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Editorial

Advances in osteoarthritis research in 2021 and beyond

Osteoarthritis (OA) affects 7% of global population, over 500 million people worldwide. It is a leading cause of chronic pain and disability in older adults. OA not only affects large joints in knee and hip, but also medium and small joints in hand, facet joints in spine, and temporomandibular joint (TMJ). Degenerative disc disease (DDD) also exhibits loss of joint space, subchondral sclerosis, and osteophytes, similar to OA in the articular joint. Both DDD and facet joint spinal OA contribute to low back pain (LBP). According to a recent systematic analysis, it has been a major global public health concern with population ageing and obesity as one of highest causes for the years lived with disability (YLDs) in 1990–2019 [1].

The hallmark of OA is loss of articular cartilage that cushions the joint during the movement. Unluckily, articular cartilage cannot heal by itself once being damaged. Cytotherapy holds a good promise to repair damaged cartilage in OA joint. Costal chondrocytes are a good donor cell source but have strong tendency of hypertrophy and calcification. Recently, synovium-derived stromal cells could prevent the hypertrophic differentiation of costal chondrocytes to achieve better outcome of cartilage repair [2]. In addition, in-depth understanding of the molecular mechanism underlying OA cartilage pathology will define novel targets for OA treatment. In this issue, Wnt/β-catenin, TGF-β and BMP, Indian Hedgehog, FGF, NF-κB, and Notch pathways have been summarized in the context of TMJ OA [3]. Alterations of these signaling pathways lead to the pathological changes in OA tissues, affecting cartilage matrix degradation, catabolic metabolism and chondrocyte apoptosis. Naringin, a flavanone glycoside that is abundant in citrus fruits, was recently reported to facilitate cartilage repair possibly via modulation of the TGF-β/ALK5/Smad2/3 signal transduction pathway in a rabbit model [4]. Beyond these well-known signaling pathways, clusterin, an ATP-independent holdase chaperone that prevents proteotoxicity as a consequence of protein aggregation, was proposed to possess cytoprotective functions in osteoarticular tissues [5]. The secreted form of clusterin could be measured in synovial and systemic fluids and may have translational potential as a biomarker of early repair responses in OA. Furthermore, latest research identified the focal adhesion protein Kindlin-2 in regulating chondrogenesis and skeletogenesis through its expression in osterix-expressing osteoprogenitor cells [6]. This finding opens a new avenue to develop Kindlin-2 as a novel target for treatment of skeletal diseases, such as chondrodysplasia and osteoporosis.

Subchondral bone disturbance also plays an important role in OA pathophysiology [7,8]. Subchondral bone marrow edema with cystic lesion formation was characterized histologically as increased osteoclastogenesis and nerve growth, which associated with clinical symptoms, joint pain, in Chinese knee OA patients [9]. Subchondral bone pathologies in OA are subject to the interplay between local and systemic risk factors. In addition to abnormal mechanical loading due to joint injury and instability, hypertension is an emerging systemic risk factor of OA in knee and hip independent of other metabolic factors, including obesity, diabetes, and so on [10]. Noteworthily, high blood pressure is a two-edge weapon to affect subchondral bone remodeling [11]. On one side, high systolic blood pressure and pulse pressure, as well as heart beating, might contribute to maintain bone mineral density. However, on the other side, high pulse pressure and heart rate could aggravate the imbalance in subchondral bone plate-rod ratio to alter its mechanical properties and to worsen OA joint deterioration. Cystic lesion was also proposed as a consequence of vascular insult [12]. In this regard, it is necessary to revisit the histological and imaging features, and clinical staging classification systems of osteonecrosis of femoral head, a common cause of secondary hip OA [13].

There is no cure for OA till now. Intra-articular injections of hyaluronic acid (HA) is one of the most frequently performed therapies for symptom relief in knee OA. However, the conflicting results were reported. An update-to-date meta-analysis of 16 randomized controlled clinical trials out of 1820 articles was conducted, revealing that HA is not an effective intervention for knee OA with increased risk of adverse events [14]. Through integrated multi-organ transcriptomics, the authors attempted to answer the question ‘why is it ineffective?’. Results unraveled that HA not only upregulated the local expression of Mmp13 and pro-inflammatory cytokines IL-1β and TNFα, but also triggered systemic inflammation via the activation of B cell proliferation.

Every little makes a mickle. In this special issue, all of our endeavors lay a solid foundation to combat OA by introducing novel research strategy, elucidating signaling interactions in OA pathogenesis from tissue down to molecular levels, discovering novel diagnostic/prognostic markers or therapeutic targets. We envision curing OA in near future and set it as the target for global OA alliance and Asian Task Force.

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