Gene expression profiling in MS: a fulfilled promise?

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Since the development of microarray technology in the late 1990s, a quest to identify gene expression signatures, characteristic of each of a multitude of diseases, was unleashed. The excitement was fueled by the expectation that this approach would deliver much-needed biomarkers to track disease progression and even determine the response to therapeutic drugs. With notable exceptions, this noble pursuit has, so far, fallen short of expectations.

Today, very few gene expression-based tests for prognostic purposes are approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), its European counterpart. One such product is Allomap®, a 20-transcript signature that measures the risk of patients with stable cardiac allograft function to develop moderate-to-severe acute cellular rejection, at the time of testing.[1] Another approved test is MammaPrint®, a 70-transcript signature that allows identification of subgroups of breast cancer patients with a very low risk of relapse and death without treatment, who could thus be spared adjuvant chemotherapy.[2]

In multiple sclerosis (MS), an extensive body of literature supports sustained enthusiasm for this paradigm, but the resounding successes are still to come. Early proof-of-concept studies established the transcriptional signature of MS in blood[3] and brain tissue.[4,5] Subsequent studies focus on changes induced by therapeutic drugs.[6] More recent work attempting to identify markers of disease activity,[7,8] progression,[9] or therapeutic response[10,11] illustrate the clinical potential of this approach.

In this issue, Ratzer and colleagues report a comparative analysis of gene expression in peripheral blood mononuclear cells (PBMC) from patients with relapsing–remitting MS (RRMS) (n = 18), secondary progressive MS (SPMS) (n = 18) and primary progressive MS (PPMS) (n = 17) against PBMC from healthy controls (n = 18). The authors found a robust signature of 380 transcripts that differentiated at least one MS subtype from healthy control samples. In line with other studies of this kind, the average effect sizes (fold changes) were moderate (range: 0.75–2.29) and the transcripts in this signature could be associated with innate and adaptive immune response pathways. This pattern also seemed to be in agreement with pathways identified through genetic susceptibility studies,[12,13] although the authors did not specifically test for this. A very small fraction of these transcripts was found to be differentially expressed in RRMS versus SPMS (n = 11), RRMS versus PPMS (n = 11) and PPMS versus SPMS (n = 21). In an original analysis, the authors also compared pooled sub-populations of PBMC (i.e. CD4+ and CD8+ T cells, B cells, natural killer (NK) cells, monocytes and dendritic cells) from each study group and found that monocytes had the highest mean for a significantly greater proportion of differentially expressed genes (55%). Furthermore, the authors suggest that the observed signature in PBMC could be traced to just CD8+ T cells, B cells and monocytes.

In many aspects, this study is an accurate representation of the field of MS transcriptomics, which takes advantage of a mature technology and increasingly sophisticated statistical approaches for data analysis; however, two recurrent criticisms of this type of study are a small sample size and the lack of replication across different laboratories. This is largely due to the fact that studies are typically conducted in a single center, to minimize costs and confounding variables that could be introduced by different sampling and processing protocols. For example, general health of patients (e.g. fever, infection, etc.), time at blood draw (e.g. morning versus afternoon), cell population (e.g. whole blood or PBMC sub-populations), RNA isolation technique (e.g. rRNA depletion, polyA priming, etc.) and microarray platform are all variables that may influence the final results. Paradoxically, it has been the inability of the scientific community to standardize these procedures (i.e. logistics), and not the shortage of technology or analytical methods, which has prevented the field to move forward in a more forceful and meaningful way.

The time is ripe for transitioning to larger, multi-center, consortium-like efforts to make this breakthrough. It worked for genetic susceptibility studies; it can work for gene expression studies too.

Conflict of interest

The author declares that there is no conflict of interest.

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