Toward wiping out osteoarthritis in China: research highlights

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Introduction

Osteoarthritis (OA) is currently considered as more than a degenerative disorder of weight-bearing joints, instead one organ disease of "all-joint" due to cause(s) of aging, injury, inflammation, metabolic disorders, *etc*. Its prevalence is high: 9.6% in men and 18.0% in women aged over 60 years. Most health professionals say that OA is incurable and focus exclusively on palliative treatment, as we lack effective disease modifying osteoarthritis drugs (DMOADs).[1] But should we hope that treating OA precisely in China is possible through intensive research and drug development?

Current status of OA research in China

Over the past 4 years, 3009 papers on OA from China appeared in PubMed, giving a total of 5359 (by the end of 2019), more than double the number of previous papers combined (a total of 2350 by the end of 2015). These papers cover the mechanisms of aging,[2,3] inflammation, catabolism,[2] joint degeneration,[2,3] cell survival or death,[3,4] synovial fibrosis,[3] stemness and regeneration,[5] and immunity,[6] as well as risk factors like age, obesity, metabolic syndrome,[7,8] ethnicity, gender, injury, joint stress and bone deformities. Other papers have covered epidemiological surveys,[9] sports medicine,[3] traditional Chinese medicine, rehabilitation[3] and drug safety.[10] A precision medicine (PM) initiative was launched to examine patient cohorts in China, although a high quality patient cohort and biobank is lacking. To address this, a multi-omics systems-based approach to PM has begun to build a patient cohort from early to advanced-stage OA of the knee, hip and spine, while a new biobank collects fluids, tissues, and cryopreserved cells.

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Progress in understanding the endogenous mechanisms of OA

We have discovered many OA pathogenesis genes that are targeted during drug development, and discovered their inhibitors, including those encoding proinflammatory factors like tumor necrosis factor-α and interleukin-1, which are also combatted by anti-inflammatory drugs (*eg*, dexamethasone and celecoxib[11]). Other targets include genes for aging and development (both for articular cartilage), autophagy and protein synthesis regulation, such as those encoding mammalian target of rapamycin (mTOR) complex 1 (mTORC1)[2-4] (it functions as a master regulator in autophagy, a mechanism for which Dr. Yoshinori Ohsumi has been awarded 2016 Nobel Prize in Physiology or Medicine), matrix metalloproteinase, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), growth factors, Cathepsin-k, the Wnt/β-catenin pathway, vascular endothelial growth factor, inhibitor of nuclear factor kappa-B kinase (IKK), nitric oxide (NO), and genes crucial for subchondral bone development such as estrogen receptors and cyclooxygenase (COX)-2. However, we still lack DMOADs.

Promising therapeutic DMOADs

The Wnt inhibitors specifically targeting the canonical Wnt pathway are promising, including SM04690, a small-molecule inhibitor of the Wnt pathway for treating moderate to severe knee OA that appears safe and has a positive effect on joint pain and function.[12] Another is Sprifermin (recombinant human fibroblast growth factor 18), which was subjected to a double-blind, randomized placebo-controlled trial (intra-articular administration of 100 μg Sprifermin every 6 or 12 months in patients with severe knee OA)[13] and revealed no serious safety concerns along with improved total femorotibial joint cartilage thickness after 2 years.

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Platforms for OA drug screening

Translating promising candidates into clinical success often fails. The ideal drug needs to stop pain and joint destruction by preventing cartilage cell death and synovitis (either inflammation or fibrosis) while protecting bones, with minimal or no side effects. However, DMOAD development has been hampered by a lack of experimental models that replicate OA disease status. Animal models have problems with funding support, time constraints, ethical concerns and debate over whether animal studies mirror the effects in humans.[14] However, the new cartilage-on-a-chip (COAC) platform may allow high-throughput drug screening for OA. For this, a microfluidic cartilaginous micro-construct is generated in a 3D micro-environment[15] through culturing adult human articular chondrocytes in a synthetic polyethylene glycol hydrogel with an adequate culture medium contact surface. The resulting COAC is rich in type II collagen and aggrecan, and can mimic OA traits through mechanical cyclical rounds of hydrogel confinement, compression and stimulation at the genetic and cellular levels without cytokines, a paradigm shift for *in vitro* models. It is even more effective than *ex vivo* and *in vitro* models with pro-inflammatory cytokines. The effects of anakinra, rapamycin, and celecoxib have been demonstrated on COACs. For drug screening purposes, COAC needs to develop into a high-throughput system with increased model complexity and new tissue–tissue interfaces to create a "joint on a chip".

An integrative bioinformatics platform (https://www.biorxiv.org/content/10.1101/243998v1) for rapid identification and validation of novel rheumatoid arthritis drug treatments also has potential for OA drug screening together with Nanning National Engineering Center of Chinese Herbal Medicine Garden.

