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Metabolomics in rheumatology: the “omic” with the potential to provide a holistic view of the patient and their disease.

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The musculoskeletal system is a highly active metabolic system. Energy consumption is driven by the combined demands of skeletal muscle, turnover and remodelling of bone, cartilage and other structural components in response to changing levels of loading. The high energy respiratory chain is estimated to result in the turnover of approximately 65 kg per day of ATP for the whole body, increasing during periods of activity [1]. With skeletal muscle accounting for 30% of body mass in a postmenopausal woman (more in men) it is perhaps not surprising then that changes in metabolic activity are observed in musculoskeletal disease. Overall resting energy use is increased by about 8% in rheumatoid arthritis patients and, interestingly, a similar increase in metabolic activity is seen in patients who smoke, a well-established risk factor for the development of rheumatoid arthritis [2]. The mechanism underlying this increase in energy metabolism is unclear, but the active role of the immune system in the inflammatory processes in RA suggests that immune cell activation and turnover may contribute. There are also significant changes in liver metabolism, as a result of the acute phase response, and large shifts in systemic metabolism as a result of rheumatoid cachexia where muscle degradation occurs along with the related increase in the mass of body fat. Many of these metabolic changes can pre-date obvious joint symptoms, and metabolic pathways may change in response to therapy. It is not surprising therefore that there is increasing interest in using altered metabolites as biomarkers of disease activity and response to therapy. These studies may also provide novel insights into the pathological processes driving complex musculoskeletal disease.

Rheumatoid arthritis was first associated with altered levels of individual metabolites in a report from 1962 describing changes in the metabolism of tryptophan [3]. In recent years a more broad-ranging approach, metabolomics, has been applied to the assessment of the disease. Metabolomics is the new kid on the 'omics' block and comparable in scope to genomics, transcriptomics and proteomics. Through the study of small molecules (<1500 Da) within specific or multiple compartments (blood, urine, joints, saliva, eyes, tears, cerebrospinal fluid, intact cells), metabolite profiles or fingerprints, each containing thousands of metabolites, can be identified. In individuals at-risk due to genetics, their environment or both, disruptive pathological processes can result in altered metabolite profiles long before overt signs and symptoms of disease appear. The metabolites themselves can be identified and quantified using nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS).

Metabolite identification is done by reference to metabolite databases or by direct metabolite assay. The Human Metabolome Database lists most than 41,000 metabolite entries in the latest version, however, just 3,000 have been linked with diseases to-date [4]. In common with other "omics" approaches, metabolomics experiments generate prodigious amounts of data, but this is amenable to multivariate analysis techniques including principal components analysis, partial least squares discriminant analysis, regression methods and genetic algorithms.

Metabolomics studies have been reported for virtually all of the main rheumatological diseases, though notably none yet for systemic sclerosis [5]. Our own group has demonstrated the use of urinary metabolic fingerprint analysis to predict responses to anti-TNF [6] and we have suggested that metabolites resulting from TNF-driven cachexia are amongst the useful predictive biomarkers. Serum metabolic profiling can differentiate four types of human arthritis [7] and we have shown predictive value of the serum metabolite profile in early synovitis patients, with differences between those with self-limiting disease and those who went on to develop persistent RA [8]. The value of combining "omics" approaches has been demonstrated in a study using proteomics and

metabolomics to show alterations in both vitamin D3 metabolites and proteins in patients with ankylosing spondylitis [9]. The combination of genetic and metabolomic data [10] has shown the potential to identify genotype-influenced metabotypes in a number of chronic diseases.

Different cells types vary in their energy and metabolic requirements with cells undergoing proliferation being very different to those in a stable steady state. This applies to tissue cells such as synovial stroma and to immune cells including macrophages and T lymphocytes. Thus the state of immune activation and tissue hyperplasia may be strongly reflected in the metabolic profiles observed in tissues and in biofluids from patients, and so these may provide useful insights into the state of the disease and its aetiopathology.

Comprehensive clinical assessment approaches used by BILAG (British Isles Lupus Assessment Group) and SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) offer a clinical approach to individualised "systems medicine" by objectively quantifying components in a disease. Transcriptomics, proteomics and metabolomics are the biological equivalents to these clinical assessments. However, the sole analysis of tissues from the specific site of disease will miss the systemic changes commonly associated with complex diseases that may be responsible for driving the persistence and much of the associated comorbidity. Metabolism in different sites, such as the liver, vasculature, muscles and synovium are significantly altered in chronic inflammation and there is a widespread redistribution of body mass between muscle and fat driven by the inflammatory process. Environmental factors such as the microbiome, age, diet, gender and smoking, which are all significant risk factors for chronic inflammatory disease, also have profound effects on metabolism. Metabolomics therefore offers a unique approach to the assessment of disease, contributing to personalised medicine and the optimisation of diagnosis and therapy for these complex conditions.

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Conflicts of Interest.

The authors declare no conflicts of interest.

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