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Commentary

Blood transcriptome profiling captures dysregulated pathways and response to treatment in neuroimmunological disease

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Assessing the transcriptome of blood cells yields a comprehensive picture of the expression status of immune-related genes. In the past decade, impressive technological and analytical advances have given rise to novel high-throughput RNA sequencing and high-density microarray platforms. These approaches perform equally well for well-defined transcriptional regions, while some uncertainties remain regarding the quantification of short and low-abundance transcripts [1]. Blood-based omics have accelerated our understanding of the mechanisms underpinning neuroinflammatory conditions and facilitated the evaluation of therapeutic effects. However, in multiple sclerosis (MS), a chronic immune-mediated neurodegenerative disease that is influenced by complex gene-environment interactions [2], the molecular mechanisms are still not clearly understood. The clinical presentation of MS is highly heterogeneous. Most patients (~90%) have a relapsing-remitting course of MS (RRMS); characterized by reversible episodes of neurological dysfunction. The modern era of disease-modifying drugs (DMDs) in MS began in 1993 with the approval of interferon-beta (IFN-β) for RRMS [3]. Since then, the therapeutic armamentarium to prevent relapses and progression of disability in patients with MS has increased to >10 DMDs, but injectable IFN-β preparations remain an important option worldwide because of the low risk of severe adverse effects and moderate costs. Recombinant IFN-β stimulates the JAK-STAT pathway, which leads to pleiotropic immunomodulatory effects and reduced migration of immune cells to sites of inflammation in the central nervous system [4]. Still, it is not clear to what extent transcriptional changes in the blood may correlate with clinical outcomes to IFN-β therapy.

In an article recently published in *EBioMedicine*, Feng and colleagues could show by leveraging big transcriptome data that long-term IFN-β therapy in MS corrects an abnormal expression signature of immunoregulatory and neuroprotective genes [5]. A key strength of their analysis is the sophisticated study design, which allowed comparison of RRMS patients vs. healthy controls, treated vs. untreated patients, clinically stable vs. clinically active patients, complete vs. partial responders, and long-term vs. short-term gene expression shifts in response to low dose vs. high dose IFN-β regimens. Feng et al. generated a rich dataset and share it with the scientific community: In total, 227 modern Human Transcriptome Arrays (HTA 2.0), each containing >6 million distinct oligonucleotide probes, were employed to quantify the levels of >67,000 transcripts in peripheral blood mononuclear cells. Furthermore, the authors studied a homogeneous single-centre group of patients (followed for ≥5 years), employed well-established pipelines for rigorous quality control and data analysis, and validated selected findings at the RNA and protein level [5]. Approximately 6000 protein-coding genes and 2000 non-coding RNAs were found to be dysregulated in untreated MS patients compared to healthy controls. This dysregulation was no longer apparent after long-term IFN-β treatment. In the short-term (i.e., within one day following IFN-β injection) >1200 genes were altered in expression. In the long-term response, 277 genes distinguished partial responders (with relapse in the follow-up) from complete responders (with no relapse and no disability progression). The differentially expressed genes have been predominantly implicated in immunity, including JAK-STAT and Toll-like receptor signalling, and neuroprotective pathways, including synaptic transmission. This study thus confirms previously identified gene expression signatures of MS [6,7] and markedly expands the number of putative biomarkers for IFN-β responsiveness [5].

The insights from the study by Feng et al. [5] can be useful in the counselling of MS patients and for comparing the bioactivity profiles of pegylated and biosimilar forms of recombinant IFN-β, which received marketing authorization in some countries more recently [8]. However, open questions remain regarding the individual risk of transition to secondary progressive MS and the generalizability of the RNA expression pattern for distinguishing par-

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tial responders, which needs to be evaluated in independent patient cohorts. Moreover, the expression signatures were not related to neuroimaging and routine laboratory parameters and poor responders (i.e., patients who switched to more effective DMDs because of continued disease activity) were excluded from this study. The large microarray dataset can be further exploited to infer dynamics in the composition of different immune cell types [9] and to analyse alternative splicing events [10]. Future studies may employ single-cell or long-read RNA sequencing solutions and integrate multi-omics information. On the other hand, functional studies are needed to investigate the precise roles of the many non-coding transcripts that were not previously known to be modulated by IFN-β.

Longitudinal transcriptome analyses of blood cells represent an attractive approach for exploring the complexities of neuroinflammatory diseases and the mechanisms of action of pharmacologic agents. The data by Feng et al. [5] suggest that long-term IFN-β treatment corrects a peripheral immune imbalance in patients with RRMS. Other DMDs presumably affect this aberrant gene expression as well, though in very different ways. A more comprehensive understanding of molecular disease processes may help to improve the monitoring of therapeutic interventions, which will translate into clinical benefits for patients. The advanced ascertainment of biomarker signatures across a variety of diseases also has the potential to explain previously failed treatment strategies (e.g., IFN-β in neuromyelitis optica) and to inform drug repositioning studies. However, the increased volumes of data from the latest generation of microarray and sequencing technologies and other biomedical sources pose new computational challenges regarding data management, mining, and dissemination. Therefore, in order to optimally prevent inflammatory and neuro-axonal damage and reduce the burden of disease, concerted interdisciplinary efforts are paramount to foster personalized treatment decisions.

Declaration of Competing Interest

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