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Review

Translational proteomics in Alzheimer's disease and related disorders

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ABSTRACT

Alzheimer's disease (AD) and its related syndromes – especially frontotemporal dementia (FTD), Lewy body dementia (LBD) and dementias associated with cerebrovascular disease – are the principal causes of dementia. Until a recent period, the diagnosis of AD and its related disorders relied almost exclusively on the combination of a neurological examination and the use neuropsychological tests. Cerebrospinal fluid (CSF) dosage of neuropathologically AD-associated proteins has already been incorporated into the neurochemical diagnosis of AD, attesting the relevance of translational research. The analysis of the human proteome has made considerable advances in the last years and is prepared to overcome several obstacles for its routine application.

In this review we discuss i) how biomarkers are modernizing the diagnosis of AD and related disorders, ii) the different sources of samples used for clinically oriented analysis highlighting the different challenges and approaches associated with these iii) studies investigating changes in circulating proteome in subjects at risk for dementia. There is urgent need for more large-scale longitudinal studies to establish the analytical and global proteome intraindividual variability for contemporary proteomics platforms. In addition, combing proteomics and endophenotypes such as imaging or other biomarkers is of paramount importance.

Contents

Introduction

Alzheimer's disease (AD) and its related syndromes – especially frontotemporal dementia (FTD), Lewy body dementia (LBD) and dementias associated with cerebrovascular disease – are the principal causes of dementia [1–3]. AD is morphologically characterized by extracellular beta-amyloid (Aβ) plaque deposition, intraneuronal tau-pathology, neuronal cell death, vascular dysfunction and inflammatory processes. Accurate, early diagnosis of AD is still difficult because early

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; APO, apolipoprotein; APP, amyloid precursor protein; 11C-PiB PET, positron emission tomography tracer (11)C-labeled Pittsburgh Compound-B; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GRN, progranulin; LBD, Lewy body dementia; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; MCI, Mild cognitive impairment; MS, mass spectrometry; PET, positron emission tomography; PSEN, presenilin; PZP, pregnancy zone protein; SELDI-TOF, surface-enhanced laser desorption and ionization time-of-flight; TDP-43, TAR DNA-binding protein 43.

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symptoms of the disease are shared by a variety of disorders, reflecting common neuropathological features. In ageing people, a memory complaint is frequently observed but is not necessarily associated with a decline of the cognitive abilities. These complaints can just as well be an indicator of mild isolated troubles as an early sign of objective cognitive dysfunctions and thus potential marker of a preclinical dementia. The concept of mild cognitive impairment (MCI) has received increasing attention in recent years, particularly as a possible prodromal stage of dementia: many patients with MCI display the same morphological changes as AD patients and the annual rate of AD diagnosis for patients with MCI is 10% to 15% [4–6]. Expanding knowledge on genetic and epigenetic risk factors is rapidly enhancing our understanding of the complex molecular interactions and systems involved in the pathogenesis of AD and related dementias. Genome sequencing has enabled us to acquire a vast amount of data and this has accelerated the discovery of biological rules at the genome level. In comparison with the genome and also transcriptome, the proteome is more dynamic and diverse in composition, modification, interaction, and localization. Similar to genomic research, the proteomics field has tended to concentrate first on candidate studies and is increasingly moving towards larger-scale, multianalyte studies. Until a recent period, the diagnosis of AD and its related disorders relied almost exclusively on the combination of a neurological examination and the use neuropsychological tests. Cerebrospinal fluid (CSF) dosage of neuropathologically AD-associated proteins has already been incorporated into the neurochemical diagnosis of AD, attesting the relevance of translational research. There is an urgent need for suitable biomarkers to improve diagnostic tools and treatment in various neurodegenerative diseases. Biomarker discovery is an application of major importance in today's proteomic research. Recent years have witnessed an enormous interest in proteomics, which is currently seen as an invaluable tool to shed more light on complex interacting signaling pathways and molecular networks involved in several neuropathological conditions. In this review, we will discuss advances in the development of biomarkers that will not only improve the accuracy of diagnostic technologies but also improve the prospects of developing disease-modifying interventions.

