

Role of Epigenetic Modification, Epigenetic Biomarkers and Dietary Supplements in Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases are outcome of epigenetic modification and environmental factors. With the age, due to epimutation neural cell get harm and affect the cognitive function. Epigenetic biomarkers such as DNA methylation, histone modification and miRNA alter the genes functions, involved in many cellular processes. Early detection of these biomarkers help in early diagnosis of diseases. In this article we have focus on how epigenetic alteration affects the expression of genes and epigenetic biomarkers help in earlier diagnosis. We also have focus on dietary supplements which help in slowing the progression of disease.

Keywords: Epigenetic biomarkers; Neurodegenerative diseases; Epigenetic modifications

INTRODUCTION

Neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease (HD) start late in life and last for several years [1]. They have become the most serious problem in current era, whose detrimental effects increasing with age and become incurable due to continuous degradation of nerve cell by epigenetic modifications [2]. The description of biomarkers responsible for epigenetic modifications, risk factor, new therapeutic target as well as diagnosis is still complicated due to complex correlation between its genetic and environmental factors. Currently, there is no diagnostic test available for its earlier detection [3]. According to Harvard School of public Health and WHO, neurodegenerative diseases will take 8th position for causing death in 2020 among other lethal diseases [4].

Emergence of different biomarkers in neurodegeneration field such as neuroimaging, genomics, clinical and biochemical has enabled us to diagnose these disorders to some extent and now a days, epigenomics serves as best among all diagnostic tool for understanding the epigenetic alterations [5]. So, dietary restriction as well as supplements rich in antioxidants, polyphenols etc. has neuroprotective effect and minimize the risk of neurodegenerative diseases [6].

EPIGENETIC MECHANISM

1. Epigenetic mutation refers to alteration in gene expression or function without disturbing DNA sequence, which mainly involve DNA hypo and hyper-methylation, post-modification of histone, and non-coding RNAs

[7]. Exogenous factors in combination with epigenetic mechanism altered the different genes expression, which leads to different diseases as shown in Figure 1 (Epigenetic biomarkers for early detection, therapeutic effectiveness, and relapse monitoring of cancer [8]. Epigenetic dysregulation in neurodegenerative diseases may be due to accumulation of intraneuronal plaques which interact with transcription and leads to dementia [5]. Exact mechanism of mutation that leads to neurodegeneration are not clearly understood.

Different hypothesis are available for pathogenic mechanism such as disease may be:

- Disturbance in biochemical pathways.
- Due to aggregation of mutated proteins, apoptosis as well as problem in transcription process and epigenetic mechanism [9-11].

Epigenetic mutation such as DNA methylation and histone modification are responsible for development of neurodegeneration. There is some epigenetic mechanism, mutation of which leads to neurodegeneration [12].

2. **DNA methylation:** Epigenetic mechanism involves the addition of methyl group at the position 5 in CpG dinucleotides. Normally CpG Island is unmethylated but it methylated as a result of epigenetic alteration and resulting in gene silencing [13].
- I. Methylation of DNA also inhibits the transcription directly or indirectly. Indirectly inhibit the transcription by activating the methyl-CpG-binding domain proteins.

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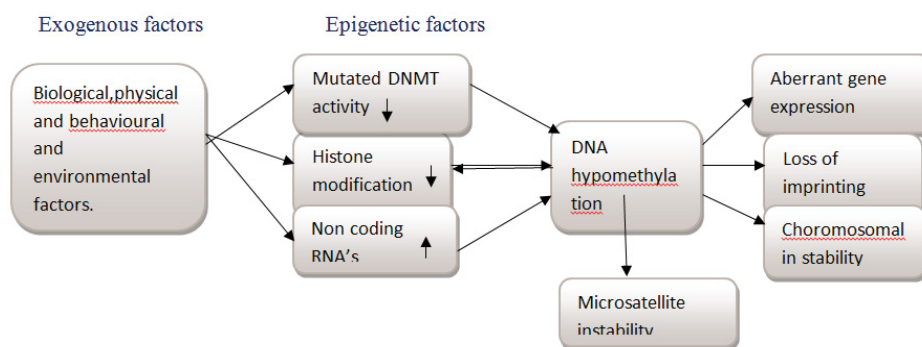


Figure 1: Showed that combination of environmental factors and genetic factors leads to epimutation (altered the gene expression) which ultimately result in disease state.

