WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Unlocking the potential of DNMTs, Non-coding RNAs, Dietary habits and Environmental exposure in regulating neurodegeneration: a glimpse into Parkinson's disease and Alzheimer's disease pathophysiology

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ABSTRACT :

PD and AD are two major challenges in neurodegenerative disorders, a group of diseases or conditions caused by progressive atrophy or cell death of neurons. Newly emerging evidence on environmental agents as inducers of damage to developing and mature nervous systems in the etiology and progression of neurodegenerative diseases is impressive.

Epigenetic modifications are thus central to the complex interplay of genetic predisposition and environmental influences. These heritable modifications refer to changes in gene expression that are independent of those in DNA-coding sequence. These epigenetic changes include methylation of DNA, histone modification, and other related processes, which have been seen to exert strong control over the neurodegenerative transcriptional landscape.

From heavy metal exposure to dietary folate intake, environmental factors epigenetically act to alter expressions in genes involved in neurodegenerative processes, predisposing the individual to a late-onset neurodegenerative disease. A growing body of research into genetic regulation of DNA methylation identifies allelic imbalances at a significant repertoire of genes, illuminating how an individual's genetic background might affect or modify vulnerability to neurodegeneration by the impact of environmental factors. Preliminary studies performed in cell culture systems and initial transgenic animal models provide encouragement regarding the therapeutic potential of pan-epigenetic modifiers against common neurodegenerative diseases. In such scenarios, interventions might have dramatic protective effects through the coordination of pervasive epigenetic changes dampening AD, PD, and related diseases. Genetic predisposition, conditioned through epigenetic mechanisms and complex in its interplay with environmental influences, underlines the multifaceted etiology of neurodegenerative diseases. Exploring this knowledge offers huge potential to develop new therapeutics that could mitigate suffering from these devastating disorders at a global health level.

Keywords: Parkinson's disease, Alzheimer's disease, DNA methylation, Histone deacetylase inhibitor.

1. Introduction :

Understanding Neurodegeneration: Parkinson's and Alzheimer's Disease

In neurodegenerative diseases, a category of disorders characterized by the progressive degeneration or loss of neurons, there is gradual loss of those physiological functions governed by afflicted regions of the nervous system[1]. Indeed, AD accounts for the greatest burden of neurodegeneration, though a spectrum of related diseases with distinct clinical manifestations and neuropathological features includes PD and frontotemporal dementias that share underlying genetic predispositions.

The integrity of the developing and mature nervous systems is significantly influenced by environmental exposures, thereby playing a role in the pathogenesis of neurodegenerative diseases. More specifically, gene expression that has a hereditary basis but does not involve an alteration in the DNA coding sequence is called epigenetics. According to one hypothesis, environmental factors can perturb gene regulation through epigenetic alterations, resulting in late-onset neurodegenerative diseases.

Parkinson's disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, with a lifetime occurrence reaching approximately 2% in subjects over 65 years old. Clinically, PD is marked by a triad of motor symptoms consisting of tremor, bradykinesia, and rigidity. Neuropathologically, PD is associated with widespread degeneration of dopaminergic neurons in the substantia nigra and Lewy bodies—a kind of cytoplasmic inclusions containing the insoluble protein aggregate alpha-synuclein[12].

Genetically, Parkinson's disease displays marked heterogeneity, with mutations in six genes thought to be responsible for autosomal inherited forms of the disease. Autosomal dominant Parkinson's disease can also be the result of missense mutations and gene-duplication events of the SNCA gene product[13,14], suggesting an important role of alpha-synuclein aggregation in the disease[15]. Another autosomal dominant mutation has been described to occur in the LRRK2 gene[16,17], but the function of the protein is not well defined.

Recessive forms of PD are often supported by deletions or compound heterozygous mutations in the Parkin gene [19], hence implicating impairment of proteasomal activity in disease onset. In this respect, mutations of PINK1 and DJ-1 [20] genes further support the role of cellular and oxidative stress responses in pathogenesis of PD. The ATP13A2 gene, associated with Kufor Rakeb disease and recessive early-onset PD [21], is believed to modulate metal homeostasis and interacts with alpha-synuclein [22]. While other candidate genes such UCHL1 [23] and GIGYF2 [24] have been suggested as being loci causative to PD, these remain tentative whilst awaiting further investigation and replication in independent studies.

