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Review Article

Epigenetic Modifications lead towards Neurodegeneration

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Abstract

Background: The foremost factor involved in Neurodegeneration is the impact of epigenetic modifications; through its nature to epigenetically mark the neuron-associated genes, also, by affecting cognitive functions and damaging neurons that promote mutations. Due to these changes in the genes; neurodegenerative diseases are developed. This review will assess epigenetic modifications that switch "on" & "off" the genes associated with neurons that lead towards neurodegeneration in humans.

Methodology: This systematic review is based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to conduct a search strategy and for the preparation of the manuscript. A search engine (PubMed) was used and the article reference list was searched for relevant primary research articles. 100 out of 22278 studies dated from January/2000 to February/2019 met the inclusion criteria. Two quality assessments were piloted and included: (1) Authors evaluation and (2) Risk of bias.

Results: Quality of interventions provided was rated "good", Risk of bias in studies was rated "fair" and the team of authors approved included papers. Furthermore, 13 out of 100 studies critical appraisal analysis demonstrated the relationship between epigenetic alterations and neurodegeneration and the rest of the studies described neuro-epigenetics, epigenetic remodeling and epigenetic mechanisms.

Conclusion: Exogenous influence like aviation stress or co-factors, such as nutrition and physical stress plays a major role in silencing the "gene switching" proteins of epigenetic marks and influences the onset and progression of neurodegeneration. Furthermore, intervention in epigenetics might help promote brain health.

Keywords

Epigenetic modifications, Neurodegeneration, Neurodegenerative Diseases

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Introduction

"Brain" a biological organ; most resilient yet much venerable to any type of stress response, such as; dietary factors, undesired excess body fat, physical fitness, smoking, alcoholism, environmental pollutants, psychological stress, chemical stress, physical stress, etc. They are major factors that are associated with wellbeing and longevity and are responsible for late-life neurological, metabolic disorders and neurodegenerative disorders[1]. The environment is capable of altering the "Epigenome" which supports heritable changes in gene expressions, situated within a genome[2]. The changes that take place in the epigenome are known as epigenetic modifications; these epigenetic modifications of DNA structure or histones are linked with regulating the gene transcription and they may affect one another – positively or negatively by the environmental influences for controlling the human phenotype[3]; these epigenetic modifications include histone acetylation; which is responsible for modification of transcriptional activity that accesses the transcription machinery of genes[4]. Histone methylation is responsible for several courses associated with activation and repression of the transcription machinery[5] and DNA methylation; majorly contribute to the gene regulation by disrupting binding sites of transcription[6]. Exogenous influence is claimed to be accountable for modifications related to neurodegeneration; a link between environmental hassles associated epigenetic alterations and oxidation[7]. The epigenetic modification of a family of macromolecule: nucleic acids; is responsible for making gene regulation more complex and makes heredity further complicated, henceforth, representing its impact on characteristics of heredity, growth and diseases[8]. However, we summed up the whole aspect of epigenetics to the master regulatory organ "Brain" and discussed mainly epigenetics of neurons "Neuro-epigenetics" which implicates the same chemical changes of DNA and histones; nevertheless, there is a slight and well-known difference in neuronal epigenetic modifications which includes no transmission to the progeny cells yet it includes the same modifications such as DNA methylation and hydromethylation, histone modifications, histone variants miRNA and variations in nucleosome positioning. Environmental pollutants, nutrition, psychosociological or physical stress, learning abilities, drug levels achieved in the body or psychological trauma are major factors involved in the regulation of the DNA structure, hence, it controls epigenetic alterations in the central nervous system (CNS) involving exogenous stimuli and gene expression regulation[9].

Nonetheless, CNS functions comprised of a substantial epigenetic constituent, as well as regulation of neural stem cell providence, neural plasticity, learning and memory. Epigenetic changes including dysregulation of DNA methylation and histone modifications are present in multiple neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS). A study explained the function of the cells in the central nervous system focus on the significant influence of a diversity of epigenetic modifications, they also exhibited the restructuring of epigenome on the cytosine methylation and histone modifications that continues to occur throughout early brain development and the ageing[10]. There are also hypotheses that mitochondrial function - agitated in neurons of human subjects with neurodegenerative disorders are usually perturbated by methylation patterns of mitochondrial DNA[10]. The world health organization proclaimed an estimation that by 2025, scarcely three-quarters of adults ageing over 60 and above will be existing, that too, only if novel strategies are established to prevent or treat AD and PD[9] therefore, the foremost factor involved in neurodegeneration is stress; due to its ability to epigenetically mark the neuronal cell genes and affect cognitive functions and damage neurons that can influence mutation and due to these

changes in genes neurodegenerative diseases may develop.

In this review, we will assess the epigenetic modifications aforementioned and regulations that switches "on" & "off" the genes associated with neurons that lead towards neurodegeneration in human, as well as the epigenetic variation that is maybe helpful in prevention.

We focused on the connection between particular and well-defined mechanisms of stress and epigenetic modifications which are fairly unclear, for that reason, we, however, evaluated some of the studies with an objective to abridge the relationship between epigenetic modifications and neurodegeneration. It is noteworthy to mention that this paper is directed to expand the knowledge about exogenous influence induced epigenetic changes that helped us to understand the complexities of neurodegeneration, the triggered epigenetic disturbance and is aimed to promote cognitive maintenance. Also, we will elucidate some of the future approaches for the prevention of neurodegeneration and neurodegenerative diseases, such as AD, PD, HD and ALS for the matter of fact that they are the outcome of neurodegeneration. We will also explore its associated medical complications by reviewing interventions designed to help those diseases.

Methodology

Search Strategy

The literature search was led by indexed literature using the PubMed search engine (www.pubmed.gov). It did not contain any grey literature sources. Duration of publication date was from January 1, 2000, to February 1, 2019, using the following terms: 'Exogenous influence' (e.g. stress or stressors, environmental factors and lifestyle) "Neurodegeneration" (e.g. Neurodegeneration or neurodegenerative diseases or Alzheimer's disease or Parkinson's or Huntington's disease and Neuronal death) "Epigenetic modifications" (e.g. neuro-epigenetics, histone methylation or histone acetylation or phosphorylation of histone H2B or heterochromatin regulation or nucleosome regulation or chromatin modification or histone tail modification or epigenetic modifications or DNA methylation or DNA demethylation and epigenetic alterations). Additional information is acquired from primary publications and direct suggestions from the Neuroscientists, Physicians and Geneticists. Moreover, thorough screening for selection of studies was obtained individualistically by considering relevant titles, abstracts of all the citations acknowledged by literature review, it was attained to achieve quality studies and to meet eligibility for this review, qualified data was allocated and screened in pilot forms and was independently reviewed duplicate again and then further inspection and review was followed by all the authors. Variance in data extraction was resolved based on decisions made through consensus.

