EDITORIAL

Role of Epigenesis in Alzheimer's Disease

Amarendra N. Singh[1,2,3)]

ABSTRACT

Introduction: **Alzheimer's Disease (AD) is a multifactorial, heterogeneous, untreatable neurodegenerative disease with a broad clinical spectrum. AD is characterized by cerebral atrophy, decreased neural density, decreased synaptic connections, the presence of amyloid plaques and neurofibrillary tangles. It is a progressive, chronic, irreversible, slow degeneration of brain cells associated with deterioration of memory, judgement, learning alteration and cognitive capabilities with neuropsychiatric changes, which affect day to day life. AD is responsible for 60-80% of Dementias worldwide. In spite of a confirmed genetic basis, AD has marked influence and strong impact from environmental and non-genetic factors. A recent comparative review showed that 35% of lifetime risk of AD is non-genetic and environmental based, and that they are modifiable. How all these factors are involved in AD is not fully understood. The importance of non-genetic factors is gaining ground for the prevention of AD and thus the role of epigenesis is becoming more crucial and important. The important role of epigenesis and understanding of the role, will help in understanding the etiology and prevention of AD, and may finally help towards the successful treatment of AD.**

Objective: **To discuss the important role and impact of epigenesis in Alzheimer's Disease.**

Method: **Published research studies on epigenetic changes in Alzheimer's Disease.**

Results: **Epigenetic changes play an important and significant role in the pathogenesis, therapeutic pathway, and finding of biomarkers for Alzheimer's Disease**

Conclusion: Research in DNA methylation/hydroxymethylation, histone modification and non-coding microRNA suggests that epigenetics is a potential interventional target in finding the pathogenesis, treatment and biomarkers for Alzheimer's Disease

KEY WORDS

Alzheimer's Disease, epigenesis, etiology, prevention, treatment

INTRODUCTION

Alzheimer's Disease (AD) is a multifactorial, heterogeneous, untreatable neurodegenerative disease with a broad clinical spectrum. AD is characterized by cerebral atrophy, decreased neural density, decreased synaptic connections, the presence of amyloid plaques and neurofibrillary tangles[1,2)]. It is a progressive, chronic, irreversible, slow degeneration of brain cells associated with deterioration of memory, judgement, learning alteration and cognitive capabilities with neuropsychiatric changes, which affect day to day life. AD is responsible for 60-80% of Dementias worldwide[3)].

In spite of a confirmed genetic basis, AD has marked influence and strong impact from environmental and non-genetic factors. A recent comparative review showed that 35% of lifetime risk of AD is non-genetic and environmental based, and that they are modifiable[4-6)], as confirmed by the Farmingham heart study[5,6)]. Metanalyses[7)] and systemic reviews based on evidence proposes 21 non-genetic factors[4,7)]. Out of the 21 factors, 10 factors with strong evidence are: education, cognitive activity, stress, diabetes, head trauma, depression, hyperhomosystic anemia, hypertension in mid-life, orthostatic hypotension. Nine factors of weaker evidence are: smoking, cerebrovascular disease, frailty, obesity in mid-life, sleep, weight loss in late life, physical exercise, atrial fibrillation and Vitamin C. The other 2 factors were not recommended. How all these factors are involved in AD is not fully understood[4-6)]. The importance of non-genetic factors is gaining ground for the prevention of AD and thus the role of epigenesis is becoming more crucial and important. The important role of epigenesis and understanding of the role, will help in understanding the etiology and prevention of AD, and may finally help towards the successful treatment of AD.

Epigenesis or epigenetics are derived from the Greek word described by Waddington in 1942, and refers to the interaction of genetic and environmental factors which produce gene activity without changing DNA sequences[8-10)]. Changes by this genetic mechanism are developed due to outside influences including environmental factors rather than genetically determined, and one that is outside conventional genetics[8-10)]. These changes may remain through cell divisions for the remainder of cell life or may last multiple generations.