Alzheimer's disease

Alzheimer's disease is the most common progressive neurodegenerative disorder; about 13% of individuals are affected at age 80 years. AD, from its clinical presentation, shows the first memory deficits at its onset, and subsequently, gradual loss in cognitive abilities. Diagnosis relies on two key neuropathological hallmarks: senile plaques and neurofibrillary tangles. Senile plaques, occurring in the extracellular space between neurons, are essentially composed of fibrils of amyloid beta surrounded by degenerated neurites and glial cells. These plaques are a result of the proteolytic cleavage of amyloid precursor protein (APP) [3] by a family of enzymes called secretases. Neurofibrillary tangles, composed of hyperphosphorylated Tau protein, reside inside neurons [2]. According to the amyloid cascade hypothesis, Ab generation is the primary instigator of AD pathology [4]; these neurofibrillary tangles then lead to formation of cell death and dementia. Several genes, APP,, PSEN1,, and PSEN2,, have been associated with the early-onset AD, and more than 100 different mutations have been described in affected families. Most of these mutations increase the secretion of the amyloidogenic Ab1-42 peptide.

The amyloid-Tau connection is thought to involve changes in kinase and phosphatase activity. Diminished methylation of PP2A, a major brain phosphatase, is associated with increased Tau phosphorylation and augmented amyloid production. This biochemical characterization further supports the amyloid cascade hypothesis by underscoring the complex interplay between the generation of amyloid and Tau phosphorylation in AD pathogenesis.

2. Exploring PD and AD Susceptibility Genes

The relation of genetic variants in the candidate genes to the risk of Alzheimer's disease or Parkinson's disease has been under study by hundreds of association studies over the past years, but the results usually contradict each other, pointing to genetic diversity of populations under study and limited sample sizes.

One of the most strongly replicated susceptibility loci for AD is the APOE gene. Those who inherit two copies of the ApoE ε4 allele have an approximate 15-fold increased risk of late-onset AD compared with the ApoE ε3 allele[25]. The ApoE ε4 has been associated with higher plasma cholesterol levels and increased deposition of Aβ[26]. On the other hand, genetic studies have identified two genes associated with PD: SNCA, which contains a polymorphic dinucleotide repeat sequence in its promoter that seems to affect gene transcription, and MAPT, encoding a molecule that is considered an important stabilizer of tubulin cytoskeletal structures[27,28].

While mutations in MAPT cause frontotemporal dementia[29], they have failed to show a causative effect for AD or PD. However, meta-analyses of association studies do identify significant effects of the variants of MAPT on the risks for late-onset AD and PD; in particular, the H1 haplotype is associated with an increase in the expression of the MAPT[30,33] gene. Additionally, genome-wide association studies have also found that both MAPT and SNCA participate in PD[32,34] as susceptibility genes. More recently, interest has focused on epistasis, or gene-gene interactions, as a major confounding factor in mapping susceptibility genes. Specifically, a significant gene-gene interaction between GSK3b and MAPT has been identified in AD [37] and PD, with replication in separate studies[39,40].

3. Epigenetic Changes in Neurodegeneration

The changes in the gene expression that can be heritable and are not specifically in the DNA-encoding sequence are termed as Epigenetic. These changes include DNA methylation, histone modification changing chromatin structure, RNAmediated changes involving noncoding RNAs like microRNAs (miRNA) [41]. DNA methylation involves the addition of methylation at the fifth position of the pyrimidine ring, carried out by DNA methyltransferases (DNMTs), in vertebrates. This specifically occurs in the cytosine base of CpG pairs. In human DNA, a majority, standing at 70% of the CpG dinucleotides is constitutively, in vertebrates and particularly in mammals, methylated; and the remaining is most concentrated in CpG islands. DNA methylation through human evolution has been reported to interfere with the binding proteins of clustered methylated CpGs, like MeCP2, leading to gene transcription silencing.

