Osteoarthritis (OA) essentially represents failure of an organ, the synovial joint. As OA develops, all of the joint structures are affected including articular cartilage, calcified cartilage, subchondral cortical and trabecular bone, joint capsule, and synovium (Goldring & Goldring 2010). OA is hard to precisely define, but is considered to result from mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix (ECM), and subchondral bone. OA may be initiated by multiple factors, including genetic, congenital, developmental, metabolic factors, and trauma. In general, a key feature of OA pathogenesis is excessive joint loading.

Insight into the pathogenesis of OA has improved as knowledge of the tissue composition and structure of cartilage and subchondral bone and the molecular pathways that regulate cartilage and bone metabolism has advanced. The relative contributions of cartilage and bone adaptation to development of OA have not been precisely established, but both are important. Experimental studies in animal models have been important for defining time-dependent changes in cartilage and bone during OA initiation and progression, as well as defining genetic factors that impact OA pathogenesis.

An emerging idea is that the syndrome of OA really consists of a number of different disease sub-types that are stratified by various factors such as the degree of pathology in the different tissues that make up the joint, the rate of progression of disease over time, the severity of clinical signs, and the initiating cause(s), patient gender and age (Driban et al. 2010). Therefore OA may be early-, late-, post-traumatic-, age-related-, inflammatory-, cartilage-erosive-, osteophytic-, etc (Little & Zaki 2012).

**Articular cartilage**

The interterritorial matrix of hyaline cartilage is composed of a fibrillar collagen network that contains the large proteoglycan aggrecan, as well as several other molecules. Collagen fibers largely consist of type II collagen fibrils, with type XI and IX collagen within and on the fibril surface respectively. These minor collagens allow association with other matrix components and retention of proteoglycans. In addition, the pericellular matrix contains type VI collagen microfibrils. Hyaline cartilage is organized into distinct zones from superficial to deep, in which chondrocytes and matrix constituents vary. Chondrocytes in the superficial zone express lubricin, which is essential for boundary lubrication of the joint surface. Chondrocytes are habitually exposed to low oxygen tension and consequently express hypoxia-inducible factor-alpha (HIF-1α). HIF-1α is an important regulator of genes associated with cartilage anabolism and catabolism, such as vascular endothelial growth factor (VEGF) and SOX9. With aging, chondrocyte stress is increased and characteristic matrix changes develop, including accumulation of advanced glycation end products (AGEs), which enhance collagen cross-linking.

During OA initiation and progression, deterioration in the molecular composition and structural integrity of hyaline cartilage occurs. Chondrocytes can respond to mechanical forces, structural changes in the pericellular matrix, as well as intrinsic and extrinsic molecular signals. With development of OA, cellular proliferation leads to chondrocyte clustering and synthesis of specific matrix components is increased. As OA progresses, increased cartilage catabolism
develops, with gradual loss of proteoglycans and eventual loss of type II collagen. Important catabolic enzymes include matrix metalloproteinase (MMP)-1, MMP-3, MMP-9, MMP-13, and MMP-14, as well as the aggrecanases ADAMTS4, ADAMTS5, and ADAMST9 [a disintegrin and metalloproteinase with thrombospondin-like motifs]. Changes to chondrocytes during OA development include increased expression of regulatory proteins (IL-1, TNF-α, toll-like receptors [TLRs]), matrix proteins (collagen type II and X, aggrecan, link protein, osteopontin), stress and apoptotic markers (caspases 3 and 9, Bcl-2) and transcription factors (SOX9, RUNX2). These changes to chondrocytes are associated with fibrillation of the cartilage surface and production of fibrocartilage.

Calcified cartilage and tidemark advancement

The tidemark represents the demarcation line between hyaline articular cartilage and calcified cartilage. Widening of the zone of calcified cartilage as well as advancement of the tidemark and the presence of multiple tmidmarks are commonly found in OA joints. Targeted remodeling of joint microcracks from mechanical injury is likely important factor leading to these changes (Burr 2004, Muir et al. 2006). Vascular ingrowth from epiphyseal bone into the tidemark is associated with up-regulation of nerve growth factor and sensory nerve fiber sprouting, suggesting a link between osteochondral angiogenesis and joint pain (Walsh et al. 2010). With tidemark advancement, there is associated thinning of articular cartilage, as well as increasing mechanical stress on the deep zones of hyaline articular cartilage.

Subchondral bone

Periarticular bone consists of the subchondral plate, as well as subchondral trabecular bone and bone at the joint margins (Goldring & Goldring 2010). The subchondral plate consists of compact cortical bone that is separated from hyaline articular cartilage by calcified cartilage. Functional adaptation of periarticular bone will occur in response to joint loading events through modeling and remodeling. In general, modeling involves addition of new bone onto existing bone surfaces, whereas remodeling involves osteoclast activation on quiescent surfaces and removal of bone packets, followed by formation of new bone. Bone removal and formation are normally in balance. In addition, the quality of periarticular bone may be influenced by matrix mineralization. If bone turnover is low, hypermineralization may develop and lead to an increase in bone modulus. Conversely, poor mineralized may lead to a decrease in bone modulus (Burr 2004).

