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Implication of Epigenetic Modifications in Neurodegenerative Disorders: Traces and Imprints

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Abstract

Neurodegenerative disorders like Alzheimer's, Parkinson's, Huntington's and ALS; present a complex biological disorder resulting loss of synaptic connections, neuronal damage and decay in old and elderly persons. Such a degrading process of neurons affects the central nervous system and results in loss of cognitive abilities, memory, sensory abilities and impairs the motor neuron functions. Thus, understanding the biology of neurodegenerative diseases has been crucial in ensuring healthy aged life. Although several cases of familial neurodegenerative disorders have been reported, yet the mechanism for sporadic neuronal degeneration remains largely unknown. Therefore, in this review we aim to understand the role of environmental triggers, i.e. epigenetics in affecting the normal functioning and coordination of host nervous system. A distinct signature mark of neurodegenerative disorders involves misfolding and structural aberration in native proteins leading to formation of intracellular fibrillary tangles, Lewy bodies, extracellular plaques, to name a few. This paper focusses primarily on four kinds of neurodegenerative disorders as mentioned above and reviewed the role of DNA/histone methylation, acetylation, ubiquitination along with mutational changes to the native protein product.

Keywords: Epigenetics; Methylation; HDACs; Alzheimer's; Parkinson's; Huntington's; ALS; Therapeutics

Introduction

Neurodegeneration usually refers to a progressive impairment of the structure and function of nerve cells ultimately leading to their damage and death. The consequences of such neurodegenerative processes are usually observed as loss in motor neuron functions, impaired sensory abilities, decline in memory and cognitive abilities along with hindrances in functioning of several organs and organ systems. Some of the common neurodegenerative disorders include alzheimer's disease, Parkinson's disease, Huntington's disease and a comparatively rarer condition called Amyotrophic Lateral Sclerosis (ALS). However, these comprise the most prominent nervous disorders amongst the rest. Huntington's disease is occasionally encountered by juveniles, while the majority of these neurodegenerative disorders are seen in aged and elderly people with (familial) or without (sporadic) a history of occurrence in their family. Therefore, the science of ageing relies significantly on addressing such ageing and senescence-linked neurodegenerative disorders. Nevertheless, better healthcare and medical facilities have reinforced our idea of living a better and healthier aged life with higher life expectancy. Additionally, given the slow onset and progressive increase in the disease phenotype, a major limitation in the treatment of neurodegenerative disorders has been the delayed diagnosis at the clinics and careless attitude of patients and their family towards initial signs and symptoms at home or work place.

Therefore, the needs for understanding the biology of these disorders are enormous and unfortunately till date we have succeeded very little in this direction. Cases with neuronal diseases are on the rise and the lack of an effective therapeutic strategy has limited our approach in responding to these disorders effectively. Usually neurodegenerative disorders are complex in nature, involving both genetic and environmental paradigms and thus hinders in designing and development of therapeutics. This review paper aims to bridge the gap in understanding the causative factors and their interactions among themselves leading to neurodegenerative disorders. It becomes highly imperative to understand the disease biology, identify unique signature marks and look for molecules and structural entities associated with such diseases to develop an effective remedy targeted against neurodegenerative disorders.

Epigenetics of Neurodegeneration

Neurodegenerative diseases exhibit multifactorial pathology involving genetic and epigenetic components working together in response to environmental stimuli. Of which genetic factors are the unalterable causal elements and the epigenome encompasses the factors which are more dynamic, modifiable and heritable (when found in germ cells). These changes, such as acetylation, phosphorylation, methylation, sumoylation or ubiquitination of histones/ histone tails/ DNA are executed by their respective writer, reader and eraser enzymes like HDACs (Histone deacetylases), HATs (Histone acetyl transferases), Sumo1/2 (Sumoylation factors), DNMT (DNA methyl transferases) etc. Such events of variable histone and DNA modifications are believed to establish a "histone-code" instructing the genes to be either transcriptionally active or inactive. Environmental influences in form of chemical, physical or nutritional factors participate in enriching or depleting these histone codes depending on the cellular context and even can target the proteosomal degradation of host cellular proteins via ubiquitin deposition. Therefore the expression of genes especially those at labile genomic regions potentially affects the adult phenotype. Since the epigenome presents a landscape of cellular and genomic

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plasticity, it constantly fluctuates within cells and tissues in response to changing environmental cues. In this section we specifically focus on epigenetic modifications as central mediators of the nexus between the environment, genes and host system. The role of epigenetics in regulation of various neurobiological and cognitive processes like development of early brain, creation of memory, learning as well as synaptic plasticity have been well documented in recent years. Moreover, incidences of many neurological disorders, including Alzheimer's, Huntington and Parkinson's diseases have also been established to be a consequence of pathologically modified epigenetic milieu of the causal genes.

