JOINT VENTURES

Osteoarthritis: A New Paradigm

Until the late 20th century, osteoarthritis was thought to represent a passive consequence of wear and tear on the joints, an inevitable consequence of aging. Our 21st-century model considers OA to be an inflammatory, cell-driven condition affecting the entire joint, including not only cartilage but also bone, synovium, muscles, and ligaments, and to be influenced by age, mechanical stress, and genetic traits. Clinical features include osteophyte formation, subchondral bone remodeling, alteration in chondrocyte phenotype, degeneration of articular cartilage, and ultimately progressive joint destruction.

BY FRANCIS BERENBAUM, M.D., PH.D.

Research has helped elucidate the roles played by chondrocytes, soluble mediators, and mechanical receptors. Understanding the biochemical and biophysical events involved may open the door to specific disease-modifying therapeutic interventions.

Structural and Mechanical Factors

Chondrocytes are the sole cellular component of cartilage and are responsible for maintaining the structural and functional integrity of the cartilage matrix. They arise during prenatal skeletal development from mesenchymal progenitors, and are metabolically inactive, maintaining a state of equilibrium between anabolic and catabolic processes.

Advances in cartilage biology have shown that mechanoreceptors are present on the surface of chondrocytes. These receptors, such as integrin and CD44, can respond to compression, stretching, or other mechanical stress with upregulation of inflammatory mediators, including cytokines. They also can activate signaling pathways, such as the mitogen-activated protein kinase and NF-kappaB pathways, as well as second-signal messengers such as calcium and inositol triphosphate.

Additionally, cilia that have long been recognized as being present on the surface of chondrocytes have recently been identified as being another type of mechanoreceptor by which the cell processes information about local mechanical factors.

In the context of the structural changes seen in early OA, chondrocytes can upregulate the synthesis of growth factors and proteins that stimulate matrix production, but can also release proteolytic enzymes such as matrix metalloproteinases that promote matrix degradation and downregulation of processes essential for cartilage repair. Unless this process can be inhibited, the result is destruction of the cartilage matrix.

Though our conceptualization of OA formerly focused on the destruction of articular cartilage, we now know that changes in bone—and particularly subchondral bone—also contribute significantly. We have learned that chondrocytes and osteoblasts communicate through intricate molecular networks and growth factors to coordinate the degradation and repair of cartilage and bone.

OA as a Metabolic Disease

Clearly, aging and obesity are risk factors for OA, with senescent cartilage being characterized by surface roughening, stiffness, and decreased hydration, and with chondrocytes showing decreased anabolic activity. But aging and OA are not the same process; rather, the structural changes associated with aging enhance the susceptibility of the tissue to matrix degradation.

The connection of obesity and OA has received much attention in recent years. Although overload stress may contribute to knee and hip degradation in the obese, the finding that obesity also is associated with OA in non–weight bearing joints (the hands) suggests the relationship is more complex. Investigations into the physiology of adipose tissue have confirmed this.

Adipose tissue is not simply a passive fat-storage repository, but rather an endocrine organ with various factors (known as adipokines) deriving from adipose tissue and acting within a neuroendocrine-immune network as molecular links between obesity and various inflammatory and autoimmune disorders, including atherosclerosis, diabetes, and OA.

This organ is composed of lipid-filled adipocytes. Adipocytes share a common mesenchymal stem-cell origin with osteoblasts, chondrocytes, and myoblasts, and secrete numerous adipokines, including leptin, adiponectin, and resistin, all of which are found in the synovial fluid of patients with OA and rheumatoid arthritis.

Leptin, the most studied of these factors, is the product of the ob gene and is involved in weight, appetite, and satiety. It also has multiple activities associated with lipid and glucose metabolism, insulin sensitivity, bone formation, and cartilage homeostasis, where it has been found in chondrocytes and shown to be capable of triggering signal transduction.

Various investigations have implicated leptin as being a central player in OA. Its expression is upregulated in articular tissues—including subchondral bone—that undergo physiologic changes in the disorder, and it appears to trigger cartilage destruction and loss of cartilage matrix through the induction of apoptosis and the activation of metalloproteinases. It circulates at high levels in patients who are obese.

