The Role of Metabolomics in Osteoarthritis Research

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Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

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Dr. Setton or an immediate family member has received royalties from Stryker Orthopaedics and Cytex Therapeutics; is a member of a speakers' bureau or has made paid presentations on behalf of, is an employee of, serves as a paid consultant to, and has stock or stock options held in Cytex Therapeutics; and serves as a board member, owner, officer, or committee member of the Orthopaedic Research Society and the Biomedical Engineering Society. Neither of the following authors nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Adams and Dr. Nettles.

J Am Acad Orthop Surg 2013;21: 63-64

http://dx.doi.org/10.5435/JAAOS-21-01-63

Metabolomics is the comprehensive analysis of small molecules in a biologic system. It has generated great interest by identifying novel biomarkers for disease diagnosis and pharmaceutical treatment, such as citrate and choline as biomarkers for prostate and breast cancer, respectively. Both tests are now clinically available and supported by most health insurance providers.[1,2]

Metabolites are the end products of cellular processes, and their levels can be regarded as the ultimate response of biologic systems to genotype, phenotype, and environmental conditions. They encompass a diverse group of low-molecular-weight compounds, including lipids, amino acids, peptides, nucleic acids, organic acids, vitamins, thiols, and carbohydrates,[3] and are commonly analyzed using nuclear magnetic resonance spectroscopy, liquid chromatography/mass spectrometry, and/or gas chromatography/mass spectrometry.

Metabolomics may be well suited for research into osteoarthritis (OA) for such reasons as the great heterogeneity in the disease process and recognition that no single biomarker can reflect the breadth of temporal and pathologic processes associated with OA.[4] Combining several biomarkers into a panel likely will increase the discriminatory capability,[5] as would occur with metabolic profiling. In addition, because metabolic perturbations occur in real time, they indicate the current disease state, which is a distinct advantage over current clinical diagnostics and disease-monitoring techniques for OA, such as radiography.

Metabolomics has been employed to detect metabolic perturbations in the urine, blood, synovium, and synovial fluid (SF) of animal models and patients with OA. Lamers et al[6] used nuclear magnetic resonance to study the urine from Dunkin Hartley guinea pigs that spontaneously develop OA. Disturbances in lactic acid, malic acid, hypoxanthine, and alanine were found to contribute heavily to the metabolic profile of OA. These investigators further studied the urine of humans with and without OA and found distinct patterns in the nuclear magnetic resonance spectra that discriminated between groups.[4] Zhai et al[7] employed metabolomics on human serum in a study of patients with and without knee OA. These investigators demonstrated that the ratios of valine and leucine to histidine were predictive of OA, thereby pointing toward interest in the use of branched-chain amino acids as potential biomarkers.[7] Many of these studies of venous plasma or urine identify metabolites that may be related to aging, altered muscle mass, and other factors that may confound the unique signature of a pathologic OA joint. For these reasons, SF may yield the most accurate, real-time, and joint-specific metabolic profile.

Damyanovich et al[8] performed metabolomics on SF from experimentally induced OA in canine knee joints. The nuclear magnetic resonance spectra demonstrated increased concentrations of lactate, pyruvate, glycerol, alanine, isoleucine, hydroxybutyrate, hydroxyisobutyrate, and lipoprotein-associated fatty acids. These investigators concluded that the intra-articular environment of OA

was more hypoxic and acidotic than in the normal joint and that arthritic joints may rely in part on altered lipid metabolic pathways.

We have performed metabolomics on both human synovium and SF. In our first study, the metabolic profile of conditioned media collected from synovium explant cultures was obtained for tissues from patients undergoing total knee arthroplasty (end-stage OA) and from patients undergoing ligament or meniscal repair with little or no evidence of OA.[9] Thirteen metabolites were significantly elevated in the end-stage OA group, including glutamine, succinate, and pro-hydroxyproline. Despite results suggestive of a distinct metabolic profile in OA, the synovium culture method does not easily translate into clinical practice.

In a second study, we performed metabolomics on ankle SF of patients with and without ankle OA.[10] Results identified 106 metabolites as significantly elevated in the OA samples and represented perturbations in virtually all metabolic pathways, including amino acid metabolism, carbohydrate metabolism, mitochondrial oxidation, lipid metabolism, peptide, vitamin, nucleotide synthesis, and oxidation-reduction homeostasis. More importantly, when a rigorous decision tree analysis was applied to the metabolic profiles of the two populations, a 90% discriminatory accuracy was achieved, indicating the potential use of this technology as a diagnostic tool for OA. Studies are ongoing to confirm these findings in a larger population and to generate a narrowed panel of metabolic biomarkers and measurement methods for translation into the clinic.

Metabolic profiling of biofluids and tissues can provide a panoramic view of the current physiologic state of a biologic system, such as the intra-articular environment of an osteoarthritic joint. We envision the role of metabolomics for OA as a clinically applied diagnostic tool in which a sample of a patient's SF would be analyzed for a panel of metabolite biomarkers, similar to following the serial values from a complete blood count. Alterations in the metabolic profile could indicate disease progression or a therapeutic response at a resolution not possible with currently employed clinical techniques.

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