Only studies with study design following (case-control, cohort, cross-sectional, family-based, RCT, cross-sectional and experimental studies) were included based on evidence-based practice to maintain the quality of studies. Animal studies, individual case reports, and meta-analyses were not included in this review. Only published studies were included to increase the robustness of the review.

Data Extraction

Following are the data that is extracted from included studies which were established on the basis of a predefined protocol using short critical appraisals of each study. Exclusion criteria from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline were considered: no animal studies, no pre-clinical studies, articles that are not original, no paediatrics study only. Studies were further evaluated by Jadad scoring; it is a scoring system to individualistically calculate the methodological quality of clinical researches or trials (developed by Jadad in 1996).

Only studies with relevant sources were scrutinized for inclusion. The study approach with epigenetic tags/marks and neurodegeneration in human were included. Any other irrelevant studies that did not support the topic were excluded.

Only studies directly describing at least one aspect of external influence associated epigenetic marks/modifications leading toward neurodegeneration or stress derived epigenetic alterations causing neurodegeneration was included. The clinical questions for this systematic review were collected based on evidence-based practice (EBP) including clinical expertise, to provide better relevance and quality to the review citation. The study was considered eligible for the systematic review as it evaluated the potential association between stress-induced epigenetic modifications in genes and neurodegeneration. Only the English language was used.

Furthermore, data management was maintained by software: Mendeley, SPSS and Microsoft Word. Obtained a manual recording of a timeframe in the notebook as well to achieve finalized collected data set of studies.

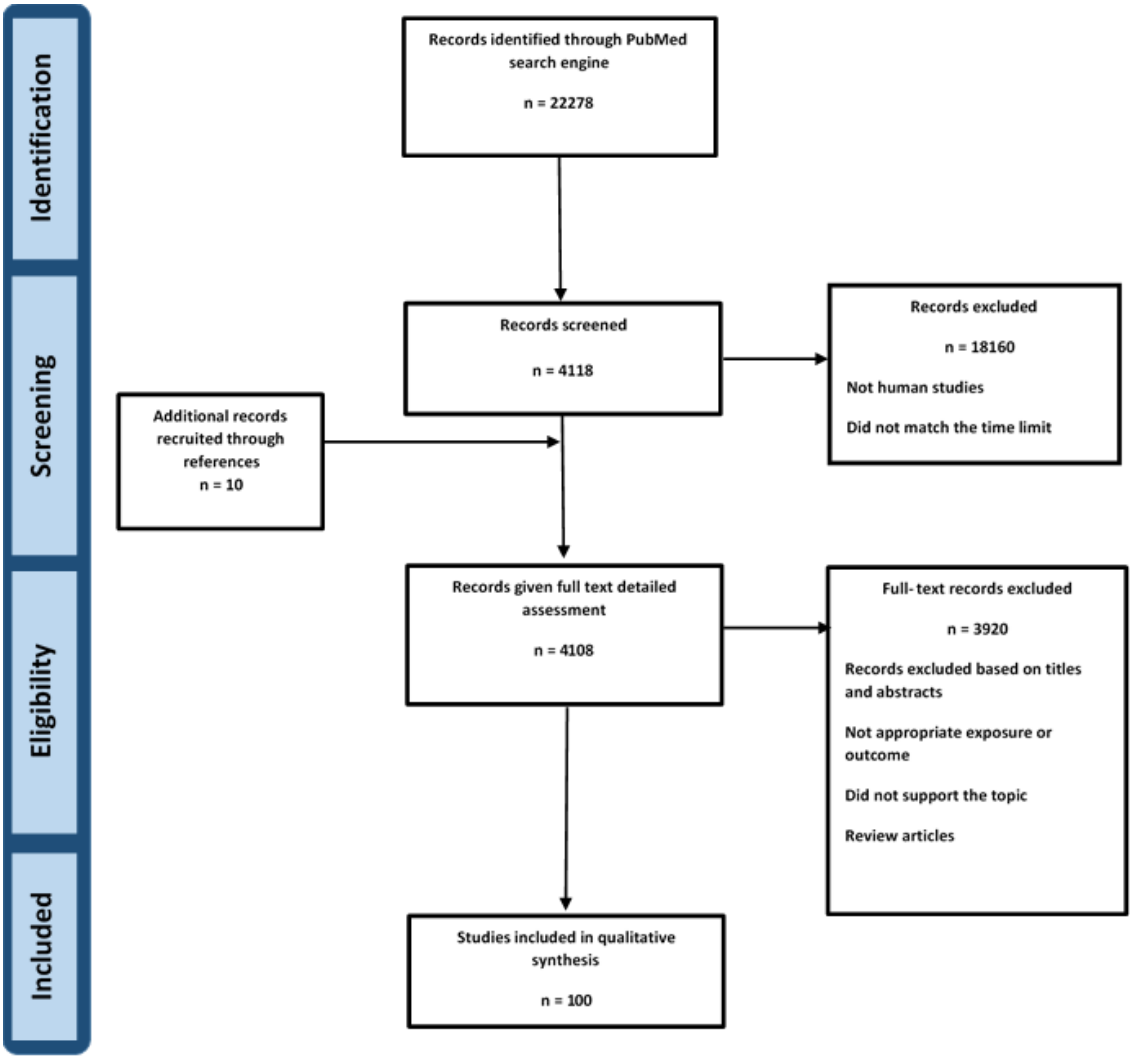


Figure 1: Flow diagram of selected studies.

Exogenous influence and Epigenetics

Exogenous influence including environmental factors such as; pollutants like particulate matters, metals, organic compounds, endocrine-disrupting chemicals and the lifestyle which involves diet, the habit of smoking, and physical activity[9]. However, the factors which affect the neuron's epigenetic modifications are arsenic the emotional burst as identified by a study of in the suicide victims, night shift workload subjects, physical exercise and nutrition[10-14]. All these are responsible for the changes in the epigenetic modifications, furthermore, imperfectly regulated DNA methylation and histone modifications are seen in numerous neurodegenerative diseases, such as; AD, ALS, PD and HD[15]. Poor lifestyle accelerates ageing which is a significant risk factor for several neurodegenerative diseases, moreover, increased age has a strong connection with the alterations in DNA methylation as distinctive DNA methylation is capable of changing highly correlating chronological age in the human brain[16]. In a study; upon the comparison of controls and AD patients, the AD patients presented higher methylation of repetitive DNA elements, this could be the consequence in changed global DNA methylation levels[17]. Besides in PD, the epigenetic mechanisms play a significant role, through methylation, which is decreased in PD patients' brains[18]. Therefore, a good lifestyle is an advantageous approach for healthy ageing and wellbeing as it could prevent several factors contributing to the progression of neurodegeneration.