Another recently discovered adipokine is visfatin (or pre–B-cell colony-enhancing factor), secreted by chondrocytes as well as by adipose tissue, skeletal muscle, and directly from the joint. We have described the role of visfatin in cartilage homeostasis in OA and its production by chondrocytes, which is increased by interleukin-1β and induces proinflammatory mediators (such as prostaglandin E_2) and prodegradative mediators (such as matrix metalloproteinases). Visfatin also is an insulin analog, may be a mediator of late-stage inflammation, and appears to have an important catabolic role in OA (Arthritis Rheum. 2008;58:1399-409).

Future Research

Another new area of research in OA involves the embryonic differentiation of the chondrocyte, which derives from a specific lineage of mesenchymal cells. It appears that dysregulation of the chondrocyte may occur even at the embryonic stage, with genes that are involved in early cell differentiation exhibiting abnormal reactivation 50 or 60 years later, for reasons we do not yet understand.

Many promising areas of investigation into the pathogenesis of OA have opened up in recent years and are ongoing. In the near future, we should expect novel therapeutic approaches not only for pain relief but for targeting pathologic targets and interrupting the disease process itself. ■

Key Points

- ► Osteoarthritis is now considered to be a systemic inflammatory condition that affects all components of the joint, including subchondral bone.
- ► Chondrocytes and osteoblasts communicate with one another via molecular networks and growth factors to coordinate the degradation and repair of cartilage and bone.
- ► A complex relationship between OA and obesity exists, with circulating adipokines, secreted by adipose tissue, being involved in bone formation and cartilage hemostasis.
- ► Future approaches to treatment will include the targeting of specific pathological processes with the goal of interrupting the disease process itself.

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Don't Be Fooled by Normal Serum Urate in Acute Gout

BY BRUCE JANCIN
Denver Bureau

PARIS — Serum urate levels are often normal during acute gouty arthritis attacks, according to Dr. Naomi Schlesinger.

In the study of 339 patients with acute gouty arthritis whose serum urate levels were measured, 29% of individuals on chronicallopurinol had a true-normal serum urate level, defined as 6 mg/dL or less. Among patients not on the hypouricemic agent, 11% had a true-normal serum urate level during their acute episode of gout.

"This may be attributed to the persistence of tophi and a resultant increased body uric acid pool," commented Dr. Schlesinger, chief of rheumatology at Robert Wood Johnson Medical School, Camden, N.J.

With a less stringent definition of normal serum urate—a value of 8 mg/dL or less—49% of allopurinol users were classified as having a normal level during their acute attack, as were 29% not on allopurinol, according to data she presented at the annual congress of the European League Against Rheumatism.

The 339 patients included in Dr. Schlesinger's analysis were participants in one of two earlier randomized clinical trials assessing the efficacy of 1 week of etoricoxib or indomethacin therapy in acute gout. Although Dr. Schlesinger wasn't involved in the original studies, she obtained the complete data for both and combined the two study populations because efficacy was similar for both drugs. Prior investigations included just 41 patients (J. Rheumatol. 2002;29:1950-3), and her own earlier study of 59 patients (J. Rheumatol. 1997;24:2265-6).

Laboratory measurements in 339 patients—including serum urate as assessed by the uricase enzyme method—were obtained at baseline and on days 2, 5, and 8. The mean serum urate at baseline was 7.6 mg/dL in patients on long-term allopurinol and 8.5 mg/dL in those who weren't. Similarly, on day 8, following a week of nonsteroidal anti-inflammatory drug therapy, the mean serum urate was 7.4 mg/dL in those on allopurinol and 8.7 mg/dL in those who were not. Patients with a history of more than four gouty attacks per year or with polyarticular attacks had higher serum urate during the episode studied than those without those characteristics.

In response to audience questions, Dr. Schlesinger said it has previously been shown that an acute gouty arthritis attack can be initiated by any significant change in serum urate, whether an increase or decrease. In some cases, however, serum urate falls secondary to the acute attack as a result of cytokines released during the episode.

Dr. Schlesinger disclosed that Merck & Co. provided her with access to the complete data from the two company-sponsored clinical trials as well as support in data analysis. ■