Recent research highlights

In addition to the COAC method, other milestones in OA research have been reached. OA was recognized by the US Food and Drug Administration as a serious disease, as it increases the mortality rate of dysmotility patients up to double that of healthy controls

Mechanism-based drug development research has spread from autophagy-related aging research to multiomics-based PM, with the promise of novel insights into OA taxonomy and potential recommendations and guidelines in China. One project is investigating rapamycin modifications[3,16] to enable chondrocytes to survive longer in articular cartilage. For PM, deep phenotyping and understanding the complex pathophysiology of OA, multi-omics platforms require next-generation sequencing (NGS) platforms and a team including bioinformaticians, biostatisticians and computational biologists. The metabolomics platform plus metabolomics bioinformaticians alongside artificial intelligence (AI) can be used for phenotyping, outcome prediction and uncovering disease mechanisms. Single molecule array technology, which allows ultrasensitive and precise detection of protein and nucleic acid biomarkers for accurate taxonomy, can be combined with the omics of imaging technology to develop stable, detectable and quantifiable biomarkers.

Non-surgical management of OA is another promising area. Optimization of musculoskeletal health has been discussed worldwide and in China, with acupuncture and Tai Chi now included in the Osteoarthritis Research Society International (OARSI) guidelines for managing knee OA. The "Good Life with osteoArthritis in Denmark" (GLAD) program was introduced to China for people with hip or knee OA, resulting in reduced pain and improvement in daily activity and quality of life. The GLAD program involves two education sessions and 12 tailored neuromuscular exercise sessions.

Updates of OA clinical trials, classification and taxonomy, and clinical guidelines are needed in China. Several OA multi-center clinical trials are investigating alone or a combination of traditional Chinese medicine Celastol, Qufengzhitong capsule and more. OA classifications and updated OA guidelines for China have been also been drafted by an expert panel. Papers on these are in preparation.

Our focus for the future

Several topics need to be addressed to treat OA precisely. Unquestionably, aging[17,18] is generally the most important OA risk factor. Aging is related to several mechanisms, such as soma–germline distinction, epigenetics, autophagy, reactive oxygen species, vitamin D receptors, *etc*. Targeting these systems to delay aging may be meaningful for preventing OA. People currently live much longer with OA because of joint injury and obesity than decades ago. Thus, injury prevention, reducing obesity and even changes in the microbiome may also help treate OA precisely.[19]

Regarding aging turning points,[17,18] we could have suggested that the degenerative OA process roughly begins at 30 to 34 years old. Biomarkers or magnetic resonance imaging (MRI) can detect OA genesis as changes in the composition of bone, cartilage and soft tissues at 35 to 50-year-olds. Later, MRI scans can reveal structural changes in the bone, cartilage, and other soft tissues at 51 to 60 years, followed by X-ray detection of structural changes in bone (*ie,* joint failure) at 61 to 70 years. End-stage disease (*ie,* joint death) generally occurs at 71 to 78 years old, therefore total knee/hip arthroplasty (TKA/THA) or total knee replacement (TKR)/hip and knee replacement (HKR) often happen. The aging process might be delayed to prevent OA, which is a major focus of mTOR and autophagy research.[2-4] The reversible turning point could be detected via high-dimension multi-omics data.

One gap remaining in OA research understands how cartilage degenerates and when this process starts. If we can detect degeneration during the early phases of OA, could we stop or delay it?

Issues in China

Chinese government may give OA researchers more funding along with "Healthy China 2030". Last year, we wrote a guideline for the national key R&D program for OA, osteoporosis and bone fracture, which aimed to accelerate Chinese OA research. However, for Chinese translational research to be fully effective, we need mental

and cultural change to create an environment of copyright and patent protection. Besides, we need to move toward more national and international collaboration and develop new open and fair systems to evaluate translational researchers and institutions against superficial achievements, focusing instead on innovation, originality and impact to develop the career path of OA researchers in hospitals. We also need to tighten the relationships between academia and the industry and create new training programs for translational researchers and/or ambitious youth, OA research proposal layman-targeted version, OA research foundation alongside donations to foster frontiers, OA patients-engaged in symposiums, as well as creating biobank systems.

It usually takes 15 years for evidence from reviews, papers and textbooks to be implemented into clinical practice. However, Chinese government may improve the efficacy of OA translational medicine by integrating healthcare, academia and the industry through its unique powerful executive system. Moreover, Shenzhen has been recently approved as the pilot demonstration area of socialism with Chinese characteristics embracing an innovation. Its local companies such as Tencent Inc. and BGI-Shenzhen indeed have the strength in bioinformatics, machine learning and artificial intelligence. This may provide novel analytics and computational approaches to link imaging with OA tissue and joint mal-function. Consequently, they might help realize the precision medicine of combining clinical and imaging parameters for DMOAD trials.

In conclusion, although tremendous progress has been made toward treating OA precisely, we need further effort including developing high-throughput platforms for DMOAD screening, which will help us reach our goal.

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Conflicts of interest

None.

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