Another field in which epigenetic changes are very important is the dynamics of chromatin, through the identification of post-translational histone modifications such as acetylation, ubiquitinylation, and phosphorylation. Such modifications modulate chromatin contacts and the recruitment of nonhistone proteins, which ultimately influences chromatin structure and function, thereby regulating gene expression. Epigenetic modifications have

been found to play a pivotal role in such developmental findings as X inactivation, genomic imprinting, and neuronal development. Besides, important human pathologies, such as cancer and neurodegenerative diseases[44], are linked to abnormal epigenetic regulation.

It is hypothesized that environmental factors, metals, and dietary components might induce life-long perturbations in gene regulation via epigenetic modifications. The modifications would begin during the early stage of development but show up pathologically later in life and add to the disease episode of late-onset neurodegenerative diseases.

4. Epigenetic Dysregulation in Parkinson's Disease

Initial insights into the molecular link of Parkinson's disease to epigenetic dysregulation came from Drosophila. Kontopoulos et al. demonstrated that, in a Drosophila model of PD, the primary molecule involved in PD, a-synuclein, interacts with histones to reduce levels of acetylated histone H3 and inhibit the activity of HAT [51]. Jowaed et al. further evidenced that methylation of the SNCA promoter is a regulator of gene expression in cultured cells and showed hypomethylation in PD brains compared with normal tissue[52]. Further evidence is also found for a protective effect of smoking against PD[53], while showing epigenetic alteration of the signature of specific genes by smoking. Whereas nicotine in cigarette smoke was thought to offer neuroprotection with respect to the dopaminergic nigrostriatal system, Parain et al. examined the neuroprotective effects of cigarette smoke and nicotine in a mouse model for PD after induction by 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine[54]. Cigarette smoking has also been related to changes in global DNA methylation [55], including epigenetic silencing of the gene encoding monoamine oxidase A, which is involved in the regulation of the serotonergic system and psychiatric disorders [56].

5. Exploring Global DNA Methylation in Alzheimer's Disease

Epigenetic research in the field of cancer development now emphasizes its role in both neurogenesis and neurodegeneration. Studies of identical twins have demonstrated a "drift" in DNA methylation levels with aging. Fraga et al. demonstrated a drift of concordance in DNA methylation levels of 30% among identical twins between the ages of 3–74 years [45].

There have been substantial changes reported in DNA methylation in Alzheimer's disease. Mastroeni et al. reported reduced immunohistological staining for DNA methylation maintenance factors DNMT1 and MBD2 in AD cases versus normal brains[46]. Global DNA methylation decreases were similarly noted in monozygotic twins discordant for AD. Further, studies that demonstrate Ab production to be induced by global hypomethylation provide a causative link between Ab and dysregulated methylation observed in AD brains. However, efforts to associate site-specific epigenetic modifications with neurodegeneration have yielded mixed result[47,48]. Wang et al. looked into DNA methylation in the promoter regions of 12 potential AD susceptibility loci and found no significant differences in individual gene-specific methylation between AD patients and controls[49]. Combined analysis revealed, however, an age-dependent drift in AD compared to controls. Similarly, Barrachina et al. analyzed the DNA methylation status of candidate genes in AD and PD brains and did not find any significant differences in DNA methylation percentages between the disease and control samples or among the different pathological entities in any of the analyzed brain regions[50].

6. Environmental Influence on Epigenetic Modification in Neurodegeneration

Environmental factors can also cause damage in the developing and mature nervous systems to result in neurodegenerative diseases. Other than the genetic risk factors, there are several other variables that appear to impact on susceptibility to disease and include gender, educational level, inflammation, stroke, smoking, head trauma, infection, vitamin deficiencies, diet, and chemical exposure[44].

Gene-environment interactions may have a central role in determining an individual's susceptibility to diseases related to the exposure of both endogenous and exogenous agents. Only a few environmental risk factors have been associated with Alzheimer's disease[57], although current research does point to a large role for diet and education levels in its pathogenesis. In contrast, many environmental factors have been related to an increased risk of Parkinson's disease. New evidence points to the role of environmental factors in the etiology of late-onset neurodegenerative diseases, including heavy metals and dietary components that may cause long-term perturbations in gene expression through epigenetic modifications and hence contribute to their development[59].