Epigenetic Modifications

Nucleosomes are situated inside a cell nucleus as an essential unit of chromatin. The individual nucleosome is made up of 147 DNA base pairs enfolded in an octamer of histone proteins; congregated by dualistic reproductions of each of the four central histones namely (H2A, H2B, H3 and H4). H1 adheres to DNA in between the central particles of a nucleosome, also, they are responsible for the stabilization of higher-order chromatin structures. Additionally, histone protein contains a fundamental rotund domain and N-terminal tail projection that consist of various sites for potential modifications[19]. Therefore, chromatin structure can be affected by the post-transitional modifications of the amino-terminal tail's histone proteins as well as the density of these proteins per unit length of DNA and can constitute a presumed histone code. We evaluated six types of epigenetic modifications in this section for the reason that these six modifications contribute to neurogenesis and neurodegeneration.

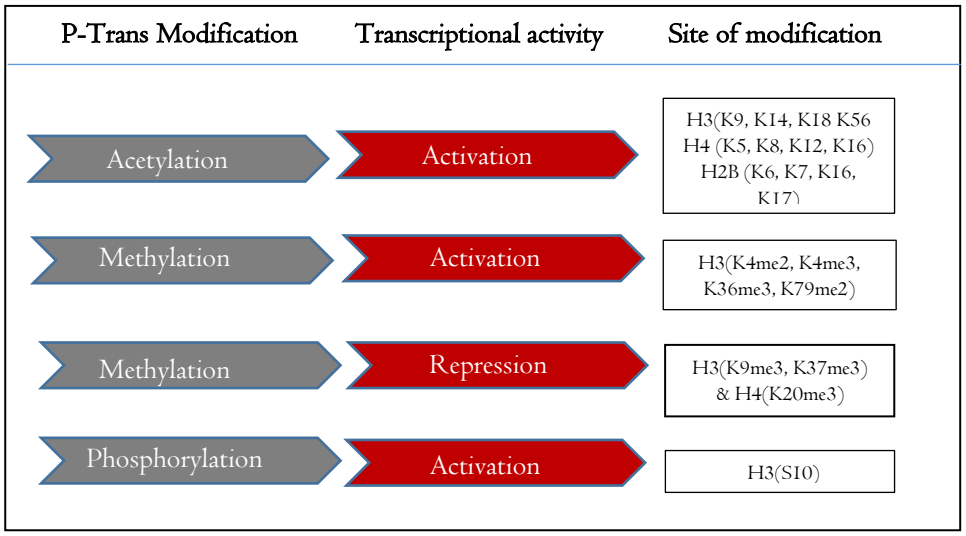
Post-transitional histone modifications

The powerful and reversible reactions arbitrated by two incompatible groups of enzyme complexes that can bind or eliminate conforming chemical groups are known as post-transitional modifications[20]. Amino acid residues at histone tails are responsible for many post-transitional modifications such as acetylation, phosphorylation, methylation, SUMOylation and ADP-ribosylation[21]. Moreover; modifications are initiated and completed by histone acetyltransferases (HATs) and reverted through histone deacetylase (HDACs).

The post-transitional modifications discussed below in the section of epigenetic regulation plays an important role and have substantial effects on several proteins associated with histone and could encirclements protein code have represented by the protein p53[22] and nuclear factor-kappa β (NF-kB)[23]. Amyloid proteins found to be widely modified by several post-transitional modifications in studies. The declaration was drawn out from the studies of AD and HD – the proteins induced histone acetylation is crucial in the pathogenesis of the neurological disease. Protein acetylation contributes in the pathogenesis of neurological disease.

Box 1: Histone modification and cognition

Histone modification plays a role in modulating memory, moreover, in humans, mutations in the gene programming crucial binding part (CBP) or its homologue p300 causes Rubenstein–Taybi syndrome, a congenital condition – considered to be an autosomal dominant disease characterized by severe intellectual and learning disabilities[24] Such outcome established an incentive for histone acetylation in synaptic plasticity as well as foundation of memory development, and established an origin for the determination of altered acetylation in the cognitive decline induced neurodegenerative disease[25].



Box 2: Arrows are representing post-transitional (P-Trans) histone modifications and its role in transcription activity are denoting towards modification sites on the right side of boxes.

Histone acetylation

Acetylation at lysine residues is widely considered histone modifications related to the transcriptional activation in studies[26]. Excerption of Histone H3 tail normalizes gene expression and the acetylation of histones derived modification commonly mediates transcriptional activity accessing the transcription machinery to genes for activation of mechanism[4]. The addition of the acetyl group in an amino-terminal residue corporate the reduced positive charge of histones, and by implicating a slight interface through DNA; it results in a decreased chromatin compaction[27].

Box 3: Histone acetylation and neuronal cell death

There is a strong association of histone acetylation and neuronal death as a result of histone modifications leads to the death of neurons, thus, resulting in neurodegeneration. A study revealed the relationship between ischaemic insults that triggers REST (which "switches off" the target genes via HDACs recruitment)[28].

Histone variants

Evidence has been collected regarding the role of histone variants – H2A and H3.3 and their input in the variance of chromatin structure[29]. The H2A.Z situated on DNA regions is responsible for the transcriptional activation; considered to be crucial due to its inducible manner for a slightly inconstant chromatin structure parallel to that of the canonical histone H2. Besides, H3.3 is a histone variant

derived from the promoter regions, along with H2A.Z, they are mostly found on promoter regions for the fact that their structure endorses the foundation of highly considerate chromatin[30].

DNA methylation

DNA methylation is a significant epigenetic mechanism. In essence, it includes the addition of a methyl group at the 5 positions on the pyrimidine ring of cytosines, in the context of cytosine-phosphate-guanine (CpG dinucleotides) area of DNA where a guanine nucleotide is followed by the cytosine nucleotide in 5' → 3' direction to describe the "fifth base of DNA and is generally allied with silencing[20]. CpG nucleotides are mainly accumulated in clusters in CpG islands; described as areas enrich with guanine-cytosine (G-C) content of 50 percent as a minimum. In a normal cell, they tend to be unmethylated, and approximately 50% of them turn out to be tissue specifically methylated in differentiated tissue throughout early development. Interestingly, the direct transcriptional inhibition is achievable by interlude disruption of DNA binding proteins activity at their target sites.