During development of OA, thickening of the subchondral plate develops together with modeling of subchondral trabecular bone, and formation of new bone formation at joint margins (osteophytes). In the late phase of OA, subchondral cysts may be found. Vascular invasion of the tidemark is associated with these bony changes (Muir et al. 2006, Walsh et al. 2007). Changes to subchondral bone are often associated with alteration to the contour of the overlying joint surface (Burr 2004). Adaptive change to periarticular bone begins very early in the initiation of OA.

Considerable controversy exists regarding the effects of subchondral bone adaptation to loading on adjacent hyaline cartilage. It has been hypothesized that adaptive enlargement of the thickness of the subchondral bone plate will lead to increased stiffness and associated adverse effects on the biomechanical environment of overlying cartilage (Radin & Rose 1986, Buckland-Wright 2004). Although subchondral bone volume is increased with OA, recent work has suggested that bone tissue modulus may actually be decreased, principally because of rapid bone
turnover, reduced bone volume and trabecular thickness, and reduced tissue mineralization (Day et al. 2001, Boyd et al. 2002, Buckland-Wright 2004). Such observations have important implications for OA treatment, particularly through use of drugs that may modulate bone remodeling.

With the wider use of MRI imaging in both humans and animals, the presence of discrete areas of increased signal intensity using fluid-sensitive MRI sequences has been found in subchondral bone in various OA conditions. This phenomenon was recently described in dogs with stifle arthritis associated with non-contact cruciate rupture (Winegardner et al. 2007). The presence of these lesions correlates with joint pain (Taljanovic et al. 2008). These lesions are associated with the presence of trabecular microfractures, fibrous replacement of bone marrow, and increased bone remodeling histologically (Taljanovic et al. 2008).

Formation of osteophytes at the joint margins is another key feature of OA joint degeneration. Osteophyte initiation is associated with proliferation of periosteal cells, differentiation into chondrocytes, and formation of a bony osteophyte through endochondral ossification. Local production of growth factors, such as transforming growth factor beta (TGF-β) and bone morphogenetic proteins (BMPs) is important for regulation of osteophyte formation (Blaney Davidson et al. 2007).

**Inflammation and joint damage**

In the past, OA has been considered to be a joint disease with little or no inflammatory component. However, synovitis is also common in patients affected with OA and typically exhibits features of a T lymphocyte immune response (Sakkas & Platsoucas 2007). These findings strongly suggest that the traditional view in both human and veterinary medicine that OA is a non-inflammatory disease must be reconsidered. OA should be considered an inflammatory condition. There are also distinct differences in synovial fluid cytokine expression between early- and late-OA. Up-regulation of IL-15 is a distinct feature of early OA, together with increased numbers of CD8+ T lymphocytes (Scanzello et al. 2007). IL-15 has a central role as an early mediator of immune responses and is principally activated through TLR signaling, particularly TLR-2 and -4 (Jung et al. 2007, Ling et al. 2009). Systemic changes to the musculoskeletal system can also be found in patients with OA (Ling et al. 2009). A unique serum protein signature precedes development of radiographic arthritis, suggesting that altered extracellular matrix metabolism plays a key role in the initiation of OA (Ling et al. 2009).

White adipose tissue has also been proposed as a major source of both pro- and anti-inflammatory cytokines, including interleukin-1 receptor antagonist (IL-1RA) and IL-10 (Dayer et al. 2006). Expression of leptin is also elevated in OA cartilage and osteophytes and stimulates IGF-1 and TGF-β synthesis in chondrocytes (Dumond et al. 2003). Dysregulation of the balance in signaling between leptin and other adipokines, such as adiponectin and resistin, may promote destructive joint inflammation in OA (Gomez et al. 2009).

**Genetics**

This is a rapidly evolving field. Results of epidemiological and familial studies, as well as analysis of rare genetic disorders, suggest that genetic mutations are an important factor in the risk of early-onset OA. Candidate gene and genome-wide association studies (GWAS) have implicated mutations in genes encoding ECM proteins and signaling molecules. Molecules of interest include fibroblast growth factor (FGF), TGF-β, BMPs, and components of the Wnt signaling pathway that regulates chondrocyte differentiation and maturation during skeletal development. It remains unclear to what extent genetic risk contributes to general OA
susceptibility in both animals and human beings. However, GWAS of dogs and human beings have discovered significant SNP associations with completely novel genetic risk factors (Zhou et al. 2010, Castano Betancourt et al. 2012).

Effects of mechanical loading of joints

OA often arises secondary to impact loading from serious joint injury. However, minor damage from habitual loading of joints is also an important causative factor in OA pathogenesis. The manner in which physiologically reasonable loads are applied to joints is critical to joint health. Loads that are applied too rapidly overwhelm viscoelastic shock absorption and lead to microdamage to cartilage and subchondral bone. In this regard, muscles provide the majority of impact absorption during joint loading. Therefore, muscle fatigue can be an important factor leading to joint damage in running athletes. As joint microdamage accumulates, reactivation of endochondral ossification occurs as a reparative mechanism. Over time, habitual loading that leads to joint damage will induce thickening of the subchondral plate, thinning of articular cartilage, and eventual loss of cartilage. Experimentally, vertical fibrillations in articular cartilage may not progress, as long as the laceration does not cross the tidemark into subchondral bone (Meachim 1963).

References