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METABOLISM

Can metabolomic profiling predict response to therapy?

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Standfirst

Shifts in cellular metabolism are central to activation, differentiation and proliferation of inflammatory cells and can contribute to the pathogenesis of inflammatory diseases. Integrating metabolomics data with other omics data is a major challenge but might enable clinicians to stratify stages of disease and response to therapy in patients with rheumatoid arthritis.

Refers to: Teitsma, X.M. et al. Baseline metabolic profiles of early rheumatoid arthritis patients achieving sustained drug-free remission after initiating treat-to-target tocilizumab, methotrexate, or the combination: insights from systems biology. *Arthritis Res. Ther.* **20**, 230 (2018)

Main text

Rheumatoid arthritis (RA) is prevalent in ~1 % of the population and is responsible for substantial financial and social burden. RA is a systemic disease, but the most obvious manifestations are in the joints. Current therapeutic best practice is to identify the disease at an early stage and treat it aggressively with a step-up regimen aimed at achieving complete clinical remission. This strategy typically commences with methotrexate and, if needed, is followed up with addition of conventional synthetic or biologic therapeutic agents that target pro-inflammatory cytokines. Unfortunately, although the goal of remission is becoming more attainable, success is not universally achieved (1). The search is on, therefore, not only to establish treatment regimens that can induce sustained clinical remission in patients with RA, but also to develop technologies to predict which therapeutic options will work in individual patients. A promising new study from Teitsma et al. (2) combines omics technologies to show that metabolite profiling of serum, when combined with transcriptomics and protein analysis, is able to stratify patient responses to methotrexate, tocilizumab or a combination of these drugs.

Cellular metabolism is required to sustain cells and tissues, but metabolic programs operating (at the level of genes, gene transcripts, proteins and metabolites) can vary according to cell type, are altered when cells activate, proliferate or differentiate and are perturbed by disease (3). By being at downstream at the convergence of multiple pathways, small molecule metabolite profiling (known as metabolomics) of biofluids can provide signatures that might be able to discriminate between disease and health. Different tissues and immune cells might respond metabolically in unique ways to inflammatory mediators such as cytokines, and thereby biofluid metabolite profiles reflect these metabolic processes and provide predictors of responses to therapy that are targeted at these mediators.

Teitsma et al (2) used clinical data which was originally derived from the 2-year multicentre phase III double-blind placebo-controlled U-Act-Early strategy trial (ClinicalTrials.gov identifier NCT01034137), which took 317 DMARD-naive patients with newly diagnosed RA, and randomized them to start treatment with tocilizumab (a humanized anti-IL-6 receptor monoclonal antibody), step-up methotrexate or a combination of the two drugs. Patients were treated-to-target until sustained

remission was achieved, defined as DAS28 <2.6 with ≤4 swollen joints for ≥24 weeks (4). In this sub-group of 60 patients (2), baseline serum metabolic profiles obtained on mass spectrometry platforms were used to validate 'oxidative stress', 'amines' and 'oxylipins' in 37 patients with RA (median duration of symptoms 23 days, inter-quartile range 18-40), and achieving sustained drug free remission (sDFR) was compared to serum profiles from 23 patients from the study who did not, as a control.

Distinct baseline metabolic pathways identified in sera from patients achieving sDFR were highlighted across the three treatment arms including 'histidine metabolism' in the tocilizumab and methotrexate arm, 'arachidonic acid metabolism' in the tocilizumab arm and 'arginine and proline metabolism' in the methotrexate-only arm (2). Although only the top pathway in each of the treatment arms was highlighted, we note that the 'histidine metabolism' pathway in the methotrexate arm also showed similar levels of significance (p=0.025, versus p=0.022 for 'arginine and proline'). Interestingly, Kanarek et al. (5) previously emphasised the importance of histidine metabolism in the sensitivity to methotrexate in cancer, and the new data from Teitsma et al. (2) provide further links between histidine metabolism and methotrexate efficacy.

