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Advances in osteoarthritis research: From diagnosis, treatment to mechanism studies

Osteoarthritis (OA) is the most common form of degenerative joint disease globally, affecting an estimated 500 million individuals over the age of 40. Patients with OA usually suffer from unbearable joint pain, crepitus on joint motion, stiffness, limited function, and even disability, thereby reducing their life quality. Current OA diagnosis relies on imaging technique and the symptoms and clinical signs; however, the current algorithm for imaging analysis is unable to predict early stage OA. OA has been primarily characterized by articular hyaline cartilage degeneration, as well as synovitis, osteophyte formation, and subchondral bone remodeling. The underlying molecular mechanisms and potential therapeutic targets of OA are still elusive. Due to insufficient understanding of the underlying mechanisms of OA, the development of disease-modifying treatment to alleviate the progression of OA is largely hindered. In this special issue, we have 13 articles including studies of OA diagnosis, molecular mechanisms, and various treatment strategies by small molecules, biophysical method or scaffold-based biomaterial interventions.

OA is a disease affecting all tissues in the joint. The functions of all joint tissues are essential in the development of OA. The anterior cruciate ligament (ACL), connecting the anterior intercondylar area of tibia with the inner surface of lateral condyle, is one of the major static and dynamic stabilizers for the maintenance of knee stability. It is well-recognized that ACL tear is a key risk factor for OA initiation and progression; therefore, the ACL transection animal model has been generally used in preclinical OA studies. However, the relationship between intrinsic ACL degeneration and OA progression is still unclear. To investigate this clinical-related issue, Luo et al. reported a nested case–control study revealing the association between alterations of signal intensity of ACL, ACL volume and the incidence of knee OA using the data generated in the Osteoarthritis Initiative (OAI) study [1]. Through conditional logistic regression analysis, they found alterations of signal intensity, but not the ACL volumes, were associated with increased the incidence of knee OA during 4-year studying period. Their results indicated that changes in compositional characteristics of ACL is more important in the development of knee OA. This study may be helpful to understand the initiation of OA and provide evidences for the early prediction and prevention of OA.

The acetabular labrum is responsible for hip joint stability and plays a fundamental role in cartilage homeostasis by distributing load, transducing mechanical stress, and regulating joint lubrication. Whereas, the molecular characteristics underlying labrum deterioration in hip OA remain poorly understood. Antoniadis et al. observed approximate 40 % of degenerated hip OA labra were fall into calcification, and further revealed that the secretion of pro-collagen-I alpha (Pro-Col-Iα) and vascular endothelial growth factor (VEGF) was significantly elevated in the degenerated human acetabular labrum, which was partially regulated by TGF-β signaling [2]. They provided Pro-Col-Iα and VEGF as potential diagnostic biomarkers for hip OA to help evaluating sub-radiographic labrum degeneration and calcification.

For patients with end-stage knee OA, total knee arthroplasty (TKA) is usually recommended to alleviate their pain and improve joint function; however, the subsequent development of arthrofibrosis will largely reduce the effectiveness of TKA. Few options could be chosen to tackle this problem due to lack of specific information about diagnostic biomarkers. In this issue, Chen et al. identified G-protein-coupled receptor 17 (GPR17) as a potential biomarker for the diagnosis of arthrofibrosis after reviewing 373,461 published literature by ChatGPT [3]. Further analysis leads to the identification of 21 drugs that might target GPR17, among which, pranlukast and montelukast showed therapeutic effect in animal models, providing diagnosis and potential therapeutic targets of arthrofibrosis.

Non-surgical OA managements are classified as non-pharmacological and pharmacological treatments. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for the pharmacological management of OA for decades. The development of novel disease-modifying OA treatment has been limited due to incomplete understanding of molecular mechanisms of OA disease. Chondrocyte dysfunction and cartilage erosion are the main reasons for articular cartilage degeneration and OA progression. Senescent chondrocytes usually exhibited impaired regenerative capacity and imbalanced metabolism of extracellular matrix proteins. Recently, Zhang et al. reported a new chondrocyte senescence regulator, transcription factor 12 (TCF12) [4]. In damaged areas of OA articular cartilage and IL-1β--treated chondrocytes, the TCF12 expression was significantly upregulated. Knocking down TCF12 by lentivirus effectively suppressed the expression of chondrocyte senescence markers (p16, p53, and p21) in the OA mouse model induced by DMM surgery. Furthermore, the luciferase reporter assay and ChIP qPCR analysis unveiled that TCF12 could directly bind to the promoter region of CXCR4 and enhance CXCR4 transcription, resulting in chondrocyte senescence ultimately.

Pyroptosis is a type of programmed cell death that triggered by caspases and inflammasomes. Chondrocyte pyroptosis was shown to be involved in OA pathogenesis, but its underlying mechanisms were elusive. Tang et al. investigated the role of guanylate binding protein 5 (GBP5) in cellular inflammatory responses and chondrocyte pyroptosis and found that GBP5 expression was upregulated in TNF-α-induced chondrocyte inflammation and in articular cartilage derived from OA patients and OA mouse models [5]. Overexpression of GBP5 evidently accelerated chondrocyte pyroptosis; in contrast, downregulation of

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GBP5 significantly abolished chondrocyte pyroptosis and alleviated OA progression. Further, the binding of interferon regulatory factor 1 (IRF1) to GBP5 promoter potentiated GBP5 expression. This study highlighted the importance of modulating IRF1/GBP5 axis in OA treatment.

