Can metabolomic profiling predict response to therapy?
McGrath, Catherine Mary; Young, Stephen

DOI: 10.1038/s41584-018-0136-z
License: None: All rights reserved

Document Version
Peer reviewed version

Citation for published version (Harvard):
McGrath, CM & Young, S 2018, 'Can metabolomic profiling predict response to therapy?', Nature Reviews Rheumatology. https://doi.org/10.1038/s41584-018-0136-z

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
First published in Nature Reviews Rheumatology (2018), McGrath et al, Can metabolomic profiling predict response to therapy?
https://doi.org/10.1038/s41584-018-0136-z

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
METABOLISM

Can metabolomic profiling predict response to therapy?

Catherine M. McGrath and Stephen P. Young

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.


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.

Catherine M. McGrath and Stephen P. Young*

Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.

*e-mail: s.p.young@bham.ac.uk
Acknowledgements

C.M. McGrath is funded by a Research Fellowship from the National Institute for Health Research.

Competing interests

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