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opinion Article

Exploring the TGFB1–IFNB1 Axis in Multiple Sclerosis: Gene Expression Offers New Clues

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DESCRIPTION

Multiple Sclerosis (MS) remains one of the most enigmatic autoimmune disorders, primarily affecting the Central Nervous System (CNS). It is marked by complex interactions between inflammatory and neurodegenerative processes. Despite decades of research, the disease's full mechanistic underpinnings continue to elude scientists. However, growing evidence places specific immune cytokines namely Transforming Growth Factor Beta 1 (TGFB1) and Interferon Beta 1 (IFNB1) at the heart of MS pathophysiology.

Cytokine crosstalk in MS: A hidden layer of complexity

TGFB1 is a multifaceted cytokine that demonstrates both pro- and anti-inflammatory roles, depending on the disease stage and immune context. In early phases of MS, it is largely anti-inflammatory, promoting regulatory T cell differentiation and dampening excessive immune responses. However, in chronic disease stages, especially in aging populations, TGFB1 may become maladaptive contributing to glial scarring, suppressing remyelination and impeding neural repair. This duality makes TGFB1 a complex yet critical focus in MS research.

IFNB1, on the other hand, is a type I interferon with established therapeutic use in Relapsing-Remitting MS (RRMS). Endogenously produced IFNB1 regulates immune responses by suppressing autoreactive T cells, enhancing regulatory T cells and attenuating pro-inflammatory cytokine production. Yet, endogenous IFNB1 signaling in MS patients distinct from pharmacological IFN- β treatment has not been extensively studied. Understanding how the body's natural IFNB1 production behaves during relapse and remission is essential, particularly as it may influence Disease-Modifying Therapy (DMT) outcomes.

In this context, a recent study offers valuable insight by investigating the Peripheral Blood Mononuclear Cell (PBMC) expression of TGFB1 and IFNB1 mRNA in MS patients, with attention to clinical phases and underlying genetics. The study also explores whether two specific genetic variants rs1800469 in TGFB1 and rs2275888 in HACD4 (an IFNB1 expression regulator) affect gene expression or disease susceptibility.

Expression patterns, not genetics, hold the answers

The study analyzed a large cohort of 417 MS patients and 293 controls for genetic association and a subset of 71 MS patients alongside 101 controls for mRNA expression analysis. The researchers discovered compelling context-dependent changes in gene expression. Specifically, TGFB1 mRNA levels were significantly elevated in RRMS patients compared to healthy controls. This suggests a potential role of TGFB1 in active immune regulation during the relapsing phase.

Even more striking was the observation that IFNB1 mRNA levels were significantly higher in RRMS patients experiencing a relapse compared to those in remission. This implies that endogenous IFNB1 production may ramp up as a countermeasure during inflammatory surges, potentially reflecting an intrinsic attempt by the immune system to self-regulate. The positive correlation between TGFB1 and IFNB1 expression within MS subgroups further reinforces the hypothesis of an interactive cytokine network modulating disease dynamics.

Importantly, the study found no significant associations between the rs1800469 and rs2275888 variants and either MS risk or the expression levels of TGFB1 and IFNB1. This finding contradicts earlier suggestions that these single nucleotide variants might function as Expression Quantitative Trait Loci (eQTLs) in MS. While both variants have been identified in eQTL studies involving other conditions or broader immune traits, they appear to exert little influence on TGFB1 or IFNB1 expression in the PBMCs of MS patients.

These findings redirect attention from static genetic predisposition to dynamic gene expression and its regulation by environmental or pathological stimuli. Rather than relying on fixed genetic markers, it may be more productive to monitor

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gene expression profiles in real time to gauge disease activity and tailor therapeutic responses.

The clinical implications of this study are noteworthy. First, measuring TGFB1 and IFNB1 mRNA levels in PBMCs could offer a non-invasive biomarker for tracking disease phase in RRMS patients. Elevated IFNB1 during relapse, in particular, could signal a window of immune activation that may be useful for guiding or adjusting DMT.

CONCLUSION

In conclusion, this study enriches our understanding of the immunological landscape in MS by emphasizing the nuanced, phase-specific expression of key cytokines rather than static genetic determinants. It underscores the importance of investigating cytokine networks in disease progression and treatment response. While TGFB1 and IFNB1 variants may not drive MS susceptibility directly, their expression patterns offer a window into the disease's dynamic immune regulation. Further research, ideally with longitudinal follow-ups and mechanistic insights into their signaling pathways, will be vital in translating these findings into clinical practice.