

Epigenetics of Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative diseases are dreaded throughout the world due to their lethality and sporadic nature. The sporadic nature and slow progression of these diseases make their early detection and hence clinical management difficult. The advances in the field of epigenetics have given people hope as at molecular level the aberrancy of epigenetic regulators helps in the progression and development of these disease. The major researches have been done in understanding the epigenetic nature of these disease and several hallmark epigenetic alterations have been recorded for each disease. These major breakthroughs have helped us in understanding the neuropathy at molecular level and countering it more effectively with the drugs and clinical management. In this review we summarize the alterations in various epigenetic modulators' leading to the pathogenesis of various neurodegenerative diseases. We also tried to summarize the various environmental and molecular factors which influence the epigenetic machinery and increase or induce the pathogenesis of neurodegenerative disease.

KEYWORDS: Neurodegenerative, epigenetics, Alzheimer's disease, Huntington's disease, Parkinson's disease, Prion disease.

INTRODUCTION

The emergence of various phenotypically and morphologically distinct cells from a single cell i.e. fertilized ovum has been a topic of fascination for centuries [1]. Various scientists have time and again done investigations to solve this mystery and have come to conclusion that epigenetics is responsible for conferring cellular identities and different functions to the cells. Epigenetics, is a mechanism which modulates the inheritance pattern of chromatin and controls the expression of different genes from the same stretch of DNA in different cells [2]. This mechanism of epigenetic functions by suppressing or activating various transcription factors by the epigenetic modulators i.e. readers, writers and erasers. Writers are the group of proteins that are known to add epigenetic marks to the DNA and Histones by methylation and acetylation; readers, the group of protein that interpret these instituted epigenetic marks and erasers, the group of proteins that function to remove instituted epigenetic marks by the process of demethylation and deacetylation, work in synergy to produce different effects [3]. From first being described as the mechanism responsible for any phenotype by Waddington [4], epigenetics' landscape has expanded a lot in last few decades. The molecular characterizations of different epigenetic interactions have been done time and again by high end technological advancements and so has its definition changed over time. These definitions [5-10] have been able to throw light on the true extent and nature of the epigenetics. Earlier it was considered that the DNA methylation was solely responsible for the epigenetic inheritance however, consecutive investigations have reported that modifications of the histone and ncRNA play equally crucial roles [11-15]. The landscape of epigenetics further expanded as a consequence of various land mark discoveries which put more emphasis on the involvement of chromatin modifications [16-26]. For instance, X-chromosome inactivation [18, 19], genome imprinting [16, 17] and vernalization [24-26]. The epigenetics of neurological functions is termed as neuroepigenetics and contrasting to the classical epigenetics, it is not heritable. Since epigenetics plays a crucial role in maintenance of the memory and neural network regulation, it has capability to interfere with their development and induce pathogenicity (Figure 1) [27]. The increasing knowledge and interest in the field of epigenetics led to major discoveries and epigenetics was implicated in about all types of diseases which were caused due to aberrant expression of genes. The studies have linked multiple disease with the aberrancies caused by epigenetics however, discussing all of them is beyond the scope of this review. In this review we will deal with the neurological disorders such as, Alzheimer's disease, Huntington's disease, Prion disease and Parkinson's disease and the epigenetic mechanism behind them.

