Recent Progress in Osteoarthritis Research

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Osteoarthritis (OA) is a degenerative joint disease and is characterized by articular cartilage degeneration, subchondral bone sclerosis, and osteophyte formation with major clinical symptoms, including chronic pain, joint instability, stiffness, and radiographic joint space narrowing.[1] OA is the most common form of arthritis and is a leading cause of impaired mobility in the elderly. It has been forecast that 25% of the adult population, or >50 million people in the United States, will be affected by OA by the year 2020, and it will be a major cause of morbidity and physical limitation among individuals older than 40 years. In addition to the well-documented impact of OA on physical function and quality of life, depression, and anxiety, there is a significant financial burden, with aggregate annual medical expenditures exceeding $185 billion in 2008.[2]

A variety of risk factors has been identified in the initiation and/or progression of OA, including age, gender, traumatic injury, obesity, metabolic dysfunction, and environmental and genetic factors.[1] Despite extensive research over the past 20 years to delineate the pathogenic mechanism or mechanisms of OA, a full understanding of the initiators of the disease and the factors that accelerate OA progression is yet to be achieved. Thus, there is no clinical diagnosis for early OA and no effective disease-modifying treatment of late OA other than pain-relieving medication or the replacement of damaged joints.[1]

Normal articular cartilage that emerges during the postnatal stage as a permanent tissue distinct from the growth plate cartilage is a smooth, hard, white tissue that lines the surface of all diarthrodial joints. Collagens and proteoglycans are the principle extracellular matrix (ECM) molecules of articular cartilage. Mutations of ECM-related factors, including types II, IX, and XI collagen, have been reported in OA patients.[1] Articular chondrocytes are the cells responsible for the maintenance of articular cartilage. As such, the dysregulation of this cell is directly connected to the process of cartilage degeneration in OA. Thus, understanding the phenotypic behavior of articular chondrocytes in homeostasis and disease has made us aware of several key environmental and genetic factors that affect OA initiation and progression.

In earlier decades, the surgically induced destabilization of medial meniscus model, as well as genetic mouse models, were developed and demonstrated potential roles of affected genes in OA pathogenesis. Transforming growth factor (TGF)-β/Smad, Wnt/β-catenin, Notch, and Indian hedgehog pathways have demonstrated the critical and unique roles of chondrocytes during OA development and progression by stimulating chondrocytes toward hypertrophy.[1] Recent genetic findings further suggest that *Runx2*, *Mmp13*, and *Adamts5* are common target genes involved in the above-mentioned signaling networks to disrupt the metabolic and catabolic balance in chondrocytes; they eventually degrade cartilage matrix by upregulation of matrix metalloproteinases and a disintegrin and

Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

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Dr. Chen or an immediate family member has received research or institutional support from Amgen. Neither Dr. Shen nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

J Am Acad Orthop Surg 2014;22: 467-468

http://dx.doi.org/10.5435/JAAOS-22-07-467

metalloproteinase with thrombospondin motifs (ADAMTS) activity and by downregulation of type II collagen and aggrecan synthesis.[1] Recent studies of genome-wide association screens have been performed in large numbers of OA and control populations throughout the world and have confirmed several critical signaling molecules previously implicated by mouse genetic and injury-induced animal models, including the Wnt (Sfrp3), bone morphogenetic protein (Gdf5), and TGF-β (Smad3) signaling pathways.[1] In addition to the single-nucleotide polymorphisms analysis, growing evidence points to the fact that the gene expression profile can be largely regulated by epigenetic machinery, modulating the local transcriptional activity and manipulating mRNA expression through a microRNA-mediated regulatory mechanism.[3] Recent genome-wide methylation screening in patients with OA revealed different DNA methylation signatures in both synoviocytes and chondrocytes, indicating that epigenetic changes can influence OA susceptibility and severity.[4] Epigenetic modification of *Mmp13* and *Adamts5* was also observed during OA development and progression, indicating that epigenetic factors may also play a role in the pathophysiology of OA.[3]

In addition to articular chondrocytes, other cell types, such as the mesenchymal stem cell in subchondral bone and synovial fibroblasts, contribute to OA progression. TGF-βs, in response to abnormal mechanical loading, were found to be released, activated, and accumulated in the subchondral bone in patients with OA, leading to aberrant bone formation and angiogenesis through recruitment of osteoprogenitor cells.[5] Both injury and obesity-induced low-grade inflammation have been widely recognized as contributing factors to synovial tissue expansion and to hyperplasia in the early onset of OA. The inflammatory factors and ECM-degrading enzymes facilitate OA progression.[6] As these underlying mechanisms are further delineated, manipulation of several critical molecules could serve as potential key targets for therapeutic intervention for the treatment of OA disease.

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