http://tandfonline.com/ibmk
ISSN: 1354-750X (print), 1366-5804 (electronic)

Biomarkers

Biomarkers, 2015; 20(8): 513–518
 DOI: 10.3109/1354750X.2016.1140930

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EDITORIAL

Biomarkers of (osteo)arthritis

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Abstract

Arthritic diseases are a major cause of disability and morbidity, and cause an enormous burden for health and social care systems globally. Osteoarthritis (OA) is the most common form of arthritis. The key risk factors for the development of OA are age, obesity, joint trauma or instability. Metabolic and endocrine diseases can also contribute to the pathogenesis of OA. There is accumulating evidence to suggest that OA is a whole-organ disease that is influenced by systemic mediators, inflammaging, innate immunity and the low-grade inflammation induced by metabolic syndrome. Although all joint tissues are implicated in disease progression in OA, articular cartilage has received the most attention in the context of aging, injury and disease. There is increasing emphasis on the early detection of OA as it has the capacity to target and treat the disease more effectively. Indeed it has been suggested that this is the era of ''personalized prevention'' for OA. However, the development of strategies for the prevention of OA require new and sensitive biomarker tools that can detect the disease in its molecular and pre-radiographic stage, before structural and functional alterations in cartilage integrity have occurred. There is also evidence to support a role for biomarkers in OA drug discovery, specifically the development of disease modifying osteoarthritis drugs. This Special Issue of Biomarkers is dedicated to recent progress in the field of OA biomarkers. The papers in this Special Issue review the current state-of-the-art and discuss the utility of OA biomarkers as diagnostic and prognostic tools.

Keywords

Arthritis, biomarker, diagnostic, musculoskeletal disorders, osteoarthritis, prognostic

History

Received 4 January 2016
Accepted 8 January 2016
Published online 7 March 2016

Introduction

The musculoskeletal system consists of the muscular and skeletal elements that support the weight of the body, maintain position and produce controlled and precise movements, thus facilitating locomotion. It includes bones, muscles, tendons and ligaments, articular cartilage and intervertebral discs in the spine. The musculoskeletal disorders (MSDs) represent a large variety of conditions that affect muscles, bones, joints and the spine. MSDs are caused by a number of factors including age, occupation, activity level and lifestyle, which are influenced by eating behavior and diet. The prevalence of MSDs is gradually increasing; an estimated 15% of Americans (40 million people) had some form or arthritis in 1995 and by the year 2020 it is estimated that 18.2% Americans (59.4 million individuals) will be affected (Lawrence et al., 1998). Arthritic diseases of synovial joints are some of the most common MSDs and the most common form of arthritis is osteoarthritis (OA). OA represents a major cause of disability and morbidity, and causes an enormous burden for health and social care systems globally. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability (Cross et al., 2014). The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. Cohort studies have demonstrated that after age, obesity and metabolic disease are major risk factors for the development of OA (Aspden et al.,

*The authors are members of the D-BOARD (http://www.d-board.eu/dboard/index.aspx) and APPROACH (http://www.approachproject.eu) Consortia. Both authors contributed equally to this paper.

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2001; Felson et al., 1988). OA is now accepted to be a whole-organ disease that is influenced by obesity (Bliddal et al., 2014), synovitis (De Lange-Brokaar et al., 2012), complement proteins (Wang et al., 2011), systemic inflammatory mediators (Berenbaum, 2013; Liu-Bryan & Terkeltaub, 2014), inflammaging (Greene & Loeser, 2015; Mobasheri et al., 2015), innate immunity (Orlowsky & Kraus, 2015) and the low-grade inflammation (Sellam & Berenbaum, 2013) induced by metabolic syndrome (Berenbaum, 2013; Courties et al., 2015) and diabetes mellitus (Louati et al., 2015). Inversely, OA is a risk factor for metabolic syndrome and cardiovascular diseases, suggesting that effective treatment of OA may prevent or delay the development of a large number of associated comorbidities (Haugen et al., 2013; Prior et al., 2014). However, despite the fact that all joint tissues are implicated in disease progression in OA, it is the articular cartilage component that has received the most attention in the context of aging, injury and disease (Buckwalter & Mankin, 1998).