6.1 Heavy Metal Exposure

Some rodent studies have demonstrated that Pb exposure during periods of brain development influences the expression and regulation of AD-related genes in later life. Wu et al. showed that the expression of AD-related genes APP and PSEN1, and its transcriptional regulator SP1, was increased in aged monkeys exposed to Pb during infancy. Similarly, Basha et al. reported increased APP expression, along with its amyloidogenic Ab product, following Pb exposure during development, which extended into old age. This was said to be due to the inhibition of DNMTs by Pb, resulting in hypomethylation at AD-associated gene promoters.

Furthermore, Wu et al. [59] proposed that environmental factors during neurodevelopment alter the methylation pattern of the APP promoter, thus leading to a latent increase in APP and Ab levels. Stewart et al. found a association between historical Pb exposure in adults and a loss in brain volume, and also white matter hyperintensities assessed by magnetic resonance imaging. Their findings were supported by their longitudinal study indicating an association between Pb exposure and decline in cognitive ability [62].

6.2 Dietary intake

Dietary components thus make an important epigenetic and genomic modulator that has the potential to affect the risk of several diseases[63], including neurodegenerative disorders. In one of the prospective studies of dietary patterns with respect to risk of PD[64], it has been shown that high intake of fruits, vegetables, whole grains, fish, and poultry with moderate alcohol consumption and low levels of saturated fats is protective against PD.

Vitamins B12 and folate[65] are essential in the methionine/homocysteine cycle[66] and influence the amount of S-adenosylmethionine—a major cofactor of epigenetic gene regulation—produced. In AD, epigenetic alterations to the genes associated with AD take place, where low levels of folate and SAM and high homocysteine[67] can be observed. These findings from Fuso et al. [68-70] and Chan and Shea [71] show that a dietary deficiency in folate increases the expression of proteins related to AD, such as APP, BACE, PSEN1, with consequent accelerated cognitive decline and altered methylation patterns in gene promoters. Single nucleotide polymorphisms in the gene MTHFR, controlling folate levels, are associated with an increased risk of late-onset AD [72-74].

Excessive alcohol intake has been reported to be associated, especially in combination with low levels of folate, with gene hypermethylation implicated in colorectal cancer [75] and with global DNA hypermethylation [76]. DNA methylation is increased after alcohol exposure in embryonic development and associated with hypermethylation of the promoter of SNCA in alcoholism patients, which may contribute to neurodegenerative diseases [77].

6.3 Pesticides, Oxidative Stress, and Neurodegeneration

The primary model to probe environmental insults in PD is MPTP-induced models of free radical injury. The metabolite of MPTP, MPP+, selectively accumulates in dopaminergic terminals and mitochondrial complexes in the SN, inhibiting complex I of the electron transport chain, producing oxidative stress similar to that seen in PD[78] patients. Paraquat, structurally similar to MPTP, has been associated with an increased risk of PD[78]. Exposure to MPTP, paraquat, or rotenone promotes acute, irreversible parkinsonism, underscoring the role of oxidative stress in aging and neurodegenerative diseases. Environmental insults, such as lead exposure during development, could thus accelerate AD neurodegeneration through oxidative damage, resulting in APP gene hypomethylation and the overproduction of Ab and reactive oxygen species[80]. Similar insults might also silence genes for ROS scavengers involved in altering SAM biosynthesis and DNA methylation patterns. These epigenetic modifications, for instance histone acetylation, can also be induced by pesticide exposure. For instance, the disrupted function of proteasomal machinery led to dieldrin-induced histone hyperacetylation, dopaminergic cell apoptosis, and mice apoptosis. These findings point toward the induction of neurodegenerative disease by environmental factors via epigenetic mechanisms[80-83].

