The future of deep phenotyping in osteoarthritis: How can high throughput omics technologies advance our understanding of the cellular and molecular taxonomy of the disease?

Ali Mobasheri a,b,c,d,*, Mohit Kapoor e,f,g, Shabana Amanda Ali h,i, Annemarie Lang j,k, Henning Madry l

ARTICLE INFO

Keywords:
Osteoarthritis
Phenotype
Endotype
Deep phenotyping
Stratification
Cellular taxonomy

ABSTRACT

Osteoarthritis (OA) is the most common form of musculoskeletal disease with significant healthcare costs and unmet needs in terms of early diagnosis and treatment. Many of the drugs that have been developed to treat OA failed in phase 2 and phase 3 clinical trials or produced inconclusive and ambiguous results. High throughput omics technologies are a powerful tool to better understand the mechanisms of the development of OA and other arthritic diseases. In this paper we outline the strategic reasons for increasingly applying deep phenotyping in OA for the benefit of gaining a better understanding of disease mechanisms and developing targeted treatments. This editorial is intended to launch a special themed issue of Osteoarthritis and Cartilage Open addressing the timely topic of “Advances in omics technologies for deep phenotyping in osteoarthritis”. High throughput omics technologies are increasingly being applied in mechanistic studies of OA and other arthritic diseases. Applying multi-omics approaches in OA is a high priority and will allow us to gather new information on disease pathogenesis at the cellular level, and integrate data from diverse omics technology platforms to enable deep phenotyping. We anticipate that new knowledge in this area will allow us to harness the power of Big Data Analytics and resolve the extremely complex and overlapping clinical phenotypes into molecular endotypes, revealing new information about the cellular taxonomy of OA and “druggable pathways”, thus facilitating future drug development.

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis across the world, 1,2 and a leading cause of disability in older adults [1]. In terms of prevalence, OA is the most common chronic, inflammatory and degenerative disease of synovial joints [2]. Approximately 80% of the population has some radiographic evidence of OA [1,3]. Moreover, it has been estimated more than 500 million people suffer from the debilitating
clinical symptoms of OA across the globe [4]. The incidence of OA is rising because of the ageing population and the epidemic of obesity [5–7]. Degradation and loss of articular cartilage is one of several hallmarks of OA, resulting in severe pain, loss of joint function and impaired quality of life [8] [9]. Despite the heavy burden of the disease on individuals, families, and healthcare systems, there are currently no disease-modifying OA-specific treatments authorized for clinical use [10]. Unfortunately, many OA clinical trials fail [11], with most trials conducted to date producing inconclusive results. For example, the trial of sprofermin (recombinant human fibroblast growth factor 18) did not lead to significant improvements in pain or other clinical outcomes over time when compared with placebo, although a beneficial modification of the articular cartilage structure was identified [12]. This means that the novel pharmacological [i.e. disease-modifying osteoarthritis drugs (DMOADs) [13–15]] and biological interventions that are currently being tested are unlikely to be approved by regulatory authorities unless they impact on both structure and symptoms, even if they include surrogate endpoints and post-marketing confirmatory data under the accelerated drug approval regulations set forth by the Food and Drug Administration (FDA) [16].

The definition of OA was updated in 2015 [17] but it is now time for an updated definition that includes endotypes, phenotypes and a more comprehensive cellular taxonomy of the disease, taking us beyond the realm of chondrocyte biology. There have been multiple appeals for a complete overhaul in OA clinical trial design [18], for example by using artificial intelligence (AI), data-mining and machine learning (ML) to stratify patients into different subtypes [19]. How these subtypes are defined, whether by genotype, phenotype, endotype, or completely different parameters, remains in question [20].

2. Improving clinical trials in OA and outdated recipes for failure

As a non-profit scientific organization for scientists and healthcare professionals focused on research to develop better prevention and treatment of OA, the Osteoarthritis Research Society International (OARSI) has launched various strategic initiatives to facilitate high quality clinical trials in OA to advance the development of DMOADs. The most recent efforts involved the OARSI/FDA Trial Guidance 2014 led by Francis Berenbaum. This was followed by comprehensive clinical trials guidelines conducted as an OARSI initiative in collaboration with industry and published as a special issue in Osteoarthritis and Cartilage in 2015 [21,22]. OARSI also initiated the FNIH OA Biomarkers Consortium, a public-private partnership in collaboration with several pharmaceutical and OA advocacy organizations to advance and formally qualify strategic imaging and soluble biomarkers that predict structural change and pain progression in knee OA [23]. This work also led to improved clinical trial designs for post-marketing approval of a drug based on biomarkers in 2019 [16], supporting the early OA initiative [24], and establishing new and accelerated pathways to drug approval for OA treatments [25].