Directly inhibit the transcription by interfering the binding of DNA binding proteins at their specific sites. DNA methyltransferase enzymes such as DNMT1, DNMT3a and DNMT3b also responsible DNA methylation [14].

- II. **Histone modification:** Octamer of core histones proteins form the nucleosome. Group of 4 core histones includes H2A, H2B, H3 and H4 which form H2A and H2B dimers and one H3-H4 tetramer. These proteins play an important role for DNA helix. Posttranslational modifications of histone proteins such as methylation, sumoylation, phosphorylation and acetylation are due to epigenetic mutation [15]. Posttranslational modification is reversible process [16]. Histone acetyl transferases (HATs) enzyme also responsible for histone modification. De novo methylation as a result of mutation is due to interaction of DNA methyltransferase 3 (DNMT3L) with histone H3 tails (H3K4).
- III. **RNA-based mechanism:** Micro RNA leads to post-transcriptional gene silencing as a result of epigenetic mechanism. In addition of gene silencing micro RNA also activate the genes involve in proliferation and differentiation [3].

Aberrant epigenetic post-translational modifications of proteins are emerging as important elements in the pathogenesis of neurological disease [17]. Epigenetic mutation altered the gene expression by methylation in CpG islands of relevant genes. Due to difficulty in getting the brain tissue for diagnosis, it can be possible to observe the transcriptomic changes in blood of disease patients. Alteration of gene expression due to epimutation helps in diagnosis of disease [5].

EPIGENETIC BIOMARKER IN ALZHEIMER DISEASE

In patients with Alzheimer's disease protein aggregates found in brain cells. Epigenetic modification play an important role in pathogenesis of AD. Three genes altered in AD include Presenilin-1, PSEN-1, PSEN2 and amyloid beta A4 protein (APP). Increased level of phosphorylated histone H3 has been observed in hippocampal neuron in AD [18]. In AD temporal lobe histone acetylation found to be low as compared to normal person. miR-16 target the amyloid precursor protein and its expression is abnormally reduced in AD patients, which leads to protein accumulation [18]. MiR-124 also suppressed in AD brain. In AD NEP (neprily-sin) enzyme which is responsible for amyloid-beta degradation suppressed. Amyloid beta may also repress global hypo methylation (Figure 2) [5].

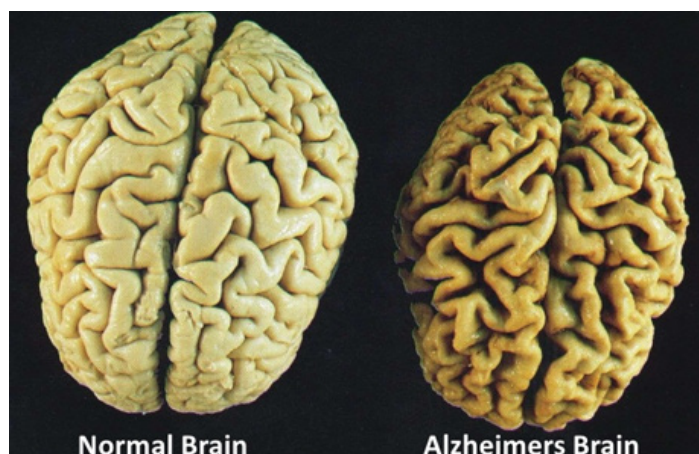


Figure 2: Epigenetic biomarker in Alzheimer's.

EPIGENETIC BIOMARKER IN PARKINSON'S DISEASE

Alzheimer disease and Parkinson disease are heterogeneous disease because they are combination of genetic and environmental factors. In early 1800 James Parkinson named the PD as "shaking palsy". Symptoms include muscle rigidity, postural instability, tremor and bradykinesia. In PD loss of neurons in substantia nigra due to aggregation of protein known as Lewy bodies [19]. Methylation of synuclein- α gene leads to accumulation of plaques in PD [20]. In PD alpha-synuclein decreased the level of acetylated histone H3 and inhibits histone acetyltransferase enzyme activity by binding to histone proteins [5]. Methylation of SNCA intron 1 leads to decreased in SNCA transcription, which has been observed in PD [21]. Genes such as ARK16, GPNMB and STX1B also show methylation in PD [22]. Hypermethylation of GRN gene has been observed in front temporal region of brain due to aberrant DNA methylation [23]. Decreased expression of miR-133b, miR-10a, -212, -132, -7 has also been observed in PD (Figure 3) [24-26].

