Editorial

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# Some News on Old Concepts and the Epigenetics of Alzheimer's Disease

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## Editorial

Alzheimer's disease in the most important neurodegenerative disorder worldwide and a major problem of health in developed countries, representing the 6th cause of death in the USA, with an age-adjusted death rate of 25.4 per 100,000. Its prevalence progresses with age, ranging from 1.8% at 65-69 years to 42.1% at age 95-99 years, with an annual incidence of 34.1 per 1,000 persons >60 years) [1-3]. Total costs of AD rise from €9,000 at 6 months to over €21,000 per patient 2 years later [4]. Approximately 10-20% of the total cost of dementia is due to pharmacological treatment; however, current drugs are not cost-effective and no new drugs for AD have been approved by the FDA during the past 15 years [5]. The pharmacological treatment of AD has been dominated by cholinesterase inhibitors (Tacrine, Donepezil, Rivastigmine, Galantamine) since the introduction of Tacrine in the market in 1993, based on the assumption that AD was a cholinergic deficiency caused by selective neurodegeneration of the nucleus basalis of Meynert. In the early 2000's, Memantine, a non-competitive NMDA receptor antagonist, was approved for the treatment of severe dementia. Since the identification of the disease by Alois Alzheimer in 1906, the confronted, dominant pathogenic theories of AD were the amyloidopathy and tauopathy responsible for conformational changes in the amyloid-beta (Aβ) protein and the hyperphosphorylation of the tau protein, respectively, leading to the phenotypic expression of extracellular amyloid deposits in senile plaques and the intracellular formation of neurofibrillary tangles (NFTs), as the major pathogenic hallmarks of AD [6]. The amyloid hypothesis was reinforced by the identification in 1987 of point mutations in the Amyloid Precursor Protein (APP) gene whose abnormal processing by α-, β-, and ϒ-secretases and post-transcriptional changes gives rise to the Aβ deposits [7]. Years later, other pathogenic genes were identified, such as those encoding presenilin-1 (PSEN1) and presenilin-2 (PSEN2); and at present, more than 600 different genes distributed across the human genome are believed to be associated with premature neuronal death and neurodegeneration in AD [8-10]. Among these, in the early 1990's, the late Allen Roses proposed the gene encoding apolipoprotein E (APOE) as the most important risk factor in those patients harboring the APOE-4 allele, which is involved in different pathogenic events associated with neurodegeneration and vascular dysfunction [10]. In parallel with a better understanding of AD pathogenesis in which genomic, epigenomic, metabolic, toxic, and environmental factors converge in a common pathogenic cascade of deleterious events (neuroinflammation, oxidative stress, neurotrophic deficit, proteasome dysfunction, neurotoxicity) leading to progressive neuronal death, and after repetitive failures in different clinical trials with secretase inhibitors/modulators, and especially with vaccines against Aβ deposition (active and passive immunization), the amyloid hypothesis has been challenged from many directions as a reductionist view of AD [11,12] which may still have some future [13]. In the international literature there is also a revival of the vascular component of AD and the importance of vascular dementia as the most prevalent form of dementia in patients over 75 years of age. At this moment, the major challenges posed by AD to the scientific community are the characterization of reliable biomarkers for the preclinical identification of the population at risk in order to implement preventive programs, and the discovery of effective drugs to halt disease progression at pre-symptomatic stages, assuming that the neurodegenerative process leading to AD starts 20-30 years before the onset of the disease [14].

In evolutionary terms, epigenetics is probably a brilliant interface that Nature inserted between the genome and the environmental milieu. In this context, epigenetics is a fundamental process for development, health and disease. Since AD is a disorder of

 

the most highly evolved species, it appears obvious that in the crossover of environmental risk factors and genomic defects causing AD, epigenetics may have a preponderant role. During the past decade over 500 studies have documented the potential involvement of epigenetics in AD pathogenesis [15]. Although the field of epigenetics in AD is still in its infancy, it seems very likely that alterations in the epigenetic machinery (DNA methylation, histone/chromatin modifications, miRNA regulation) may participate (as primary factors or as secondary events) in the pathogenesis of different neurodegenerative disorders, including AD [15-22]. DNA methylation (5-methylcytosine) (5mC) and DNA hydroxymethylation (5-hydroxymethylcytosine)(5hmC) are unevenly altered in AD brains. 5mC is generally associated with the inhibition of gene expression, whereas 5hmC has been associated with increased gene expression in different processes such as differentiation, development, and aging [23]. Hypermethylation of thousands of CpG sites have been observed in 485 genes associated with AD in transgenic mice [24]; however, important differences have been found between animal models and humans. Hypo- and hyper-methylated AD genes have been identified in different brain regions, reflecting tissue- and area-specific epigenetic changes, with conflicting results [16]. Histone modifications have also been reported in AD [15,18].