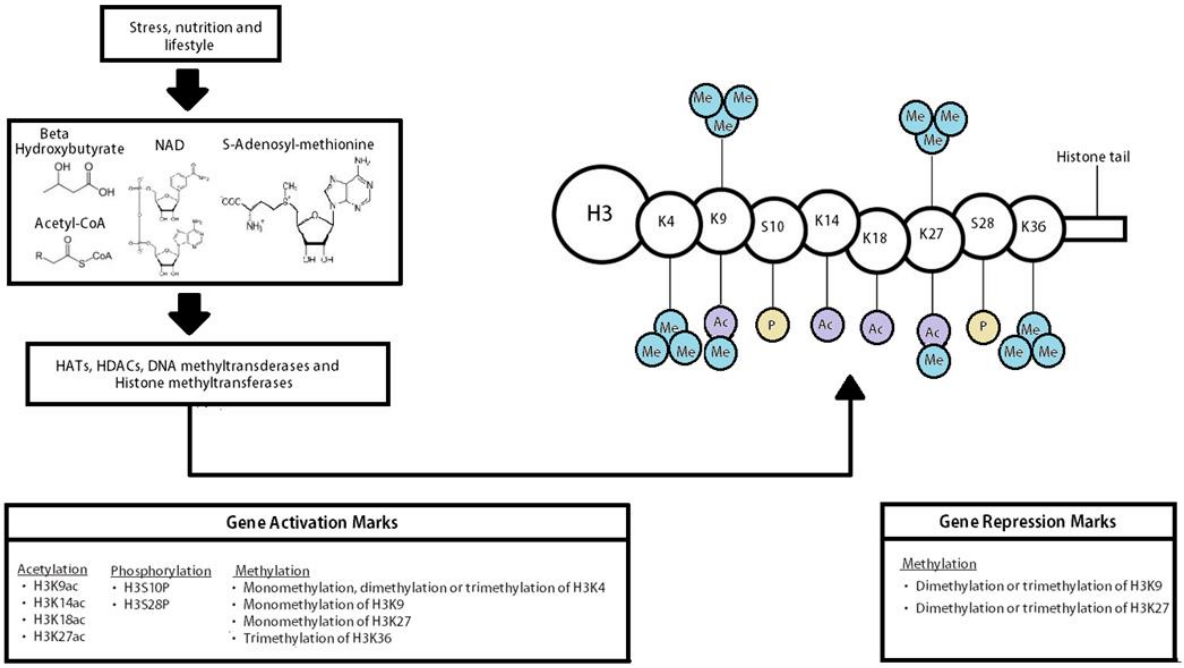


Figure 2: Histone modification associated with repression and activation that may lead towards neurodegeneration.

Non-C-G methylation is proposed in humans at CHG and CHH sites, while DNA methylation occurs mostly in CpG islands in mammals. Decreased concentrations of non-CpG methylation befall during differentiation and the mechanisms of non-CpG methylation are uncertain until present[31]. Additionally, there are reports showing methylation of guanine and adenine, consequential in 7-methyl guanine (7-mG) and 3-methyladenine[32]. Herein, we discussed the DNA methylation, explicitly 5-mC, except as otherwise specified. DNA methylation is not limited to CpG islands only, they are also present at CpG island margins. Moreover, DNA methylation is mediated by transcription repression and is commonly present in heterochromatin[33]. Low amounts of methylated DNA are found in euchromatin. Subsequently, supposed are some genes; that exhibit enhanced expressions upon their hypermethylation[34]. Besides, DNA methylation in the transcribed region of a gene "Gene body" has been involved in substitute splicing[35].

Gene transcription by DNA methylation is reliant on the location inside or onto the gene[36]. Methylated DNA is capable of disrupting transcription by intruding binding of transcription factors – this course takes place in the promotor regions[37]. The theory behind enhanced gene expression gene bodies methylation is currently uncertain. Even though the most established and steadiest epigenetic modification is via DNA methylation, the DNA methylome is extremely kinetic[38]. Heritable DNA methylation is dependent on a process known as "maintenance of DNA methylation," which synthesizes DNA strand. The novel DNA methylation mark is referred to as de novo DNA methylation. Mechanism of DNA methylation is carried out by a family of proteins known as DNA methylation enzyme DNA methyltransferases (DNMT)[39]. DNMT family arbitrates DNA methylation by catalytic reaction for the transformation of the methyl group from S-adenosyl-L-methionine to cytosine, and they remain responsible for the conservation and de novo DNA methylation[40]. DNMTs are of four identified types, Namely, DNMT1, DNMT3, DNMT3a and DNMT3b, All of the DNMTs utilize methyl donor: S-adenosylmethionine (SAM)[37,40]. Although DNMT2 appeared to be RNA methyltransferase[41]. Yet, another known DNMT, DNMT3-like (DNMT3L) possesses no enzymatic reaction[42]. Note, however, a peer-review paper stated that in mammals; exists five DNMT family, but only DNMT1, DNMT3a and DNMT3b have methyltransferase activity and their DNA methylation can be evaluated by genomic DNA profiling, for the reason that it is allied with human epidemiological epigenetic research[43].

Initial studies on DNA methylation exhibited its fundamental significance in neural stem cells[44]. Moreover, learning, memory, neuronal repair, the survival of neurons and synaptic plasticity has been associated with DNA methylation[45]. These dynamic progressions are further reliant on novel methylation. However, the role of maintenance DNA methylation plays a vital role, such as loss of DNMT1 exhibited increment in histone acetylation, a disrupted nuclear organization and finally cell death[39]. Disturbance of these factors are significantly associated with neurodegeneration; therefore, DNA methylation evaluation is important for the investigating neurodegeneration[46].

DNMT and DNA methylation mechanism and its association with human-only are unclear. Thus, we majorly discussed the mechanisms which were closely associated or, to some extent, showed a connection with human studies. As aforementioned, DNA methylation patterns were established during the developmental stage, yet these patterns tend to change over time, chiefly due to ecological stressors and co-factors[47]. This venerability of DNA methylation might be responsible for the onset or progression of pathosis. Pooling evidence concerning epigenetic modifications, specifically, DNA methylation may be beneficial to elucidate the unidentified “heritable changes” that previously failed to identify through genome-wide association and resequencing approaches.

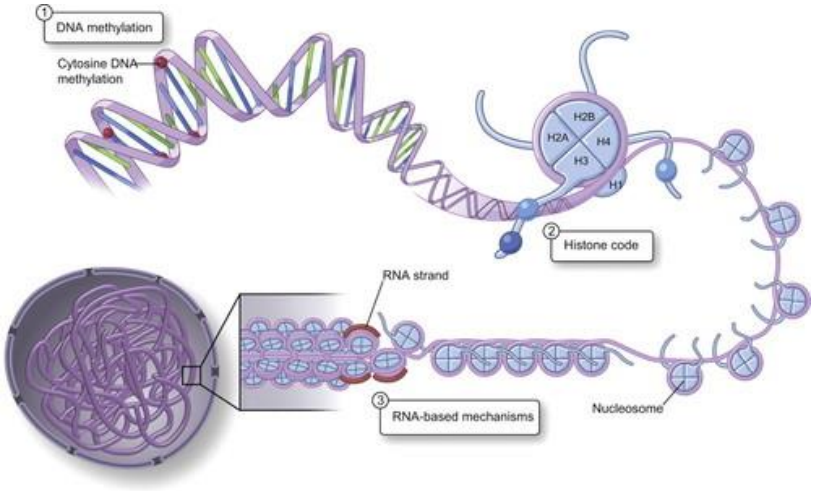


Figure 3: Three fundamental mechanisms of DNA methylation (Reproduced with permission, Yan, M.S et al., J Appl physi).

