the other hand, many studies have shown the pathological effects of high levels of A β in causing cognitive damage and several neurodegenerative diseases (Morley *et al.*, 2019).

Based on the recent immunohistochemical study on HD tissues, neural inclusions have been identified inside the neuronal nuclei, peri-nuclear and dystrophic neuritic processes (Becher *et al.*, 1998; DiFiglia *et al.*, 1997; Gutekunst *et al.*, 1999). The functional importance of these inclusions has not been discovered yet. However, there are several evidences showing that the inclusions developed because of a proteolytic protective mechanism (Klement *et al.*, 1998; Saudou *et al.*, 1998). It is proposed that the conformational changes in polyglutamine that can cause the formation of a highly stable A β structure is a disease-causing mechanism in HD (Perutz, 1996). In a histochemical study, Congo Red staining followed by confocal and polarising microscopy was performed on post-mortem human brain tissues from five HD cases and two healthy controls (McGowan *et al.*, 2000). In this research, it is demonstrated that some inclusions in HD brain tissues contained amyloid-like structures. The observation further supports the fact that polyglutamine

produced amyloid-like protein aggregates that were stained with Congo Red and displayed green birefringence under the polarised light (Scherzinger *et al.*, 1997). Congo Red-stained birefringent inclusions were demonstrated in neurons of all the five cases of HD but were not present in the two normal brains. In addition, the inclusions were demonstrated in both neuronal nuclei and perinuclear. The results strongly suggest that inclusion bodies have amyloid-like protein aggregates in HD. Based on the previous findings, it is likely that polyglutamine disorders, including HD fall into the group of amyloid diseases although the role of the amyloid aggregates remains unclear in the diseases (McGowan *et al.*, 2000).

III. THE ROLE OF TAU PROTEIN IN HUNTINGTON'S DISEASE

Apart from A β , tau protein can also form prion-like misfolded oligomers, and some evidences show that misfolded A β is able to induce misfolding of tau protein. Tau is a microtubule-associated protein. Under usual physiological conditions, this protein stabilises neuronal microtubules. However, under pathological conditions, tau protein undergoes modifications (usually by phosphorylation) and forms abnormal aggregates, which are toxic to neurons. This process can be seen in several neurological disorders, such as AD which is also called as tauopathy (Avila *et al.*, 2004).

Tau protein, which is formed by alternative splicing of microtubule-associated protein tau (MAPT) gene has been implicated in HD (Blum *et al.*, 2015; Fernández-Nogales *et al.*, 2014; Gratuze *et al.*, 2015). The association of tau with different genetic, neuropathological, and clinical levels in HD had been investigated. The presence of tau aggregates as well as co-localisation of mutant huntingtin with tau and its oligomeric intermediates were compared between HD patients, cases with a known tauopathy and healthy controls

using autopsy brain samples (Vuono *et al.*, 2015). Furthermore, genotype, and phenotype of HD patients had been analysed, in which association between genetic variation of tau and clinical expression as well as progression of HD was reported. Based on the results obtained in this research, tau pathology was evident in the HD cases and occurred independently of their age, CAG length or disease grade. In addition, widespread pathological inclusions that contain abnormally phosphorylated tau protein were observed in HD brain tissues, where some of these inclusions were co-localised with mutant huntingtin. Tau oligomers were also observed in the brain of patients with HD. The MAPT haplotypes had shown to affect the rate of cognitive decline in a large number of cases with HD (Vuono *et al.*, 2015). In short, tau protein was shown to be involved in HD, although the exact function of this protein and how it relates to HD is not fully understood yet.

IV. CONCLUSION

In conclusion, the presence of both A β and tau proteins in the brain of HD patients has been confirmed, and some of the important roles of the proteins have also been demonstrated. However, there is a need for detailed investigations and comprehensive analysis to further confirm and demonstrate the role of A β and tau proteins in HD.

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