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Proteomics Analysis Moves the Needle by Generating Clinical Diagnostic Markers

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Multiple sclerosis (MS) is a very heterogeneous disease, in terms of clinical presentation, rate of progression, and response to therapy. Unfortunately, there is a paucity of fluid biomarkers in MS, which might reflect a past period of relative absence of use of CSF biomarkers for diagnosis of MS, limiting CSF availability for research. However, nowadays, the use of oligoclonal band analysis and kappa free light chain analysis is underscored. This stimulates research to identify biomarkers in body fluids, which have the benefit over imaging by reflecting ongoing pathologic processes nearly at real time. Blood is a noninvasive matrix, and blood markers such NfL and GFAP have a proven correlation with disease progression, but for biomarker discovery, CSF is the matrix of choice because it adds specificity being in intricate connection with the brain tissue. In this issue of *Neurology® Neuroimmunology and Neuroinflammation*, Hinsinger et al.[1] describe a series of experiments aimed at the identification of novel CSF biomarkers for MS, which led to the validation of several novel candidate biomarkers, such as CERC1 and CD138 as biomarkers for MS diagnosis. For this, they applied label-free mass spectrometry proteomics, in several cohorts and in an animal model. A first data set was derived from CSF of controls, patients with RRMS, and CIS patients slowly converting to RRMS, and fast converting CIS patients (n = 10 each group). Given the key importance of oligodendrocyte dysfunction in MS pathogenesis, a second data set was obtained in vitro from cell culture supernatants of rat oligodendrocyte precursors that were exposed to agents mimicking MS inflammatory and apoptotic processes. They selected proteins with differential expression from each of the proteomics analysis and next added several markers from a literature search for proteins related to MS pathology, of which most had not been studied yet as CSF biomarkers for MS. This led to a total list of 87 proteins, for which they developed parallel reaction monitoring assays for further validation in additional cohorts consisting of up to 15 patients per group: CIS fast or slow converters, RRMS, controls, but now also including patients with progressive MS (PMS) and noninflammatory and inflammatory neurologic disease controls. All mass spectrometry experiments were well performed and included appropriate internal controls, technological replicates, and correlation analysis of the parallel reaction monitoring findings to those in the discovery analysis, adding confidence to their findings. Several previously identified biomarkers were thus validated, such as CH3L1, IgG kappa chain C region, CD27, but also new ones were identified such as CERC1 and CD138. For validation of the relation with MS pathology, they performed immunostainings of CD138 in MS lesions from 2 patients with MS and observed expression in plasmablasts, probably blood-derived, and in primary cultured oligodendrocytes, but not in astrocytes.

CD138 is a cell surface proteoglycan bearing heparan and chondroitin sulfates that links the cytoskeleton to the extracellular matrix[2] and is a receptor for CH3L1.[3] CH3L1 had been identified before in MS CSF[4] but also in dementia types, such as FTD.[5] The function was largely unknown, and expression in FTD brain tissue was low and mostly confined to the blood vessels, which was puzzling and did not provide insight into how the validated increase of CH3L1 in CSF relates to brain pathology.[6] The findings of Hinsinger similarly show low expression of CH3L1 in neuronal cells, yet higher expression in plasmablasts, and no overlap

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between CH3L1 and CD138 expression in MS tissue of the 2 studied patients. The CH3L1-CD138 connection thus appears important for MS and could be a potential therapeutic target, but clearly needs to be studied further. The dual actions, proinflammatory vs protective in EAE models, also warrant further study.

All in all, this is an elaborate and intriguing study, and because of the multistep validations, the results are convincing. Despite the low cohort sizes, the magnitudes of changes and high areas under the curve provide confidence. For example, CERC1 and CD138 CSF levels were approximately 3-fold higher in patients with RRMS compared with controls. Moreover, the fact that ELISA assays were available for CD27, CHI3L1, and CD138, with results correlating with the mass spectrometry, should help further validation and working toward implementation because immunoassay is the cornerstone for protein analysis in clinical laboratory medicine. The specificity of CD138 elevations in patients with MS compared with patients with other inflammatory neurologic disorders or controls[7] suggests that it has added diagnostic value compared with oligoclonal bands and kappa free light chains, although it needs direct comparison in future studies.

This study has some limitations. Clearly, the sample size, including a maximum of 15 patients per group, and only 2 MS brains call for larger studies. Key open questions are thus large-scale validation; comparison of the diagnostic value of the novel markers with those of oligoclonal bands or with kappa free light chains; relation with progression for CD138, which was the only marker found elevated in PMS as well; and age relationship because patients with PMS within this study were about a decade older than the other patients with MS. Moreover, it would be interesting to apply the study design by measuring the neuronal secretome because axonal damage is the likely substrate of disease progression in MS, and markers for disease progression are strongly needed for MS.

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