Unfortunately many of these efforts have been largely unsuccessful. Improving the designs and outcomes of clinical trials in OA is absolutely crucial for the success of future DMOAD development. However, our present inability to stratify OA patients is a recipe for a series of catastrophic failures. The clinical features of OA are affected by many factors among which age [26], subject characteristics such as obesity and metabolic syndrome [27] or structural features such as joint alignment [28] are important contributors. Research using molecular and omics approaches in other inflammatory diseases have helped to understand the cellular taxonomy and resolve the extremely complex clinical phenotypes into molecular endotypes, revealing “druggable pathways” that have been specifically targeted to transform the way we treat allergy [29] and asthma [30]. Furthermore, the same omics approaches are facilitating our understanding of phenotypes and endotypes in other rheumatic diseases such as rheumatoid arthritis (RA) [31,32] and Sjögren’s syndrome [33,34]. So why are we not learning from other disease areas? Why do we keep referring to OA as a difficult to treat disease? We need to take the same endotyping and phenotyping approach in OA research and clinical development to pave the way towards personalized medicine.

One approach to enhance ongoing and future efforts in OA clinical trials is to build a stronger multidisciplinary understanding of disease pathogenesis at the cellular level in all synovial joint tissue compartments. Deep phenotyping in OA using high throughput omics technologies is an obvious way to advance the understanding of the molecular mechanisms of disease. Building a molecular and cellular taxonomy of OA that clearly defines alterations in phenotypes, not just the clinical morphotypes but the cellular phenotypes, in articular cartilage, meniscus, synovium, subchondral bone and the inflammatory cells that reside these joint tissue compartments (Fig. 1) that all are affected by OA is essential [32,35–39].

3. A serious disease needs seriously deep phenotyping

OA is a serious disease [40]. However, only two decades ago OA was viewed as a homogeneous, non-inflammatory “wear and tear” disease affecting mainly the articular cartilage component of the joint [41,42]. In sharp contrast, it is now considered to be an inflammatory disease [43,44] of the whole joint as an organ [45] resulting in more than just joint disease, but a chronic, long-term and persistent illness in the OA patient [46]. The complexity of the disease is one of reasons why OARSI initiated “OA as a serious disease” culminating in the publication and dissemination of a White Paper on the subject to the FDA in December 2016 [14].

The use of the term “degenerative joint disease (DJD)” supported the myth that OA is a disease of aging affecting a small proportion of the population for which there is no effective treatment, except non-steroidal anti-inflammatory drugs (NSAIDs) for pain mitigation [47] and ultimately total joint replacement. This unfortunate and fatalistic DJD concept proved counterproductive for basic and clinical research on OA, development of DMOADs, and implementation of lifestyle-based preventive interventions for OA because it provided “solutions” that appear attractive but essentially ignore the underlying causes. Furthermore, the lack of OA biomarkers, especially biomarkers of early disease, hampered the development of new and effective management and therapeutic strategies [48–50].

OA is a heterogeneous, multifactorial, multi-dimensional, multi-source, multi-origin and highly complex disease. Therefore, this presents several challenges: “How to phenotype OA?”; “Where do we start?”; and “Are there any obvious low hanging fruit that can be picked first?” To begin with, the tissues within OA joints may be stratified by an array of variables, some transient (e.g. flares) and others consistent (e.g. malalignment) throughout the disease process [51]. Clinical phenotypes are the morphotypes that are already known from careful clinical examination, and taking detailed information from patients about the natural history of the condition and their clinical manifestations. These are not necessarily hypothesis-driven but derived from clinical classification. It is important to note that there are no widely accepted early OA clinical classification criteria [52–55]. Currently it is not possible to stratify patients with OA into therapeutic groups. However, harmonising data collection from OA studies can enable stratification by collecting a list of optional clinical data in all OA interventional and observational (Fig. 2), providing a basis for future analyses to identify predictors of progression or response to treatment [56].

