IMMUNOLOGY

# Learning from similarities between vaccine responses and SLE

*Marie Wahren-Herlenius and Lars Rönnblom*

Baseline immune variation predicts immune responses during vaccination, and the gene signatures capturing such immune variation seem to correlate with systemic lupus erythematosus (SLE) disease activity. Will the definition of these gene sets enable the development of the much needed concept of personalized medicine in SLE?

*Refers to* Kotliarov, Y. et al. Broad immune activation underlies shared set point signatures for vaccine responsiveness in healthy individuals and disease activity in patients with lupus. *Nat. Med.* **26**, 618–629 (2020).

Systemic lupus erythematosus (SLE) is a disease characterized by B cell activation with increased antibody synthesis and by ongoing type I interferon production, causing the prominent expression of type I interferon-regulated genes, known as the 'interferon signature'[1]. Both these features — the B cell activation and the type I interferon production — are also typical of most viral infections. Conversely, several clinical signs and symptoms that commonly occur during viral infections are also observed in patients with SLE. Thus, both patients with viral infections and those with SLE experience fever, fatigue, rash and pain in joints and muscles. Viral infections might also increase the risk of developing SLE[2]. Together, these observations suggest that similar immune processes are important in SLE and during viral infection. In a new study, Kotliarov et al.[3] investigated whether information that can be used to predict the immune response to an acute infection might also be of value in predicting the magnitude of disease flares in patients with SLE.

SLE is a heterogeneous disease that has both familial, monogenetic forms (including complement protein C1q deficiencies and *TREX1* mutations) and polygenetic forms that are associated with common single nucleotide polymorphisms, many of which have been mapped to type I interferon induction or response genes[4]. The chronic activation of the type I interferon system is present in many, but not all, patients with SLE and correlates with disease activity[5]. The ability to define patient subpopulations and understand the immune mechanisms that lead to disease flares in patients with SLE is important to avoid organ damage in these individuals and for the development of more precise therapies. In fact, this lack of targeted therapies is one of the most important unmet medical needs for patients with SLE.

In their new study, Kotliarov et al.[3] used a strategy influenced by their previous work on influenza vaccine responses to investigate similarities between vaccine responses in healthy individuals and disease flares in patients with SLE. On the basis of their previous identification of a baseline peripheral blood profile of $CD20^{+}CD38^{++}$ B cells that could be used to predict influenza vaccine responses in terms of specific antibody titres[6], they developed a blood-based transcriptional surrogate signature of ten genes that correlated with the amount of $CD20^{+}CD38^{++}$ B cells. These B cells are considered to be precursors of plasmablasts that have the capacity to secrete large amounts of antibodies. The predictive value of this ten-gene signature was investigated in several independent cohorts of individuals who had received influenza or yellow fever vaccination. In most, but not all, individuals, expression of the ten-gene signature at baseline (before vaccine administration) could predict whether that individual would have a high or low vaccine antibody response[3].

Kotliarov et al.[3] next assessed whether, at periods of no or low disease activity, expression of the same ten-gene signature in a clinically well-characterized longitudinal cohort of paediatric patients with SLE might be associated with the severity of subsequent disease flares. Previous efforts to define subgroups of paediatric patients with SLE by correlating disease activity with distinct combinations of transcriptomic signatures have revealed that a plasmablast signature is the most robust biomarker of disease activity[7]. Hypothesizing that the predictive capacity of a ten-gene signature would therefore be greatest in patients for whom disease activity correlated with a transcriptomic module enriched for plasma cells or plasmablasts, Kotliarov et al.[3] focused their analysis on this set of patients. Indeed, the ten-gene signature correlated with disease activity in this but not in other subgroups of patients. The authors also accounted for the effects of SLE treatment in the model. Overall, the results presented by Kotliarov et al.[3] suggest that the ten-gene signature evaluated during clinically quiescent periods can inform on the expected magnitude of disease flares in a defined subgroup of paediatric patients with SLE. Early onset SLE is generally more severe and has a higher degree of genetic contribution than adult onset SLE[8], so verification of the predictive value of the ten-gene signature in adult onset SLE will be important to understand its general clinical applicability.

Most cell types in the immune system can be involved in the SLE disease process, and identifying the most important cells responsible for triggering disease flares would be extremely helpful when selecting targeted therapies. However, linking the ten-gene signature back to a specific cell type proved difficult[3], despite the use of the powerful CITE-Seq method, which measures 82 cell surface immune markers in parallel with single-cell RNA sequencing of the same cells. A higher mean expression of the ten-gene signature was observed in plasmacytoid dendritic cells but this signature was not restricted to these cells and, following further bioinformatic analyses, Kotliarov et al.[3] concluded that the ten-gene signature captures the responsiveness to vaccination or prediction of SLE flares in multiple cell subsets in the peripheral blood.