Articular cartilage is a load-bearing connective tissue that serves as a template for the development of skeletal elements during embryogenesis (Archer & Francis-West, 2003) and is responsible for the smooth and friction-free joint articulation in synovial joints (Sandell, 2012). However, articular cartilage has a limited capacity for self-repair because of its avascular nature (Buckwalter & Mankin, 1998) and the low proliferation rate of chondrocytes, the main cells responsible for its physiological maintenance (Sandell & Aigner, 2001). Chondrocytes are the resident cell of the cartilage extracellular matrix (ECM). They exist in a unique niche that consists of collagen Type II, large aggregating proteoglycans (e.g. aggrecan), glycosaminoglycans, hyaluronan, other non-collagenous proteins (e.g. cartilage oligomeric matrix protein (COMP)), and a large amount of water and mobile cations (i.e. Na^+, K^+, Ca^{2+}); this composition allows cartilage to resist biomechanical forces during joint loading and physical activity (Jahr et al., 2015b).

Biomarkers

The National Institutes of Health (NIH) Biomarkers Definitions Working Group has defined a biomarker as ''a characteristic, i.e. objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention'' (Biomarkers Definitions Working Group, 2001). In essence biomarkers help healthcare professionals to diagnose illness, measure its progress and check how well novel or preexisting treatments work. Important biomarkers include:

- Biomarkers that help us to diagnose illness
- Biomarkers that help us to predict illness or
- Biomarkers that allow us to assess a patient's physical condition.

Approximately 10 years ago it became apparent that the OA researchers needed a definition of biomarkers for their own community. Accordingly, the NIH-funded OA Biomarkers Network was assembled. The group published an article in 2006 that summarized efforts to characterize and classify OA biomarkers. The group proposed the ''BIPED'' biomarker classification, which stands for Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic (Bauer et al., 2006). The ''BIPED'' classification was subsequently revised to BIPEDs include ''safety''. Use of this classification system has been encouraged to communicate these advances within a common framework and make OA biochemical marker research more transparent and efficient (Lafeber & van Spil, 2013), offering suggestions on optimal study design and the development of analytical methods for use in OA focused investigations (Bauer et al., 2006).

We now have an extensive list of OA biomarkers and efforts are currently under way to use some of these markers to identify sub-clinical and/or sub-acute inflammation, particularly in scenarios that are relevant to the clinical setting (Daghestani & Kraus, 2015). Consequently, there has been a significant change in our perception of OA, exemplified in a large shift in our outdated understanding of OA as a ''wear and tear'' disease to an inflammatory disease (Berenbaum, 2013; Daghestani & Kraus, 2015).

Biomarkers of joint disease

Although radiographs and other types of joint imaging are routinely used as ''gold standard'' diagnostic techniques for joint diseases (Braun & Gold, 2012), they do not have the capacity to measure dynamic changes in the joint. The diagnosis of OA is generally based on clinical and radiographic changes, which occur very late during the disease pathogenesis pathway and have poor sensitivity for monitoring disease progression (Rousseau & Delmas, 2007, Rousseau & Garnero, 2012). There are numerous different biochemical markers that can be measured in body fluids such as serum, urine and synovial fluid to complement biomedical imaging (Rousseau & Garnero, 2012). Biochemical markers or ''wet'' biomarkers can complement imaging and visual analog scales also known as ''dry'' biomarkers (Henrotin, 2012). Research conducted over the last four decades has demonstrated that the cartilage ECM is a rich source of biomarkers in joint diseases and many of these are now becoming established in the research community (Hedbom et al., 1992; Lohmander et al., 1994; Lotz et al., 2013). The maintenance of the ECM is compromised in aging, injury and disease and ECM components are degraded by catabolic enzymes in response to inflammatory mediators, producing ''fragments'' that are released into synovial fluid and the general circulation (Chockalingam et al., 2011). Although the identification of such fragments in synovial fluid, serum and urine does not consistently correlate with radiographic changes and symptoms such as pain and loss of mobility, fragments of Type II collagen, aggrecan and smaller proteoglycans can be measured as indicators or ''biomarkers'' of early joint disease (Larsson et al., 2012). They reflect metabolic changes that occur in joint tissues, which is an early and dynamic process that cannot be investigated by use of conventional medical imaging techniques. There is increasing emphasis on better characterization of early OA phenotypes and the early detection of molecular alterations in articular cartilage as this approach has the capacity to treat and target the disease more effectively (Conaghan, 2013). Indeed it has been suggested that this is the era of ''personalized prevention''

for OA (Roos & Arden, 2015). However, the development of strategies for the prevention of OA require new and highly sensitive biomarker tools that can detect the diseases in its molecular and pre-radiographic stage, long before structural and functional alterations in tissue integrity have occurred. However, finding biomarkers with the sensitivity and specificity to achieve this remains a challenging problem (Mobasheri, 2012). Although many laboratories are actively involved in identifying and developing new diagnostic and prognostic biomarkers of OA, radiographic imaging remains the ''gold standard'' for assessment of disease progression in OA and other forms of degenerative joint disease (Lotz et al., 2013).