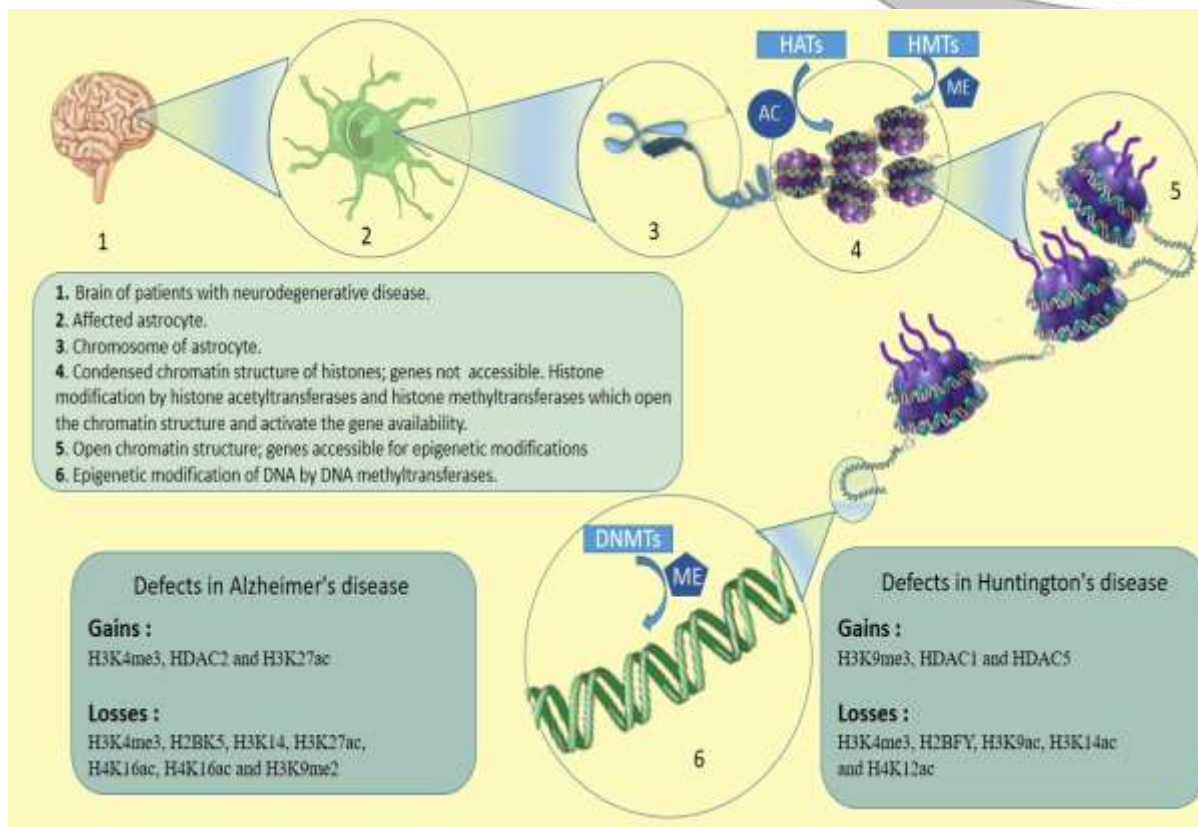


Figure 1 Neuroepigenetic mechanisms leading to the various neurodegenerative disease. The gain and loss of various neuroepigenetic modulators have been also observed.

MECHANISM OF NEUROEPIGENETIC REGULATION

Except being non-heritable the neuroepigenetic modifications resemble the classical epigenetic modifications and the mechanism of both is controlled by same class of enzymes. However, neuroepigenetics has distinct functions too [28]. The various neuroepigenetic modifications play various roles in the storage and retention of the memory. The functions of neuroepigenetic modifications have been discussed below.

Histone modifications

Acetylation and deacetylation of histones is controlled by two enzymes i.e. histone acetyl transferases (HAT) and histone deacetylases (HDAC) respectively. Histone acetyl transferases transfer the acetyl group to the histones as a consequence of which euchromatin structure is formed and transcription occurs. Contrary to this, the histone deacetylases act upon the acetyl group added by histone acetyl transferases and remove it due to which histone regains heterochromatin structure and transcription is repressed [29-31]. Studies have reported that both of these epigenetic modulating enzymes are accountable for the plasticity of the neural synapsis and memory function [32]. Acetylation of histones in insular lobes are responsible for the memory formation and inhibition of deacetylation by HDAC inhibitor has been shown to increase the level of CA1 synapses. Thus, it has been hypothetically assumed that inhibiting HDAC can lead to memory improvement. In in-vitro investigations it has been observed that by inhibiting the HDACs or enhancing the acetylation levels of H3K9 or H3K14, the memory loss either due to brain atrophy or loss of neurons could be reinstated [33].

DNA modification

DNA methylation in mammals is governed by specific rules and can either lead to the gene suppression or activation based on the site of methylation [34]. Changes in these established pattern of methylation and demethylation has been reported with the change in age [35, 36]. It has been established that the methylation of DNA is important for acquiring and storing memory [37]. In neuroepigenetic modifications, not only CpG island but also non CpG sites have been shown to be methylated. The various methyltransferases function to deposit these methylation marks on the DNA. Investigations have shown that knocking out DNA methyltransferase1 and DNA methyltransferase 3A in mice has resulted in impaired hippocampus based memory storage and learning [38]. Ten-eleven translocation proteins are associated with the formation of 5-hydroymethylcytosine from 5-

methylcytosine in the genes linked with synaptic plasticity and memory [39]. Thus, these proteins are associated with DNA methylation and activation of the genes associated with memory.

Non-coding RNA

Various non-coding RNAs such as micro RNA are associated with the post translational regulation of the gene expression [40]. They are known for the mRNA silencing by getting attached to the 3' untranslated region leading to the degradation [41, 42]. The differentiation and proliferation of neurons have been shown to be controlled by miRNA-124. miRNA-124 functions by suppressing PTBP1 as a consequence of which neuronal cells are formed from the cells which otherwise might have developed in some other kind of cells [43]. Studies have also shown that during the brain development process miRNAs play important functions in the formation and maturation of synapse and neural dendrite formation [43-45]. Non-coding RNAs have been also implicated in cell survival. Long ncRNAs are known to boost genes linked with synapse in hippocampus [46].