Epigenetics and Biology of Neurodegeneration

Alzheimer's disorder

Alzheimer's disease International reports approximately 44 million people (i.e., 1 in 4 individuals) worldwide to be suffering from Alzheimer's disease with highest prevalence exhibited in Western Europe (http://www.alz.co.uk/research/world-report-2015) (Figure 1). It is also one of the leading causes of physical and cognitive disabilities among elderly individuals with 2 women reported for every 3 Alzheimer's patients [1]. The disease initiates gradually with several discernible symptoms like short term memory loss (Figure 1) [1]. In addition, with the progression of disease several other noticeable symptoms including difficulty in language usage and processing, disorientation, inability in self-care, volatile mood swings and acute dementia are exhibited (Figure 1) [2]. In the later stages, the patients often show critical symptoms of complete speech and memory loss and become dependent on the caregivers lacking the competence to perform even simple tasks independently (Figure 1).

With respect to the age of onset and the associated genetic predisposition, Alzheimer's is usually categorized into two types. The early onset familial Alzheimer's comprises only 5-10% of all the cases and exhibits an autosomal dominant inheritance pattern. The physiopathology of the disease involves contributory effects from many genes (Figure 1). Typically, the occurrence of intracellular neurofibrillary tangles along with the phosphorylated Microtubule Associated Protein Tau (MAPT) and extracellular plaques carrying aggregated Amyloid beta (Aβ) protein characterizes the presence of the Alzheimer's Disorder (Figure 1) [3-5]. Usually the early onset subtype is noticed within mid-40s and 50s and is attributable to mutations in any of three key genes like Amyloid Precursor Protein (APP) (Figure 1), Presenilin 1 (PSEN 1) and Presenilin 2 (PSEN 2) [6]. Increased production of Aβ-42 protein due to mutations in PSEN 1 or aberrations in PSEN2 leading to alteration in the homeostatic ratio of Aβ-42 to Aβ-40 are associated with familial Alzheimer's [7]. In addition, TREM 2, has also been known to increase the susceptibility of an individual 3 to 5 times for developing the early onset familial Alzheimer's [8].

While only a few cases of Alzheimer's comprise the familial type, the majority i.e., 90-95% of the cases are late onset (occurring after 60-65 years of age) and non-familial kind. Risk factors attributable to such cases originate from environmental triggers and genetic factors leading to sporadic cases of the disease. Located on the chromosome 19q13, the APOE (Apolipoprotein E) gene has been linked to the incidence of non-familial, sporadic Alzheimer's. The APOE ε4 allele enhances the predisposition for disease although less than 50% of the late onset cases are carriers of this allele. On contrary, ε2 and ε3 alleles have been designated to confer a relative protection from the neurodegenerative

