OSTEOARTHRITIS ACROSS THE SPECIES
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Osteoarthritis (OA) is a chronic progressive degenerative disease of synovial joints that leads to articular cartilage erosions, osteophyte formation, subchondral bone sclerosis and porosity, synovial hyperplasia and capsular fibrosis. The clinical outcome is pain and a reduction of function. OA has a diverse etiology, the mechanisms of the disease are highly complex and it's trajectory is variable. Interesting insights into the pathobiology of OA are provided by studies of both naturally occurring and experimental OA in various species. Biomechanical stresses, inflammation and deficient joint repair mechanisms act in concert to yield the OA phenotype.

1. BIOMECHANICAL STRESSES
It is well recognized that biomechanical stresses have a major etiologic role in OA. The magnitude and frequency (single or repetitive) of the biomechanical stress to the joint influences the disease trajectory.

*Single acute trauma:* A sudden application of a mechanical force to the joint surface occurs in acute injury and the extent of the damage is related to the energy at impact. Low energy impact causes subtle matrix and cellular damage in the superficial zone of the articular cartilage. High-energy events lead to intraarticular fracture implicating both cartilage and bone. Up to 14% of young people with a history of knee injury and 50% of patients with IA fractures in the knee develop post-traumatic osteoarthritis (PTOA). Joint ligament or capsule damage also increases OA risk 10 fold. Specific examples of acute impact trauma include soccer players with acute ACL rupture, horses in a fall, or dogs hit by a car.

It is now possible to quantify articular fracture severity and estimate damage to the articular surface by image analysis techniques in people. Surface area measurements of the comminuted bone fragments on CT reflect the amount of energy to create the intraarticular fracture and explain 70% PTOA in humans at 2 years. The same investigators reported that fracture displacement, contrary to belief, correlated poorly with subsequent joint degeneration.

*Repetitive trauma:* Repetitive trauma to the joint may arise in a variety of situations: due to occupation (racehorses, greyhounds, jackhammer operators, ballet dancers), abnormal joint shape (incongruency in hip dysplasia, osteochondritis dissecans), limb axis deviation (angular limb deformities in foals), joint instability (experimental and naturally occurring ACL deficiency) and obesity.

*Occupational repetitive trauma:* This form of OA most frequently arises in the fetlock and midcarpal joints in racehorses. A recent Canadian study found that up to one third of 1-2 year old racehorses have cartilage lesions in their fetlocks. We employed microCT to investigate equine midcarpal OA in racehorses and detected substantial remodelling in the subchondral bone in parallel with moderate surface cartilage changes underpinning the implication of both tissues in this disease. Cyclic loading results in the accumulation of microdamage by causing microcracks in the calcified tissues that may induce focal targeted modeling. An additional study published simultaneously, but in younger horses, provides additional insight into the effect of exercise on young developing cartilage. This study also revealed calcified cartilage thickening and microcracks in the calcified cartilage, even though the overlying cartilage was intact. Mineralized projections extending up from these cracks and associated with equine cartilage pathology have
also been observed by other investigators. Combined these studies highlight changes in the calcified cartilage in these joints that may be important in OA. Substantial subchondral bone remodelling with focal porosity has also been observed in the distal metacarpus in association with OA on CT and micro-CT examination and appears to be a common feature of repetitive trauma at specific sites in horses. The racehorse skeleton overall appears to accumulate microdamage that manifests not only as fatigue fractures but also OA.

Abnormal joint shape/incongruency: Abnormal joint geometry (e.g. hip dysplasia in dogs), combined with joint laxity, creates repeated focal supraphysiological stresses on cartilage and leads to OA. Genetics contribute to joint shape, joint tissue matrix quality and healing response. A recent study of OA secondary to fragmentation of the coronoid process of the ulna in dogs reported histological findings that mirrored those we observed in equine midcarpal OA and included increased porosity with bone remodelling, cartilage islands and subchondral fissures with decreased overlying cartilage proteoglycan, revealing some common features in the pathophysiological response.

Instability: A stable joint produces joint contact forces of normal intensity on its articular surface under physiological conditions. Unstable joints (e.g. ligament injury) may undergo abrupt repositioning that causes supraphysiological loading and chronic repetitive trauma to the cells and matrix. This is exploited in experimental models of OA in various species where the ACL is transected. It is an attractive model as it mimics, in part, naturally occurring disease in humans and dogs and has provided extensive information on the pathobiology of OA. A recent study in a rabbit model of partial instability (partial transection of the ACL) provided clear evidence for what we intuitively know, that cartilage degeneration is related to the amount of joint instability. From studies in my laboratory, osteophytes appear as early as 2 weeks post injury in this model of OA in rabbits. Bone marrow edema is also observed on MRI early in the disease trajectory. The subchondral bone density initially decreases before a later increase. However, this is an acute model as articular cartilage erosions occur as early as 8 weeks after injury. Emerging evidence now indicates that the pathogenesis of naturally occurring ACL rupture in dogs is much more complex (see Muir and Cook for more information). In the case of hip dysplasia in dogs, hip laxity increases as OA progresses exacerbating an already bad situation.

Obesity: Any discussion of joint biomechanical stresses would be incomplete without mention of the epidemic of obesity and knowledge that pets’ weights often parallel those of their owners. Obesity not only results in an increase in load but a change in joint kinematics. Obesity and varus malignment predisposes to medial femorotibial OA in humans.