Special issue: biomarkers of arthritis

This Special Issue will focus on recent progress in the field of OA biomarkers and their utility as diagnostic and prognostic tools. The content of some of the key papers in this Special Issue is summarized below.

As discussed earlier obesity is associated with an increased risk of developing OA, even in non-weight bearing joints. High levels of adipose tissue-associated cytokines may explain this association (Kluzek et al., 2015a). Stefan Kluzek, Nigel Arden and Julia Newton from Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford discuss the role of adipokines as potential prognostic biomarkers in patients with acute knee injury. Recent data suggests that adipokines produced by white adipose tissue, such as leptin, may provide a mechanistic link between obesity and OA, providing an explanation for the high prevalence of OA among obese and over-weight individuals (Scotece & Mobasheri, 2015). In their review Kluzek et al. discuss the role of leptin, resistin and vistfatin as key mediators of catabolic pathways associated with cartilage degeneration. Their article considers adipokines as predictive biomarkers for early onset post-traumatic knee osteoarthritis (Kluzek et al., 2015b).

In their article entitled: ''Chopping off the chondrocyte proteome'' Mona Dvir-Ginzberg and Eli Reich from the Hebrew University in Jerusalem discuss the biomarkers generated from chondrocytes upon increased protease activity. Specifically, they discuss the role of degraded and cleaved cellular proteins, rather than ECM fragments as less abundant biomarkers that may nevertheless exert significant adverse effects on cell metabolism and the cartilage secretome. They propose that subtle changes in the chondrocyte secretome could potentially act as markers of altered metabolism. They propose that combined biomarkers from both cell and ECM-degraded secretomes could provide a valuable platform for testing drug efficacy to halt OA progression during early stages (Dvir-Ginzberg & Reich, 2014).

''Big data'', machine learning and computational methods are starting to make an impact in the areas of chondrocyte biology (Henrotin et al., 2010) and OA biomarkers (Swan et al., 2015). Investigations into novel OA biomarkers using OMICS techniques generate large amounts of data. Due to their size and numbers of attributes, these data are suitable for analysis with machine learning methods. Roman Krawetz & Guomin Ren (2015) discuss the potential for applying computational biology and ''big data'' approaches to develop and refine multiplex diagnostics for complex chronic diseases such as OA.

In his State of the Union Address on 20 January 2015 President Barack Obama launched a new initiative on ''Precision Medicine'' [reviewed by Collins and Varmus (Collins & Varmus, 2015)]. Precision medicine is the preferred new term used to describe targeted and personalized approaches for treating chronic diseases. The article by Yves Henrotin et al. (2015) discusses the importance of soluble biomarkers in the development of personalized medicine strategies for OA.

Synovitis is another important and emerging risk factor for the development and progression of OA (Felson et al., 2015; Scanzello & Goldring, 2012). Interestingly, synovitis has hit the news several times over the last few years. In February 2013 Lady Gaga canceled the rest of her *Born This Way Ball* world tour because she developed debilitating synovitis[1,2]. She was unable to perform on stage due to severe joint inflammation and had to undergo surgery. In this Special Issue, Cecilie Kjelgaard-Petersen and her colleagues (2015) at Nordic Bioscience developed an *ex vivo* culture model of synovitis to characterize three biomarkers of inflammatory OA. It is hoped that further work on synovitis models will identify early marker of synovial inflammation, which is a key target for early intervention in OA.

In a second article in this Special Issue, Stefan Kluzek and coauthors (2015c) focus on serum COMP and how it levels correlate with the development of radiographic and painful knee OA in a community-based cohort of middle-aged women. Serum COMP appears to be a promising biomarker but further research is needed to further understand the association between COMP and long-term outcomes in this population.

