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Review Article

Epigenetics, oxidative stress, and Alzheimer disease

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ABSTRACT

Alzheimer disease (AD) is a progressive neurodegenerative disorder whose clinical manifestations appear in old age. The sporadic nature of 90% of AD cases, the differential susceptibility to and course of the illness, as well as the late age onset of the disease suggest that epigenetic and environmental components play a role in the etiology of late-onset AD. Animal exposure studies demonstrated that AD may begin early in life and may involve an interplay between the environment, epigenetics, and oxidative stress. Early life exposure of rodents and primates to the xenobiotic metal lead (Pb) enhanced the expression of genes associated with AD, repressed the expression of others, and increased the burden of oxidative DNA damage in the aged brain. Epigenetic mechanisms that control gene expression and promote the accumulation of oxidative DNA damage are mediated through alterations in the methylation or oxidation of CpG dinucleotides. We found that environmental influences occurring during brain development inhibit DNA-methyltransferases, thus hypomethylating promoters of genes associated with AD such as the β-amyloid precursor protein (APP). This early life imprint was sustained and triggered later in life to increase the levels of APP and amyloid-β (Aβ). Increased Aβ levels promoted the production of reactive oxygen species, which damage DNA and accelerate neurodegenerative events. Whereas AD-associated genes were overexpressed late in life, others were repressed, suggesting that these early life perturbations result in hypomethylation as well as hypermethylation of genes. The hypermethylated genes are rendered susceptible to Aβ-enhanced oxidative DNA damage because methylcytosines restrict repair of adjacent hydroxyguanosines. Although the conditions leading to early life hypo- or hypermethylation of specific genes are not known, these changes can have an impact on gene expression and imprint susceptibility to oxidative DNA damage in the aged brain.

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Introduction

Epigenetics is a major mechanism that accommodates gene-expression changes in response to gene-environment interactions [1,2]. Epigenetics refers to modifications in gene expression that are

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influenced by DNA methylation and/or chromatin structure, RNA editing, and RNA interference without any changes in DNA sequences [3]. DNA methylation and histone deacetylation are known to occur shortly after DNA synthesis and could be modified by diverse physiological or pathological factors, altering gene expression for the lifetime of the organism.

Epigenetics and mental disorders

Despite the fact that the bulk of the work in epigenetics has been developed in cancer research [4], there is recognition of epigenetic aberrations in mental illnesses, namely in fragile X disease and Rett syndrome [5–7]. Fragile X disease is associated with an expanded (>250 copies) number of hypermethylated CGG repeats 5′ of the FMR1 gene that results in downregulation of the gene [5,6]. Disease severity in fragile X is directly correlated with the extent of methylation in the 5′ region of the FMR1 gene [8]. Rett syndrome, on the other hand, is linked to mutations in the gene encoding the methylated cytosine binding protein (MECP2) [7]. The MECP2 recruits a variety of proteins that form a complex, thus repressing gene expression [9]. Both fragile X and Rett syndrome are responses to well-established alterations to a single gene. However, recent work in autism spectrum disorders suggests a major epigenetic component to the origin of the disease, indicating some contribution of differential methylation, but not to a single gene [10].

DNA methylation is one of the most studied aspects of epigenetic modifications. The addition or removal of methyl groups from cytosines can impact gene expression and alter cell and organism function. For example, hypomethylation of the membrane-bound catechol-*O*-methyltransferase gene has been implicated in both schizophrenia and bipolar disorder [11]. In contrast, hypermethylation of the RELN (reelin) gene has been shown to be associated with schizophrenia [12]. In addition to DNA methylation, other mechanisms linked to epigenetic regulation have been found to play a role in neuronal function, as demonstrated by the use of inhibitors of histone deacetylases to ameliorate deficits in a wide range of psychiatric and neurological conditions [13]. Recent research points to endogenous systems, such as the sirtuins, a group of nicotinamide-dependent deacetylases/ADP-ribosyltransferases, playing a major role in the beneficial response to longevity-extending protocols such as caloric restriction [14]; however, whether their neuroprotective effects are due to the deacetylase activity remains to be elucidated [15].