Previous publications from the U-Act-Early study have already included other packets of omics data (6)(7). High-throughput whole transcriptomic ribonucleic acid sequencing (RNA-seq) from $CD4^+$ T helper cells and $CD14^+$ monocytes isolated at baseline from whole blood samples was used to identify differential gene expression networks from these same 60 patients (6). That study showed different clusters of expressed genes were significant for $CD4^+$ T cells, depending on the subsequent treatment arm, with three pathways identified (6). For example, in the tocilizumab and methotrexate arm, pathways related to transcription and translation were important, whereas pathways related to migration of white blood cells and G-protein coupled receptors were significant in the tocilizumab arm. In the methotrexate arm, pathways relating to response to a bacterial or biotic stimulus were highlighted. No relevant networks could be identified in the sequenced CD14+ monocytes. This study (6) indicated that at least in $CD4^+$ T helper cells, differential expression of blood cell genes can be linked to drug efficacy but with the limitation being the focus on blood cells without any analysis of synovium (the main site of inflammation in RA). In another publication, proteomics data (obtained at baseline from serum) from the same 60 patients showed multiple proteins associated with achieving sDFR, but the addition of seven candidate protein biomarkers identified to clinical predictors did not enhance the prognosis of methotrexate treatment response (7), suggesting that proteomics data alone are not sufficiently discriminatory and that further integration of data is required. Similarly, while IL-6 signalling (the target of tocilizumab) has an important role in metabolism, the baseline level of IL-6 in blood seems to be a weak predictor of the response to tocilizumab in RA, emphasising that individual blood parameters can be less informative in isolation (8).

Previous work has suggested that baseline urine metabolic profiles can predict responses to biological therapies using TNF inhibitors (9). Metabolites linked to degradation of amino acids were identified as predictors of drug response. TNF is known to drive rheumatoid cachexia, in which muscle loss is substantial and so would drive protein degradation leading to the appearance of amino acid by-products in the urine. The presence of these by-products would indicate the importance of TNF in driving disease in those patients and thus their responses to TNF-targeted therapy. Metabolic profiles in blood in very early arthritis are heterogeneous (10), and may reflect

whether the patient will develop chronic arthritis or not, in addition to being useful in predicting responses to therapy (2).

Metabolomics undoubtedly has more to offer in future studies of chronic disease, and especially when integrated with other omics technologies, metabolic profiling of blood or urine might enable integration of signals from all the tissues and cells that contribute to early stages of disease. Integration of the different omics technologies by Teitsma et al (2) in their study of early RA is an elegant example, and suggests a pathway to fully personalized therapy.

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Competing interests

C. M. M. declares that she has received honoraria from Pfizer. S.P.Y. declares no competing interests.

1. Ajeganova S, Huizinga T. Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations. Ther Adv Musculoskel. 2017;9(10):249-62.
2. Teitsma XM, Yang W, Jacobs JWG, Petho-Schramm A, Borm MEA, Harms AC, et al. Baseline metabolic profiles of early rheumatoid arthritis patients achieving sustained drug-free remission after initiating treat-to-target tocilizumab, methotrexate, or the combination: insights from systems biology. Arthritis Res Ther. 2018;20(1):230.
3. DeBerardinis RJ, Thompson CB. Cellular Metabolism and Disease: What Do Metabolic Outliers Teach Us? Cell. 2012;148(6):1132-44.
4. Bijlsma JWJ, Welsing PMJ, Woodworth TG, Middelink LM, Petho-Schramm A, Bernasconi C, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet. 2016;388(10042):343-55.
5. Kanarek N, Keys HR, Cantor JR, Lewis CA, Chan SH, Kunchok T, et al. Histidine catabolism is a major determinant of methotrexate sensitivity. Nature. 2018;559(7715):632-6.
6. Teitsma XM, Jacobs JWG, Mokry M, Borm MEA, Petho-Schramm A, van Laar JM, et al. Identification of differential co-expressed gene networks in early rheumatoid arthritis achieving sustained drug-free remission after treatment with a tocilizumab-based or methotrexate-based strategy. Arthritis Res Ther. 2017;19:10.
7. Teitsma XM, Jacobs JWG, de Jong PHP, Hazes JMW, Weel AEAM, Welsing PMJ, et al. Adding baseline protein biomarkers to clinical predictors does not enhance prediction of treatment response to a methotrexate strategy in early rheumatoid arthritis. Ann Rheum Dis. 2018;Published Online First: 29 August 2018. doi: 10.1136/annrheumdis-2018-213767.
8. Wang JM, Platt A, Upmanyu R, Germer S, Lei GY, Rabe C, et al. IL-6 pathway-driven investigation of response to IL-6 receptor inhibition in rheumatoid arthritis. BMJ Open. 2013;3(8).
9. Kapoor SR, Filer A, Fitzpatrick M, Fisher BA, Taylor PC, Buckley CD, et al. Metabolic profiling predicts response to anti-TNFα therapy in patients with rheumatoid arthritis. Arthritis Rheum. 2013;65(6):1448-56.
10. Young SP, Kapoor SR, Viant MR, Byrne JJ, Filer A, Buckley CD, et al. The impact of inflammation on metabolomic profiles in patients with arthritis. Arthritis Rheum. 2013;65(8):2015-23.