DNA Demethylation

Another well-established epigenetic mechanism is DNA demethylation; in this process, the methyl group is detached and swapped. When DNA methylation is blocked, there are abundant DNMts in non-dividing cells[48] and a considerably decreased levels of DNA methylation[33,38] regardless of the 5-methylcytosine (5-mC) mark permanency – have interested in the exploration of factors responsible for the process of active demethylation46. Although, still in this context, the modification repair pathway is crucial for primary demethylation in post-mitotic neural cells and it never omits the opportunity of several demethylation pathways[49].

The epigenetic marker that has shown to be an important one in the past few years is 5-hmC, which is pragmatically and chemically different from 5-mC[50]. Even though the DNA hydroxymethylation (an epigenetic mechanism which alters the 5 positions of cytosine by the additional hydroxymethyl group to DNA) is commonly involved in increased gene activity, a study by Jin et al., described that this association does not depend on the 5-hmC location in the genes and the CpG component[51]. Moreover, 5-hmC exists in almost all the tissues and cells, explicitly in the brain[52], with the highest level in cerebellar Purkinje cells[53] and lowest in the stem cell-rich area[52]. Nevertheless, the exact mechanisms of DNA methylation are still blurred in the scientific world and need more research for scientific elucidation.

Epigenetic Regulation

The gene expression of the epigenetic regulation mechanism encompasses static and instinctive variations in gene expression that exist for the alterations in the primary DNA sequence. The identified epigenetic mechanisms established till now; includes histone post-transitional modifications, DNA CpG methylation and gene imprinting. The histone code is a resolute proposition signifying a particular pattern of post-transitional modifications to histones perform as a "molecular encrypting code" recognized and castoff by non-histone proteins for the regulation of determined chromatin functions. These modifications are acetylation, phosphorylation, methylation. Additionally, there are modifications involved in epigenetic regulation such as SUMOylation (post-translational modification involved in response to stress, transcriptional regulation, cell death, protein stability, and development throughout the cell cycle and several other cellular courses) and ubiquitylation (a post-transitional modification adding ubiquitin to protein sequence).

Furthermore, numerous families of proteins have associated that function with adding

and subtracting these post-transitional modifications. The most superlatively considered of these families involves the histone deacetylases (HDACs), K-acetyltransferases, K-demethylases (KDMs) and K-methyltransferases (KMTs)[54]. Furthermore, numerous families of proteins are associated with that function to add or remove these post-transitional modifications, which results in the covalent addition of acetyl groups to a lysine residue on proteins. KMTs are responsible for the addition of methyl groups to lysine residues whichever, as mono-methylation, di-methylation or as tri-methylation, whereas KDMs and HDACs eliminate these alterations[55]. They are crucial for many proteins, in addition to histones.

Epigenetic Modulation

The positive modifications of cellular phenotype without altering the genotype is done via epigenetics. This process is termed as epigenetic modulation or epigenetic reprogramming or epigenetic regulation.

The epigenetic modulation is easy to achieve due to its reversible nature; modifications can be regulated by eliminating the type of stresses, environmental hazards. The excessive intake or deficiency of chemical elements and there are growing shreds of evidence that transcription factor derived remodeling, transcriptionally responsive genes related gene silencing, nutrition, physical activities can play a role in epigenetic modulation, discussed below.

Transcription factor derived remodeling

A perilous regulator for the development of neurons, called RE1, an explicit protein, namely repressor element silencing factor/restrictive element silencing factor (REST), correspondingly, known as neuron restrictive silencing factor (NRSF). REST is crucial for development and is necessary for differentiation and maturation of cells[56], REST silences the gene transcription by initiating binding too restrictive element I (RE1), conscripting its co-repressors; REST co-repressor (CoREST)[57].

Transcription produces daises that result in recruiting histone deacetylases (HDACs), containing HDAC1 and HDAC2. HDACs, deacetylate and switches off the gene by the constriction of chromatin, which impedes transcription of gene promoters[58]. the site-specific histone demethylase LSD1, eliminates monomethyl and dimethyl moieties from H3K4, therefore, stimulating gene repression. Although, inhibition of REST target genes can take place even after depleted REST due to the presence of co-suppressors, such as MECP2 and CoREST[59].

Followed by the binding of DNA, the BRG1 encourages nucleosome relocation, which in turn interacts with REST and RE1 sites and encourages gene repression[60]. Moreover, the REST–co-repressor complex has essential suggestions for drug discovery.

Meticulosity of transcriptionally responsive genes-induced gene silencing

The subgroup of the target genes that are associated with REST is salient—in a particular disease, state differs in a cell type-dependant[61]. For instance, the unit of REST mark genes that display altered expressions prior to ischemia and varies from the unit of genes exhibit modified expressions in the prefrontal cortex of humans with HD[62] as well as in the prefrontal cortex of aged humans (healthy subjects)[63]. Additionally, transcriptionally responsive genes distinguished in genome-wide studies involving chromatin immunoprecipitation of REST assessed by sequencing (ChIP-seq) in neuroblastoma cell lines[62]; is dissimilar than that of detected genes by significant Chip-seq investigation in Jurkat cells[64]. Factors that define the specificity of interference between REST and its targeted marks include a likelihood of the epigenetic landscape, a term invented by a British developmental biologist Conrad Hal Waddington (the numerous developing pathways a cell recruit for the differentiation) – influences REST attraction towards the unit of target genes. For instance, chromatin-remodelling protein

BRG1 employees REST to a definite ensemble of the target genes.

The polycomb repressive complex 2 (PRC2) is conscripted to RE1 positions in REST target genes by (lncRNA) HOX transcript antisense RNA (HOTAIR)[65]. It binds through its 3' domain to the LSD1-REST co-repressor (CoREST), REST complex, due to its consistency with IncRNAs, which serves as platforms by providing binding daises for the unique assemblage of chromatin-remodeling enzymes. Thus, resulting in modifications of target gene expressions.