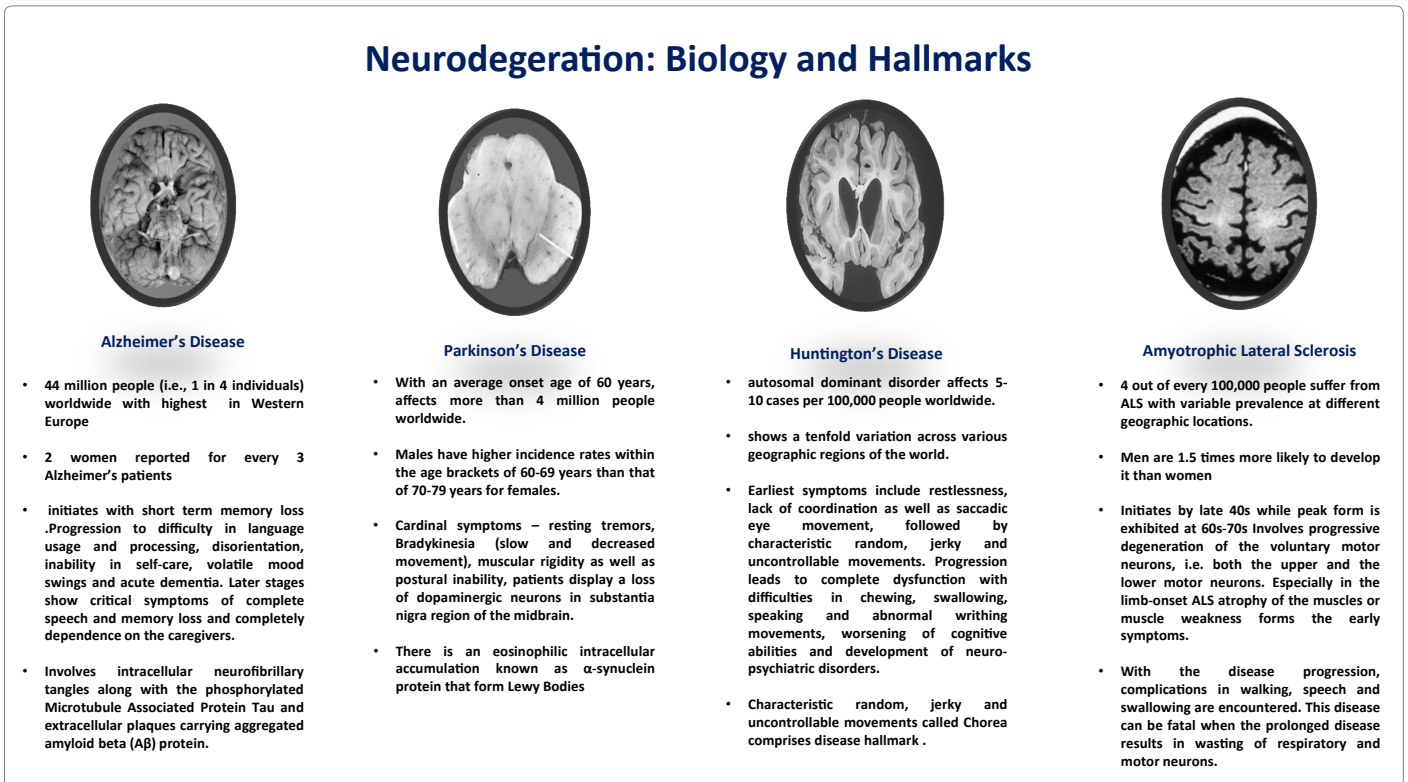

Figure 1: The common neurodegenerative disorders and their associated disease hallmarks. In this paper we have discussed in details about Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis. This figure summarizes there statistical prevalence, disease onset and progression phenotype and the hallmark features like formation of intracellular fibrillary tangles, extracellular plaques and Lewy bodies. The representative images are brain MRIs of each specific neurodegenerative disorder.

disorder [9]. In addition, recent genome wide association studies (GWAS) have brought forth a total of 19 candidate genes that pose risk for onset of sporadic, late onset Alzheimer's Disorder [10].

Epigenetics and Alzheimer's disease

Patients with Alzheimer's disease frequently exhibit insufficient levels of serum folate along with deficiencies of S- adenosylmethionine (SAM) and methionine S-adenosyltransferase in the cerebrospinal fluid (CSF) leading to atrophic cerebral cortex. A further elevated level of S-adenosylhomocysteine (SAH) (a methyltransferase inhibitor) has been observed in the brain of Alzheimer's patients (Figure 2) [11]. Such an inhibition of methyltransferase results in the silencing of genes ultimately leading to aberrant gene transcription and cognitive failure, as observed in the disease. In addition, the promoter region of the APP gene in patients below 70-years bear significantly lesser DNA methylation (5 mC i.e., 5-methylcytosine) in comparison to those above 70 years, substantiating the possibility of elevated Aβ deposition and disease progression (Figure 2). Fuso et al. in an *in vitro* study confirmed that insufficiencies of folate and vitamin B12 in culture medium regulate DNA methylation of the BACE1 and PSEN1 genes leading to an increased production of Aβ (Figure 2). Additionally Alzheimer's patients exhibit altered 5 mc levels in the brain and lymphocytes along with altered expression of genes like APOE and PSEN1 (required for Aβ processing), DNA methyltransferase-1 (DNMT1) and methylenetetrahydrofolate reductase (MTHFR- required for methylation homeostasis) (Figure 2). Moreover, the adult human brain with Alzheimer's exhibits globally enhanced hypermethylation, increased 5 mC and 5 hmC (5-hydroxymethylcytosine; oxidation product of 5 mC) levels in neurons but not in microglia and astrocytes.

Apart from the much explored role of DNA methylation, there are indications of role of HATs HDACs, HMTs, HMDs and HPRTs as modulators in Alzheimer pathology (Figure 2). For example, recent findings from a clinical trial have shown a strong negative correlation of the levels of SIRT1 (Sirutinin-1 belonging to HDAC III family) with that of Aβ and fibrillary tau proteins in the cerebral cortex of Alzheimer's patients. This implies that this HDAC family of proteins can help to ameliorate the signature marker and progression of AD. Further a recent study Turner et al. have shown that resveratrol can effectively and safely cross the blood brain barrier to induce cerebral effects and in case of a randomized double blind-placebo controlled study, it has shown to downregulate the levels of AD biomarkers like Aβ 40/42 and hyperphosphorylated tau both in blood plasma and CSF.