2. INFLAMMATION
Joint inflammation, in concert with biomechanical stresses, is a major contributor to OA. It is a highly complex process and encompasses an intricate cellular crosstalk by all cells in and around the joint (chondrocytes, synovial membrane cells, ligament cells, osteoblasts and osteoclasts, neurons and blood elements). Molecules secreted by the cells activate predominantly catabolic signaling pathways. In the early phase of OA, the metabolic balance between anabolism and catabolism for joint tissue maintenance is tipped towards degradative events that overwhelm the joint tissues’ synthetic capacity and repair mechanisms. The central role of the proinflammatory cytokines IL-1 and TNFα as drivers of cartilage matrix degradation and synovitis is already well established in both human and veterinary OA literature.

Chondrocytes maintain the articular cartilage matrix by synthesis and degradation throughout life. They are protected by the matrix and sensitive to molecular and mechanical
signals. Matrix molecules such as GAG, collagen and fibronectin fragments are released into the synovial fluid following trauma. The response of chondrocytes to single acute impact trauma has now been extensively studied in many species. The collagen and fibronectin fragments released by injury activate chondrocyte and synovial cell degradative catabolic signaling pathways. Biomarker analysis measure some of these collagen fragments in synovial fluid in experimental OA in horses providing evidence of continuing progressive matrix breakdown. In addition the disruption of the matrix may render the chondrocytes more susceptible to further biomechanical stresses. Chondrocyte death (necrosis and apoptosis) occurs immediately following joint impact and continues for a few days beside cartilage fissures. The extent and depth of chondrocyte loss depends on the magnitude of stress and loading rate. Apoptosis also progresses to adjacent non-impacted areas. This "spread" of degradation mimics what has already been reported for naturally occurring OA lesions in people. Chondrocytes that remain viable are activated and, in the case of OA, although synthesis occurs, degradative events win the day. Chondrocytes release many biologically active factors following injury that add to the vicious cycle by both paracrine and autocrine signaling. This battery of molecules includes reactive oxygen species, proinflammatory cytokines (IL-1, IL-6, TNF α) NO, PGE2 and proteinases (aggrecanases and metalloproteases, cathepsins). The activated enzymes then attack and degrade the matrix molecules further exacerbating the insult. The synovial membrane also responds to these stimuli and osteoblasts and osteoclasts in the subchondral bone also wind up the degradatory process.

The complement pathway is also a player in OA. Complement proteins are overexpressed in OA synovial fluid in people and complement activation occurs in early OA and persists throughout the disease process. The membrane attack complex (MAC) of complement (C5b-9) is the chief culprit and forms pores when deposited on cell membranes and induces MMP-13 and proinflammatory cytokine expression in addition to causing cell lysis. OA cartilage fragments can activate MAC and it has been proposed that the release and exposure of cartilage ECM components may contribute to the pathophysiology of OA by activating complement.

Type II collagen is an important articular cartilage structural molecule and, when intact, it's triple helical domain is resistant to degradation by most enzymes. It was believed that MMP 13 was the only proteinase capable of initiating this primary cleavage. When the molecule is cleaved, many other enzymes can subsequently digest the fragments produced. This primary cleavage is believed to be a key irreversible event in OA and has been a target for MMP 13 inhibitors as many proinflammatory signals converge on this enzyme. However there is now emerging evidence that there is another enzyme, Cathepsin K (Cat K), capable of cleaving the intact triple helix of type II collagen in vivo. Traditionally, Cat K has been associated with osteoclasts but is now known to be expressed by both chondrocytes and synovial macrophages. We have shown Cat K activity in both equine and human OA cartilage. Cat K inhibition has been shown to have OA disease modification effects in ACLT models in rabbits. In transgenic mice over expression of Cat K induces OA and in Cat K knock-out mice with surgical instability OA is less. We are currently developing ELISA assays to detect it's breakdown in vivo.

3. FAILED REPAIR
Chondrocytes make, repair and remodel the extracellular matrix in which they reside. However, articular cartilage is known to have a limited regenerative capacity and the lesion size, age of patient and depth of the defect determine outcome. Type II collagen synthesis by chondrocytes has been measured in OA in horses and other species by measuring CPII, a biomarker of matrix synthesis revealing a synthetic response to tissue injury. Stem cells residing at the articular
cartilage surface, in the synovial membrane or arising from the subchondral bone may all also potentially contribute to the healing process, depending on the injury.

In the presence of OA, the repair mechanisms are overwhelmed by the chronic combination of inflammation and persisting abnormal or supraphysiological biomechanical stresses. Additional reasons for failed repair of articular cartilage in OA are manifold: lack of blood supply, inflammation induced suppression of matrix synthesis by chondrocytes, ageing effects (diminished response of chondrocytes to anabolic growth factors, less growth factors, reduced chondrogenic capacity of stem cells) and decreased cell density with OA. Furthermore, the capacity to heal articular cartilage defects may be genetically determined. A fascinating study of cartilage healing in murine ears and joints revealed that the capacity to regenerate articular cartilage is inversely correlated to development of PTOA and may be heritable.

WHAT LESSONS THAT CAN BE LEARNED FROM THE PATHOBIOLOGY OF OA?
1. Tailored, patient specific therapy necessary
2. Prevent injury from abnormal biomechanical stresses
3. Prevention of PTOA- early intervention to prevention chronic progression
4. Curb inflammation
5. Treat cartilage, synovial membrane, bone and muscles.

SELECTED REFERENCES