Kotliarov et al.[3] also investigated the converse scenario of whether a baseline gene signature in SLE that was predictive of disease flare would also be predictive of antibody responses to vaccination in healthy individuals. Using a weighted gene co-expression network analysis to identify temporally stable transcripts across low disease activity time points in the paediatric patients with SLE, the researchers first defined a module that correlated with the disease-activity-associated change in the plasmablast score. Downstream analysis demonstrated that the module was indeed enriched for genes that had previously been associated with antibody responses in studies of influenza vaccination[3]. Overall, the data presented by Kotliarov et al.[3] emphasize that shared baseline gene signatures exist for influenza vaccination responses and for SLE disease activity.

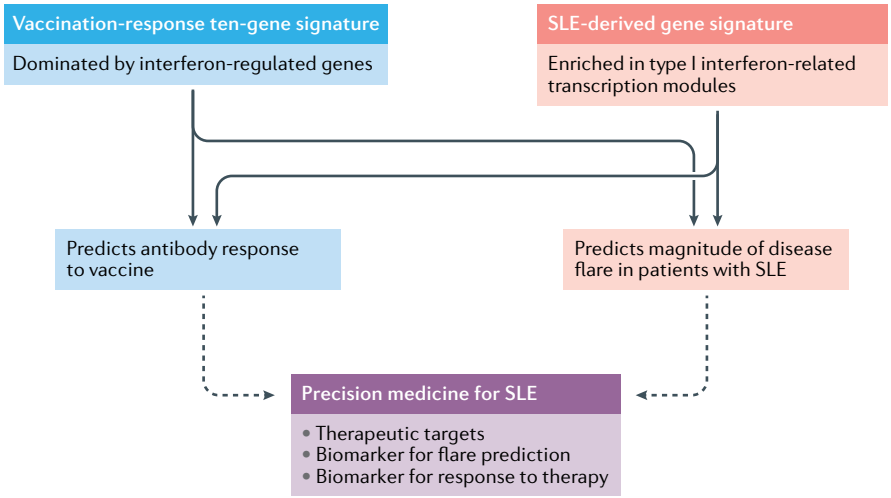


Fig. 1 | **A basal gene expression profile determines immune responses.** A ten-gene signature that predicts antibody responses to influenza vaccination also predicts flare magnitude in paediatric systemic lupus erythematosus (SLE), and conversely, a separate gene signature that predicts flare magnitude in paediatric SLE can predict antibody responses to influenza vaccination. Both gene signatures are dominated by interferon-regulated genes, but share only one gene in common. These gene signatures could be used to improve precision medicine for patients with SLE.

Perhaps not surprisingly, the SLE-derived module was enriched for type I interferon-related transcripts[3], and the type I interferon activation status of an individual is known to predict vaccine responses in patients with autoimmune diseases to both adjuvanted[9] and non-adjuvanted influenza vaccines[10]. Notably, all genes in the original ten-gene signature are interferon regulated, albeit with different expression profiles among different immune cell subsets when investigated using sites such as Interferome and The Human Protein Atlas. Several of the genes are of unknown or less extensively characterized function, leaving the question open as to whether these particular genes might be interesting therapeutic targets, or whether they will best serve as a biomarker signature for predicting flare or therapeutic responsiveness (FIG. 1). Regardless of the answers to these questions, the findings of the study by Kotliarov et al.[3] take us one step closer to the concept of personalized medicine for patients with SLE in all its forms.

The next goal will be to translate the ten-gene signature, or a refined version, into a clinically useful test that can identify patients with an increased risk for disease flares, irrespective of organ manifestations. Such a step will need the development of a reasonably priced assay and the validation of these results in longitudinal studies with large cohorts of patients. Achieving both these tasks would be a tremendous help to all clinicians faced with the challenge of caring for patients with SLE.

*Marie Wahren-Herlenius*[1] *and Lars Rönnblom*[2] ✉

[1]*Division of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.*

[2]*Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden.*

✉*e-mail: lars.ronnblom@medsci.uu.se*

https://doi.org/10.1038/s41584-020-0421-5

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**Acknowledgements**
The authors thank the Swedish Research Council, the Heart-Lung Foundation, the Swedish Rheumatism Association, the King Gustaf the V[th] 80-year Foundation and the Swedish Society of Medicine with the Ingegerd Johansson donation for provision of funding.

**Competing interests**
The authors declare no competing interests.

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