In AD, as described above, the influences of outside non-genetic factors including environmental factors from the very beginning of whole life and are observed through the involvement of ongoing genetic factors as shown in Figure 1:

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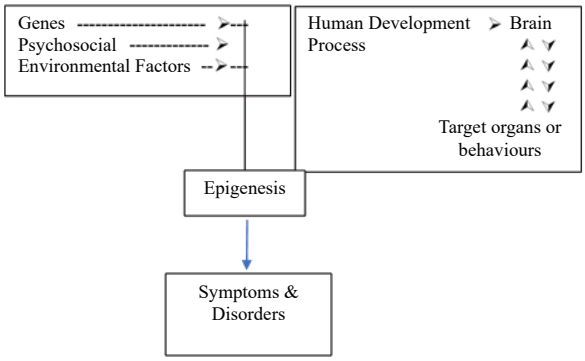

Figure 1: Interaction of Biopsychosocial and Environmental Factors Affecting Brain-Body Function Causing Symptoms, Disease or Both (Alzheimer's Disease).

Changes by the epigenesis of interaction between genetic and environmental factors work through modified gene expression during the occurrence of AD. The degree of mismatch determines the individual susceptibility of AD[11] as shown in Figure 2.

Good Match	Matchup	Mismatch
No illness	←gene→ + Environmental Factors	Risk of disease increase and degree of mismatch guides the severity of disorders

Figure 2

The molecular basis of epigenesis is complex and multiple inherited systems and may play a role in informing cell memory. The important disease related in humans is produced by genomic imprinting and also by transgenerational observation. Epigenetic gene regulation is also involved in producing complex behaviour and has been implicated in AD.

Overview of Epigenetic Mechanisms

The following epigenetic mechanisms play a part in AD:

1. DNA methylation and hydroxymethylation
2. Histone modification
3. Non-coding RNA regulation with emphasis on microRNAs
4. Acetylation, phosphorylation, ubiquitylation and sumolyation

The above epigenetic changes have an important role in gene readouts like gene silencing, transcription and post-transcriptional RNA processes[9-11].

DNA Methylation and Hydroxymethylation

DNA Methylation has been extensively researched by multiple cross-sectional studies, a few longitudinal studies and EWAS group studies[16]. DNA methlylation is dynamically regulated by active enzymatic methylation and demethylation processes[12-14]. This dynamic regulation adjusts to changes brought by epigenetically, in AD suffering patients[12-14]. In AD suffering patients DNA methylation acts as a mediator of environmental stimuli for facilitating various cells in the body to maintain the respective identity and also adopt to stimuli[15]. DNA methylation plays part in gene silencing, x chromosomes in activation, synaptic plasticity and genomic imprinting[15]. Basic cellular processes including the above changes affect cognitive function and also adjust to many environmental factors including: medication, pollution and changing factors which influences the environment[16-18].

DNA hydroxymethylation was recognized in 2009 as an oxidation metabolite of DNA methylation[16,19-21]. Though several specific genes of AD have been studied, but most important has been study of APOE. However, results have not been consistent. The majority of studies have shown hypomethylation of APOE gene[22-25,28,41,42] while other studies have shown no differences in APOE genes[26,27].

Most of the studies conducted are of a small scale and also on different tissues, which were examined. For consistent results, large scale studies on same tissue should be conducted in future studies. Studies done on other genes were not able to show as being the sole carrier of AD pathology[16].

Mitochondrial epigenetic changes are also called as mitoepigenesis. Mitoepigenesis changes is a new field for future investigations. In limited studies done on mitochondrial epigenetic processes, no consistent results were seen.

Histone Modification

Histone modifications play a significant role in neuronal development of AD pathogenesis[16,29,30]. Histone modification can affect structure of chromatin leading to the changes in genes[15,31]. Balance between histone methyltransferase and histone demethylases are important for brain integrity and memory[16,34]. These modifications and changes occur in AD thus deteriorating the memory and transcription of genes[39]. Changes in histone modification are related to AD pathologies and development of AD[32,33]. However, different studies have variable results[41]. Majority of studies have shown decrease[15,34] while other studies have shown increase in AD[15,32,34,40] compared to normal control. Again, studies have also shown increased level of histone[36,37,39]. These studies are again consisting of a small number of participants, and the research protocols utilized are variable, which affects the consistency of results. Epigenome-wide association studies have demonstrated that Tau protein affects histone modification changes and altered chromatin structure in prefrontal cortices of AD[15,33].

Non-coding RNA Regulations in AD

Non-coding RNA (ncRNA) are important for many cellular functions by binding DNA, RNA and proteins, thus involved in gene expression, ncRNA translation and assembly of proteins complexes[35,38]. Studies of microRNA (miRNA) are majority-wise in blood samples, but few others have been in CSF. However, results are contradicting and not replicable. More than 60 different miRNA have been studied and results are thus either down regulated[43,44,46] or up regulated[45,46,48]. Interestingly few studies on miRNA have both (down regulated and up regulated). miRNA targeted genes are involved in the pathophysiology of AD. Many miRNA are implicated in APP degradation and AB changes by regulating activities of enzymes.

