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PRIME Time in Rheumatoid Arthritis

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Rheumatoid arthritis, like many autoimmune diseases, has a course characterized by intermittent flares, yet our understanding of the mechanisms underlying flares remains limited. In an article published in this issue of the *Journal*,[1] Orange and colleagues describe a study in which serial fingerstick collection of blood was combined with weekly monitoring of patient-reported disease activity with the use of a questionnaire. They applied a dense longitudinal transcriptional monitoring approach, which revealed transcriptional signatures in blood that were associated with disease flares. By anchoring their informatics analysis on the point in time at which clinical flares occurred, they were able to obtain an unprecedented level of granularity that sheds light on the kinetics of immune activation leading to flares.

Previous efforts to better understand pathogenic mechanisms in rheumatoid arthritis and other autoimmune diseases through blood transcriptional analysis have provided only limited insights. This is at least in part a result of the use of cross-sectional sets of specimens obtained from patients at different stages of disease activity and with different molecular subtypes of rheumatoid arthritis. Such sets "mass average" transcriptional profiles across different stages and subtypes of disease, thereby obscuring key transcriptional programs mediating flares and other important disease manifestations in individual patients. Anchoring the analysis on disease flares enabled the authors to identify molecular markers that were predictive of imminent flares and to identify transcriptional modules representing activation of naive B cells, which increased in blood approximately 2 weeks before a flare. It further allowed for the identification of a new cell type — termed preinflammatory mesenchymal, or PRIME, cells — that appeared in blood just before disease flares. In contrast to CD45+ "fibrocytes,"[2] these fibroblast-like PRIME cells are CD45−. Intriguingly, PRIME cells are phenotypically similar to the murine fibroblast-related cell type identified in a recent landmark study[3] in which passive cell transfer was found to exacerbate inflammatory arthritis.

Human synovial fibroblasts are key contributors to the pathogenesis of rheumatoid arthritis, since these cells perpetuate chronic inflammation and promote the degradation of joint cartilage and bone. It has previously been shown that synovial fibroblasts possess the capacity to migrate and spread destructive arthritis between joints.[4] Recent studies have revealed multiple subtypes of synovial fibroblasts in rheumatoid arthritis,[5] for which the Notch signaling pathway instructs differentiation and function.[6] Orange et al. provide evidence that the fibroblast-like PRIME cell gene signature increased in the blood just before a rheumatoid arthritis flare and then decreased during the flare, which suggests that these cells may traffic to inflamed synovium and thus represent a circulating precursor of inflammatory synovial fibroblasts.[7] Further studies are needed to define how PRIME cells might

contribute to cytokine production, antigen presentation, or other functions that would augment inflammation in rheumatoid arthritis.

The temporal sequence of events in blood that was shown by Orange and colleagues implicates a role for B cells in flare initiation in rheumatoid arthritis and suggests that B cells become activated in the weeks before a flare and may, in turn, activate PRIME cells. These findings are consistent with the emerging role for B cells as key drivers of autoimmune and anticancer immune responses,[8,9] which probably occur through one or more of the known B-cell effector functions, including serving as professional antigen-presenting cells and producing both cytokines and antibodies. Nevertheless, autoimmune flares involve the orchestrated activation of multiple cell types that together mediate inflammation. The authors' data sets also revealed activation of myeloid, neutrophil, and platelet transcriptional pathways during flares, a finding that may also implicate these cell types in the pathobiology of rheumatoid arthritis flares. A comprehensive analysis of the roles of these cell types in mediating disease flares would likely provide further important mechanistic insights.

There is a lack of consensus in the field around the best definition of a rheumatoid arthritis flare,[10] and the authors used patient-reported Routine Assessment of Patient Index Data 3 (RAPID3) scores, which are subjective. Nevertheless, Orange and colleagues show that repeated measures of disease activity over time are powerful for the assessment of the baseline disease activity in a given patient and for the identification of flares. We do not yet know whether their findings represent a consistent theme for all flares in all patients with rheumatoid arthritis, since a small number of patients were studied and medications were not considered, and it remains likely that distinct cellular and molecular mechanisms are at play in different subpopulations of patients with rheumatoid arthritis. If the results are generalizable, it may become possible to intervene to prevent clinical flares when the telltale precursor changes associated with flare immunopathogenesis are detected and before clinical symptoms emerge.

Orange and colleagues show that intensively collected longitudinal data from a small sample of patients can be used to identify dysregulated transcriptional signatures that are not recognized by classical cross-sectional studies. This study illustrates the exciting potential of longitudinal genomics to identify key antecedents of disease flares in an approach that may be applicable to the investigation of pathogenic and protective immune responses in a wide range of human diseases.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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