Parkinson's disorder

Amongst all neurodegenerative disorders, the Parkinson's disease is the second most common after Alzheimer's. According to the Parkinson's disease Foundation (PDF), with an average onset age of 60 years, it affects more than 4 million people worldwide [11]. The gender-based prevalence of Parkinson's with age reflected a steep bias in favor of males with higher incidence rates within the age brackets of 60-69 years than that of 70-79 years for females (Figure 1). The effect is speculated to be due to the presence of higher estrogen level in females. Interestingly, a greater extent of heterogeneity has been noticed for patients above 80 years as the disease varies in an age and gender-dependent manner during later years of life [12]. Parkinson's disease primarily afflicts the motor neurons of the central nervous system. Characterized by four cardinal symptoms – resting tremors, Bradykinesia (slow and decreased movement), muscular rigidity as well

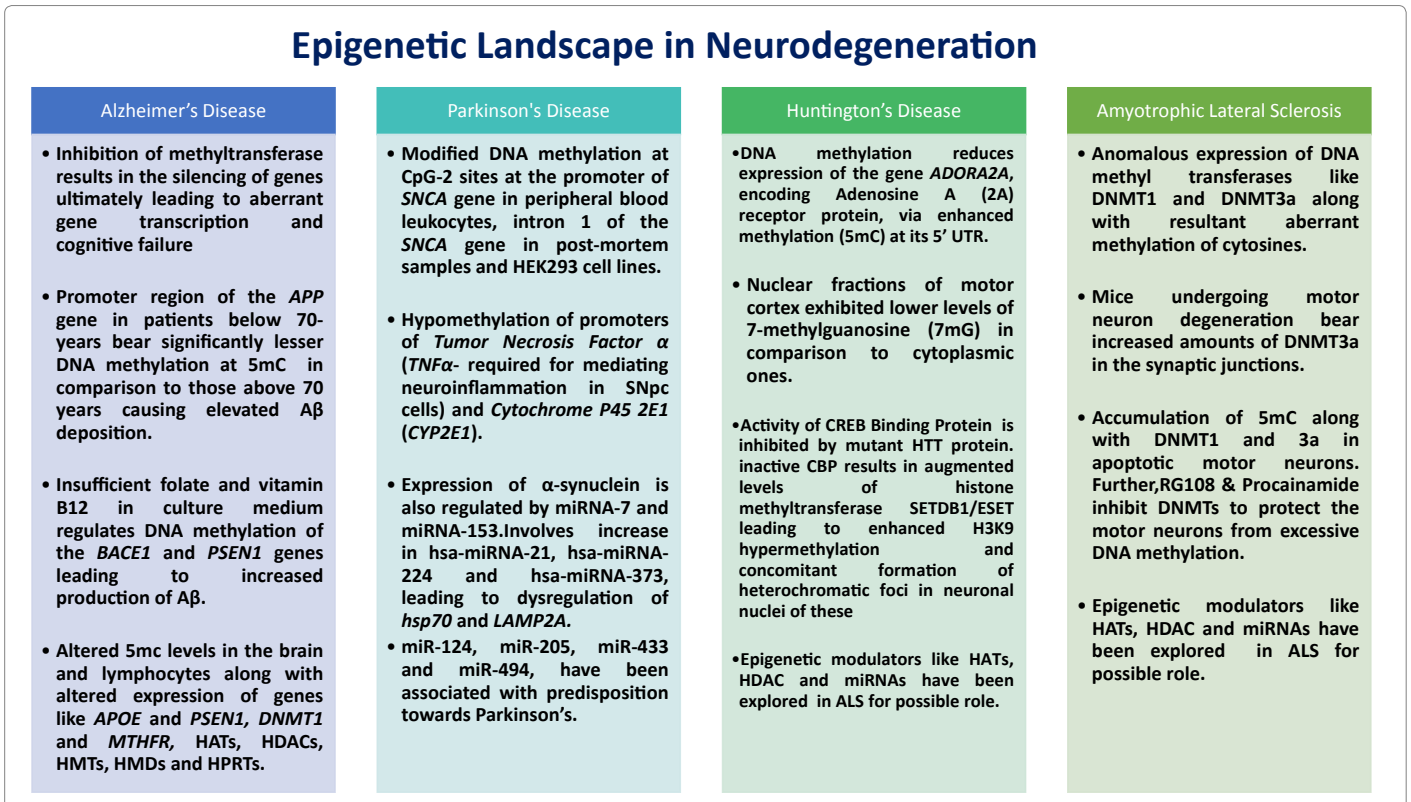

Figure 2: List of major and significant epigenetic changes associated with different neurodegenerative disorders. Each of the four neurodegenerative disorders namely Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis have different forms of epigenetic modifications like methylation, acetylation, ubiquitination and interference of microRNAs etc. This figure highlights the key modifications.