Over the past few years, most studies on AD epigenetics have concentrated on ncRNAs. miRNAs are deeply involved in gene expression, influencing diverse pathogenic cascades leading to neurodegeneration [20-22]. The role of miRNAs in the regulation of pathogenic genes associated with AD (APP, BACE1, MAPT, APOE), lipid metabolism, neuroinflammation, and oxidative stress has been extensively documented [18,20-22]. Inducible miRNAs exert regulatory roles in brain development, aging, and neurodegeneration. AD brains show up-regulation of several brain-enriched miRNAs that are under transcriptional control by the pro-inflammatory transcription factor NF-kB, including miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155. miRNA-125b is the most abundant and significantly induced miRNA species in human brain cells. Up-regulated miRNA-125b may target the 3'-untranslated region (3'-UTR) of the mRNA encoding a 15-lipoxygenase (ALOX15) for the conversion of docosahexaneoic acid into neuroprotectin D1 (NPD1), and the vitamin D3 receptor (VD3R) of the nuclear hormone receptor superfamily. ALOX15 and VD3R are essential factors in lipid-mediated signaling, neurotrophic support, defense against oxidative stress, and neuroprotection. miRNA-125b-induced down-regulation of LOX15 and VD3R in the AD brain may alter neurotrophic activity and oxidative stress, contributing to neuronal damage [25]. Some other examples illustrate the role of miRNAs in Aβ formation and deposition [26].

Several signatures of miRNAs have also been proposed as potential biomarkers for AD in peripheral blood [27] and/or in the cerebrospinal fluid [28].

Epigenetic intervention and epigenetic drugs may also come to rescue AD treatment from the misery in which it has remained stagnant for decades, although technical difficulties may preclude a rapid implantation of these procedures [29-33]. Pharmacoepigenetics is becoming a very attractive field, with high complexity [29,30]. The genes involved in the pharmacogenetic outcome of AD therapeutics include (i) pathogenic genes associated with AD as potential causative factors, (ii) mechanistic genes whose products participate in the mechanism of action of drugs, (iii) metabolic genes encoding Phase I and Phase II metabolic enzymes, (iv) genes encoding protein transporters, and (v) a vast array of pleiotropic genes involved in multiple metabolomic processes [14,34]. All these genes are under the regulatory control of epigenetic mechanisms, contributing to drug efficacy and safety [35,36].

Some genes may also play dual or multiple roles in the pathogenesis, diagnosis and pharmacoepigenetics of AD, such as several members of the ATP Binding Cassette Subfamily (ABCB1, ABCA2, ABCA7). For instance, the ABCA2 gene is linked to AD risk and ABCA2 mRNA expression is upregulated in AD. Methylation of 2 of 36 CpG islands in the ABCA2 gene with high diagnostic accuracy of AD were found to be negatively associated with AD risk [37]. This pleiotropic gene has also been proposed as a therapeutic target [38].

Some epigenetic drugs, alone or in combination, have demonstrated anti-amyloidotic and neuroprotective effects in AD [39]; however, conventional epigenetic drugs do not easily cross the blood-brain barrier, and their incapability of optimal brain penetration make them a distant therapeutic option in AD while nanoparticle technology is still unable to provide help in brain tissue diffusion. Additionally, gene expression regulation of transporter genes and abnormalities in epigenetic mechanisms regulating metabolic genes may also be responsible for drug resistance in cancer and brain disorders (e.g., epilepsy, depression) [40,41] in different ethnic contexts [42].

As in many other novel fields, much expectation is usually created around epigenetics and pharmacoepigenetics, in part to mitigate the frustration of repetitive failures in the obtaining of reliable biomarkers and effective drugs for AD. It is likely that part of the problem is due to the misconception of the animal models currently used in AD research. It would be wise not to replicate the same errors of the past so as not to devalue the potentiality of epigenetics in the future of AD management.

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