Vanessa Abella and colleagues discuss the potential of Lipocalin2/NGAL as biomarker for inflammatory and metabolic diseases. LCN2 has emerged as a useful biomarker and rheumatic diseases. Their review provides an overview of LCN2 in inflammation, immunity, and metabolism (Abella et al., 2015).

Despite the fact that many drug targets reside on the plasma membrane there is insufficient knowledge about the chondrocyte membranome and its molecular composition. Csaba Matta and coauthors (2015) contribute an original research article that reports a modified phase partitioning technique for profiling integral membrane proteins in primary articular chondrocytes. The method uses an optimized Triton X-114 phase partitioning technique and LC-MS/MS analysis for protein identification. The method yielded a high proportion of membrane proteins (56%) including CD276, S100-A6 and three voltage-dependent anion channel isoforms. Defining the chondrocyte membranome is likely to reveal new biomarker targets for conventional and biological drug discovery.

[1]http://www.theweek.co.uk/health-science/51499/lady-gaga-cancels-gigs-due-inflamed-joint-condition

[2]http://www.huffingtonpost.com/2013/02/13/synovitis-lady-gaga-health-inflammation-joints_n_2678387.html

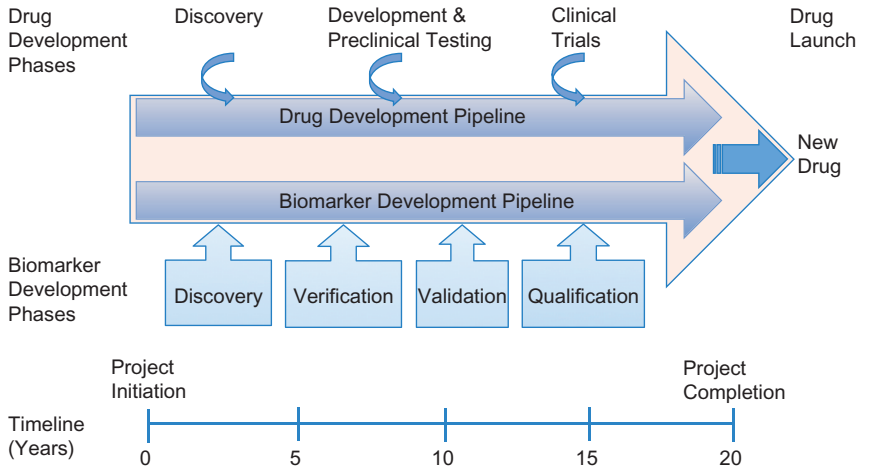

Figure 1. Applying the biomarker toolbox in the drug discovery and development pathway. This schematic highlights the mutual interdependency of the drug and biomarker development pipelines. Linking a biomarker to a complementary endpoint facilitates the drug discovery process and allows pharmaceutical companies to make rational decisions about the continuity of preclinical studies and clinical trials. Biomarkers can be used at critical decision points to make go/no-go decisions. They can also be used in translational research, bridging the gap between the bench and the bedside. Biomarkers can also be used to identify responders and non-responders and quantify clinical efficacy and patient stratification (i.e. identification of those in need of treatment and selection of patients most likely to respond to treatment). In phase II clinical trials biomarkers can be used for dose determination and safety/efficacy studies. They can also help pharmaceutical companies save costs by enabling drug repositioning and determining the cost/benefit ratio for treatment. In routine clinical practice biomarkers are important diagnostic and prognostic tools for monitoring disease development and monitoring patients compliance. They are also indispensable tools for pharmacovigilance, personalized and precision health care and differentiating compounds from competitors.

Finally, Holger Jahr and colleagues (2015a) contribute their perspective on detecting OA by optical coherence tomography (OCT), an emerging technology for performing high-resolution cross-sectional imaging. OCT is analogous to ultrasound imaging, except that it uses light instead of sound. Since many MSDs such as OA are associated with irreversible bone and cartilage damage, a clinical need exists for the development of imaging modalities that can detect structural changes at an early stage (Rashidifard et al., 2013). OCT may turn out to be a complementary technique for early OA diagnosis.