Approaches to OA phenotyping may come from clinical observation and patient outcomes [57,58] from consensus-based classification [36] or from unsupervised clustering and computational methods (Fig. 2) [19,59,60]. The granularity of the currently identified OA phenotypes, their
The cellular taxonomy of the synovial joint in health and disease. Many cell types are involved in the process of osteoarthritis development and progression but most of the research carried out to date has focused on articular chondrocytes. A more comprehensive cellular taxonomy should include all the cell types that are found within the synovial joint.

Strategy of phenotyping and stratification of a heterogeneous population of osteoarthritis patients. Using this approach biological and high throughput multi-omics platforms may be used for patient stratification into different phenotypic categories that further refine the initial clinical classification criteria.
precision and the methods for determining them currently produces a somewhat fuzzy and undecipherable picture, especially when looking at the diversity of subjects in the sixth decade of life and beyond. This is the typical age of most OA patients recruited for clinical trials and looking at the clinical phenotypes of these patients produces an overlapping picture that often involves multiple co-morbidities, including OA, cardiovascular disease, diabetes and other forms of metabolic disease. This hampers the identification of molecular profiles and endotypes and druggable pathways in OA.

OA disease mechanisms need to be investigated at the cellular level, ideally starting with well characterized OA biobanks and focusing on the single cell level, incorporating multi-omics techniques, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipomics and the emerging science of glycomics, among others (Fig. 2). The development of analysis pipelines that can handle diverse and complex data from these omics platforms is crucial for the success of computational and ML techniques. The use of multi-omics approaches will lead to an enhanced understanding of the molecular and cellular mechanisms involved in OA. This knowledge will also allow us to address some crucially important gaps in knowledge by facilitating the translation of research from preclinical models to clinical OA, creating new and exciting opportunities for “back translation” and “reverse engineering” of more disease relevant preclinical models that better reflect the complexities of the human disease.

4. The future of OA phenotyping: going deeper

High throughput omics technologies have been used for the study of normal physiological function of cells, tissues and organs in the musculoskeletal system and are increasingly being applied in mechanistic studies of arthritic diseases such as OA. Applying multi-omics approaches in OA will allow us to gather a wealth of new information on disease manifestations in preclinical models, translational models and human subjects/patients [61]. The development and application of sophisticated algorithms and open access databases to integrate that information will make deep phenotyping possible. The aim of this special issue of Osteoarthritis and Cartilage Open is to cover recent advances and emerging methods in high throughput omics technologies that enable deep phenotyping in OA. New knowledge in this area will allow us to harness the power of Big Data Analytics and make sense of molecular endotypes, cellular taxonomies and understand their relationships with morphotypes and clinical phenotypes.

Contributions

AM drafted the manuscript and the figures. All authors revised the manuscript critically for important content and approved the final version. All authors contributed to the revisions following peer review and take full responsibility for the accuracy and integrity of the information contained in this article.

Footnotes

The opinions expressed are those of the authors, and do not reflect the official policy of their academic institutions.

Funding

Ali Mobasheri has received funding from the following sources: 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). The Innovative Medicines Initiative Joint Undertaking under grant agreement No. 115770, resources of which are composed of financial contribution from the European Union’s Seventh Framework programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution. Ali Mobasheri also acknowledges funding from the European Commission through a Marie Curie Intra-European Fellowship for Career Development grant (project number 625746; acronym: CHOND-RION; FP7-PEOPLE-2013-IEF) and financial support from the European Structural and Social Funds (ES Strukturines Paramos) through the Research Council of Lithuania (Lietuvos Mokslu Taryba) according to the activity “Improvement of researchers’ qualification by implementing world-class R&D projects” of Measure No. 09.3.3-LMT-K-712 (grant application code: 09.3.3-LMT-K-712-01-0157, agreement No. DOTUS-T-215) and the new funding programme: “Attracting Foreign Researchers for Research Implementation (2018-2022)”, Grant No 01.2.2-LMT-K-718-02-0022.