EPIGENETICS BIOMARKER IN HUNTINGTON'S DISEASE

Normally huntingtin (htt) protein comprise of 36 polyQ repeats. In HD mutation leads to abnormal increased poly-glutamine (39 poly-Q) sequence of gene responsible for protein htt. miR-9, miR29b, miR-132 and miR-124a dysregulated in HD [27]. In blood and brain tissues of HD patient increased level of histone protein has been observed [4]. Epimutation altered the transcription as a result of increased histone methylation and decreased acetylation

[28,29]. Localization of altered huntingtin to the nucleus form aggregates of mutated polyQ protein which ultimately inhibits the transcription factors (Figure 4) [30].

EPIGENETIC BIOMARKER IN NEURODEGENERATIVE DISEASE

Epigenetic mutation in different neurodegenerative diseases (Table 1) [31].

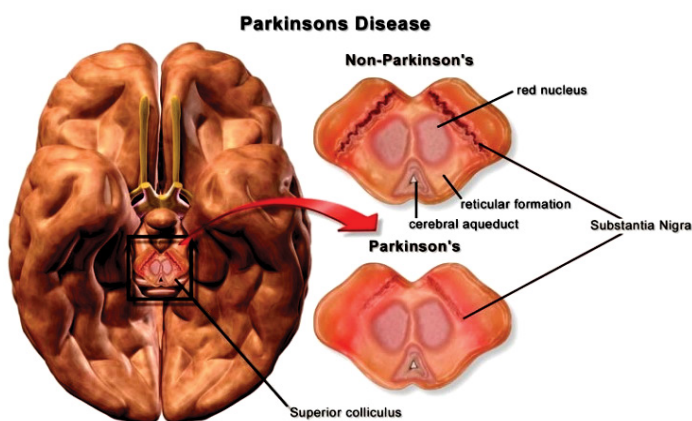


Figure 3: Epigenetic biomarker in Parkinson's.

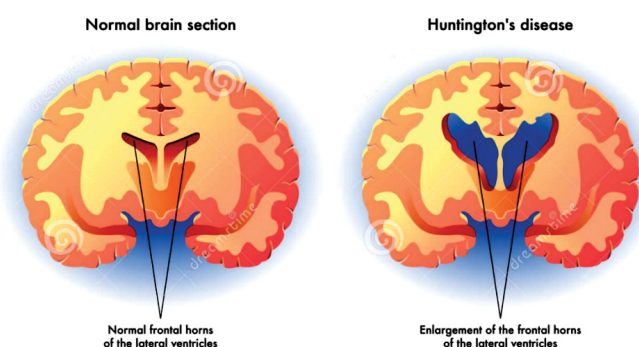


Figure 4: Epigenetic biomarker in Huntington's.

TREATMENT OF NEURODEGENERATIVE DISEASE THROUGH DIET

With the passage of time, in brain cells energy metabolism is impaired due to accretion of damaged molecules [32]. Multiple factors involved in neurodegenerative disease which includes depletion of endogenous antioxidants, elevated of nitric oxide and iron, neurotoxicity due to glutamate, irregularity of ubiquitin-proteasome system, presence of proapoptotic proteins leads to degeneration of neurons [5]. To compensate neuronal damage neurotrophic factors as well as cell protecting proteins such as antioxidant etc help to restore damage neuronal cells. To overcome this (damaged) lost, neurons may either produce new neurons or remodeling neuronal system. In case of failure to adapt the changes to overcome neuronal damage neurodegeneration occurred [32]. Neuroprotective factors may be helpful to combat with diseases such as Parkinson's disease, Alzheimer disease and Huntington disease. In this article we will focus on different dietary factors that prevent the occurrence of neurodegenerative diseases (Figure 5).

Dietary restriction, exercise, intellectual activity prevents the neuronal damage by mechanism (Figure 6) [32].