How current biomarkers are modernizing the diagnosis of Alzheimer's disease and related disorders

The criteria for the clinical diagnosis of AD were established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984 [7]. However, in the intervening 27 years, important advances in our understanding of AD, in our ability to detect the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease have occurred [8,9]. The translational development of AD biomarkers may be theoretically achieved via two different strategies: the first strategy can be defined as "knowledge-based," while the second one is hypothesis-generating "unbiased" approach. The "knowledge-based" approach relies on a direct understanding of the neuropathological processes that underlie the development of AD. One of the main histological findings in AD is the intracellular accumulation of neurofibrillary tangles composed of an abnormally phosphorylated form of tau protein [10]. Hyperphosphorylation of tau protein results in neuronal degeneration through deleterious effects on axonal transport mechanisms and cell shape. The accumulation of extracellular senile plaques comprised of aggregated Aβ peptides is a further pathohistological feature in AD [11]. These biological observations naturally led to first propose Aβ peptides and tau proteins as potential biomarkers for AD. The three major alterations in AD brain (i.e. amyloid plaques, axonal degeneration and intraneuronal tangles) can be monitored with the CSF biomarkers Aβ1-42, total-tau and phosphorylated tau respectively. The revised diagnostic criteria proposed in 2011 by the National Institute of Aging and the Alzheimer's Association workgroup include the incorporation of biomarkers of the underlying disease state and formalization of different stages of disease – "preclinical AD," "mild cognitive impairment (MCI) due to AD" and "AD dementia" – in the diagnostic criteria [12–14]. Reconstruction of biomarker trajectories is central to understanding the sequence of events at the molecular, cellular, tissue and organ level that finally lead to cognitive symptoms. The onset and progression of AD biomarkers likely follows an ordered temporal pattern. Biomarkers of Aβ amyloid are indicative of initiating or upstream events before clinical symptoms. Biomarkers of neuronal injury and dysfunction are indicative of downstream pathophysiological processes which emerge later. There is evidence suggesting that combined assessment of tau and Aβ measurements in CSF can improve the translational value of these biochemical assays [15].

They may also be used to identify AD before onset of dementia at the stage of MCI, as shown in both mono-center and large-scale heterogeneous multicenter studies [16–20]. Aβ1-42 is associated with impairment of cognitive function from a potentially early to a later disease phase [21–23]. Of note, i) decreased CSF Aβ1-42 and high levels of total tau are also seen in other neurodegenerative disorders [24,25], ii) measured biomarker CSF levels differ greatly between studies and the diagnostic accuracy varies significantly [26,27]. These variations could be the result of preanalytical, analytical, or manufacturing processes that affect assay-related factors [28–30].

The criteria for the clinical diagnosis of FTD were established in 1998 by Neary et al. [31]. Intervention at an early (ideally, presymptomatic) stage of disease holds the greatest promise for prevention of irreversible brain tissue destruction in neurodegenerative diseases. The best prospect of achieving this lies with FTD, where up to half of all patients have a family history of the disease and thus a genetically mediated pathology: in these cases, carrier status can potentially be diagnosed and at-risk individuals followed many years prior to clinical conversion. Up to date, seven disease causing genes have been identified [32–34], including progranulin gene (GRN) [35–37]. Recent advances in this field prompt scientists to review and revise the existing criteria for FTD incorporating the presence of pathogenic mutations in the diagnosis of FTD with definite frontotemporal lobar degeneration (FTLD) pathology [38,39]. All GRN mutations identified thus far cause disease through a uniform disease mechanism, i.e., the loss of functional progranulin or haploinsufficiency [40]. Although molecular genetic mutation screening is still the method of choice to definitely detect GRN pathogenic mutations, this technique is only performed in specialized genetic centers upon referral. GRN mutations are associated with a strong reduction of circulating progranulin protein. Thus, the principle of progranulin protein as a biomarker is straightforward and is based on the haploinsufficiency mechanism. Recently, the dosage of circulating progranulin has been proposed as a useful tool for a quick and inexpensive large-scale screening of affected and unaffected carriers of GRN mutations [41–44]. Before it is systematically translated into clinical practice and, more importantly, included into diagnostic criteria for dementias, further standardization of plasma progranulin test and harmonization of its use are required. Once a specific treatment becomes available for these pathologies, this test – being applicable on large scale – will represent an important step towards personalized healthcare.

Proteins and space: circulating disease markers

The analysis of the human proteome has made considerable advances in the last years and is prepared to overcome several obstacles for its routine application. We will therefore review the different sources of samples used for clinically oriented analysis and attempt to highlight the different challenges and approaches associated with these.