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Review

Cerebrospinal fluid proteomics in multiple sclerosis ☆

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ABSTRACT

Multiple sclerosis (MS) is an immune mediated chronic inflammatory disease of the central nervous system usually initiated during young adulthood, affecting approximately 2.5 million people worldwide. There is currently no cure for MS, but disease modifying treatment has become increasingly more effective, especially when started in the first phase of the disease. The disease course and prognosis are often unpredictable and it can be challenging to determine an early diagnosis. The detection of novel biomarkers to understand more of the disease mechanism, facilitate early diagnosis, predict disease progression, and find treatment targets would be very attractive. Over the last decade there has been an increasing effort toward finding such biomarker candidates. One promising strategy has been to use state-of-the-art quantitative proteomics approaches to compare the cerebrospinal fluid (CSF) proteome between MS and control patients or between different subgroups of MS. In this review we summarize and discuss the status of CSF proteomics in MS, including the latest findings with a focus on the last five years. This article is part of a Special Issue entitled: Neuroproteomics: Applications in Neuroscience and Neurology.

1. Introduction

Proteomics has evolved continuously over the last decade, including developments in sample preparation, fractionation strategies, instrumentation, and bioinformatics [1]. This has led to the possibility to include larger number of samples in the experiments, improve the quantitation accuracy, and increase the number of proteins monitored and quantified. Due to this development it has become increasingly attractive to analyze clinical samples, including body fluids, in the search for biomarker candidates for various diseases.

In disorders affecting the central nervous system (CNS), like multiple sclerosis (MS) and Alzheimer's disease (AD), cerebrospinal fluid (CSF) has been the body fluid of choice for the proteomics-based discovery of disease-related CNS changes. Proteins or peptides that are released from the cells of the CNS tissue can be found in the CSF [2] and reflect the disease pathology. When a protein/proteoform has an altered concentration as a result of CNS pathology, these proteins might serve as biomarkers for the disease and these biomarkers could potentially be detected through proteomics studies.

MS is a heterogeneous and complex disease with largely unknown disease course and prognosis, and there is today no single symptom, sign or test that provides a diagnosis of MS. Clinicians would benefit from specific biomarkers in MS to facilitate early diagnosis since the treatments available are most efficient in the early phase [3]. In addition, biomarkers to predict and monitor disease progression and treatment effects would be attractive to discover. All these categories of biomarkers will potentially provide information about the disease pathogenesis, thus unraveling potential treatment targets.

In the following, the mass spectrometry based proteomics work on CSF that relates to discovering proteins altered by MS will be summarized, with focus on the work published the last five years.

Abbreviations: AD, Alzheimer's disease; ApoD, apolipoprotein D; BBB, blood–brain barrier; BCSFB, blood–CSF barrier; BCNSB, blood–CNS barrier; CHI3L1, chitinase-3-like protein 1; CIS, clinical isolated syndrome; CNS, central nervous system; CP, choroid plexus; CSF, cerebrospinal fluid; EAE, experimental autoimmune/allergic encephalomyelitis; ELISA, enzyme-linked immunosorbent assay; HC, healthy control; LP, lumbar puncture; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal bands; OIND, other inflammatory neurological disease; OND, other neurological disease; PJ1, protein jagged-1; PPMS, primary-progressive MS; PRMS, progressive-relapsing MS; RCG, rostro-caudal gradient; RRMS, relapsing-remitting MS; SC, symptomatic control; SID, stable-isotope dilution; SPMS, secondary-progressive MS; SRM, selected reaction monitoring; VDB, vitamin D-binding protein

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2. Cerebrospinal fluid

2.1. Production of human CSF (CSF hydrodynamics)

There are mainly two barriers that regulate the traffic of solutes between blood and the brain or the spinal cord; the blood-brain barrier (BBB) which is made up of tight junction epithelia tissue in brain micro-vessels separating the blood from the brain, and the blood-CSF barrier (BCSFB) made up of fenestrated epithelia cells found primarily in the choroid plexus (CP) where the BCSFB is quantitatively leakier than those of the BBB [4]. A common name for the two types of barriers is the blood-CNS barrier (BCNSB).

Although the formation of CSF is still insufficiently understood it is generally accepted that 80% of the CSF is primarily produced by the CP and the remaining 20% comes from extrachoroidal sources such as the brain ependyma and parenchyma [5]. The endothelium of the CP capillaries makes up the first stage in CSF formation where a hydrostatic ultrafiltration of plasma through the endothelium occurs. This ultrafiltrate is subsequently secreted as CSF by the CP epithelial cells in an active and energy consuming secretion process creating a pulsating production. This is a unidirectional process due to polarized expression of membrane transport proteins in the apical and basolateral membrane of the epithelial cells in the CP [6]. The production rate of CSF is age dependent and estimated to be approximately 500 mL/day at a rate of 0.2–0.4 mL/min with a total volume of 150 mL in adults [7,8]. Thus the turnover rate is high, and the common description of CSF circulation implies a unidirectional flow from the CP to the subarachnoid space toward the arachnoid villi [9,10]. Direct reabsorption of CSF into blood takes place at arachnoid villi, where the CSF is introduced to the venous blood [11,12]. This description is however a simplified version and is reviewed in [2].

