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Editorial

EDITORIAL

Toward cellular biomarkers for rheumatoid arthritis

Biomarkers in RA

This editorial refers to Differential effects of biological DMARDs on peripheral immune cell phenotypes in patients with rheumatoid arthritis, Shingo Nakayamada *et al.*, on pages 164–74.

RA, like many chronic immune-mediated inflammatory diseases, has benefited from the advent of biological disease-modifying therapies (biologics), which target specific elements of the disease process. Used as part of a strategic management approach, these treatments have significantly improved outcomes for patients. However, restoration of immune homeostasis and treatment-free remission are yet to be achieved. Frustrated rheumatologists describe a therapeutic ceiling to be breached only through an improved understanding of RA pathophysiology [1].

The important contribution of immune cells to RA pathogenesis is evident in the local and systemic manifestations of disease and is confirmed by genome-wide association studies, epigenetic screens and *in vivo* model systems. Their role is further highlighted by the efficacy of drugs targeting the molecules and cells of the immune system, including TNFα and IL-6, the Janus kinase signalling pathway, T-cell co-stimulation and antibody-producing B cells.

But which biologic is most appropriate for any individual patient? And at what stage of disease is each drug most efficacious? Current treatment regimens do not accommodate these questions, and instead, drugs are administered in a conserved sequence until a favourable response is achieved [2]. As it is now accepted that there are multiple disease endotypes encompassed within the diagnosis of RA and that there is a strategic window for treating patients, after which favourable outcomes are reduced [3], we have better reason than ever to search for new biomarkers for stratification of patients to predict drug efficacy, biomarkers for early diagnosis and drug targets for patients unresponsive to existing therapies [1].

Although molecular techniques have proved useful in predicting drug responses [4], immune cells have been heralded as particularly promising biomarkers because they both orchestrate the disease processes and are the targets of existing therapies [5]. However, the relative contributions, spatiotemporal arrangement and effector profile of individual cell types across disease stages are not well understood, a factor which limits our therapeutic exploitation of molecular products including cytokines, chemokines, receptors, adhesion molecules and kinases.

One of the sticking points in improving our understanding of immune-mediated inflammatory disease pathogenesis is the standardization of assays to assess cell phenotypes and show true pathological changes rather than technical artefacts. The Human Immunology Project Consortium (HIPC) is a grouping of six leading US research institutes that have come together to address this, producing methods for comparable immune profiling across studies and research centres [6]. An article by Shingo Nakayamada *et al*. [7] has applied these protocols to the study of RA for the first time (published at *Rheumatology* online ahead of print in March 2017).

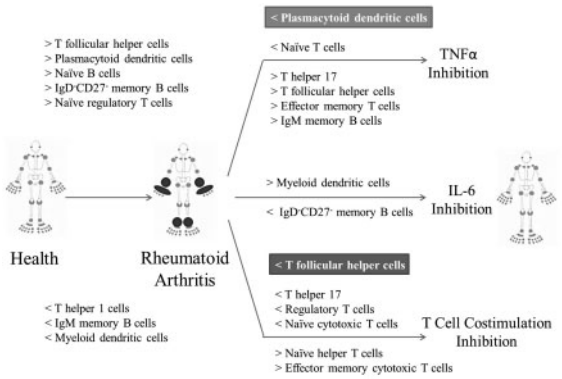
In a large and complex experiment, the group used 25 antibodies and eight colour flow cytometry panels to profile the differentiation status and effector phenotype of major lymphocytic and myeloid cells in the peripheral blood. The group analysed 108 RA patients and 33 age- and sex-matched healthy control individuals. Among the RA cohort, clinical and cellular measurements were made at baseline and after 24 weeks of treatment with a biologic, targeting IL-6 (tocilizumab, n = 22), T-cell co-stimulation (abatacept, n = 40) or TNFα (etanercept, infliximab, adalimumab, golimumab or certolizumab pegol, n = 46) [7]. A summary of findings is shown in Fig. 1.

Unsurprisingly, each drug gave rise to a distinct peripheral immune profile, reflective of the diversity of molecules targeted. Indeed, many of the cellular responses observed have been shown in smaller studies looking at individual therapies or focused upon particular components of the immune response. However, analysis of this large data set together has provided a picture of the immune compartments affected downstream of different drug targets, with possible implications for combining biological therapies to improve patient outcomes in the future.

Of course, there are shortcomings and limitations to the scope of this study. For example, the fact that the patient group was composed largely of individuals under treatment with but unresponsive to MTX imposed limitations upon comparisons with healthy controls. Furthermore, the small number of healthy controls may have contributed to the poor statistical power of the study and could have been addressed. However, a number of important correlations could be observed using abundant clinical data within the RA group alone, showing relationships between disease activity markers and the percentage of circulating $CD4^+$ memory T cells, Th17 cells, T-follicular helper (Tfh) cells, $CD8^+$ T cells, plasmablasts, IgM memory B cells, classical and non-classical monocytes [7].

Importantly, the findings of this paper have contributed to the hot topic areas of plasmacytoid dendritic cell (pDC) biology, cells known for their role in type 1 interferon responses, [8] and Tfh cell [9] biology, cells that orchestrate germinal centre formation and antibody responses. Here,

Fig. 1 Summary of findings from [7]



Dark boxes depict cells which were independent, significant predictors of a positive response to therapy. (>: increased proportion; <: decreased proportion in peripheral blood).

Nakayamada *et al.* [7] show plasmacytoid dendritic cells and Tfh cells to be significant independent predictors of improvement in response to TNFα inhibitors and abatacept, respectively, adding these cells to the armamentarium of peripheral blood biomarkers, which might allow clinicians to select the most appropriate treatment for an individual early in the disease process. However, capitalizing on this will rely upon the introduction of immune profiling to clinical rheumatological practice, as is routine in haematology for the management of lymphoproliferative disease.

Although low patient numbers meant that no predictor of tocilizumab response was identified [7], the use of the standardized HIPC protocol ensures that it is plausible to add statistical power at a later date to interrogate anti-IL-6 responses further. Indeed, it is also tantalizing to imagine comparing data from other interesting patients, such as those receiving B-cell-depleting rituximab therapy or patients with other immune-mediated inflammatory diseases receiving the same treatments.

In fact, it appears from the findings of this article that successful treatment of RA hinges on control of B-cell responses. The authors show profound effects on regulatory, effector and memory B-cell populations which, taken together with the central role of Tfh cells in orchestrating germinal centre formation and the role of plasmacytoid dendritic cells in driving plasma cell responses, emphasize that controlling the autoantibody response will be crucial to improving outcomes in RA.

The immune profiling of peripheral blood as standardized by HIPC and implemented by Nakayamada *et al.* [7] has broad applications to identify biomarkers and improve knowledge of pathophysiology in immune and inflammatory diseases and across clinical disciplines. However, this technique can only hint at the spatiotemporal organization of cells, because elevation in the blood may correspond to proliferation, cell death or a depletion at other sites. Consequently, there is a pressing need for complementary studies and standardized procedures for analysis of inflamed tissue and draining lymphoid organs to gain a full understanding and exploit the role of immune cells in RA.

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Jane Falconer[1]

[1]*Rheumatology Research Group, Institute of inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Queen Elizabeth Hospital, Birmingham, UK*
Revised version accepted 13 June 2017
Correspondence to: Jane Falconer, Institute for Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2WD, UK.
E-mail: j.falconer@bham.ac.uk

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