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Blood and plasma-based proteomic biomarker research in Alzheimer's disease

Simone Lista [a,*], Frank Faltraco [a], David Prvulovic [b], Harald Hampel [a]

[a] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe-University of Frankfurt, Frankfurt am Main, Germany
[b] Labor für Neurophysiologie und Neuroimaging, Institutsambulanz (Gedächtnissprechstunde), Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Johann Wolfgang Goethe-Universität Frankfurt, Heinrich-Hoffmann-Str. 10, D-60528 Frankfurt, Deutschland, Germany

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ABSTRACT

Alzheimer's disease (AD) is the most important cause of dementia in the elderly. The molecular alterations preceding this neurodegenerative pathology may take place even 20 years before its clinical appearance. In this context, the discovery of biomarkers in biological fluids enabling an early presymptomatic diagnosis as well as discrimination from other types of dementia is eagerly awaited. In particular, since the traditional markers obtained both from cerebrospinal fluid inspection and neuroimaging approaches have not achieved a broad clinical application, research efforts have been focused on the development and validation of biomarkers in blood. The benefit of searching for blood-based candidate biomarkers is evident due to the easiness and non-invasiveness nature of blood samples collection compared with any other body fluid. As a result, blood may constitute a rich source of disease biomarkers. Interestingly, among the technological platforms used to perform research into the biomarker discovery arena, proteomics has attained more recent consideration. In the present review, we provide a comprehensive assessment of patterns of biomarkers detected in plasma and serum specimens for the diagnosis of AD by employing proteomic approaches. Currently, growing evidence suggests that blood protein signatures are helpful to increase the likelihood of successful diagnosis of AD. Accordingly, this area of research promises to yield exciting results in the next future.

Contents

Abbreviations: AD, Alzheimer's disease; ApoA-I, apolipoprotein A-I; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; EMA, European Medicines Agency; ESI, electrospray ionization; F2-IsoPs, F2-isoprostanes; FDA, Food and Drug Administration; GC, gas chromatography; HCs, healthy controls; HPLC, high-performance liquid chromatography; HUPO, Human Proteome Organization; HUPO BPP, HUPO Brain Proteome Project; HUPO PPP, HUPO Plasma Proteome Project; ICAT, isotope coded affinity tags; iTRAQ, isobaric tags for relative and absolute quantitation; LC, liquid chromatography; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; *m/z*, mass-to-charge ratio; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; MCI, mild cognitive impairment; MS/MS, tandem mass spectrometry; NFTs, neurofibrillary tangles; PET, positron emission tomography; PiB, Pittsburgh Compound B; p-tau, hyperphosphorylated tau; PTMs, post-translational modifications; SELDI-TOF, surfaced-enhanced laser desorption/ionization time-of-flight; t-tau, total tau; 2D-PAGE, two-dimensional polyacrylamide gel electrophoresis.

* Corresponding author at: Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Johann Wolfgang Goethe-University, Heinrich-Hoffmann-Str. 10, D-60528 Frankfurt am Main, Germany. Tel.: +49 152 51904006; fax: +49 69 6301 3833.
E-mail address: slista@libero.it (S. Lista).

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1. Introduction

Alzheimer's disease (AD) – the main cause of dementia in the elderly – results in extracellular beta-amyloid (Aβ) plaques deposition and hyperphosphorylation of tau protein with formation of neurofibrillary tangles (NFTs). These modifications lead to neuronal cell death, vascular dysfunction, and inflammatory processes (Blennow et al., 2006). AD diagnosis is time-consuming and challenging, particularly for physicians who lack dedicated training in this area, since it involves the integration of psychological tests, imaging technologies, and exclusion of other neurological pathologies. This problem is aggravated in patients coming from rural communities and lower socio-economic background, who may not easily obtain access to state of the art diagnostic methods for AD such as imaging or other systems existing in university research settings, which amplify the sensitivity and reliability of AD diagnosis. Actually, recent investigations indicate that about two-thirds of dementia cases may be undiagnosed (Ho et al., 2010). It is estimated that the first AD-typical molecular alterations may occur in subjects even several decades years before the manifestation of clinical symptoms of dementia. Thus, owing to the long duration of such an asymptomatic phase, during which pathophysiological mechanisms are building up, it is of paramount significance to detect biological markers reproducing accurately features of AD pathophysiology, before the expression of dementia (Sperling et al., 2011). Accordingly, new diagnostic criteria for AD have recently been proposed, which define pre-dementia stages (''prodromal AD'' (Dubois et al., 2010, 2007)); Mild Cognitive Impairment (MCI) due to AD (Albert et al., 2011) and even presymptomatic stages of AD (''asymptomatic AD'' (Sperling et al., 2011), ''asymptomatic at-risk for AD'' (Dubois et al., 2010, 2007)). These new diagnostic concepts are necessary prerequisites and legitimation for prevention and early intervention trials in AD and may help to identify early preclinical stages which might be more responsive to potential disease-modifying therapies than later clinical stages of AD.