2.2. Protein content of human CSF

Two of the main differences between blood and CSF are the cellular composition and the total protein concentration. CSF contains about 5 cells/μL and the protein amount in CSF is about 200 times lower than in plasma [13,14]. The proteins found in CSF can be grouped according to their site of origin; proteins transferred from plasma, proteins produced in the CNS and proteins that are synthesized locally by the tissue surrounding the CSF containing lumen (the leptomeninges). About 80% of the total protein amount in normal CSF originates from plasma as a result of filtration across the cells constituting the BCNSB [15–18]. The main contributing protein is albumin, constituting 35–80% of the total protein concentration [14,16,19]. The remaining 20% of the CSF proteins are brain derived and are typically found in higher concentrations in CSF compared to plasma [15,17]. The albumin quotient between plasma and CSF (CSF / serum albumin quotient — Q_{Alb}) can therefore be a good tool to assess the BCNSB function as albumin is only synthesized in the liver and therefore exclusively originates from blood [14]. Increased Q_{Alb} indicate higher influx of albumin (and proteins in general [20]) from blood across the BCNSB to CSF, suggesting a BCNSB dysfunction [18].

An important factor that also contributes to the CSF proteome is the absorption of CSF and proteins found in CSF into venous blood [21]. The production of proteins in the CNS, their transport to the CSF and their reabsorption to venous blood are highly regulated processes and disturbances in these processes are found in neurological diseases such as AD, Creuzfeldt–Jakob disease, Parkinson's disease and frontotemporal dementia [22]. An increased concentration of CNS proteins in CSF can be caused by both an increased production in the CNS and/or a reduced absorption to the venous blood [22,23]. Accumulation of the proteins can cause changes to the CSF proteome that are linked to pathological conditions.

2.3. CSF proteome mapping studies

Several studies have aimed at mapping the protein content of CSF [24–34]. Some studies have a general global proteome mapping approach, while other studies have targeted specific disease groups or subproteomes. Schutzer and colleagues published in 2010 a comprehensive CSF proteome mapping study identifying 2630 proteins in CSF from healthy donors and compared these to other mapping studies in plasma [34]. The most recent and extensive mapping of proteins in neurologically healthy CSF, was published by our group in 2014, and included several proteomics approaches to cover a broad range of the CSF proteome [35]. Applying extensive fractionation tools on both protein and peptide level, in addition to glycopeptide enrichment, resulted in the identification of over 3000 proteins in CSF. The overlap between the Schutzer [34] and Guldbrandsen [35] study was almost 1500 proteins, while both of them identified hundreds of unique proteins. This demonstrates that the choice of analytical approach influences the proteins identified, and that combining various approaches could lead to identifying a larger portion of the CSF proteome.

2.4. Factors that affect the CSF proteome

There are several factors that affect the CSF production and composition. To reduce the influence of such factors, a consensus protocol giving important guidelines for CSF collection was published in 2011 by the BioMS*eu* consortium [36]. We will discuss some of the factors that influence the CSF proteome and thus are important to be aware of during a proteomics biomarker discovery study.

2.4.1. Age

Age related concentration changes of several proteins in CSF have been well documented [37–39]. Generally, the protein concentration of CSF increases with age [40]. It is debated whether this is due to a reduction in the BBB integrity or a reduction of the CSF turn-over rate. Reiber suggests that the increase in protein concentration found in CSF from elderly patients is an effect of a slower CSF turn-over rate due to reduced capacity of the CPs to produce CSF [17,19,41]. The lower turn-over rate gives time to increased diffusion of plasma proteins into the CSF [17,19]. With respect to the origin of proteins and age related effect, Chen et al. investigated how age affected proteins from CP, brain and plasma and found an increase in plasma derived proteins and a decrease in brain and CP-derived proteins when corrected for age-specific CSF turn-over [42]. This can lead to the discovery of age- rather than disease-specific changes to the proteome and underlines the necessity to match patient and control samples by age.

2.4.2. Circadian rhythm

The fluctuation in CSF production during a ~24 h period has been studied in order to decipher the circadian effect on protein expression in CSF. The circadian rhythm influences the production and absorption of CSF with a peak flow during the night [13,43,44]. The studies of protein expression as a consequence of the circadian rhythm are dual, with reports of no impact [45,46] to significant regulation in protein concentration during the circadian rhythm [47,48] dependent on the proteins that have been measured. To our knowledge there is no large scale study of the proteome changes in CSF due to the circadian rhythm. CSF used for biomarker discovery studies should ideally be withdrawn at the same time of the day [13,33], but since this can be difficult to establish in clinical practice, recoding the time of lumbar puncture (LP) is necessary [36].

2.4.3. Gender

The sex related changes of the CSF proteome is not well studied. The brain derived protein S100B was reported to be differentially expressed between male and female [49] and the density of the CSF (as a function of glucose and protein concentration) was found to be gender dependent [50]. Whether or not gender affects the CSF proteome should be further investigated in order to pinpoint the importance of gender matching of patient and control groups.