Published in final edited form as:

N Engl J Med. 2020 October 15; 383(16): 1595–1596. doi:10.1056/NEJMc2027492.

PRIME Cells Predicting Rheumatoid Arthritis Flares. Reply

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THE AUTHORS REPLY:

Sfikakis et al. note that PRIME cells share gene-expression features with both lining and sublining fibroblasts. Gene-expression signatures of lining and sublining fibroblasts overlap, and the various fibroblast populations are probably related. The AC3 gene cluster that was identified just before a rheumatoid arthritis flare was significantly enriched with sublining — but not lining — fibroblast genes (Fig. 3A of our article, available at NEJM.org), which suggests that this signature is more closely related to sublining fibroblasts. Potential intersections with cadherin-11–positive cells and the deep characterization of the function and RNA signatures of PRIME cells are of primary interest. We look forward to future studies, such as trajectory analysis and fate mapping, to more conclusively establish the relationship between PRIME cells and the various synovial fibroblast populations.

Dörner and Burmester raise the interesting possibility that the B-cell signature identified before a rheumatoid arthritis flare could represent atypical memory B cells, which are expanded in patients with rheumatoid arthritis; lower frequencies of these cells at baseline are associated with a good response to treatment.[1] We agree that additional studies are needed to further refine the characterization of B-cell subsets that become activated before rheumatoid arthritis flares and to determine how such B cells may interact with PRIME cells. They also note that the longitudinal molecular genetic approach we established for rheumatoid arthritis might be relevant to other inflammatory diseases. Although we do not suggest (or rule out) that PRIME cells play a role in other inflammatory disorders that fluctuate over time, we agree with the suggestion that our study of rheumatoid arthritis may establish a fruitful avenue to pursue the identification of antecedent signatures associated with flares in many disorders. Arguably, this approach could be taken to explore antecedents in any disease that is not characterized by a monotonic course.

References

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Since publication of their article, the authors report no further potential conflict of interest.