

FCRL5, a B-Cell Marker With Novel Diagnostic and Prognostic Value for Multiple Sclerosis

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Abstract

Background and Objectives

Fc receptor-like 5 (FCRL5) is an IgG-binding receptor frequently reported to be highly expressed on double-negative and atypical memory B cells, both of which are frequently expanded in inflammatory conditions. However, its expression profile in multiple sclerosis (MS) remains unclear. This study aims to characterize FCRL5 expression in CSF, serum, and peripheral blood mononuclear cells (PBMC) of patients with MS and to define the phenotypic and transcriptional features of FCRL5⁺ B cells in MS.

Methods

A proximity extension assay-based proteomic analysis was conducted on the CSF of patients with relapsing-remitting MS (RRMS, n = 59) and controls (n = 29). The observed FCRL5 upregulation was validated using single-molecule array analysis in a cohort comprising patients with RRMS (n = 40), controls (n = 30), and individuals with other inflammatory neurologic diseases (OIND, n = 20). Serum FCRL5 levels were also assessed in a cohort of patients with MS characterized by 3T MRI (n = 58). In addition, flow cytometry-based techniques and RNA sequencing were performed on PBMC from patients with RRMS and controls to investigate the phenotype and transcriptional profiles of FCRL5⁺ B cells. Finally, the effect of Bruton tyrosine kinase inhibitors (BTKi) on FCRL5 regulation was also evaluated in vitro.

Results

FCRL5 was significantly upregulated in the CSF of patients with RRMS compared with that in controls and OIND. Elevated CSF FCRL5 levels were associated with an increased risk of new brain lesions within 24 months. Serum FCRL5 levels were not correlated with CSF measurements but were inversely correlated with the cortical and juxtacortical lesion burdens. Moreover, flow cytometry analysis revealed that peripheral CD19⁺FCRL5⁺ B cells of patients with RRMS differed from those of controls by their strong CD11c expression. The transcriptional profiles of CD19⁺CD11c⁺FCRL5⁺ cells also differed significantly between the 2 groups, characterized by reduced expression of humoral response genes and enhanced inflammatory signaling. In addition, FCRL5 regulation was found to be BTK-dependent.

Discussion

The soluble form of FCRL5 can be measured in the CSF and could serve as a promising biomarker for MS diagnosis and disease activity prediction. In addition, this study highlights that CD19⁺CD11c⁺FCRL5⁺ B cells in MS display a distinct transcriptional profile compared with controls.

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory disorder of the CNS characterized by demyelination and concomitant neurodegeneration.¹ In its early phase, the disease is characterized by multifocal inflammation resulting from the invasion of the CNS by

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Supplementary Material

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