as postural inability, patients display a loss of dopaminergic neurons in substantia nigra region of the midbrain, often reflected as involuntary writing movements (Figure 1) [13]. Characteristically, there is an eosinophilic intracellular accumulation known as α-synuclein protein that form Lewy Bodies (Figure 1) [14,15]. The genetic risk factors for the development of familial forms Parkinson's include 16 genes, ranging from PARK1 to PARK16. These genes have been known to be correlated with the autosomal (dominant and recessive) and X-linked variants of the disease [16,17]. Collectively, the genes of this group code for various proteins such as α-synuclein (SNCA/PARK1 or 4), parkin (PRKN/PARK2), leucine-rich repeat kinase 2 (LRRK2/PARK8), PTEN-induced putative kinase 1 (PINK1/PARK6), protein deglycase (DJ-1/PARK7) and probable cation-transporting ATPase 13A2 (ATP13A2/PARK9) [17]. Specifically events like point mutations, gene duplication or triplication of SNCA and point mutations in LRRK2 have been implicated in the autosomal dominant forms of the disease. The autosomal recessive form of this disease is associated with DJ-1 and PINK1 mutations [18-21].

In contrast, preponderance of the sporadic form of Parkinson's largely arises from a combination of genetic and environmental triggers rendering it non-heritable. Mutations of the promoter region of SNCA (Fuchs et al.), polymorphisms located in DJ-1 (De Marco et al.), point mutation variants of LRRK2 (Chan et al.) and MAPT expression of Tau protein (Towin et al.) predispose an individual for Parkinson's Disease in older years of life.

Epigenetics and Parkinson's disease: In Parkinson's Disease, a correlation between neurodegeneration and epigenetics has not been extensively exploited so far. However, several genes common to both Parkinson's and Cancer carry an abnormal methylation pattern in the latter, indicating a possible shared similarity in the former [21,22]. In another study, SIR2 (a NAD dependent HDAC) mediated rescue of dopaminergic neurons by inhibiting aggregation of α-synuclein suggested a plausible mechanism of disease progression and regulators to influence the same. Modified DNA methylation profiles in Parkinson's patients has also been experimentally confirmed in the brain and blood samples, CpG-2 sites at the promoter of SNCA gene in peripheral blood leukocytes, intron 1 of the SNCA gene in post-mortem samples and HEK293 cell lines (Figure 2). Specifically, hypomethylation of promoters of Tumor Necrosis Factor α (TNFα- required for mediating neuroinflammation in SNpc cells) and Cytochrome P45 2E1 (CYP2E1) in clinical cases of Parkinson's has been reported (Figure 2). Furthermore, it has been observed that the promotion of neurotoxicity in drosophila and cell culture models of Parkinson's is associated with α-synuclein induced inhibition of histone acetylation. Interestingly, this effect could be reversed by administration of HDAC inhibitors which implies a role of histone post-translational modifications in the disease pathology. For example SIRT1 inhibitors are upregulated in most patients suffering from Parkinson's and thus SIRT1 is potent in reducing α-synuclein aggregates by upregulating molecular chaperons like HSP70 and co-factors of molecular chaperons like HSF-1 (Heat shock factor-1). Correlation of histone modifications with Parkinson's can also be noticed from the fact that a reduction in p300 levels as well as its corresponding HDAC activity is brought about by α-synuclein in α-synuclein transgenic mice (Figure 2). In addition, micro RNAs (miRNAs) have also been correlated with the onset and progression of Parkinson's disease. miRNAs are ~19-25 bp long non-coding RNAs that inhibit translation of target mRNAs by binding to their 3' untranslated regions (UTRs) and thereby suppressing protein synthesis. MiRNA-133b, which is involved in the terminal differentiation and activity of dopaminergic neurons, was observed to be diminished in the midbrains of the Parkinson's patients. Expression of α-synuclein is also regulated by miRNA-7 and miRNA-153 (Figure 2). Disease-causing aggregation of α-synuclein also involves increase in the levels of hsa-miRNA-21, hsa-miRNA-224 and hsa-miRNA-373, leading to dysregulation of helper proteins like Heat Shock Cognate Protein 70 (hsp70) and Lysosomal-Associated Membrane Protein 2A (LAMP2A), that otherwise assist α-synuclein for proper folding, packing and trafficking (Figure 2). Various other miRNAs, for example miR-124, miR-205, miR-433 and miR-494, have been associated with predisposition towards Parkinson's.

