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Hylonome

Perspective Article

Summary - Osteoarthrosis: Animal models and imaging

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Osteoarthritis (OA) is the most common joint disorder. Although it has been considered a so-called non-inflammatory form of joint disease, it is frequently associated with signs and symptoms of inflammation, including pain, stiffness and loss of mobility leading to significant functional impairment and disability[1]. Anatomically, OA is characterized by progressive loss of articular cartilage, increased subchondral plate thickness, formation of new bone at the joint margins (osteophytes) and the development of subchondral bone cysts[1-9]. In addition, at the junction of the articular hyaline cartilage and adjacent subchondral bone, there is evidence of vascular invasion and advancement in the zone of calcified cartilage that further contributes to a decrease in articular cartilage thickness[2,10-14]. These structural alterations in the articular cartilage and peri-articular bone may lead to modification of the contours of the adjacent articulating surfaces, and thus contribute to the progression of the osteoarthritic process[7-9,15-19].

Multiple factors affect the natural history of OA, including the presence of polyarticular disease, increasing age, associated intra-articular crystal deposition, obesity, joint instability and/or malalignment, muscle weakness and peripheral neuropathy[1,20-30]. It has been suggested that these risk factors can be segregated into two fundamental mechanisms related either to the adverse effects of "abnormal" loading on normal cartilage or "normal" loading on "abnormal" cartilage. Aging has been suggested as the primary factor contributing to this "abnormal" state of articular cartilage, although genetic factors that determine the regulation of chondrocyte function and composition and structure of the cartilage matrix also contribute, independent of the influence of the aging process. It is important to note that, whereas changes in the composition and structure of the cartilage matrix is inevitable, the development of OA with aging, while common, is not universal[31].

Multiple studies have provided insights into the effects of aging on articular cartilage. These changes include softening of the articular surface and a decrease in the tensile strength and stiffness of the cartilage matrix. These changes in part have been attributed to alterations in the proteoglycan and collagen content, composition and structural organization[31-43]. For example, aggrecan, which is the major cartilage proteoglycan, decreases in molecular size and its content diminishes with aging. In addition there is evidence of an accumulation of advanced glycation end products (AGEs) leading to enhanced collagen cross-linking, which contributes to an increase in cartilage stiffness and altered biomechanical properties.

The chondrocyte is the only cell type residing in the cartilage matrix. This cell, which is believed to have a low metabolic activity and to possess little regenerative capacity, is ultimately responsible for remodeling the cartilage matrix and maintaining its structural and functional integrity. There is evidence that the capacity of the chondrocyte to remodel and repair the cartilage ECM (Extracellular Matrix) diminishes with age. This has been attributed primarily to a decrease in the anabolic capacity of this cell[39,43]. Although there appears to be an increase in chondrocyte apoptosis in OA, there is also evidence of chondrocyte cloning that has been interpreted as localized attempts at tissue regeneration and repair[33,35-37]. It has also been suggested that the accumulation in the endoplasmic reticulum and golgi of chondrocytes of cartilage matrix proteins that have been modified by oxidant stress during aging leads to decreased type II collagen synthesis and eventual chondrocyte apoptosis[38,44,45].

Although there remains debate regarding the essential role of synovial inflammation in OA, numerous studies have documented the presence of synovitis in this condition[46-49]. The effects of synovial inflammation provide an additional factor that likely contributes to dysregulation of chondrocyte function, favoring an imbalance between the catabolic and anabolic activities of the chondrocyte in remodeling the cartilage ECM.

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In addition to the potentially adverse effects of synovial inflammation on chondrocyte function, the synovial products may also contribute to the symptoms of pain, which is the most prominent but least well studied feature of OA. According to data from the World Health Organization it is estimated that 10% of the world's population over the age of 60 suffers from pain related to OA[50]. In general, noxius mechanical stimuli are detected by a specific group of sensory nerves (type III and IV afferents) that are located in the joint capsule, ligaments, periosteum and subchondral bone[51-56]. These pain-sensing fibers, termed nociceptors, have a high threshold of activation. Movement of the joint induces the opening of mechanogated ion channels located in the terminals of the sensory nerves resulting in depolarization and nerve firing[57]. The action potentials are propagated to the central nervous system that translates the electrical activity into mechanosensation. When the limits of physiologic joint movement are exceeded, then the nerve firing dramatically increases and the central nervous system interprets these signals as pain.

Developing models for assessing the pathogenetic factors and mechanisms responsible for joint pain in OA has been very challenging because of the subjective nature of pain and the complex role of cognitive interpretation of sensory information. Recent studies by Schuelert and McDougall[58] have shown that the mechanosensory nerves become sensitized in animals with experimental OA, resulting in an increase in afferent firing rate even in response to physiologic joint motion. They also implicated vasoactive intestinal peptide (VIP) as a locally produced sensitizing agent that enhances pain perception. In more recent studies, employing the Dunkin Hartley guinea pig model of spontaneous OA, they observed that afferent firing for a given level of joint torque was significantly enhanced in older compared to younger animals. They speculated that joint nociception might be age-dependent, although they could not exclude the possibility that the more advanced OA in the older animals may have contributed to the enhanced sensitivity.

Whereas pain represents the most prominent clinical manifestation associated with OA, the structural deterioration that characterizes this joint disorder represents the major factor contributing to disability and impaired quality of life. The availability of non-invasive techniques for monitoring the effects of therapeutic interventions on the structural and functional properties of cartilage matrix are therefore of critical importance. The introduction of magnetic resonance imaging (MRI) techniques in recent years offers significant promise for addressing this need.

MRI imaging techniques have been used to successfully quantify articular cartilage morphology, volume and thickness and to identify focal defects. In addition, the technology can be adapted to characterize changes in the composition of the ECM[59-63]. This information is of particular interest since cartilage thinning in OA is preceded by modification in the composition and structural organization of the collagen-proteoglycan matrix. These changes in matrix composition are associated with alterations in cartilage relaxation times T_2 and $T_{1\rho}$, and well as in the uptake of contrast agents such as Gd-DTPA[61,63]. In addition, alterations in the subchondral bone marrow accompany both OA and injury, and these changes can be detected by an increase in the signal intensity in the bone marrow on fat-saturated T_2-weighted images[64,65]. The presence of so-called bone marrow edema has been of particular interest, since this finding has been associated with the progression and severity of OA[64]. Additional potential applications of MRI imaging are also being developed for applications in monitoring results in stem cell regeneration treatment strategies. Recently, investigators have utilized MRI to detect transplanted cells after labeling with super paramagnetic iron oxide (SPIO) particles[66]. The SPIO contrast agent is metabolized by the cells, increasing their magnetic susceptibility, and as a result the cells appear as hypo-intense regions permitting their tissue detection and localization. Such techniques hold promise for tracking cell survival and outcomes in models of cartilage regeneration.

In summary, OA is the most common joint disorder. It affects large segments of the population and leads to significant disability and impaired quality of life. An understanding of the cellular processes that regulate the functional activities of chondrocytes in both physiological and pathological conditions is essential to the development of more effective strategies for treating patients with OA and altering the natural history of this disorder. Improved techniques for monitoring the effects of therapeutic interventions on the structural and functional properties of cartilage matrix are needed. In addition, the role of peri-articular bone remodeling and synovial inflammation on the natural history and outcomes in OA need to be more clearly defined. Importantly, more information is needed regarding the origin of pain and related symptoms in OA, so that more effective treatment strategies can be developed.

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