Nutrition

In one of the reviews of Gabbianelli and Damiani 2018, they summarized some of the critical discoveries in the last few years. It explained the probable influences and mechanisms involved between early-life nutrition during 1000 days of a timeframe in human development as soon as environmental experience shapes neural circuits and disposition for neurodegeneration when ageing occurs[66]. A scientist stated that brain health is not modulated by diet during the lifetime only – it is also modulated during the prenatal phase as well as by what the mother consumes during the early life of a child and what the mother feeds the child during first two years of his/her life. Moreover, the development of neurodegeneration is associated with other factors, such as alcohol and the pesticides and metal component in food, as they promote neurodegeneration. All these factors are associated with epigenetic modifications that lead to oxidative stress, brain volume reduction, mitochondrial dysfunction, lack of dopaminergic neurons, reduced fetal telomere length, proinflammatory cytokine release resulting in altered brain development which affects the onset of AD and PD and general neurodegeneration[67]. Therefore, a mother needs to eat nutritious food to avoid neurodegeneration to the offspring.

Nevertheless, copper deficiency can be severely destructive for the human brain. Joven et al., 2014 described the mRNA expression of epigenetic factors (DNMT1 and DNMT3A) predisposed to be upregulated upon cells exposure to copper; this upregulation was larger when H_2O_2 was added. Moreover, simple foods, i.e. vegetables (white/green/carroty/reddish-pink), also, tea represent a significant role in neurodegeneration protection[68,69]. A study proposed that double-bonded omega 3 fatty acid decelerates cognitive decline in aged entities before the clinical manifestation of dementia[70]. Besides, the research related to epigenetics of AD indicates that the use of resveratrol in small amounts can decrease the gene expression that is critical for the age-related diseases[71]. Lastly, Selenium supplements hold the capability to modify DNA methylation at explicit gene regions; this might be though DNMT[72]; additionally, the dietary deficiency in selenium can reduce the DNA methylation by propagating the trans-sulfonation pathways[71]. Selenium can modify the histone variants as well, though inhibiting HDAC activity by seleno-a-keto acids[72]. Food and nutritional science researches demonstrated many nutritional based natural compositions to constrain the epigenetic machinery, including sulforaphane, also acts as HDACi[73]. Spannhoff et al., 2011 stated the importance of a nutritional-based tactic for directing the epigenetic mechanism in people with neurodegeneration and neurodegenerative disease[74].

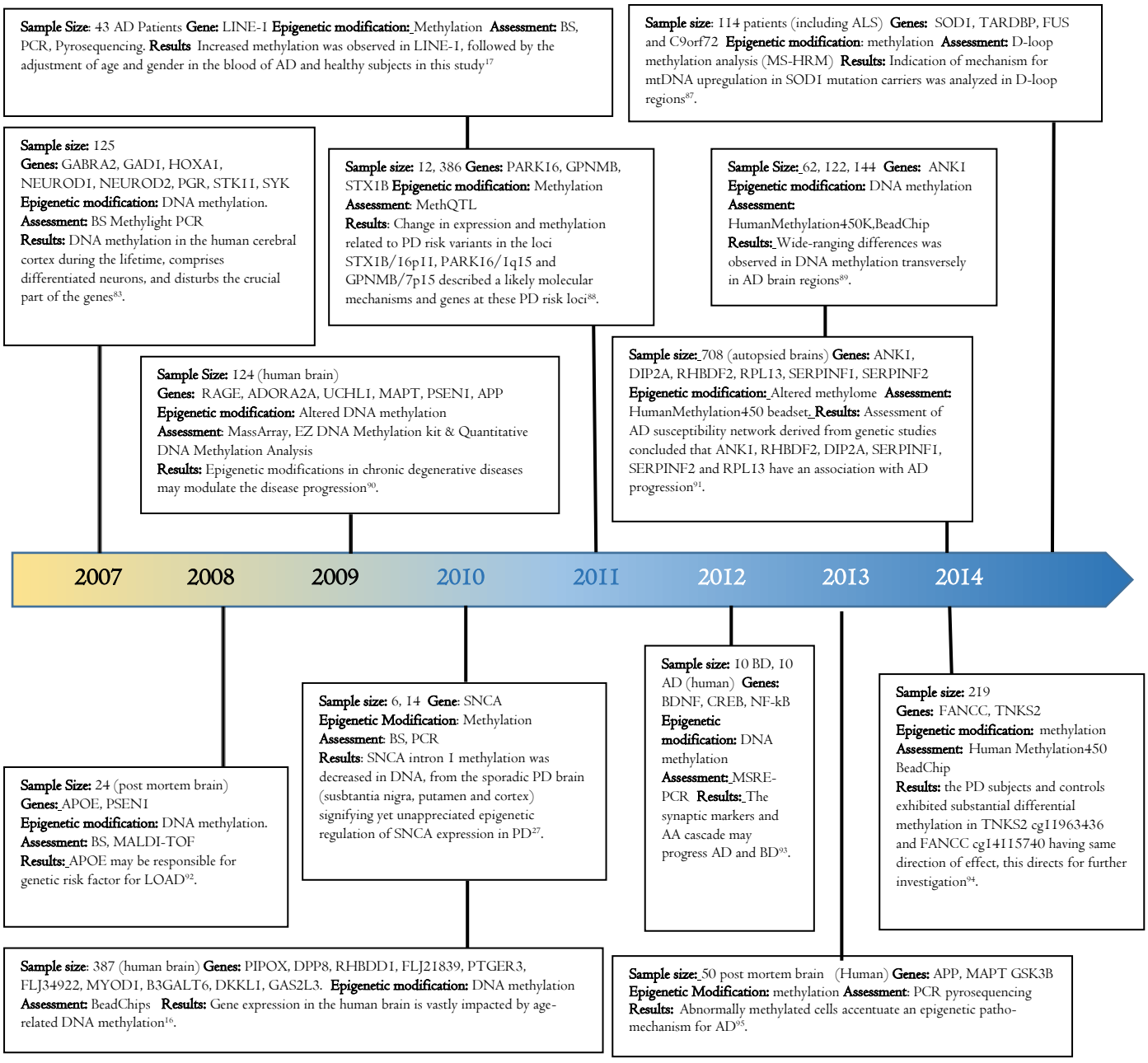
Physical Activity

The top listed factors for all the diseases are implicated by physical inactivity and is described to be accountable for 9% of all deaths worldwide with serious health, environmental, social and economic outcomes[75] in which cancer and neurological diseases are also testified[76]. There is evidence that postulates that physical activity can naturally control the epigenetic machinery considering several human diseases[77]. A study in human monocytic cells represented the outcomes of moderate exercise, which upregulates the methylation status of apoptosis induced protein containing a C-terminal caspase recruitment domain

(ASC)[78]. ASC is known for its essential conciliation of cytosol-inflammatory signaling pathways, and interestingly, its methylation pattern accompanies the level of proinflammatory and anti-inflammatory cytokines during isometrics and physical exercises to keep fit[79]. Accordingly, resulting in lowering the basal level of inflammation, thus, preventing the manifestation of pathosis and chronic inflammation[80]. There are also growing studies demonstrating physical activity promote the modulation of histone acetylation, mainly H3 and H4, promoting chromatin alteration that can develop behavioral diseases as well[81]. A first human study conducted by Bertram et al., 2008 demonstrated the relationship between exercise training and levels of histone acetylation in subjects with neurodegenerative diseases, and they observed that the strength training can induce a histone H4 and benefit the people with neurodegeneration[82].