Huntington's disease

Also known as Huntington's chorea (most common polyglutamine disorder), this autosomal dominant disorder affects 5-10 cases per 100,000 people worldwide [22]. The prevalence of this disease shows a tenfold variation across various geographic regions of the world [23]. Generally, this disease initiates in the middle years ranging from 35-45 years although juvenile cases [24] of the same have been reported (Figure 1). The earliest symptoms include restlessness, lack of coordination as well as saccadic eye movements. These are succeeded by characteristic random, jerky and uncontrollable movements called Chorea comprising a hallmark of Huntington's Disorder. However, the progression of the disease often leads to a state of complete dysfunction with difficulties in chewing, swallowing, speaking and abnormal writhing movements [25] along with worsening of cognitive abilities and development of neuro-psychiatric disorders (Figure 1) [26]. Genetically, Huntington's Disorder results from an aberrant expansion of a trinucleotide repeat (CAG repeats) within the Huntingtin gene (HTT). Glutamine (Q) encoded from this CAG repeat is expressed in the HTT protein as a Poly-Q stretch near its N-terminal. Usually, healthy individuals bear <36 CAG repeats in their HTT gene resulting in normal HTT functioning in vesicle trafficking and endocytosis. However due to mutation, individuals with more than 36 repeats express a mutant HTT (mHTT) protein. These misfolded and aberrant mHTT protein is unable to accomplish its synaptic and pro-survival functions. A distinctive trait of the disease involve cleavage and aggregation formation of Misfolded mHTT within the cell nucleus, cytoplasm and neurites [25,27]. With a very high penetrance of the disease, i.e. 50% of the offspring with one of the parents afflicted with Huntingtin's and 75%-100% of the offspring with both parents afflicted bear the risk of developing the disease. Further it also depends upon whether the parents bear single or double expanded copies of mHTT gene.

Epigenetics and Huntington's disease

Likewise, a growing body of evidence proposes epigenetic mechanisms to be of prime importance in the huntington's disease. DNA methylation is believed to be the key factor responsible for reduced expression of the gene ADORA2A, encoding Adenosine A (2A) receptor protein, via enhanced methylation (5 mC) at its 5' UTR (Figure 2). Thus, ADOR2A protein is being considered as a potential therapeutic target in huntington's disorder. Nuclear fractions of motor cortex exhibited lower levels of 7-methylguanosine (7 mG) in comparison to cytoplasmic ones, in such patients. Further, the activity of the histone acetyltransferase; CREB Binding Protein (CBP- also acts as transcriptional co-activator to RNA-pol II) is inhibited by mutant HTT protein (Figure 2). The resultant histone hypoacetylation and hypermethylation leads to dysregulated neuronal transcription in Huntington's disease. Also inactive CBP results in augmented levels of histone methyltransferase SETDB1/ESET leading to enhanced H3K9 hypermethylation and concomitant formation of heterochromatic foci in neuronal nuclei of these patients (Figure 2).

These events of heterochromatinisation causes synaptic dysregulation due to transcriptional disruption of CHRM1 (muscarinic acetylcholine receptor 1) protein (Figure 2). Lastly, some preliminary investigations of histone ubiquitination and histone phosphorylation point towards their possible involvement in the huntington's pathogenesis (Figure 2). Apart from post-translational modification of histones, several histone deacetylases (HDAC family of proteins) can play a vital role in huntington's disease. A significant HDAC among other is Sirutinin-1 (SIRT-1) confers protein from toxicity of HTT protein by restoring the expression of c-AMP regulated phosphoprotein, dopamine, brain derived neurotrophic factor (BDNF is usually declined in huntington's cases).

Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig 's disease, has a much rarer occurrence in comparison to other neurodegenerative disorders. This disease prevails variably at different geographic locations and about 4 out of every 100,000 people suffer from ALS wherein men are 1.5 times more likely to develop it than women (Figure 1). This disease usually initiates by late 40s while peak form is exhibited in patients in their 60s-70s and declines post 80s. Although this disease is associated with old and middle aged people, less than 5% cases have been reported in patients below the age of 25 years. Interestingly majority of ALS cases follow a non-mendelian inheritance (sporadic ALS) with only 5-10% of ALS cases exhibiting a mendelian pattern of inheritance (familial ALS) (Figure 1). Such a motor neuron disease occurs with progressive degeneration of both the upper and lower motor neurons. Especially in the limb-onset ALS atrophy of the muscles or muscle weakness forms the early symptoms. With disease progression, complications in walking, speech and swallowing are encountered by the affected patients of the limb/bulbar-onset ALS (Figure 1). This disease can be fatal when the prolonged disease results in wasting of respiratory and motor neurons [28,29]. The loss of cognitive abilities and eye movements are generally spared until the last stages of ALS29. Majority of the cases are autosomal recessive although dominant inheritance have been associated with chromosome 9q34 (senataxin, ALS4) [30]. The recessive form of ALS have been mapped to chromosomal loci 2q33 (alsin, ALS2), and 15q12-21 [31,32]. Even though the present studies have remained inconclusive upon the complex molecular pathology causing ALS, aberrations in several genes have indeed been implicated. The presence of toxic, autosomal dominant gain of function (GOF) mutations in the SOD1 (Cu-Zn Superoxide dismutase) gene have demonstrated a clear correlation with the presence of ALS (familial or sporadic) [33]. Mutations in SOD1 results in increased generation of the free radicals causing injury to the cell and cell-death [34]. Also several mutations are known to form intracellular aggregates of misfolded SOD1 peptides [35] leading to interruption of neuronal transport via axons and in other cellular processes [35-37]. Other genes considered as causal risk factors for familial ALS include Angiogenin (ANG) [38], Alsin (ALS2) [39], Senataxin (ALS4) [40], Vesicle Associated Membrane Protein (VAPB/ALS8) [41] and Dynactin (DCTN1) (Figure 1) [42]. Apart from these, recent studies have demonstrated mutations in Tar DNA-Binding Protein TDP-43 (TARDBP), APOE, VEGF (Vascular epidermal growth factor) and EAAT2 (Excitatory amino-acid transporter 2) gene in case of both familial and sporadic ALS [43] results in increased susceptibility to ALS (Figure 2) [44-46]. As evident, both genetic and epigenetic cues interfere in normal cellular processes and pathways leading to a manifestation of complex neurodegenerative diseases with onset, development and evolution. Nevertheless, this complexity does not limit itself here. It is further enhanced by the interplay and crosstalk interactions among genetic and environmental factors giving rise to the diseased state [47-50].

Epigenetics and ALS disease

ALS presents a challenging scenario for exploration of the underlying epigenetic pathogenesis of the disease owing to its rare nature as well as incomplete understanding of the causal genetic factors. However, the small number of studies has indeed served as a guide to search for the epigenetic link to ALS [51-54]. Experimental investigations based upon human and mice models of ALS have brought forth the anomalous expression pattern of a number of DNA methyl transferases like DNMT1 and DNMT3a along with resultant aberrant methylation of cytosines (Figure 2). Mice undergoing motor neuron degeneration bear increased amounts of DNMT3a in the synaptic junctions. In addition, accumulation of 5 mC along with DNMT1 and 3a is often seen in apoptotic motor neurons (Figure 2) [55,56]. Further, RG108 and Procainamide induced inhibition of DNMTs protect the motor neurons from excessive DNA methylation (Figure 2). Further genes with modified global DNA methylation and hydroxymethylation levels have been identified in the post-mortem spinal cord samples from both, early and late onset ALS patients. Apart from these possible connections of the ALS with epigenetic modulators like HATs, HDAC and miRNAs have been explored and discussed in detailed elsewhere (Figure 2) [57-62]. As discussed in case of other neurodegenerative diseases, ALS has also witnessed a significant role of sirutinin genes. SIRT-1 and SIRT-2 are known to target SOD-1 aggregates in mouse model of ALS and have a highly tissue specific expression patterns, suggesting these molecules as therapeutic targets for ALS.

Based upon the above it can be very well established that the neuronal and synaptic loss occurring with neurodegeneration can be successfully treated by designing and developing an effective strategy of epigenetic therapeutics, that aim to target the histone modifications and DNA methylation patterns in the affected individuals [63-75].

Epigenetic Therapeutics of Neurodegenerative Disorders

The dynamic epigenetic variations in the genome of the neurons are at least in part, if not completely, responsible for the onset, development and progression of the neurodegeneration and related diseases. Hence, any molecules targeting this epigenomic dynamics, presents a novel as well as promising approach for the preventive and therapeutic purposes of the degenerative neuronal disorders. With hallmark presence of extracellular senile plaques and intracellular accumulations of neurofibrillary tangles in the neurons, Alzheimer's accounts for most number of cases of dementia and disabilities in the elderly. The genetic components responsible for their development have already been discussed above. Clinical studies aimed at treatment of Alzheimer's have affirmed a possible approach wherein in vitro or dietary administration of the components required for production of SAM like folate, homocysteine and B - group vitamins can be utilized to restore methylation levels of PSEN1, protract brain atrophy and minimize oxidative stress (Figure 3) [76-94]. In addition, several HDAC inhibitors have been developed for the therapeutic strategies targeted for Alzheimer's. These include sodium butyrate, trichostatin-A, vorinostat, entinostat, valproic acid, HDAC1i, HDAC3i and sirtuin HDACi etc (Figure 3). Alzheimer's transgenic mice administered with sodium butyrate for 4 weeks showed alleviation of Tau protein aggregation. Furthermore, a 10 days' treatment with etinostat and 2 weeks' treatment with others like valproate, trichostatin-A etc. resulted in reduced senile plaque formation and restoration of memory deficits

