VIEW POINTS
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Complement Regulator Factor H in Multiple Sclerosis

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ABSTRACT

A recent proteomic study published in this journal demonstrated lower cerebrospinal fluid (CSF) expression of factor H (fH), an important complement regulator, along with two other complement proteins, in active multiple sclerosis (MS) patients. We have previously demonstrated raised serum fH levels in MS and here, an extended analysis, quantifying fH in CSF, demonstrates no change in fH levels in active disease, but significantly raised levels in progressive disease. These findings support our previous work showing raised serum fH in patients with progressive MS, and our results predict that CSF fH levels will be raised rather than reduced in active disease. J. Cell. Biochem. 112: 2653–2654, 2011.

KEY WORDS: MULTIPLE SCLEROSIS; BIOMARKER; COMPLEMENT; FACTOR H

The recent paper by Li et al. [2011] published in this journal demonstrated altered expression of three complement proteins, including factor H (fH), in pooled cerebrospinal fluid (CSF) from 12 patients with active multiple sclerosis (MS) compared to 12 patients with other unspecified neurological diseases. This timely data adds to the growing evidence implicating complement in active disease.

FH is an important regulator of the alternative pathway of complement, binding to fragments of C3b and regulating formation of C3 and C5 convertases. It comprises 20 structural units called short consensus repeats (SCRs) arranged in tandem. The splice variant fH-like-1 (fHL-1) comprises the first seven SCRs of fH and a short, unique C-terminal peptide and is readily detectable in plasma. Several fH-related proteins (fHR-1 to fHR-5) are also present in plasma at much lower concentrations. Deficiency of fH causes unregulated fluid phase activation of complement with secondary deficiency that predisposes to infection.

A previous proteomic study by Finehout et al. [2005] compared four complement proteins (C3, C4b, factor B (fB), and fH) on two-dimensional electrophoresis gels of CSF from normal subjects (n = 9) and patients diagnosed with Alzheimer's disease (n = 9), Parkinson's disease (n = 10), MS (n = 3), and neurosyphilis (n = 3). They showed a lower vol% of all four proteins in MS patients compared with normal subjects although this was only significant for one isoform of factor fB and fH. This contrasts with the study by Li et al. which showed higher levels of C4b and lower levels of fH, but may relate to differential disease phase sampling.

We have previously examined fH in MS patients serum and CSF [Ingram et al., 2010], demonstrating in a quantitative assay raised serum levels of fH in MS (n = 350) compared to normal subjects (n = 86). There were also significantly higher levels of fH in patients in active relapse and progressive disease compared to patients with stable relapsing MS. Levels of CSF fH were not altered in MS patients (n = 22) compared to a neurological control group (n = 22), although the CSF:serum ratio was significantly higher. In addition, we demonstrated raised levels of CSF fH at times of break-down of the blood–CSF barrier, indicating that the source of CSF fH in these MS patients was predominantly from an influx of systemically produced protein.

We have since extended the analysis of CSF fH in an additional three controls, 30 patients with MS and 8 patients with clinically isolated syndrome (CIS). Combined results demonstrate no significant differences between controls and either MS or CIS patients (Table I). Within the MS group, there were seven patients with active disease in whom fH levels were not altered. Interestingly, significantly higher levels of fH were seen in the seven patients with progressive disease supporting our previous demonstration of higher mean serum fH levels in progressive MS [Ingram et al., 2010].

In summary, our data do not support the finding of lower levels of fH in active MS reported by Li et al. [2011]. The reasons for this are

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TABLE I. CSF Factor H Levels in Controls, Patients With CIS and MS

	No.	Mean fH (mg/L)	SD	*P*
Controls	25	0.67	0.29	
CIS	8	0.69	0.20	0.907
Total MS	52	0.66	0.31	0.937
RRMS	38	0.59	0.29	0.330
Relapse	7	0.72	0.25	0.744
Progressive MS	7	1.04	0.18	0.014

CIS, clinically isolated syndrome; FH, factor H; SD, standard deviation.
P-value is determined by Student's *t*-test or one-way ANOVA for multiple comparisons and compares to the control group. Samples were normally distributed and *P*-value was considered positive if less than 0.05. Relapse refers to patients sampled during a clinical relapse.

unclear but may relate to small sample numbers or the pooled analysis methodology employed by Li et al. In contrast, we have demonstrated higher levels of both CSF and serum fH in progressive disease and an influx of systemic fH at times of breakdown of the blood–CSF barrier. Our results predict that CSF fH levels will be raised rather than reduced in active disease and correlate with raised systemic levels in relapse. This work now needs extending and validating in larger cohorts to resolve these disparities.

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