The Timeline of Neurodegenerative Genes and their Association with the Epigenetic Modifications

Limited and well-evaluated studies met the criteria for this timeline. There are numerous genes allied with neurodegeneration, a condition that implied on every neurodegenerative disease; thus, studies exhibiting genetic biomarkers of neurodegeneration were considered only.



Discussion

There are proximal epigenetic modifications in the human neurogenic epigenome, the epigenetic modifications involved in neurodegeneration are profoundly discussed above to explain the mechanism and an association with specific neurodegenerative diseases. Herein, we focused our consideration on AD, PD, HD and ALS. Epigenetics expands opportunities to classify or detect disease-related genes. We evaluated numerous genetic biomarkers of neurodegenerative diseases that are activated or suppressed by the epigenetic modifications. In the last two decades, scientists endeavored to discover new risk factors for AD using genetic screening, which has not fulfilled the expectations of success rate. In respect to epigenetics; it offers additional opportunities to classify or detect disease-associated genes.

Methylation associated with age may show one of the mechanisms by which exogenous and dietary factors can contribute to the progression of AD. The epimutations occur at different epigenetic loci of the gene. The critical psychosocial events such as stress exposure in the early phase of life may induce permanent epigenetic marks, such marks are established by the intron 1, which is considered as an extra level of complexity to a graded epigenetic risk of neurodegenerative diseases, specifically PD. Besides, it has been shown in the early 2000s in Genome-wide DNA methylation research that 9000 plus CpG sites identified presenting 918 exceptional genes may be confirming late-onset AD. They might be categorized through oxidative stress, and chromosomal changeability diminished DNA repair, accumulated nuclear and mitochondrial DNA impairment and disrupted calcium homeostasis. The "Aging" emanates substantial risk factors for AD, and it also accepts multiple epigenetic alterations.

Regarding neurodegenerative genes, the viable genes turned out to be hyper- hypomethylated in AD. Foremostly, the promotor region of transmembrane protein 59 (TMEM559) was hypomethylated in AD, initially, this gene was accompanying amyloid precursor protein; an important regulatory point in the development of amyloid β peptide in AD. Moreover, there was an increment in long interspersed nuclear elements 1 (LINE-1) in AD patients[17]. The same study also described that up-regulation of DNMTs secondary to DNA damage might promote increased LINE-1 methylation and further speculated that AD might involve two different phases concerning LINE-1 methylation. Initially, in AD patients, there might be an increment in LINE-1 methylation, while, in advanced stage AD, there may be a decrease in DNA methylation as a result of compromised methyl cycle. However, it requires further investigation to become conclusive. Nevertheless, LINE-1 methylation may help elaborate the AD pathogenesis and may help identify the novel markers appropriate for risk stratification valuation.

As we moved forward, we assessed the Alpha-synuclein gene (SCNA), a well-recognized gene that plays a part in PD risk. The unacknowledged epigenetic control of SNCA expression may play a role in the presumed dysregulation of SNCA expression in PD; besides, the epigenetic changes, such as TF binding sites induced deferentially methylated CpG sites involved in hypomethylation might promote SNCA expression in the PD brain, in the inference of study that stated this; concluded that methylation of SNCA inton1 has decreased in DNA from sporadic PD patients substantia nigra, cortex and putamen, directing toward a yet unacknowledged epigenetic regulation of SNCA expression in PD[18]. Moreover, the age-dependent alterations of gene methylation may have an association with neonatal development and in the adult CNS.

As age-dependent changes of the gene have a strong association with neurodegeneration, we further evaluated the studies and results associated with genes that connect the dots between ageing and neurodegeneration, which causes age-related diseases, such as, AD and PD. Interestingly, a study described CpG sites responsible for age-associated variations in DNA methylation. They selected genes were the genes that have been previously associated with age-related methylation changes in the brain, such as, Pipecolic acid and sarcosine oxidase (PIPOX), Dipeptidyl peptidase 8 (DPP8), Rhomboid domain containing 1 (RHBDD1), Prostaglandin E receptor 3 (PTGER3), Myogenic differentiation 1 (MYOD1), Beta-1,3-

galactosyltransferase 6 (B3GALT6), Dickkopf-like acrosomal protein 1 (DKKL1), Growth arrest-specific 2 Like 3 (GAS2L3), protein-coding genes FLJ21839 and FLJ34922, outcomes were followed by the multiple testing, in which they observed substantial age-associated fluctuations in DNA methylation, the CpG sites were significant in multiple tissues and result in higher frequencies than it would perchance; this exhibits amelioration of age-associated methylation changes at CpG islands of functionally associated transcripts, moreover, it is also possible that altered epigenetic regulation at these loci may upsurge broad deviations in transcriptional potential during the ageing process, therefore, changes in specific age-related DNA methylation might have relatively sufficient influence on gene expression in the human brain[16].

Glutamate decarboxylase 1 (GAD1), Homeobox A1 (HOXA1), Neuronal differentiation 1 (NEUROD1), Progesterone receptor (PGR), serine-threonine kinase 11 (STK11) and Tyrosine-protein kinase (SYK) exhibited substantial methylation changes in 2 loci namely S100A2 and SORBS3 out of 50 loci, correspondingly, methylation in SORBS3 was relatively higher than S100A2[83]. Genes of neurodegenerative development found in the cerebral cortex and other brain regions also include Gamma-aminobutyric acid type A receptor subunit alpha 2 (GABRA2)[84]. A study by Borovecki et al., 2005 demonstrated the significant up-regulation in genetic biomarkers of HD brain, alterations of gene expression in HD blood and brain indicates that mutant huntingtin might mark the analogous targets in these tissues, interestingly, this resulted in providing a more open window through which it is possible to monitor the manifestation of HD pathogenic process[85]. These genes have been researched in REST regulatory experiments as well[86].

An epigenetic investigation also observed patients with SOD1 mutation or C9orf72 expansion, the outcomes demonstrated higher mtDNA copy numbers compared to noncarriers, however, SOD1 mutations carriers, whichever in pre-symptomatic or affected by ALS, exhibited a significant decrease in methylation levels of the mtDNA D-loop region[87].