In recent years, progresses in the use of biomarkers have aroused a significant interest of regulatory agencies throughout the globe. In Europe and the US, the use of biomarker methods is a high priority on the work programs and listings both of the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (Broich et al., 2011). In particular, the Biomarkers Definitions Working Group of the US National Institutes of Health (2001) described a biological marker as an objectively measured feature that is assessed as an indicator of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention. Such biomarkers should be reliable, non-invasive, simple to perform, inexpensive, and employed to exactly categorize the population in line with the disease (Schneider et al., 2009).

Advances in the knowledge of the natural history of AD might have a central function in determining the real efficacy of new drugs: the early diagnosis of AD in association with new classes of disease-modifying drugs may slow down the neurodegenerative traits of the pathology. Unfortunately, an accurate, early diagnosis of AD is still difficult because early symptoms are shared by various disorders, reflecting common neuropathological properties.

The levels of amyloid β peptide 42 ($A\beta_{1\text{-}42}$), total tau (t-tau) protein, and hyperphosphorylated tau (p-tau) protein in cerebrospinal fluid (CSF) have been comprehensively investigated and have shown strong association with clinical AD (Shoji, 2002; Shoji et al., 2002). In particular, $A\beta_{1\text{-}42}$, t-tau, and p-tau measurement in CSF of AD patients, as well as individuals with other dementing pathologies and normal elderly controls emphasized sensitivity and specificity levels between 80% and 90% to identify AD versus normal elderly (Blennow et al., 2010; Hampel et al., 2008). Moreover, CSF amounts of $A\beta_{1\text{-}42}$, t-tau, and p-tau were described to be able to discriminate between those subjects with MCI who are likely to develop AD (MCI-AD) and those who do not convert (MCI-MCI) (Hampel et al., 2008; Mattsson et al., 2009). At the present time, these CSF markers represent one of the best validated diagnostic biomarkers of AD. Nevertheless, lumbar puncture, the procedure required to collect CSF samples, is still considered in several countries a relatively invasive practice that may cause patient discomfort and present some side effects such as the post-lumbar puncture headache (De Almeida et al., 2011). Despite the fact that large numbers of studies show marginal incidence of lumbar puncture associated headaches and virtually non-existent further neurological or clinical complications in a memory clinic setting (Zetterberg et al., 2010), CSF sampling still suffers from a negative public reputation, accompanied by high rates of reservation among patients (Schneider et al., 2009).

Similarly, some radiolabeled ligands, with the capability of binding to fibrillar Aβ deposits in the brain, have been expansively studied. Up to now, the most commonly utilized amyloid tracer is the ''Pittsburgh Compound B'' (PiB) (Herholz and Ebmeier, 2011; Prvulovic and Hampel, 2011). Positron emission tomography using PiB (PiB-PET) can be employed as a tool for monitoring changes in the Aβ plaque burden (Klunk et al., 2003). Interestingly, post-mortem autopsy studies disclosed an important correlation between PiB binding and histological Aβ plaque load (Bacskai et al., 2007; Ikonomovic et al., 2008). Unfortunately, a major drawback is the fact that PiB is radiolabeled using the ^{11}C isotope, which has an extremely short half-life time (about 20 min), making PiB-PET technology bulky, uncomfortable and expensive. As a result, the use of this imaging modality in primary healthcare settings and in routine screening of individuals at risk of AD currently appears to be impractical (Ho et al., 2010; Klunk and Mathis, 2008).

Given that, to date, the recognized and traditional biological markers obtained from both CSF examination and neuroimaging approaches have not achieved an extensive clinical application, research efforts have been focused, ultimately, on the development and validation of biomarkers in blood, plasma, or serum (Schneider et al., 2009).

Blood is considered a complex liquid tissue that encompasses cells and extracellular fluid. It comprises, as a source for biomarkers, a number of dissimilar molecules. Proteins, nucleic acids, lipids, and other metabolic products can be observed in plasma, serum, and cellular compartments. The latter includes erythrocytes, leucocytes, and platelets, separated either crude (e.g., buffy coat after density gradient centrifugation) or isolated by flow cytometry into distinct cell subsets. Given the existence of different unique compartments, the variety of potential candidate biomarkers in blood is significant and may embrace: protein concentrations, protein isoforms, and post-translational modifications (PTMs); a vast group of metabolic products (such as lipids and