MULTIPLE SCLEROSIS

Predicting the response to IFN-β treatment in patients with MS

Expression of type I interferon (IFN)-inducible genes could predict response to IFN-β treatment in patients with multiple sclerosis (MS). New research indicates that there is "a common dysregulation of the type I IFN signalling pathway in nonresponders [to IFN-β treatment]," says lead investigator Manuel Comabella, of the Hospital Vall Hebron, Barcelona, Spain.

> "Genes that are selectively induced by type I IFNs were the best predictors of treatment outcome"

IFN-β, a type I IFN, is the most widely used treatment for relapsing–remitting MS; however, the effects are modest and a large proportion of patients with MS do not respond to treatment with this drug. Classification of the response status requires a long clinical follow-up (1 or 2 years). In this time, many patients will be treated without any benefit (nonresponders). Those patients receiving ineffective therapy accumulate further disability and are subject to treatment-related adverse effects.

Comabella and colleagues sought to identify biomarkers in patients with MS that could allow early recognition of a poor response or no response to IFN-β treatment. To date, no definitive biomarkers have been found. The team were aware that the response or lack of response to IFN-β treatment was mediated by a combination of genes, most probably belonging to the same cellular pathway. "For this reason, we used a genome-wide hypothesis-free approach, gene expression microarrays, to identify cellular pathways that may be related to the response or lack of response to IFN-β," Comabella explains.

Tests were carried out on peripheral blood mononuclear cells collected from patients before and during IFN-β treatment. The microarrays identified gene expression signatures that distinguished between responders and nonresponders to treatment with IFN-β. Differential expression of type I IFN-regulated genes was revealed: before treatment, these genes were overexpressed in patients who went on to be nonresponders, whereas baseline expression was low in those who responded to IFN-β. Genes that are selectively induced by type I IFNs were the best predictors of treatment outcome. After 2 years of IFN-β treatment, expression of the type I IFN-induced genes remained unaltered in nonresponders but was strongly upregulated in responders.

A panel of mechanistic experiments demonstrated that the type I IFN signature was selectively altered in monocytes of nonresponders.

These results indicate that the type I IFN-regulated genes could be used to predict and monitor response to IFN-β treatment in patients with MS. "The future step in relation to this work is to validate the type I IFN signature in prospective cohorts of patients with MS treated with IFN-β, but focusing only on the most predictive set of genes," Comabella concludes.

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