NEURODEGENERATIVE DISEASES AND NEUROEPIGENETICS

Aging process and several other external factors such as smoking, eating habits, workouts and lifestyle affect the epigenetic machinery and its precision. This gradual decrease in the precision leads to aberrant modifications and defects in neural cells. These neuronal modifications though non-heritable lead to various neurodegenerative diseases. We selected the disease having strong research data backed evidences for the epigenetic modifications leading to the various neurodegenerative diseases.

Huntington's disease

It is heritable disease of neural cells affecting spiny projection neurons of striatum. It is often characterized by the gradual decrease in locomotor and cognitive activity. It occurs as a consequence of uneven expansion of CAG repeats (usually >35) in the gene that codes for huntingtin [47, 48]. This expanded CAG stretch results in the expression of mutant protein which is unable to fold correctly and is proteolyzed. This proteolysis of mutant protein yields toxic polyglutamine [49]. Thus, higher the stretch of these CAG repeats higher will be the expression of mutant protein and severe will the disease progression. This disease in long run causes death of neuronal cells and ultimately lead to many medical conditions such as melancholy, mania, droopiness and dystonia.

DNA methylation: Aberrancy of DNA methylation in Huntington's disease has been reported due to the mutation in Huntington gene [50]. Successive researches were done for the evaluation of methylation levels in the tissues of the Huntington's disease patients. However, no concrete and concluding evidence has been reported suggestive of DNA methylation's role in the development and progression of Huntington's disease (HD).

Histone modifications: Due to the overexpression of Huntington gene vast difference has been observed in the acetylation pattern of histone. Investigations done in the animal model showed that the genes *Drd2*, *Grin1* and *Penk1* which are usually under expressed in the normal cells were found to be upregulated due to acetylation of promoter regions of the specified genes in HD [51]. Some studies also reported the upregulation of di- and tri-methylated 9th position lysine in the H3 caused the formation of heterochromatin structure in striate nucleus of patients suffering from HD [52, 53]. In HD patients the overexpression of H2AFY, which is a member of H2A family, was also observed [54]. Also, the hypomethylation of 9th and 14th position lysine in H3 and 12th position lysine in H4 has been observed. Apart from acetylation and methylation, the ubiquitination in the H2A has been also reported along with its capability to modulate the transcription [55].

Alzheimer's disease

It is the most frequent occurring adult-onset neurological disorder. Gradual loss in the cognitive ability and apoptosis and/or necrosis of the neurons are the common hallmark of this disease. As most of the patients develop Alzheimer sporadically and its progression takes time it is hypothesized that the environmental factors lead to the alterations in the normal epigenetic patterns that actively contribute towards Alzheimer development [56]. Mutations of various genes further worsens the case. For instance, mutation in the presenilin genes and amyloid precursor protein leads to the autosomal dominant Alzheimer's disease [28].

DNA methylation: Methylation associated with the 5-methyl cytosine plays a crucial role in the proliferation and development of the neurons. In the patients of Alzheimer's the evidence of 5-methyl cytosine or its product has rarely been seen thus indicating their association with the neuron degeneration [57]. In 207-182 region of amyloid precursor protein methylation of cytosine is observed in the normal brain, but with aging these methylation marks get reduced leading to the deposition of amyloid- β in the brain which is known to cause neurodegradation. The low levels of 5-methyl cytosine were observed in the hippocampus, entorhinal cortex and cerebellum region of Alzheimer patients [58].

Histone modifications: In Alzheimer's patients histone deacetylases 2 and 3 are normally expressed in elevated levels in the area of brain related with memory processing and storage and deletion of these genes in mice

model has shown to increase amyloid phagocytosis by microglia [59]. Histone deacetylases 2 is also known to decrease the acetylation level of genes linked with learning and cognition [60]. Another independent study reported the elevated expression of histone deacetylases 2 in hippocampus and prefrontal cortex [61]. The elevation in the expression of histone deacetylases 6 in hippocampus and cortex was found to be 91 percent and 52 percent respectively [62]. All these imbalances of acetylation were linked with the impaired cognition. Thus, these studies show a positive correlation between the histone modifications and the Alzheimer's disease progression and development.

Epigenetic alterations by ncRNAs: A drastic difference between the expression of ncRNAs in the normal brain and in the brain of Alzheimer's patients' have been observed. In the Alzheimer's mice model a significant downregulation in the expression level of 319 mRNAs, 183 micro RNA and 555 circular RNA was observed [63]. The miRNAs have been implicated in the pathogenesis of Alzheimer's disease as they are associated with the processing of amyloid, neurogenesis and in imparting resistance to insulin. In human Alzheimer's brain miRNA-206 showed to regulate the neuropathic factor which is known to regulate memory and plasticity of synapse [64].

