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Review

Alzheimer's disease in the omics era

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ABSTRACT

Recent progresses in high-throughput technologies have led to a new scenario in investigating pathologies, named the "Omics era", which integrate the opportunity to collect large amounts of data and information at the molecular and protein levels together with the development of novel computational and statistical tools that are able to analyze and filter such data. Subsequently, advances in genotyping arrays, next generation sequencing, mass spectrometry technology, and bioinformatics allowed for the simultaneous large-scale study of thousands of genes (genomics), epigenetics factors (epigenomics), RNA (transcriptomics), metabolites (metabolomics) and proteins(proteomics), with the possibility of integrating multiple types of omics data ("multi -omics"). All of these technological innovations have modified the approach to the study of complex diseases, such as Alzheimer's Disease (AD), thus representing a promising tool to investigate the relationship between several molecular pathways in AD as well as other pathologies.

This review focuses on the current knowledge on the pathology of AD, the recent findings from Omics sciences, and the challenge of the use of Big Data. We then focus on future perspectives for Omics sciences, such as the discovery of novel diagnostic biomarkers or drugs.

1. Introduction

The "-Omics" technologies attempt to investigate the global and dynamic molecular changes under different normal and pathological conditions, and thus represent a promising approach for the study of the Alzheimer's Disease (AD). Due to the inaccessibility of the human brain, Omics studies in AD patients have focused on biofluids, mainly the cerebrospinal fluid (CSF) and blood. In particular, the CSF is an attractive source of soluble brain biomarkers as it is in close contact with neurons and could reflect modifications occurring during the disease (and, hopefully, anticipating the clinical onset). Actually, the analysis of CSF amyloid-β peptide 1–42 ($A\beta_{42}$), total tau protein (T-Tau) and phosphorylated tau protein (p-tau) is a useful tool for the differential diagnosis of AD and mild cognitive impairment (MCI) of different etiologies [1, 2]. The decrease of $A\beta_{42}$ and the increase of both T-Tau and p-tau in CSF reflect the formation of amyloid plaques and neurofibrillary tangles in the brain tissue, the histological hallmarks of AD; levels of such biomarkers may be altered even in the prodromal phase of AD with MCI. However, multi-factorial factors can converge to determine the histological pathology of AD, since genetic variants, proteins, non-coding RNAs and other signaling molecules seem to contribute to the pathogenesis and the clinical expression of the disease. For a global and comprehensive knowledge of the AD etiology and pathology, -omics technologies represent a promising tool.

Advances in technologies have led to a new system of analysis, named the "Omics era", which integrates the opportunity of collecting various data and information at the molecular levels together with the simultaneous development of novel computational tools needed to analyze and filter such data. In this review, we summarize the current evidences on the pathology of AD, the recent findings from Omics studies, and the challenge of the use of Big Data. Then, we focus on future perspectives for Omics sciences, such as the discovery of novel diagnostic biomarkers or potential drugs.

2. The Alzheimer's disease

Alzheimer's is a complex multi-factorial disease, clinically characterized by cognitive impairment and late dementia, and representing one of the greatest epidemic and health challenges today. The pathological brain changes, including the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles, may begin 20–30 years before the onset of the clinical symptoms. Thereafter, the symptomatic phase of AD can last from about 5 up to 12 years [3, 4]. The only available treatments are memantine and cholinesterase inhibitors, that are able to delay the progression of symptoms but do not modify the disease process. To achieve the optimal efficacy, any

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Table 1
Causing genes associated with EOAD.

Gene	Cromos.	Frequency[a]	Function	Pathway	Test method
APP	21	10–15%	Neuronal development, Synaptic formation and repair, β-Amyloid production	APP processing	Sequence analysis; Delection/duplication
PSEN1	14	30–70%	γ-Secretase activity, Intracellular signaling, β-Amyloid production	APP processing	Sequence analysis; Delection/duplication
PSEN2	1	< 5%	γ-Secretase activity, β-Amyloid production, Synaptic plasticity	APP processing	Sequence analysis;

[a] Frequency of EOAD.

therapy should be initiated as early as possible, although early diagnosis of AD is difficult. The identification of early diagnostic and progression biomarkers, as well as novel targets for drug designs, are needed.

AD is an age-related pathology, often characterized by a late onset (LOAD), while familial cases (FAD) are due to rare mutations of amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes [5–8] (Table 1). Allele 4 of apolipoprotein E (ApoE4) represents the first risk factor in sporadic AD and can be found up to 50% in homozygous (Apo E4/E4) and 20–30% in heterozygous conditions with APOE3/E4 [9].

The “amyloid hypothesis” has represented the basis for hundreds of studies to date, and implicates the role of the $A\beta_{42}$ as neurotoxic component leading to synaptic impairment, behavioral deficits and apoptotic cell death [10]. Moreover, $A\beta_{42}$ may form soluble oligomers, which can also include post-translational modified Aβ species, and could trigger downstream events including aggregation of the tau protein and brain inflammation [11–14].