Green tea contain catechin polyphenols which as neuroprotective activity by involving different mechanism of action (Figure 7) [6].

Folic acid deficiency as well as increased level of homocysteine affect the nervous system. Homocysteine damaged neuronal cells by inducing oxidative stress. Folic acid deficiency and homocysteine elevated level stimulate neurodegenerative process. Vitamin E, lipoic acid, coenzyme Q10 and Ginkgo biloba extract help in treating neurodegenerative diseases. Vitamin E has antioxidant property. It suppresses neurodegeneration repress lipid peroxidation as well as by maintaining cellular ion homeostasis (Figure 8).

Ubiquinone (coenzyme Q10) has antioxidant property. It exhibit it antioxidant property by improving mitochondrial function and prevent the neuronal damage. Hypoxia, glutamate damages the brain cells but lipoic acid prevents this damage by suppressing

Table 1: Epigenetic mutation in different neurodegenerative diseases.

	DNA Methylation	Histone Modification	Micro RNA Regulation
Alzheimers Disease	Supressed DNA methylation in the anterior neuronal nuclei	Elevated phosphorylated histone H3 in hippocampal neurons	Dysregulation of mRNAs in brain
	Hypermethylation of HTERT gene	Modulation of histone acetylation by HDAC inhibitors	
	Hypomethylation of inflammatory genes such as TNF, IL-1 in cortex		
Parkinsons Disease	Methylation suppressed	Alpha synuclein suppressed histone acetylation as well as histone gene expression	Differential expression of dopaminergic neuron specific miRNA miR, -133b
	Hypomethylation of SNCA gene in brain tissue. Alpha synuclein decreases the availability of Dnmt 1 methyltransferase		Differential expression of miR-7, -132, -495, -10a, -10b in brain tissues
	Methylation of ARK16, CYP2E1 and STX1B. Hypermethylation of GRN gene		
Huntingtons disease	Increased availability at HTT gene locus	Sequestration of proteins it HDAC activity	Down regulation of nine miRNA in HD
		Elevation of histone proteins carrying H3K9 marks in blood and brain tissues	Unregulation of miR-34b in plasma of HD patient



Figure 5: Diet of Neurodegenerative disease.

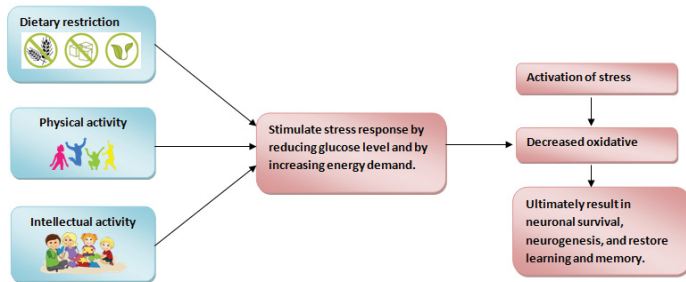


Figure 6: Dietary restriction, Exercise, Intellectual activity.

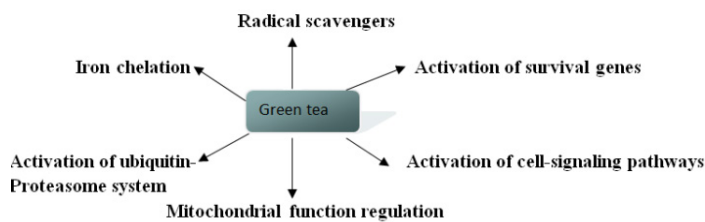


Figure 7: Polyphenols present in green tea help in preventing the neurodegeneration by different mechanism of action.

the ischemic brain injury. Lipoic acid also has ability to prevent neurodegeneration caused by Aβ [32].

Zn²⁺ deficiency induce neurodegeneration by formation of free radicals while it supplements prevent the neuronal damage [33].

