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Special Article- Etiology of Osteoarthritis

Etiology of Osteoarthritis

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Editorial

Osteoarthritis (OA) is the most prevalent joint disease associated with pain and disability [1]. It is characterized by degeneration of articular cartilage, synovial inflammation, and changes in peri-articular and subchondral bone. OA is not simply a process of wear and tear but rather an organ resulting in abnormal remodeling and joint failure [2]. Multiple risk factors involved in the disease pathogenesis include age, gender, genetic factors, prior joint injury, and mechanical influences [3].

Aging

One of the most common risk factors for OA is age. Structural OA of one or more joints is reported in a majority of people over the age of 65 in North America and Europe [4]. Studies using articular chondrocytes suggest that aging cells show excessive mechanical loading and elevated oxidative stress that promotes cell senescence and mitochondrial dysfunction [5]. Moreover, reduced repair response in aging chondrocytes may contribute to OA mechanisms. In chondrocytes from aged and OA cartilage, increased production of TGF-β together with an elevated ALK1 to ALK5 ratio might affect homeostasis of both the cartilage and bone in joints [6].

Obesity

Obesity is a strong and well-established risk factor for the progression of OA [7]. Incidence of knee OA progressing to hip replacement among adults aged ≥40 years is reported to be approximately five times as frequent among morbidly obese individuals

(BMI ≥35 kg m^{-2}) compared with individuals of a healthy weight (BMI ≤22 kg m^{-2}) [8]. The link between of obesity and knee OA creates a negative feedback loop in which pain from OA can greatly limit a person's physical activity, thus promoting further weight gain and weakening of muscles that stabilize and protect joints, which in turn can exacerbate pain and OA progression. In addition to increased biomechanical loading on the knee joint, obesity is thought to contribute to low-grade systemic inflammation through secretion of adipokines [9].

Inflammation

It has been established that the chronic low-grade inflammation found in OA contributes to disease development and progression. During OA progression, the entire synovial joint, including cartilage, synovium, and subchondral bone, are involved in the inflammation process. Articular chondrocytes increase the synthesis of matrix molecules but also contribute to their own destruction by synthesising pro inflammatory cytokines, Including Interleukin (IL)-1β, Il-6 and Tumor Necrosis Factor alpha (TNF-α), as well as chemokine's [10,11]. These inflammatory factors may trigger the Nuclear Factor-κB (NF-κB) signaling pathway to stimulate an articular chondrocyte catabolic process and lead to Extracellular Matrix (ECM) degradation through the up regulation of tissue-destructive enzymes such as Matrix Metallo Proteinase (MMPs) and metalloproteinase with thrombospondin motifs (ADAMTS)6 [12]. Extensive cellular changes are accompanied by increased expression of molecules related to chondrocyte hypertrophy and terminal differentiation, such as Vascular Endothelial Growth Factor (VEGF), Runt-Related Transcription Factor 2 (RUNX2) and MMP13 [13]. The normally quiescent chondrocytes undergo a phenotypic shift to become activated cells. Chondrocyte proliferation, cluster formation and increased production of matrix proteins and enzymes that degrade specific ECM proteins are followed by amplified catabolic activity leading to matrix remodeling and cartilage damage [14].

Sport Injury and Physical Inactivity

Joint trauma is the major cause of OA in young adults, increasing the risk for OA, especially cartilage tissue tear, joint dislocation, meniscal and anterior cruciate ligament tears, which can lead to abnormal stress gradients and excess focal stress within cartilage. Trauma-related sport injuries can cause the entire joint, involving all joint tissues containing bone, cartilage, ligament, and meniscus damage, all of which can negatively affect joint stabilization [15].

Even if sport injury is detrimental to joint health, this does not mean that all forms of physical inactivity are beneficial for joints. Pathways by which physical inactivity can increase OA risk include indirect promotion of obesity and metaflammation and depression [16]. Moreover, a reduction in loading as a result of a physically inactive lifestyle might cause formation of weaker and less stable joints that are more susceptible to damage and deterioration. Increasing evidence suggests that physical activity, particularly joint loading, is important for developing and maintaining healthy knee joints. MRI studies have shown that people who regularly engage in weight-bearing exercise maintain thicker cartilage [17]. However, Joints with structural abnormalities might not be adept at withstanding loads imparted by physical activity. In people with high baseline cartilage volume, exposure to heavy occupational and recreational activity slowed the rate of cartilage loss, whereas the same exposure expedited cartilage loss among people with lower baseline cartilage volume [18].

Genetics

Genetic, signaling pathways and epidemiological studies have helped to establish the important role of genetic factors in the risk for the development of OA. Alterations in TGF-β, Wnt/β-catenin, Indian Hedgehog (Ihh), Notch pathways have been shown to contribute to

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OA development and progression by regulating the homeostasis of bone-cartilage unit [19,20]. Such responses converge on Hypoxia-Inducible Factor-2a (HIF-2a), Runx2, and inflammatory mediators that lead to cartilage ECM degradation through the increased expression of MMPs and ADAMTS activity [21,22]. An imbalance of molecular interactions may also lead to cartilage damage and subchondral bone remodeling.

Recent studies of Genome-Wide Association Screens (GWAS) that have been performed several common variants associated with knee or hip OA [23,24]. Some of the genes are important structural and ECM-related factors (Col2a1, Col9a1, and Col11a1), and critical signaling molecules in the Wnt (Sfrp3), Bone Morphogenetic Protein (BMP) (Gdf5), and TGF-β (Smad3) signaling pathways. The identification of these genes can be applied to develop biomarkers that can be used to detect individuals at high risk for the development of OA and to explore the molecular mechanisms involved in OA pathogenesis.

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