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Review

Osteoarthritis Year in Review 2014: we need more biochemical biomarkers in qualification phase

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SUMMARY

The current diagnosis of osteoarthritis (OA) relies on the description of pain symptoms, affected joint stiffness, and radiography used as the reference technique for determining the grade of joint destruction. Limitations of the presently available diagnostic tests have provided an impetus for the substantial increase in interest in finding new specific biological markers for cartilage degradation to facilitate the early diagnosis of joint destruction, evaluate disease progression and improve disease prognosis. Biomarkers for OA are also useful for drug development, treatment monitoring, and as a basis for personalized evidence-based action plans. This review summarizes 29 manuscripts published during 2013 with a focus on soluble biochemical biomarkers, primarily those utilizing proteomic, metabolomics, lipidomic and imaging mass spectrometry technologies.

Introduction

An important objective for osteoarthritis (OA) research is the conceptualization and development of early diagnostic strategies. OA is clinically silent in most individuals during its initial stages, therefore extensive deterioration of cartilage already exists at the time of diagnosis. The current diagnosis of OA relies on the subjective description of pain symptoms by patients, affected joint stiffness, and radiography used as the reference technique for determining the grade of joint destruction. Limitations of the presently available diagnostic tests have provided an impetus for the increased interest in finding new specific biological markers for cartilage degradation to facilitate the early diagnosis of joint destruction, evaluate disease progression and improve disease prognosis.

A biomarker has been defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Biomarkers for OA are also useful for drug development, treatment monitoring, and as a basis for personalized evidence-based action plans. This “Year in Review” manuscript will focus on soluble biochemical biomarkers, primarily those studies utilizing proteomic and metabolomics technologies.

Methodology

Relevant articles and abstracts were identified through a PubMed/MEDLINE and EMBASE search of English language articles published between April 1, 2013 and April 1, 2014. The initial search strategy included the terms: osteoarthritis, biomarker, biomarkers, biological marker, proteomics, lipidomics, and metabolomics. The initial search yielded 153 articles. Human studies were then given preference over animal studies and biomarkers other than biochemical biomarkers were eliminated from consideration. Finally, 29 relevant articles were selected by the author according to their quality. In this review, the descriptions of and comments on the selected papers follow the phases of biomarker development shown in Fig. 1.

Phase I: discovery phase

Biomarker research involves a series of steps moving from discovery to the launch of a commercial biomarker product (Fig. 1). Proteomics and metabolomics have generated great expectations for discovery of biomarkers to improve the diagnosis of a wide range of diseases. There are two general approaches for proteomic biomarker discovery: global/nondirected and target-specific. Because global/nondirected approaches are unbiased and high-

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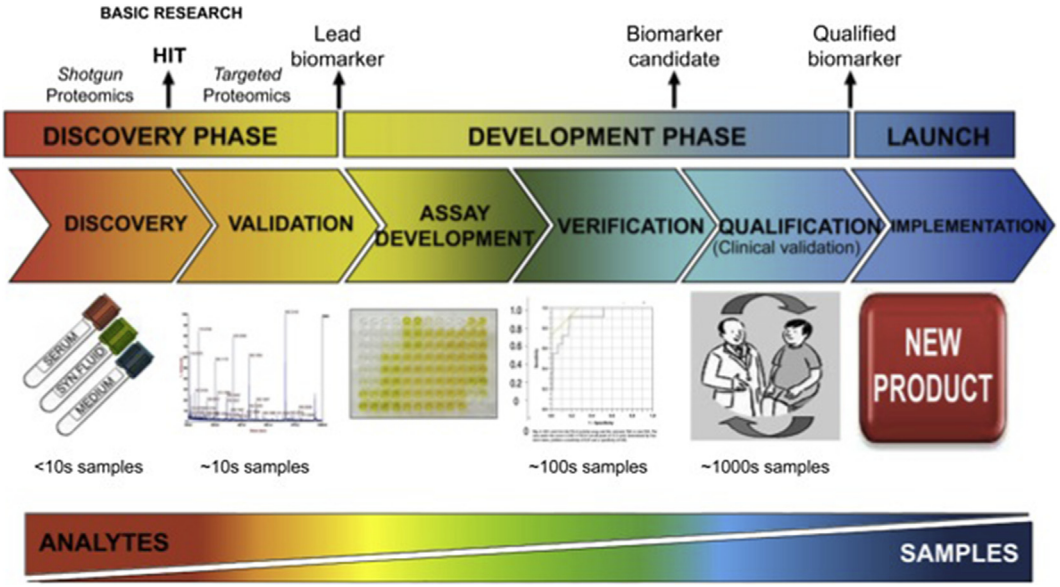

