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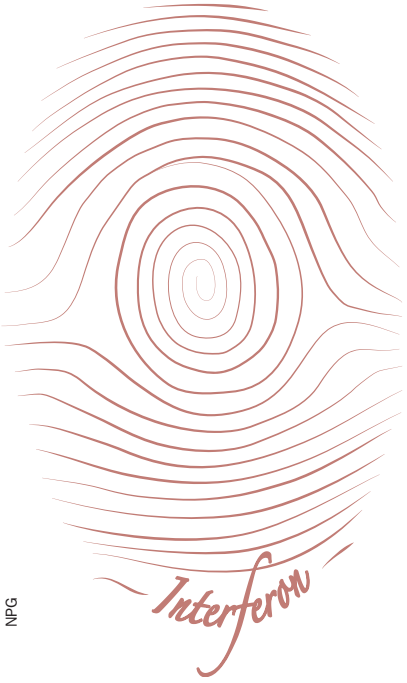
CONNECTIVE TISSUE DISEASES

Interferon signatures in SLE—two types to consider

New research investigating the gene expression profile of patients with systemic lupus erythematosus (SLE) reveals the complexity of interferon (IFN) signatures in SLE, and that not only type I but also type II IFN signatures could be relevant to the disease. "The IFN signature of SLE was identified over 10 years ago using similar gene expression profiling," says author Laurent Chiche, speaking to *Nature Reviews Rheumatology*. "The most striking and unexpected finding was to be able to find something fundamentally new about it after all this time," he exclaims.

SLE is a chronic autoimmune disease, with the pivotal role of type I IFNs (in particular, IFN-α) in the pathogenesis of SLE having long been established; however, the role of type II IFNs (IFN-γ) in SLE has potentially been overlooked. Here, the researchers took advantage of a systems biology approach and used modular transcriptional repertoire analysis to examine microarray data within three specific IFN-related modules or gene sets (termed M1.2, M3.4 and M5.12) —essentially examining the molecular fingerprint of IFN signatures in SLE.



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Gene expression profiles were obtained for 62 patients with SLE (aged 18–70 years; 85% were women, 89% were white) and were compared with 20 healthy individuals as controls who were matched for age, gender and ethnicity (with no personal or family history of SLE). SLE disease activity was assessed using the SELENA-SLEDAI score, alongside immunological and biological marker analyses of (such as autoantibody levels). Patients with SLE were split into three groups: 'at inclusion', including all patients at the first clinic first, irrespective of disease activity; 'quiescent', patients with SLE with low disease activity at first visit; and 'longitudinal', patients who had three consecutive clinic visits during the course of the study (median follow-up time, 8.3 months; range, 2–28 months).

Chiche and co-workers found that, at a group level, the IFN-related modules M1.2, M3.4 and M5.12 were among the most upregulated in terms of gene expression in patients with SLE versus controls. At the individual level, a modular IFN signature (upregulated gene expression in at least one IFN module) was observed at 87% of patients with SLE at inclusion, and in 83% of patients with SLE monitored longitudinally.

These modular IFN signatures seemed to be dynamic, with a gradient of activation of IFN modules across samples. Each module displayed distinct activation thresholds (M1.2<M3.4<M5.12) and patterns of upregulation; for instance, when only 1 of 3 IFN modules were upregulated it was always M1.2. Moreover, each module differed in terms of upregulation over time, reflecting the complexity of the IFN signatures. In the longitudinal group, expression within M1.2 remained stable, but M3.4 and M5.12 varied markedly over time within a given patient.

Importantly, upregulation of the IFN modules correlated with different patterns of clinical and biological markers of SLE disease activity; for example, all modules correlated with anti-dsDNA antibody titres, whereas only M5.12 correlated with renal flares and the SLEDAI score, and both M3.4 and M5.12 correlated with cutaneous flares.

The researchers then considered how modular IFN signatures might provide insights into SLE pathogenesis. The authors mined existing datasets on IFN-related gene expression in patients treated with IFN-α (for hepatitis C) or IFN-β (for multiple sclerosis) and the Interferome database, and compared the findings with the results observed in their new study. They found evidence that the modular IFN signatures in SLE might not be solely driven by IFN-α and that IFN-β might also have a role, especially for modules M3.4 and M5.12 for which both type I and type II IFNs seem to contribute to the gene expression responses in these modules.

From a clinically practical point of view, these IFN signature profiles could be used as a means to monitor and manage patients with SLE. In an accompanying commentary, Peter Gregersen and Michaela Oswald write: "The data illustrate the power of combining correlated gene expression information with biological associations". "Despite early promise, the various approaches to measuring the interferon signature have not provided a clinically useful biomarker for disease management," they write, "the current data suggest that with a more granular and focused approach to the different types of interferon signature may in fact have some clinical utility".

"Our findings have direct implications for the development of a biomarker aiming at the evaluation of disease activity and/or prognosis or at tailoring of therapies targeting interferons and related pathways," concludes Chiche. "There are also many rheumatic or autoimmune diseases in which interferon signatures have been described in different degrees that will have to be revisited in light of this new finding," he adds.

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Original article Chiche, L. *et al.* Modular repertoire analyses of adults with systemic lupus erythematosus reveal distinct type I and type II interferon signatures. *Arthritis Rheum.* doi:10.1002/art.38628