7. Global Epigenetic Harmonies at the Genotypic Level

It is thus imperative to learn the ways in which epigenetic data are to be interpreted with respect to disease processes. Recent publications have shown that a subset of autosomal genes are subject to random monoallelic expression that is independent of parent-of-origin imprinting [84]. In cases of DNA methylation, until recently it had been presumed that there was an equal distribution to both alleles genomewide. Two major publications showed allelic skewing of DNA methylation and the subsequent effects on gene expression. The first one was done by Schalkwyk et al., where in a lymphocyte sample, allelic skewing of DNA methylation was conducted in a genome-wide survey against SNP microarray data for allele-specific DNA methylation. More than 35,000 sites where allele-specific DNA methylation may occur were revealed across the genome [85,86]. In other words, Zhang et al. map methylation quantitative trait loci for a number of CpG sites in human cerebellum samples and reveal 736 CpG sites that are significantly associated with SNPs. Among those, ten genes showed three-way association, such that the very same SNP was significantly related to DNA methylation and gene expression, and DNA methylation correlates to gene expression [86].

These findings support the purported genetically driven DNA methylation-gene expression variation relationship[49,50]. However, most studies into neurodegenerative diseases are not genotype-directed. Global measures of changes in DNA methylation, currently assessed by technological surveys such as the Illumina Infinium Beadchip, cover only about 27,000 CpG dinucleotides that are represented in approximately 50% of transcribed genes, missing many CpGs relevant to epigenetic regulation. Such technological barriers must be overcome in order to fully realize an understanding of epigenetic modifications.

8. Epigenetic Therapeutics for Neurodegenerative Diseases

Therapeutic developments for neurodegeneration have focused on two main epigenetic modifications: DNA methylation and histone modification. DNA methylation, catalyzed by DNA methyltransferase (DNMT), and histone acetylation/deacetylation, regulated by histone acetyltransferase (HAT) and histone deacetylases (HDACs) respectively, play key roles in gene regulation. In vitro studies of HDAC inhibition have identified protective genes and pathways, including cell cycle protein p21[87] and the molecular chaperone HSP70[88,89]. HDAC inhibitors have shown promise in models of spinal muscle atrophy, where they reverse hypermethylation and downregulation of SMN2 gene promoter, potentially restoring gene expression levels[90]. In neurodegenerative disorders like Alzheimer's (AD) and Parkinson's disease (PD), neuropathological intraneuronal aggregates interfere with transcription, causing deficits in synaptic plasticity and cognition[91]. Tsai et al. demonstrated that HDAC inhibitors restored histone acetylation status, learning, and memory in a mouse model of neurodegeneration[92]

Recent studies suggest that HDAC inhibitors may be promising for PD treatment, rescuing a-synuclein-induced toxicity[93]. Several drugs targeting DNA methylation and histone deacetylation enzymes have been approved for cancer treatment, making them potential candidates for neurodegenerative disorders[94,95]. It's worth noting that HDAC inhibitors alter only a small subset of genes (<10% of the genome)[96,97] and are associated with specific genetic signatures. Thus, specific HDAC inhibitors could potentially increase the expression of neuroprotective genes without altering pathogenic gene levels[98].

Another avenue of investigation is how lifestyle factors, such as diet, may ameliorate neurodegenerative disorders[63,65]. Folate, for instance, has been studied due to its potential to modulate DNA methylation[99]. A recent study demonstrated that folic acid increased genomic DNA methylation in lymphocytes, although the effect was site and gene-specific. This observation suggests that only certain alleles of neurodegenerative genes may respond to folate supplementation, possibly explaining why a large clinical trial of AD patients failed to show a significant protective effect[100-102].

9. Future outlook

Epigenetics offers a fresh perspective in neuroscience, holding the promise of novel therapies by targeting reversible changes in gene expression. This opens the door to interventions at the intersection of our genes and environment, potentially mitigating the impact of harmful neurodegenerative genes. However, a key challenge lies in developing HDAC inhibitors that selectively enhance neuroprotective gene expression without inadvertently boosting known neurodegenerative genes.

In the realm of 'nutrigenomics,' [103]personalized diets tailored to individual genetic profiles show great potential for optimizing health. For instance, variations in the MTHFR gene influence folate metabolism, impacting disease risk and highlighting the power of personalized nutrition[104]. Expanding upon this approach, advanced genotyping combined with microarray technology can unveil how environmental factors shape the epigenetic landscape at an allelic level. Understanding how factors like diet, smoking, and pesticide exposure interact with our unique genetic makeup can provide comprehensive insights into disease risk via epigenetic mechanisms.

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