Declaration of competing interest

AM is the president of OARSI. HM is the editor of Osteoarthritis and Cartilage Open. The authors have no financial conflicts to declare in connection with this article.

Acknowledgements

We wish to acknowledge all our colleagues and collaborators who have supported and encouraged us to enter the osteoarthritis field and remain engaged in this challenging area of research.

References

[1] D.J. Hunter, S. Biemer-زينسترا, Osteoarthritis, Lancet 393 (10182) (2019) 1745–1759, https://doi.org/10.1016/S0140-6736(19)30417-9.
[2] J.W.J. Bijloma, F. Berenbaum, F.P.J.G. Lafeber, Osteoarthritis: an update with relevance for clinical practice, Lancet 377 (9783) (2011) 2115-2126, https://doi.org/10.1016/S0140-6736(11)60243-2.
[3] D.T. Felson, A. Naimark, J. Anderson, L. Kazis, W. Castelli, R.F. Meenan, The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study, Arthritis Rheum. 30 (8) (1987) 914–918, https://doi.org/10.1002/art.178030811.
[4] D.J. Hunter, L. March, M. Chew, Osteoarthritis in 2020 and beyond: a lancet commission, Lancet 396 (10264) (2020) 1711–1712, https://doi.org/10.1016/S0140-6736(20)32256-0.
[5] H. Bliddal, A.R. Leeds, R. Christensen, Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review, Obes. Rev. 15 (7) (2014) 578-586, https://doi.org/10.1111/obr.12173.
[6] L.K. King, L. March, A. Anandacoomarasamy, Obesity & osteoarthritis, Indian J. Med. Res. 138 (2013) 185–193.
[7] S.P. Messier, Obesity and osteoarthritis disease genetics and nonpharmacologic weight management, Rheum. Dis. Clin. N. Am. 34 (3) (2008) 719–729, https://doi.org/10.1016/j.rdc.2008.04.007.
[8] J.A. Buckwalter, H.J. Mankin, A.J. Grodzinsky, Articular cartilage and osteoarthritis, Instr. Course Lect. 54 (2005) 465–480.
[9] T. Neogi, The epidemiology and impact of pain in osteoarthritis, Osteoarthritis Cartilage 21 (9) (2013) 1145–1153, https://doi.org/10.1016/j.joca.2013.03.018.
[10] S. Grønn, D. Muschter, Recent advances in the treatment of osteoarthritis, F1000 Res 9 (2020), https://doi.org/10.12688/f1000research.22115.1.
[11] D.B. Fogel, Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review, Contemp Clin Trials Commun 11 (2018) 156–164, https://doi.org/10.1016/j.cctc.2018.08.001.
[12] M.C. Hochberg, A. Guermazi, H. Guerbing, et al., Effect of intra-articular szipfermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial, J. Am. Med. Assoc. 322 (14) (2019) 1360–1370, https://doi.org/10.1001/jama.2019.14735.
[13] A. Latsurte, M. Kloppenburg, F. Richette, Emerging pharmacological therapies for osteoarthritis, Nat. Rev. Rheumatol. 16 (12) (2020) 673–688, https://doi.org/10.1038/s41584-020-00518-6.
[14] M. Sabha, R.C. Sliaton, M.C. Hochberg, Lorenzivin, an intra-articular potential disease-modifying osteoarthritis drug, Expert Opin. Invest. Drugs (November 2020) 1–7, https://doi.org/10.1080/13543784.2020.1842357.
[15] A. Ghouri, P.G. Conaghan, Prospects for therapies in osteoarthritis, Calcif. Tissue Int. (February 2020), https://doi.org/10.1007/s00223-020-00672-9.
[16] V.B. Kraus, I.S. Simon, J.N. Katz, et al., Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA’s accelerated approval regulations for disease modifying osteoarthritis drugs, Osteoarthritis Cartilage 27 (4) (2019) 571–579, https://doi.org/10.1016/j.joca.2018.11.002.
[17] V.B. Kraus, F.J. Blanco, M. Englund, M.A. Karsdal, L.S. Lohmander, Call for standardization of osteoarthritis and risk stratification for clinical trials and clinical use, Osteoarthritis Cartilage 23 (8) (2015) 1233–1241, https://doi.org/10.1016/j.joca.2015.03.016.