The expression of a large number of genes undergoes significant changes during OA development. Through bioinformatics analysis of the transcriptomic data from Gene Expression Omnibus (GEO) database, Liu et al. screened 470 upregulated and 215 downregulated genes in OA mice and revealed that TGF-β pathway might play an important role in OA development, among which neuron regeneration related protein (NREP), an upstream molecule targeting TGF-β, has been identified [6]. They observed significantly downregulated expression of NREP in OA cartilage and knockdown of NREP inactivated the TGF-β1/Smad2/3 pathway, resulting in suppressed chondrocyte proliferation, impaired expression of anabolic markers (Col2a1 and Sox9), and enhanced expression of catabolic markers (MMP3 and MMP13). Their findings provide evidence of targeting NREP to attenuate OA progression. Regarding the SLC26A2 deficiency-related skeletal diseases, Li et al. revealed that genetic ablation or pharmacological inhibition of FGFR3 signaling pathway exhibited promising therapeutic implications for cartilage diseases [7].

Estrogen has been showed to protect OA development. This finding need to be further confirmed and the related mechanisms are not clear. Targeting estrogen receptor, G protein-coupled receptor 30 (GPR30), may help us further understand the action and mechanism of estrogen on OA. Zhao et al. recently reported that GPR30 was downregulated in the OA cartilage tissues, and pharmacologically activated GPR30 by its agonist, G1, significantly rescued chondrocyte viability under the treatment of ferroptosis inducer [8]. Further, they revealed that GPR30 activation protected chondrocytes against ferroptosis by suppressing YAP1 phosphorylation, and thus promoting the expression of FTH1, a classical ferroptosis suppressor.

Based on the discovery that blood infiltration caused heterotopic ossification of injured tendon, Chen et al. revealed significantly activated PI3K/AKT signaling pathway in this process and verified that PI3K inhibition by a small molecule drug LY294002 reduced tendon heterotopic ossification [9]. Their study may provide new perspectives on understanding the pathological mechanisms of articular cartilage calcification. Together, these studies provided new insights into the molecular mechanisms of OA and other cartilage related diseases.

Recently, several small molecules were proposed as candidates for the treatment of OA and cartilage defects caused by other reasons. Ferroptosis is characterized as an iron-dependent programmed cell death that essentially caused by massive lipid peroxidation. Chondrocyte ferroptosis was considered as an important pathogenesis that promotes OA progression. To address this issue, Sun et al. determined potential anti-ferroptosis drugs on OA and revealed that the mitochondria targeting antioxidant nitroxide compound XJB-5-131 could significantly suppressed the activity of reactive oxygen species, lipid peroxidation, and Fe^{2+} accumulation induced by tert-butyl hydroperoxide (TBHP) [10]. They further confirmed that the anti-ferroptosis effect of XJB-5-131 is through suppressing the expression of ferroptotic drivers and promoted the expression of ferroptotic suppressors. Intra-articular injection of XJB-5-131 significantly attenuated OA progression, mechanistically, by restoring the expression of Pebp1.

To enhance the mesenchymal stem cells (MSCs)-based cartilage repair and regeneration, Gao et al. reported a novel non-toxic small molecule, JD-312, that could potentiate chondrogenic differentiation [11]. They found MSCs that transient induced by JD-312 before intra-articular administration improved cartilage regeneration and increased Col2a1 and Acan expression, in the DMM-induced OA model. Moreover, direct intraarticular injection of JD-312 in mice OA model also showed reduced articular cartilage loss, suggesting the attenuated OA progression. Together, the findings reported by above studies provided potential drug options for the alleviation of OA progression.

In addition to small molecule drugs, there are also several OA treatment strategies proposed. Lee et al. tested whether low-intensity pulsed ultrasound (LIPUS) could be used for the treatment of OA [12]. They found that daily LIPUS treatment (0.1W/cm^2 peak intensity, 3 MHz pulse frequency, and 20 % duty cycle) in rat OA model significantly mitigated cartilage degradation and alteration of bone micro-architecture, as well as relieved OA pain. Further, LIPUS treatment suppressed osteoclastogenesis and sensory innervation. These findings provide new avenues for the early intervention of OA by using LIPUS.

Decellularized extracellular matrix has attracted considerable attention in cartilage regeneration; however, whether microfracture technique is essential in this strategy has not been carefully investigated. To deal with this issue, Peng et al. created full-thickness articular cartilage defect in the weight-bearing area of sheep femoral condyles and found that the human articular cartilage-derived extracellular matrix (hACECM) alone is sufficient and safe for cartilage regeneration, providing evidences for future decellularized extracellular matrix-based cartilage repair strategies [13].

Taken together, the topics in this special issue are ranging from the diagnosis, treatment and molecular mechanisms of OA and provided us with the latest progress on OA research in various aspects. Although further investigations are needed, the information provided in this issue significantly contributes to the translational OA research.

Declaration of competing interest

The authors declared that no conflict of interest exists in this work.

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