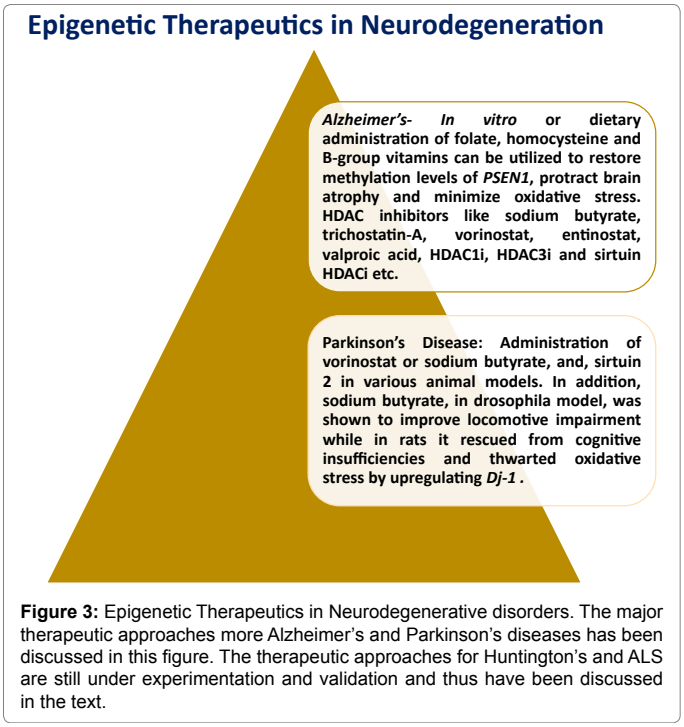

Figure 3: Epigenetic Therapeutics in Neurodegenerative disorders. The major therapeutic approaches more Alzheimer's and Parkinson's diseases has been discussed in this figure. The therapeutic approaches for Huntington's and ALS are still under experimentation and validation and thus have been discussed in the text.

in mice, respectively [95,96-103]. Similarly, Parkinson's disease, typified by bradykinesia and postural instability, pathologically displays loss of dopaminergic neurons and intracytoplasmic inclusions of α-synuclein protein called Lewy Bodies in surviving neurons (Figure 1). Subsequent neuronal toxicity due to α-synuclein is mediated by its binding to histone H3 with concomitant histone acetylation inhibition. However, this toxicity can be salvaged by administration of vorinostat or sodium butyrate, and, sirtuin 2 101 in various models of Parkinson's (Figure 3). In addition, sodium butyrate (Figure 3), in drosophila model, was shown to improve locomotive impairment while in rats it rescued from cognitive insufficiencies and thwarted oxidative stress by upregulating Dj-1(Protein deglycase). While the therapeutic exploitation of majority of the epigenetic modulators in treating Huntington's disease and ALS is presently under experimental investigations, some have been reported to furnish beneficiary effects. In mouse and drosophila models, progressive neuronal degeneration has been found to be remedied by HDAC inhibitor treatment. Survival of animals models of ALS is bolstered by supplementations of sodium phenylbutyrate, valproate combined with lithium and trichostatin-A. Besides, escalated histone acetylation, reduced degeneration of neurons and delay in disease onset are impediments in developing better epigenetic therapeutics [104-109].

Conclusion

In conclusion, the partial success of the epigenetic modulators as therapeutic mediators of neurodegenerative disorders prerequisites additional experimental investigations and clinical trials. Possibility of unforeseen side-effects remains a cause of concern because of the simultaneous targeting of multiple factors and pathways. Furthermore, the impending studies would also require taking into cognizance the metabolic and anatomic differences amongst animal and human models. The mode of drug administration with dose timings and regimen would also be needed to keep in view. Most intriguingly it needs to be considered that the probability that certain drugs do not function satisfactorily needs to be taken into account. Lastly, several dietary supplements such as folate, vitamin-B, flavonoids involved in modulation of epigenome could also be evaluated for their preventive potential in the case of neurodegenerative diseases. Therefore, our present known how of genetics and epigenetics of neurodegenerative disorders present us with a complex landscape of intricate crosstalk. Given the dynamics and ease of influencing the expression of genes without interfering with the sequence, has led to the development and appreciation of "epigenome as an effective therapeutic target for neurodegenerative diseases".

Author Contribution

R.K.S and A.S contributed in initial draft designing and manuscript preparation. S.S and K.B contributed towards final draft development, figure designing and editing.

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