Mitochondria represent the energy source of the cell and in AD bioenergies are decreased due to dysfunction of mitochondria. Many other altered miRNA are related to APP and AB processing in AD. Epigenetic regulations by non-coding miRNA are complex but are closely associated with core pathophysiological processes of AD via gene expression of different levels including: transcription, alternative splicing and translational activities. Dysregulated non-coding RNA are thus very closely related with pathophysiological process of AD.

DISCUSSION

In spite of increases in epigenetic research in AD the research remains inconsistent and variable. Confirmation of many research results are not possible in the majority of cases. Methods obtaining results in epigenesis of AD are not uniform and results are not easily replicable.

The goal of obtaining consistent results is to have a common protocol with common methods. These are necessary for future research activities so that the results are replicable and acceptable.

LIMITATIONS OF RESEARCH

1. Research sample sizes are small. They are underpowered studies; thus, they have difficulties in producing significant findings.

2. To replicate research findings is not possible because in the majority of studies there is a lack of common and similar protocols and agreed methods. These are important points for producing significant acceptable results.

3. Longitudinal studies with large samples are needed as the majority of cross-sectional studies do not fully describe the developmental processes of epigenesis.

4. Research findings should be able to differentiate epigenetic changes which causes AD. However, epigenetic changes occurring during the progression of AD are not covered.

CONCLUSION

The role of epigenesis in AD is important and significant in understanding the pathogenesis of AD, help in finding the therapeutic pathway of AD and to find biomarkers for AD. In spite of growing interest in research activities in the epigenesis of AD, the results are less satisfying due to a lack of definitive and consistent results. Research in DNA methylation/hydroxymethylation, histone modification and non-coding RNA have glimpses of significant findings, suggesting that epigenetics is a potential interventional target in finding the pathogenesis, treatment and biomarkers for AD. There is a need to have longer longitudinal studies in the epigenesis of AD for better understanding of the process of the pathogenesis of AD and also for producing definite and consistent results. EGWA has interestingly confirmed that many differentiating methylated sites exist in AD which should produce further research activities. The current evidence also points out epigenetic changes can be detected in CNS, CSF and periphery. These might produce significant and interesting findings. The most important step in epigenetic research is to produce less controversial results and more definite and consistent results.

FUTURE DIRECTIONS

Important steps should be taken to produce replicable, definite and consistent results by refining research methodologies and having larger samples with longitudinal studies. Besides making inroads in the pathogenesis of AD, the findings of epigenesis research has shown us the interesting scope of finding a therapeutic pathway with the possibility of finding biomarkers for AD. The effect of environmental factors interacting with genetic changes through the epigenetic process can produce more therapeutically effective drugs for AD. miRNA has the ability to regulate the endogenous gene expression. The possibility of one miRNA regulating the entire biological pathway brings the opportunity of producing multi-targeting drugs for multi-factorial AD.

Most of the epigenetic drugs pathways are involved with histone modification. One of the potential therapeutics for AD belong to the group of HDACi[52] which improves memory formation, learning and spatial memory along with an increase in synaptic plasticity[16]. SAM (S-adenosylmethionine) plays part in improving the cognitive status in AD (mouse model)[50]. In future inhibitors of non-coding RNA may also be of help in therapeutic pathways for AD[53-55].

Hypermethylation is involved in development of AD and the disease state of hypermethylation could also be a therapeutic pathway[57]. RDN929 a selection of HDAC inhibitor is being investigated in Phase 1 for the treatment of improving AD[56].

Recent research studies have pointed out that epigenetic changes can be found not only in CNS but also in CSF and on periphery; thus, paving the pathway for finding biomarkers for AD through the changes in epigenetic processes[58]. Mitochondrial epigenomes have potential to become an applicable biomarker for AD.

Abnormal alterations seen in epigenesis can be changed to normal by gene editing[16,56]. Epigenesis is described as a science of change thus science of change can be directed towards pathologies and therapeutic pathway of AD to achieve enhancement of knowledge in the complex disease of AD.

In conclusion, for a new therapeutic approach to AD, a complex balance between histone acetylation and deacetylation, as well as other histone modifications, should be studied[16].

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