Polyphenol known as resveratrol found in pomegranates, peanuts red wine has ability to abolish amyloid plaques formation. Recent study showed that resveratrol reduced the plaque formation in different areas of brain with different percentages such as in cortex (48%), hypothalamus (90%) and striatum (89%). Dietary supplements with resveratrol also have ability in reducing the plaques formation by elevating the cysteine level as well as by decreasing the glutathione level [34]. Polyphenol in coca also has neuroprotective effect. Glutathione deficiency is hallmark of neurodegeneration disease. Glutathione is essential for normal function of brain cells. The most important factor responsible for glutathione depletion is monosodium glutamate (MSG) and aspartame. Dietary supplement such as magnesium remove metals and toxins from body by stimulating glutathione production. Diet rich in omega 3 fatty acid also help in reducing the neurodegeneration risk by 60% by suppressing the inflammation in brain cells (Figure 9) [34].

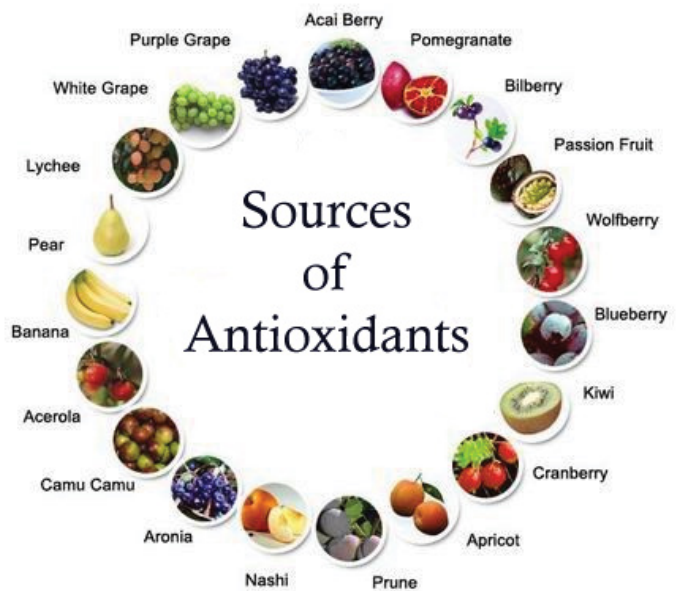


Figure 8: Sources of Antioxidants.

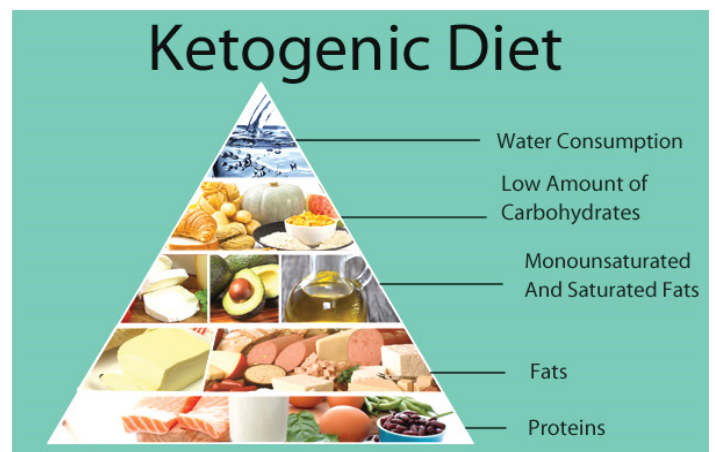


Figure 9: Ketogenic Diet.

Ketogenic diet improves glucose metabolism and metabolic dysfunction and protects the neuronal cells death by Aβ toxicity. With aging, glycation end product stored in brain cells where they induce oxidative stress and neurodegeneration. But KD prevent this damage because of its neuroprotective effect. KD also proved helpful against 6-hydroxydopamine neurotoxicity in PD by protecting the dopaminergic neurons in brain [26].

CONCLUSION

Neurodegenerative diseases are becoming important now a day. Multiple factors are involved in neuronal damage which includes environmental factors as well as epigenetic modification. Early detection of epigenetic modification helps in early diagnosis of neurodegenerative diseases. Epigenetic modification altered directly or indirectly transcriptional activity and posttranslational activity. Epigenetic modification is reversible phenomenon. Early understanding of epigenetic biomarker involved in neurodegeneration may open path of novel therapies for its treatment and prevent its progression. Now a day, dietary supplement not only help in disease prevention but also slow the progression of disease and prevent neuronal damage. So, it is important to improve our knowledge not only about epigenetic biomarkers but also about dietary supplement to prevent the generation and to slow the progression of disease.

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