Conclusions

Biomarkers provide useful diagnostic information by detecting cartilage degradation in OA, reflecting disease-relevant biological activity and predicting the course of disease progression. They also serve as complementary endpoints in the drug discovery process (Mobasheri, 2012) (Figure 1). As such, biomarkers of joint tissue turnover (i.e. ECM fragments), cytokines and chemokines continue to be measured in different cohorts and community studies. This makes them highly complementary tools to imaging and visual analog scales for measuring pain symptoms. However, there is still a huge and unmet medical need to identify, test, validate and qualify novel and well-known biomarkers (Bay-Jensen et al., 2016; Hunter et al., 2014). Combining biochemical markers with tissue and cell imaging techniques and bioinformatics may facilitate the development of biomarker combinations enabling earlier detection of OA (Mobasheri, 2012). There is increasing evidence to support a role for biomarkers in drug development for OA (Mobasheri, 2013a,b). Various OMICs approaches and technologies are being used to identify new biomarkers and validate existing biomarkers, thus contributing to our understanding of joint disease development, progression and responses to therapy. The ultimate aim of these ongoing efforts is to develop surrogate and complementary endpoints in large-scale clinical trials and facilitate the discovery of disease modifying osteoarthritis drugs. There are recent guidelines from the Food and Drug Administration and the European Medicines Agency on qualification and usage of biomarkers for drug development and personalized medicine. These guidelines are likely to impact the design and implementation of future studies. The development of new and more sensitive analytical techniques for the identification of OA biomarkers will lead to further progress in this field. It should also be strongly emphasized that biomarkers reflect metabolic changes in joint tissues and that metabolic responses should be considered in addition to symptomatic or structural responses. Future papers on this topic will need to address some of the following questions:

- How can basic research in cartilage biology, chondrocyte physiology and ECM-derived biomarkers contribute to our understanding of OA?
- What is the rationale for identifying new biomarkers of OA and can current analytical platforms be refined to improve sensitivity and specificity?
- Can biomarkers help us define ‘‘early’’, ‘‘pre-radiographic’’ OA?
- How can biomarkers be used as drug development tools and surrogate end-points in OA clinical trials?

Researchers in the field of OA biomarkers must continue to tackle these challenging issues. They also need to decide whether the current definitions are fit for purpose. Perhaps future research in this area will need to adopt a broader

definition of the term ''biomarker'' and develop risk prediction tools that combine imaging, biochemical markers and patient specific data including lifestyle and physical activity. Such tools already exist in the form of FRAX, which assesses fracture probability in men and women (Kanis et al., 2009). A similar tool is needed for OA and biomarkers could potentially become important components of a future OA risk prediction tool.

Declaration of interest

The authors do not have any commercial relationships that could be construed as biased or inappropriate. The authors served as Guest Editors of this Special issue. They report no declarations of interests.

The authors are members of the D-BOARD Consortium[3] funded by European Commission Framework 7 program (EU FP7; HEALTH.2012.2.4.5-2, project number 305815, Novel Diagnostics and Biomarkers for Early Identification of Chronic Inflammatory Joint Diseases). They conceived the concept for the D-BOARD project and actively collaborated to build the consortium.

The authors are also members of the Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) Consortium,[4] a 5-year project funded by the European Commission's Innovative Medicines Initiative (IMI). APPROACH is a public-private partnership directed toward osteoarthritis biomarker development through the establishment of a heavily phenotyped and comprehensively analyzed longitudinal cohort. The research leading to these results has received partial support from the Innovative Medicines Initiative (IMI) Joint Undertaking under grant agreement No. 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework program (FP7/2007-2013) and EFPIA companies' in kind contribution.

Yves Henrotin is the Founder, Chairman of the Board, and President at Artialis SA (http://www.artialis.com). He is also the founder and the chairman of the board of the spin-off company of the University of Liège Synolyne Pharma SA (http://synolyne-pharma.com), a company developing medical device for the joint viscosupplementation and tissue repair.

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[3]http://www.d-board.eu/dboard/index.aspx
[4]http://www.approachproject.eu

Funding information

This study was funded by the European Commission Framework 7 programme (EU FP7; HEALTH.2012.2.4.5-2, project number 305815, Novel Diagnostics and Biomarkers for Early Identification of Chronic Inflammatory Joint Diseases, D-BOARD). This study has also received financial support from the Innovative Medicines Initiative (IMI) Joint Undertaking under grant agreement No. 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework program (FP7/2007-2013) and EFPIA companies' in kind contribution through the APPROACH consortium.

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