In addition to amyloid, different mechanisms including oxidative stress [15], mitochondrial dysfunction [16], metabolic alteration, and inflammation [17] are involved in the evolution and progression of the AD pathology. Moreover, several overlapping mechanisms observed in AD may be found in different co-morbidity disorders such as obesity and diabetes. For example, there is evidence that hyperglycemia, insulin resistance, increased tau levels, and increased tau hyperphosphorylation may cooperate with Aβ to induce neurodegeneration [18].

Interestingly, alteration of neuroinflammatory regulation has been hypothesized to contribute to the pathogenesis of the disease. In AD, the impairment or failure to restore the resolution phase after initiation of the inflammatory phase leads to the development of chronic inflammation, thus favoring the diffusion of neurodegeneration [17].

Despite the described complex factors, AD still has mysterious aspects and an uncontrollable process. Given the complexity of the pathogenesis of the disease, and the failure rate of clinical trial, -omics technologies may represent a promising tool to investigate the relationship between different pathways in AD and different pathologies.

3. The omics sciences

Applications of omics platforms range from the identification of genes (genomics), messenger RNA (mRNA, transcriptomics), epigenomic factors (epigenomics), to proteins (proteomics), metabolites (metabolomics) and lipids (lipidomics). Moreover, also the study of the gut microbiota (the microbiome/microbiomics) has attracted growing interest due to its association with different diseases [19]. For complex pathologies such as AD, the analysis and integration of data coming from different omics technologies is crucial for the full knowledge of the disease, thus supporting the development of personalized diagnostic and therapeutic tools. Several Omics studies have focused on novel pathways and networks, suggesting new pathologic mechanisms associated with the AD and cross-linked with other diseases.

3.1. Genomics

The actual knowledge about the cause and risk genes for AD mainly derive from different strategies genetic linkage analysis, study of candidate genes, Genome -wide association studies (GWAS), and Next-generation sequencing technologies (NGS) [20]. Genetic linkage studies on families have allowed the identification of rare mutations in genes of APP, PSEN1, and PSEN2 (Table 1) that cause dominantly inherited early-onset AD.

Research has also suggested that genetic components may affect the development of the disease in sporadic cases of AD. Thus, such genetic effects may be underestimated since the known genetic variants in AD still explain only about 33% of the heritability [21], in contrast to the estimated 60%–80% [22]. Beyond APOE, other identified genetic loci have very modest effects in influencing the risk of developing an AD dementia [21]. It is expected that gene-gene interaction may be crucial in influencing the disease risk, whereas loci with unknown effects on AD could potentially interact with each other to significantly increase the risk of developing AD [23].

Genome-wide association studies (GWAS) have become a worthwhile approach for identifying genes with common variants involved in different diseases. GWAS compare the whole genome set of genetic variants in different individuals to focus on the likelihood of associations between variants; for example, single nucleotide polymorphisms (SNPs) can be referenced against traits of major human diseases. Currently, in addition to the *APOE*, a number of regions of interest in the genome that may increase a person's risk for late-onset AD of varied significance have been identified (Table 2). Such candidate genes are involved in pathways already linked to AD, such as β-amyloid processing and clearance, immune response and inflammation (CR1, CD33, MS4A, ABCA7, EPHA1, and CLU, HLA-DRB5/HLA-DRB1, INPP5D, and MEF2C), cholesterol metabolism (APOE, SORL1, ABCA7, and CLU), regulation of endocytosis and vesicle tracking (BIN1, CD2AP, PICALM, EPHA1, SORL1), cytoskeletal function and axonal transport (NME8, CELF1, and CASS4), and other functions (PTK2B, FERMT2, SLC24H4-RIN3) (Table 2) [24, 25]. However, these top candidate risk genes are not associated with clinical phenotypes, disease status, or age-at onset [26]. To better understand the gap between our knowledge and the pathogenesis of AD, numerous studies have stressed the role of gene-gene interaction. In particular, interactions have been described between variants in the proinflammatory cytokine genes IL-6 and IL-10 [27], the dopamine beta-hydroxylase gene with each of the two cytokine genes IL-1A and IL-6 [28, 29], or between variants in the transferrin and the hemochromatosis genes [30, 31].

Moreover, investigating the relationships between defective genes and molecular mechanisms involved in different pathologies may provide novel insights into the comprehension of potential sharing genetic mechanisms underlying different diseases. Similar alterations of the PI3K-AKT signaling pathway, related to the impairment of neuronal transport, calcium homeostasis, mechanisms of endocytosis, processing of APP, increased oxidative stress, mitochondrial dysfunction, and neuroinflammation, were found in AD, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease (PD) [32].

Additionally, the interaction of different genes may influence the