Parkinson's disease

Being second most prevalent disease, Parkinson's disease leading to the degradation of neural network. According to an estimate, around 1.5 million people in United States of America each year succumb to this disease [65]. This disease causes death of neuromelanin containing dopaminergic neurons found in substantia nigra of the brain. Parkinson's disease is a consequence of many factors combined to produce common effect. Such factors include environmental exposers, gene interaction, epigenetics and polygenic inheritance [66]. Many genes including PARK, Parkin, DJ1 and SNCA are implicated in the pathogenesis of Parkinson's disease.

A genome wide epigenetic analysis revealed that the regulation of SNCA is epigenetically controlled in the brains of Parkinson patients [67]. In the samples obtained from the alcoholic anorexic patient's hypermethylation of SNCA has been observed [68]. Thus, hinting at the epigenetic modulation of the gene. The decrease in the methylation level of SNCA intron 1 was reported in the multiple regions of brain in the patients having erratic Parkinson's disease [69]. Also, the increase in the expression of SNCA has been observed post DNA methylation inhibition. Contrasting to SNCA, methylation in the promoter region of Parkin gene has been not observed in the disease development and progression of Parkinson's disease [70].

DNA methylation: The epigenetic sequencing of brain showed inconsistencies in the DNA methylation level of CpG islands in substantia nigra region [71]. Several factors including environmental and molecular are known to positively influence the methylation level leading to the PD development and progression [72]. An investigation done to evaluate effect of Mn exposers on SHAY5Y cell line reported aberrancy in the PINK1 and PARK2 as a consequence of DNA hypermethylation [73]. Hypermethylation of the PGC1- α , CYP2E1, NPAS2 and SNCA are also implemented in PD.

Histone modifications: Studies have reported that binding of SNCA to the histones acts as an inhibitor to the histone acetylation process [74]. Thus, treating with histone deacetylases inhibitors helps in protecting the neurons against the SNCA induced neurotoxicity [75]. Decrease in SNCA levels in various study models were observed on treatment with histone deacetylases Sirtuin2 inhibitors [76]. Downregulation of multiple genes making histone H2A, H4 and H1 has been positively correlated with the elevated expression of SNCA in humans [77]. Thus, we can say that the histone modifications play very crucial role in the PD pathogenesis.

Epigenetic alterations by ncRNAs: miRNA -133b is known to regulate the maturation and proliferation of dopaminergic neurons in the mid region of brain. However, in the brain cells of patients with PD, paucity of miRNA-133b was observed [78]. Concentration of SNCA gene product α -synuclein is shown to be controlled by two miRNAs : miR-153 and miR-7. Both of these micro RNAs function in a similar manner. They bind to the 3' untranslated region of SNCA and cause downregulation of gene expression [79]. Studies done in C.elegans Parkinson's disease model reported various downregulated miRNAs [80]. Thus, majority of studies have reported and concluded that the miRNAs play crucial role in the pathogenesis of PD.

Prion disease

Prion disease is related to the misfolded protein particles which have ability to transfer this aberrancy to the other normal proteins of same type. Most prevalent prion disease is Creutzfeldt-Jakob disease which very closely resembles with bovine spongiform encephalopathy of livestock. This is very fatal neurological disorder with very high progression rate and is able to claim life of patient within a year of its onset. Infectious prion proteins arise as a result of structural change in the prion protein. These infectious prion proteins are known to cause degradation of grey matter along with the rise in the level of astrocytes. Another sporadic prion disease is fatal familial insomnia. It is heritable disease meaning that it can pass from one generation to the other. Since these diseases are linked with the aberrancy in the protein folding they exhibit unusual epigenetic mechanism. With

increase in the environmental stresses the prion switching frequency increases with epigenetic alterations occurring at extreme circumstances [81].

CONCLUSION:

In the present review we summarized the epigenetic aberrations leading to some major neurodegenerative disease. A lot of work has been done in understanding the epigenetics of various neurodegenerative disease and still there remains a gap between the knowledge and the development of proper medication to cure or prevent these disease. Also, very little to almost no knowledge is available to understand the proper mechanism of the neurodegenerative diseases. Partially due to the ethical reasons and partially due to the sporadic nature of these diseases the study of these diseases have been a challenge.

Understanding the proper mechanisms of these diseases will help in generating drugs targeting epigenetic machinery with great efficacy and may help in preventing the serious outcomes of these diseases. Several drugs targeting the epigenetics for the cure of neurodegenerative diseases are under clinical evaluation and with great hope will soon be commercially available for the treatment of the epigenetic neurodegenerative disorders.

CONFLICT OF INTEREST:

The authors have no conflict of interest regarding this review.

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