Fig. 1. Phases of proteomics biomarkers development. The Discovery phase encompasses discovery and analytical validation sub-phases. The aim of the Discovery phase is to find prospective biomarkers using a small number of samples. The Development phase is composed of assay development, verification and qualification (clinical validation) sub-phases. The aim of the Development phase is to define biomarker candidates and qualify/verify biomarkers using clinical application.

throughput screens, they possess an important potential for biomarker discovery. There are also two strategies for nondirected approaches: those that profile unidentified proteins and those that generate patterns of identified proteins. Profiling of unidentified proteins often, but not always, utilizes matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). Overall, the main advantage of nondirected approaches is speed in processing many samples, making them highly advantageous for clinical screening. However, target-specific approaches frequently use antibodies to screen specific proteins by utilizing western blot analysis, enzyme-linked immunosorbent assay (ELISA), or antibody arrays, making them useful for validation in the discovery phase (Fig. 1).

Blood (plasma and/or serum) and other body fluids are excellent sources of protein biomarkers for proteomic analyses because of their contact with most tissues. Through this contact, body fluids pick up proteins secreted or shed by tissues. A major advantage of using plasma and/or serum is ready availability. However, the proteins secreted or released from a specific tissue or cell type that hold the highest potential as biomarkers are often so diluted in blood as to make them undetectable by current methods. This has generated great interest on analyses focusing on “proximal” body fluids (i.e., synovial fluid [SF]), those that contact only one or a few tissues; thus less dilution of tissue-derived proteins would be expected.

Biomarkers in discovery phase

Because SF bathes all the intrinsic structures of diarthrodial joints, analyses of its constituents offer a unique opportunity to study the entire diseased OA joint. Three papers, using different approaches, have reported several biomarkers in SF[1–3]. Using two-dimensional differential gel electrophoresis (2D-DIGE) and MS, 66 proteins were identified as differentially present in healthy and OA SF[1]. Among these proteins, three major pathways were identified: the acute phase response, and the complement and coagulation pathways. An analysis focusing on those transcripts corresponding to the proteins found to be differentially present also indicated that synovial and cartilage tissues may both contribute to the OA SF proteome. This study also compared age-matched knee SF samples from control subjects and patients with early- and late-stage OA and found no important differences between the OA stages[1].

High-resolution MS identified 545 proteins not previously reported in OA SF[2]. However, multiple reaction monitoring (MRM) analysis validated only three of these proteins, aminopeptidase N (ANPEP), Dickkopf-related protein 3 (DKK3) and osteoglycin (OGN), in ten OA SF samples. Further evaluations of some of these newly identified proteins may reveal their potential as specific targets or useful biomarkers for OA. The authors suggest that improved knowledge of these proteins could provide insights into the underlying mechanism of OA pathogenesis and lead to better therapeutic strategies[2].

One of the major functions of SF in articular joints is lubrication of the surfaces of cartilage, menisci, tendons, and ligaments. Boundary lubrication by SF lowers the friction between apposed and pressurized articular cartilage surfaces. SF contacts 10% of the total joint area and is necessary to protect and maintain intact cartilage surfaces. Three major components of SF have been proposed to independently or additively mediate boundary lubrication: membrane phospholipids, lubricin, and hyaluronan (HA). Despite the evidence that phospholipids are important boundary lubricants, a complete qualitative and quantitative chemical analysis of all phospholipids in SF has only been possible since the recent development of sophisticated lipidomic methods. This technology has enabled the identification of all known phospholipid classes and many individual species in OA and rheumatoid arthritis (RA) SF. Certain phospholipids may act as boundary lubricants, while others perform functions, such as immune modulation during inflammation, cartilage destruction, cell differentiation, apoptosis, and signaling.

Quantitative differences were observed in 117 phospholipid species in SF obtained from the knees of control subjects and patients with early and late OA and RA[3]. Compared to controls, SF from patients with early and late OA had a higher content of total phospholipids, major phospholipid classes, and phospholipid species. .Furthermore, the concentrations of 66 phospholipid species were significantly altered depending on the stage of OA. These data indicate that disease- and stage-dependent differences exist in the