Concerning AD, Ankyrin 1 (ANK1) and Rhomboid 5 homolog 2 (RHBDF2) connect to Protein tyrosine kinase 2 beta (PTK2B) – a chief AD gene which is crucial for modulating the activation of microglia and macrophages as well as AD genes, i.e. Siglec-3 (CD33) and Ephrin type-A receptor 1 (EPHA1) also attach to this molecule[88]. Moreover, cortex-specific hypermethylation at CpG sites in the ANK1 gene is allied with AD neuropathology[89]. Besides, extremely reproducible methylation sites of Microtubule-associated protein tau (MAPT), and beta-Amyloid protein precursor (APP) Receptor for advanced glycation end-products (RAGE), Adenosine A2a receptor (ADORA2A), Ubiquitin Carboxy-terminal hydrolase L-1 (UCHL1), with methylation state of selected loci in neurodegenerative diseases represented that even slight modifications may be enough for the modulation of diseases progression[90]. The relationship between RHBDF2 and PTK2B in ANK1 is steady with the known role of this molecule in myeloid cells, thus, exhibiting the most strong molecular associations with neurodegeneration and AD[91].

In a study of Wang et al., 2008, the most substantial interindividual changes in DNA methylation were detected in the Presenilin-1 gene (PSEN1), and Apolipoprotein E gene (APOE) promoters, both PSEN1 and APOE genes are inherently allied with late-onset Alzheimer's disease (LOAD). In PSEN1, methylation patterns were generally related to hypomethylation of the promoter, which can induce overexpression of PSEN1, that may result in an imbalance in beta-amyloid production; additionally, PSEN1 encompassed epigenetic alterations in male germ cells, these kinds of patterns may be transmitted unswervingly via germline or may be post-zygotically re-established or restored, which may contribute to diverse susceptibility to pathosis in future[92]. Furthermore, the same study described, concerning APOE, which is known as the chief susceptibility gene for LOAD in the human genome, was found to hypomethylated at CpG-poor promoter and completely methylated 39-CpG-island, including sequences for e4-haplotype – the unquestionable and only genetic risk factor for LOAD. Abnormal epigenetic control in this CpG-island may contribute to LOAD pathology[92].

Genes that are linked to neuropsychological and neurodegenerative diseases involve brain-derived neurotrophic factor (BDNF), a cellular transcription factor, cAMP response element-binding protein (CREB) and nuclear factor-kappa b (NF-kB). Both AD and bipolar disorder (BD) brains involve reduced mRNA levels of BDNF; moreover, disease-specific hypermethylation in the CREB promoter region might become a reason of aggravation reduced BDNF, besides, hypomethylation of NF-kB in the cortex of AD brain may benefit in understanding the increased neuroinflammation attributable to reduced methylation from induced upregulated NF-kB activity[93]. Furthermore, the alteration of synaptic plasticity in AD is allied with abridged protein and mRNA levels of synaptophysin; perhaps, induced by a hypermethylated state of its promoter region in AD brain. Additionally, the variance of synaptophysin methylation between AD and BD may mirror an excessively swift progression or development of AD[93].

Regarding PD, the most known genetic and epigenetic biomarkers are Falconi anemia complementation group C (FANCC) cg14115740 and Tankyrase 2 (TNKS2) cg11963436 which displayed significant differential methylation between PD cases and controls (94) using blood-derived DNA. Furthermore, a study, followed by the data available and their previous studies on 11 loci – they extracted 3 of those that reported being associated with PD risk, additionally, describing methylation and expressions changes associated with PD risk variants in PARK16/1q32, GPNMB/7p15, and STX1B/16p11 loci, henceforth, signifying potential molecular mechanisms and candidate genes at these risk loci[88,94].

Besides, the epigenomic alterations occur early in the pathologic process in these genes along with accumulated amyloid. A study by Iwata et al., 2014, observed an abnormal CpG methylation in MAPT, APP in neurons and non-neuronal cells, whereas, methylation in Glycogen synthase kinase 3 beta (GSK3B) was aberrant in non-neuronal cells only and concerning MAPT and APP; they further proposed that abnormally methylated cells could negotiation the neural circuit and/or assist as "seed cells" for uncharacteristic and abnormal protein proliferation even in a small amount of highly methylated neurons amongst normal neurons; thus, reflecting the underlying pathological process of neurodegeneration and AD[95].

Some studies explain the likelihood that REST may act as a regulator for the expression of approximately 1,200 genes, the mechanism of REST has been explained above. However, due to animal studies and other limitations, REST related speculations are not conferred in this paper. Moreover, its relationship with HD progression and potential for treatment is still unclear as well[20]. Nevertheless, transcription derived remodeling requires more trials for better epigenetic modulation and other options such as nutrition, physical activities, along with a good stress-free lifestyle can be beneficial in epigenetic regulation.

Future Approach

Epigenetic modifications in neurons are reversible, henceforth, the expectation for regulating it can be achieved in the future. Remodeling the chromatin structure can aid the regulation of gene expressions associated with synaptic plasticity during development and throughout the lifetime[96]. Epigenetic disruption has a substantial effect on the limbic system and especially on the hippocampus[97]. Clinical epigenetics would not qualify as a potential therapeutic strategy to prevent deterioration of AD, as epigenetic-based therapy could affect plentiful targets due to the lack of locus specificity[98,99], however, Berson et al., 2018 determined in a review that age-related neurodegenerative disease may accumulate overtime until repair and stress-response pathways finally collapse preceding towards irreversible neuronal damage[100]. Berson et al., 2018 also added that technologies aiming to re-establish chromatin underlying forces and gene expression might be able to offer beneficial strategies when applied appropriately. Some of the epigenetic advancements are already applied to the study of the nervous system and might provide exciting advances in our understanding of epigenetic regulation in neurodegenerative diseases in future[100]. However, there is a dread need to research in technological advancements to target locus specificity along with combine pick-out strategy of therapeutics to come up with concrete epigenetic therapy for neurodegeneration and other diseases.

Conclusion

Epigenetic modifications mediate alterations in transcriptional activity of thousands of genes, this dynamic potential of epigenetic modifications constitutes an interchange pathway for various pathological mechanisms and "caution alarm" for the development of neurodegeneration. In addition, Epigenetic changes are identified to transpire shortly after DNA synthesis and can possibly be modified by various physiological or pathological influences as well – which includes; any type of chronic stress, identified and unidentified environmental factors and co-factors, such as, micro and macronutrients, smoking, unbalanced nutrition, physical stress, etc. Henceforth, these modifications are responsible for altering gene expression for the lifetime of an organism and may continue to make changes in the offspring. A balanced stress-free environment, balanced diet, physical activities and a good lifestyle can remodel the epigenome at certain stages of neurodegeneration. Moreover, advancements in neuro-epigenetics may help regulate epigenetic modifications, however, to combat neurodegeneration, explicitly; the cognitive functions and neuronal plasticity; the requirement is to go beyond protein manipulation and discover many undiscovered epigenetic units and develop novel therapeutic targets.

Conflicts of Interest

None.

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