Genetics and epigenetics of Alzheimer disease

Alzheimer disease (AD) is a gradual and irreversible progressive neurodegenerative disorder that results in dementia and death. AD pathology is characterized by senile plaques and neurofibrillary tangles, combined with massive neuronal loss, mainly in the hippocampus and association regions of the neocortex. The major constituents of senile plaques are 39- to 42-amino-acid peptides, snipped from a larger protein called β-amyloid precursor protein (APP) [16–21]. Of these, the amyloid-β (Aβ) form that comprises 42 amino acids is considered the most amyloidogenic.

The majority of AD cases occur in the elderly; however, it is still unresolved whether AD is a disease of old age or whether it has earlier beginnings. Epidemiological studies have shown that people with dementia are more likely to have had low scores on intelligence tests when they were children compared to people without dementia [22]. These findings indicate that AD patients may arrive at old age with significant predisposing deficits. Some studies point to a possible role for epigenetic changes on AD etiology. AD patients are among the few that may display high homocysteine and low B12 and folate in blood, suggesting a dysregulation in the *S*-adenosylmethionine cycle required for epigenetic regulation through DNA methylation. It is worth noting that expression of APP and β-APP cleaving enzyme (BACE) genes is regulated via methylation of their promoters [23].

Furthering the possibility for an epigenetic impact in AD, structural genomics studies have demonstrated that more than 200 genes might be involved in AD pathogenesis [24]. In addition, the AD population exhibits a higher absolute genetic variation rate of 40–60% and AD patients differ in their genomic architecture from patients with other forms of dementia [24]. Between 5 and 10% of AD cases are of familial origin and involve mutations in genes associated with APP biosynthesis and proteolytic processing [25–28]. The genetics of AD have revealed that early (<60 years of age) onset AD (EOAD) is associated with APP or the presenilins, whereas the risk to develop late onset AD (LOAD) is linked to an apolipoprotein E (ApoE) polymorphism [29].

Genetics plays a major role in EOAD; however, LOAD, which represents over 90% of cases, is sporadic in nature and remains with an unexplained etiology. Twin studies often used to confirm the inheritance pattern of a disease have shown an estimated concordance well below 100% (20–80%) for AD, suggesting that LOAD is a complex non-Mendelian disease [30–32]. Prefrontal cortex and lymphocytes from AD patients were used to analyze DNA methylation patterns in genes with a potential role in AD etiology. An age-specific epigenetic drift associated with unusual methylation patters in LOAD was identified, supporting a potential role for epigenetic effects in the development of the disease [33]. Additionally, genes that are genetically associated with LOAD (PSEN1, APOE) showed the largest interindividual variance in DNA methylation, with the APOE gene exhibiting the most variably methylated sequences. APOE presented a bimodal methylation pattern, with a hypomethylated CpG-poor promoter and a fully methylated 3′-CpG island, containing the sequences for the ε4-haplotype, the only established genetic risk factor for LOAD [33]. Interestingly, the gene MTHFR, coding for methylenetetrahydrofolate reductase, showed a significant interindividual epigenetic variability. Alteration in MTHFR expression can influence homocystine levels, which may contribute to LOAD predisposition [33]. The sporadic nature of the disease, the differential susceptibility and course of illness in males and females, as well as the late age onset of the disease add to the hypothesis that epigenetic and perhaps environmental components play a role in the etiology of LOAD [33].

Role of oxidative stress in the etiology of AD

In addition to the established pathology of amyloid plaques and neurofibrillary tangles in the brain of AD sufferers, there is a growing body of evidence indicating changes in the redox status of AD brains. This is supported by findings of increased levels of oxidative damage markers in every major cellular macromolecule (proteins, lipids, and DNA) [34]. Also, alteration in the expression of antioxidant systems lends support to a role for free radical damage in AD pathology [35]. Owing to their postmitotic nature, damage to DNA in neurons could be highly detrimental to their function and viability. Guanine has the lowest oxidation potential of the DNA bases; thus, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) is the most prevalent form of oxidative base modifications produced [36–38]. Some evidence suggests that in addition to its mutagenic properties, the presence of 8-oxodG in DNA can alter binding of transcription factors and have an impact on epigenetic signaling [39,40].

Scope of this review

This review focuses on epigenetics and explores the role of the environment in the promotion of AD pathogenesis through transcriptional dysregulation of genes associated with AD. In addition to the alteration in APP and Aβ metabolism, age-related accumulation of oxidative damage is also suspected to play a role in the pathogenesis of AD. Thus, any environmental agent that significantly alters the redox