Abstract

One of the biggest challenges in managing multiple sclerosis is the heterogeneity of clinical manifestation and progression trajectories. It still remains to be elucidated whether this heterogeneity is reflected by discrete immune signatures in the blood as a surrogate of disease pathophysiology. Accordingly, individualized treatment selection based on immunobiological principles is still not feasible. Using two independent multi-centric longitudinal cohorts of patients with early multiple sclerosis (n = 208 discovery, n = 325 validation), we were able to identify three distinct peripheral blood immunological endophenotypes by a combination of high-dimensional flow cytometry and serum proteomics followed by unsupervised clustering. Longitudinal clinical and paraclinical follow-up data collected for the cohorts revealed that these endophenotypes were associated with disease trajectories of inflammation versus early structural damage. Investigating the capacity of immunotherapy to normalize endophenotype-specific immune signatures revealed discrete effect sizes as illustrated by the limited effect of interferon-β on endophenotype 3-related immune signatures. Accordingly, patients that fell into endophenotype 3 subsequently treated with interferon-β exhibited higher disease progression and MRI activity over a four-year follow-up compared to treatment with other therapies. We therefore propose that ascertaining a patient’s blood immune signature before immunomodulatory treatment initiation may facilitate prediction of clinical disease trajectories and enable personalized treatment decisions based on pathobiological principles.

Study design

Immunological endophenotypes can be reproduced in an independent cohort

Immunological endophenotypes display discrete patterns of inflammatory disease characteristics vs. signs of early neurodegeneration

Peripheral immune-regulatory networks are disturbed in early multiple sclerosis

Early multiple sclerosis forms three distinct immunological endophenotypes

Treatment responses differ between endophenotypes

Conclusion

Multiple sclerosis endophenotypes identified by high dimensional blood signatures are associated with distinct disease trajectories

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